Pediatric Hospital Medicine

A Case-Based Educational Guide

Editors
Melissa G. Cossey, MD, FAAP, and Lauren K. Gambill, MD, MPA, FAAP

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

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To our husbands, for their never-ending support

To our children, who inspire us in all that we do

And to our patients, who have taught us the most important lessons in pediatric hospital medicine

Equity, Diversity, and Inclusion Statement

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Introduction

Welcome to the first edition of *Pediatric Hospital Medicine: A Case-Based Educational Guide*! This book covers 50 common cases in pediatric hospital medicine and is written to help supplement the educational experience of trainees during their inpatient pediatrics rotation. Although the primary intended audience for this book is the pediatric intern, the content of this book should be helpful for medical students, residents, pediatric hospital medicine fellows, and practicing pediatric hospitalists, particularly those who educate medical students and residents.

We have chosen a case-based format that walks the reader from patient presentation through diagnosis, treatment, and resolution. We believe this flow provides realistic examples in an interesting, logical structure. Although this book cannot encompass every topic critical to the care of hospitalized children, we believe it serves as a wonderful springboard into the discipline, covering an incredible breadth of medical topics, leading the reader through the process of clinical decision-making, and providing evidence-based management plans that are both practical and comprehensive.

The book is written so that it can be used in several different ways. Some readers may prefer to read it cover to cover as part of their own self-directed learning. Others may use chapters as a resource for their care of hospitalized patients. Still others may use this book as an educational guide to help lead learning sessions.

This book includes unique features not traditionally found in similar books; these features are specifically designed to support learning and ultimately enhance patient care, including *Back to Basics* boxes, *Health Equity Focus* boxes, *Clinical Pearls*, and *Documentation Tips*.

Back to Basics Boxes

Back to Basics boxes highlight topics that provide general foundational knowledge needed to best navigate the clinical case. Many of these topics are not necessarily specific to pediatrics but are topics that all clinicians should know. The information in these boxes may be a refresher for some readers and new information for others.

Health Equity Focus Boxes

Inequity plagues our health care system and impacts the care of hospitalized children in many ways. When caring for the hospitalized child, it is imperative to recognize and address areas of health disparity and inequity. The primary approach to achieving health equity is to address social determinants of health (SDOH).

The Centers for Disease Control and Prevention defines SDOH as conditions in which people live, learn, work, or play that can affect a wide range of health and quality of life outcomes.[1] There are many SDOH, but they are generally divided into five domains:

- Economic stability
- Education access and quality
- Health care access and quality
- Neighborhood and built environment
- Social and community context

Throughout this book, topics related to SDOH are highlighted in *Health Equity Focus* boxes. Although these boxes are not all-encompassing, they are designed to help the reader identify common SDOH encountered in pediatric hospital medicine and explore solutions to address associated disparities.

Clinical Pearls

To reinforce the learning provided by each patient case, we have included a section titled *Clinical Pearls* in every case. This portion of the chapter summarizes the case's key takeaways, highlighting the medical knowledge needed to care for patients with the featured diagnosis.

Documentation Tips

Complete, timely, and accurate documentation is a vital component of patient care. Hospitalized children are often cared for by a team of interdisciplinary providers, and documentation in the medical record provides a means of communication between teams and team members. Additionally, clinician documentation serves as the basis for coding and billing. Because of this, it is important to document patient findings using clear language and terms that are compatible with coding.

The introduction of the electronic health record has provided a way to communicate medical information amongst multiple care providers in a setting that is easily legible, accessible, and shareable. It is also vitally important in extracting and compiling data to assist with quality and safety improvement. However, the electronic health record also contributes to the phenomenon of "note bloat," where reliance on the copy-forward functionality and autopopulation of data fields, which may not be up to date or medically relevant, leads to a lack of meaningful documentation. In other words, clinicians can say a lot without actually saying much at all. At present, there is little formal medical education provided on constructing truly meaningful medical record documentation, and feedback during inpatient rotations is often variable. Throughout this book, documentation tips and suggestions are included to help the reader develop their documentation skills to foster clear communication and ensure the best care of the hospitalized child.

The overarching goal of this book is to walk our readers through common cases in pediatric hospital medicine in a logical way that is both interesting and informative. We aimed to create an ideal resource for learners to improve their clinical skills and study for examinations and for educators to use as a guide when working with learners. Thanks in no small part to the contributions of over 100 physicians across the country, we believe we have achieved this goal. We hope that you agree.

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Austin, TX, 2022

Reference

1. US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Social determinants of health. Healthy People 2030. Accessed January 24, 2022. https://health.gov/healthypeople/objectives-and-data/social-determinants-health

CASE 1

Emma, a 16-Month-Old Girl With Vomiting and Diarrhea

CASE PRESENTATION

Emma is a 16-month-old girl with no significant medical history who presents to the emergency department (ED) with intractable vomiting and diarrhea. In the ED, she is found to have mild tachycardia and tachypnea. Emma is given a dose of oral ondansetron, but she continues to have vomiting after an oral challenge. She is then given an intravenous (IV) fluid bolus of normal saline (0.9%) at 20 mL/kg, and you are called with a request to evaluate her for admission. After speaking to the physician caring for her in the ED, you begin your patient evaluation.

Patient History and Review of Systems

Q: What information should you collect from Emma's caregivers?

- History of present illness
  - Onset and duration of illness
  - Number of vomiting and diarrhea episodes and estimated diarrheal volumes
  - Visible blood or mucus in the stool, color of vomitus
  - Recent oral intake
  - Signs of dehydration, such as decreased urine output, sunken appearance of eyes, malaise, lethargy, irritability, or absence of tears
  - Associated symptoms, such as fever, headache, abdominal or back pain, altered mentation, rash, or urinary symptoms
  - Most recent preillness weight
- Medical history, including underlying health status, history of similar episodes, history of abdominal surgeries, and immunization status (specifically rotavirus vaccine status)
- Medications, including recent use of antibiotics and over-the-counter medications
- Dietary history, especially any consumption of unpasteurized dairy products or juices or undercooked meat, shellfish, or eggs
- Social history, including sick contacts, child care attendance, and travel and activity history, particularly recent water-related activities and animal contact

CASE FOCUS

History and Review of Systems

From her parents, you learn that Emma has been sick for 3 days. Her illness started with nonbloody, nonbilious vomiting and fevers up to 39.2 °C (102.6 °F). She has been fussy, but because she says only a few words, her parents have had difficulty determining whether she is having any abdominal pain. Her parents estimate that she has had 5 to 10 episodes of emesis and 10 to 15 episodes of large-volume watery stools on each day of her illness. They deny any visible blood or mucus in her stool. The family has had difficulty determining her urine output because of the frequency and volume of her stools. Emma has not been drinking much for the past few days and has become increasingly irritable and somnolent. She has had decreased tear production and sunken eyes.

Emma does attend child care, but her family is not aware of any recent sick contacts. They deny recent travel, swimming, antibiotics, animal exposures, or changes in her diet. Emma is healthy, growing and developing well, and appropriately immunized according to the Centers for Disease Control and Prevention (CDC) schedule.

The family has been treating her at home with appropriately dosed acetaminophen and ibuprofen and having her drink water, juice, oral rehydration solution (ORS), and cow milk as tolerated. Her parents report that her weight at a pediatrician appointment 4 weeks prior was approximately 11.4 kg.

Physical Examination

Q: What parts of the physical examination should you focus on for Emma?

- Complete set of vital signs
- Weight, with comparison to most recent weight
- Level of consciousness and ability to arouse normally
- Anterior fontanelle (closed, sunken, flat, or full)
- Appearance of eyes (sunken, injected, or icteric)
- Presence or absence of tears with crying
- Mucous membranes (moist, sticky, or dry)
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Gastrointestinal: abdominal distension, quantity and quality of bowel sounds, abdominal tenderness and guarding, presence of a mass, visual appearance of stool
- Respiratory: auscultation and depth of respirations
- Costovertebral angle tenderness
- Abdominal skin turgor
- Rashes
- Neurologic: altered level of consciousness, ataxia, focal neurologic deficits

CASE FOCUS

Physical Examination

Emma's vital signs show that she is afebrile at 37 °C (98.6 °F). The mild tachycardia (resting heart rate: 150 beats/min when calm) and mild tachypnea (respiratory rate: 30 breaths/min) initially present in the ED have now resolved after her fluid bolus.[a] She has a normal blood pressure for age and normal oxygen saturation. Her weight on arrival to the ED was 10.8 kg.

On examination, Emma appears listless but is responsive and appropriately fearful of you. Her anterior fontanelle feels closed. You notice the presence of tears when she cries, but her oral mucosa appears sticky. No scleral icterus or conjunctival injection is present. When calm, she has a normal cardiac examination. Her peripheral pulses are normal; however, her capillary refill time is mildly prolonged (approximately 3 seconds), and her hands and feet are slightly cool. Her abdomen is soft and nontender with no masses. She does have increased frequency of bowel sounds. Her lungs are clear with normal respirations. There is no appreciable costovertebral angle tenderness. The remainder of Emma's examination is normal, including a nonfocal neurologic examination. Visualized stool in her most recent diaper is light brown and watery, completely soaked into and filling the diaper.

[a] See Table A.1 in the Appendix for normal pediatric vital sign reference values by age.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with vomiting and diarrhea?

There are many etiologies of vomiting and diarrhea in children. Based on Emma's presentation, you divide the potential causes into diagnoses that seem more and less likely, as shown in Table 1.1.

Table 1.1. Differential Diagnosis for a Young Child With Vomiting and Diarrhea

Diagnoses of highest suspicion	• Acute infectious gastroenteritis (viral, bacterial, parasitic)[a] • UTI
Other diagnoses to consider	• Allergic reaction, such as a delayed hypersensitivity reaction (eg, FPIES) • Appendicitis • CNS infection • DKA • Hirschsprung-associated enterocolitis • Intussusception • Malrotation with or without volvulus • MIS-C • Peritonitis • Small-bowel obstruction • Toxic ingestion • TSS

Abbreviations: CNS, central nervous system; DKA, diabetic ketoacidosis; FPIES, food protein–induced enterocolitis syndrome; MIS-C, multisystem inflammatory syndrome in children; TSS, toxic shock syndrome; UTI, urinary tract infection.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for children who present with acute onset of vomiting and diarrhea?

- As illustrated by the differential diagnoses, vomiting and diarrhea can be common presenting symptoms for many conditions. The diagnostic evaluation should therefore be guided by the suspected etiology.
- For patients whose presentation is primarily characterized by vomiting, clinicians should be mindful to consider (and exclude, if necessary) etiologies that would require urgent evaluation and treatment, including but not limited to appendicitis, intestinal volvulus, intussusception, new-onset diabetes, metabolic crisis, or intracranial infection/pathology. For Emma, you are less concerned with these etiologies based on her history and examination.
- For patients with suspected uncomplicated acute gastroenteritis (AGE) who have minimal, mild, or moderate dehydration, diagnostic testing is not generally indicated. Severe dehydration or anuria should prompt testing of serum electrolytes, blood urea nitrogen (BUN), and creatinine. Refer to Table A.2 in the Appendix for the classification of dehydration.
- Certain illness features should prompt further evaluation, including visibly bloody or mucoid diarrhea, significant abdominal pain or fever, relevant travel or exposure history, persistent diarrheal episodes (defined as lasting >14 days), or diarrhea in an immunocompromised patient. For these patients, the following testing should be considered:
  - Stool culture for Shiga toxin–producing *Escherichia coli*, *Yersinia enterocolitica*, *Salmonella* spp, *Shigella* spp, and *Campylobacter* spp[a]: Of note, some children with *Shigella* infections may have generalized seizures during acute illness.
  - Stool testing for *Clostridioides difficile* (formerly called *Clostridium difficile*)[a]: Testing may vary by institutional protocol but should include some combination of glutamate dehydrogenase testing, nucleic-acid amplification testing, or toxin testing. *C difficile* testing should also be considered for hospitalized or institutionalized patients who develop diarrhea. Of note, *C difficile* testing for infants and children younger than 2 years is generally not recommended, as asymptomatic carriage is common.
  - Microscopy for ova and parasites[a]: To increase the test's sensitivity, it may be necessary to test 3 stool samples, each collected on 3 separate days. Alternatively, direct fluorescent antibody testing can be performed for common parasites such as *Cryptosporidium* spp and *Giardia lamblia*.
  - Complete blood cell count and serum electrolyte testing if hemolytic uremic syndrome is suspected.
  - For immunocompromised patients, viral stool testing.
  - Stool leukocytes testing usually is not indicated.

[a] At many institutions, obtaining a stool pathogen panel by polymerase chain reaction testing is more timely and cost-effective than stool culture analysis, *C difficile* testing, and testing for ova and parasites.

CASE FOCUS

Diagnostic Evaluation

The physician in the ED obtained serum laboratory studies when placing Emma's IV line. Emma's laboratory results are as follows:

Laboratory test	Result	Reference range
Sodium	141 mEq/L (141 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	106 mEq/L (106 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)	18–24 mEq/L (18–24 mmol/L)
Anion gap	20 mEq/L (20 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	24 mg/dL (8.57 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.6 mg/dL (53.0 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	72 mg/dL (4.0 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)

Abbreviation: BUN, blood urea nitrogen.

Given Emma's history of fever during her illness, you consider obtaining a stool culture but decide that is unnecessary because Emma does not have any other symptoms consistent with a bacterial infection. Based on Emma's laboratory results, her history, and her examination, you decide that no further diagnostic testing is indicated at this time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Emma?

In thinking through her case, you decide to begin by interpreting the key findings from Emma's history, examination, and diagnostic evaluation to develop a list of significant findings. You can then narrow your differential diagnosis to the most likely etiology and generate admission criteria for Emma's suspected diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Assessment of hydration status: You believe Emma is dehydrated based on her history and examination, but you are curious whether there are standard ways to classify and treat dehydration. In searching the literature, you are surprised to find that although many dehydration scales have been developed, there does not appear to be one standardized, highly validated scale that reliably predicts the severity of a child's dehydration and guides treatment. Because of this, you decide to utilize the CDC guidelines for assessing dehydration.
     - First, you calculate Emma's percentage weight loss with this illness.
       - If she weighed approximately 11.4 kg at 15 months of age, her anticipated weight 4 weeks later would be approximately 11.6 kg based on World Health Organization growth curves. With a presenting weight of 10.8 kg, her percentage weight loss with this illness is 7%. The amount of weight loss with this illness classifies Emma as having mild to moderate dehydration according to the CDC (refer to Table A.2 of the Appendix).

    - The accuracy of this method is highly variable, depending partly on the relative recency and accuracy of the patient's preillness weight, with a more recent weight required in a younger child. Because Emma's preillness weight is an approximation by her parents and is not verified in the medical record, using only this method to calculate the severity of Emma's dehydration may be inaccurate.
  - Next, you decide to apply Emma's physical examination findings to the CDC dehydration assessment scale as shown in Table A.2 of the Appendix. Based on this, you estimate she has mild to moderate dehydration still present at the time of your evaluation.
- Evaluation of other notable findings.
  - History: Emma's history is significant for acute onset of a febrile illness characterized by nonbloody, nonbilious vomiting and watery, nonbloody diarrhea. She did not tolerate an attempt at oral rehydration in the ED. She has no other clear risk factors or exposures but does attend child care.
  - Physical examination: Her examination shows her to be dehydrated. Importantly, she is appropriately responsive to your examination, and her abdomen is nontender. The lack of abdominal tenderness helps to decrease your suspicion for significant intra-abdominal pathology. Her examination is otherwise nonfocal and reassuring against an intracranial infection.
  - Diagnostic evaluation: Emma's laboratory tests show a low potassium level (hypokalemia), a low bicarbonate level with an elevated anion gap (high anion gap metabolic acidosis; see Box 1.1 for different causes), and elevated BUN and creatinine levels. The increased BUN and creatinine likely reflect a prerenal acute kidney injury (AKI).

2. **Develop the list of findings.**

Q: What major findings have you identified for Emma?

- Mild to moderate dehydration
- Acute onset of vomiting and diarrhea associated with fever
- Metabolic acidosis with a high anion gap, likely related to ketoacidosis and stool bicarbonate losses
- AKI
- Hypokalemia

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Emma's presentation?

You believe that AGE is the most likely cause of Emma's symptoms based on her history; the absence of concerning findings on abdominal, pulmonary, cardiac, dermatologic, and neurologic examinations; and the results of her diagnostic evaluation.

Q: What are the infectious etiologies of uncomplicated AGE in childhood?

While viral etiologies of AGE are among the most common in the United States, bacterial and parasitic etiologies also need to be considered. Box 1.2 lists infectious agents from each of these 3 categories.

Q: What factors in Emma's history help you decide between viral, bacterial, or parasitic causes of her illness?

The lack of blood or mucus in her stool and lack of significant abdominal pain, while not definitive, weigh against a bacterial etiology. There is no concerning travel, activity, or dietary history, so a parasitic infection and certain bacterial infections are less likely. Her young age and lack of recent antibiotic use would make *C difficile* unlikely. These combined factors as well as her child care attendance point toward viral AGE as the most likely diagnosis.

Box 1.1. Causes of Metabolic Acidosis

HIGH ANION GAP Increased production or decreased clearance of endogenous acids or ingestion of an exogenous acid	NONANION GAP Bicarbonate losses or increased chloride administration/absorption
• Uremia/renal failure • Ketoacidosis — Diabetic ketoacidosis — Starvation ketoacidosis — Alcoholic ketoacidosis — Ketogenic diet — Inborn errors of metabolism • Poisonings and medications that create anions — Carbon monoxide — Ethylene glycol — Iron — Isoniazid — Methanol — Paraldehyde — Salicylates — Toluene • Inborn errors of metabolism by production of other organic anions • Rhabdomyolysis • Lactic acidosis — Tissue hypoxia (shock, hypoxemia, tissue necrosis, severe anemia) — Exercise — Ethanol intoxication — Liver failure — Malignancy — Intestinal bacterial overgrowth, especially in patients with short bowel syndrome (D-lactic acidosis) — Inborn errors of metabolism, especially mitochondrial disorders — Medications (salicylates, nucleoside reverse transcriptase inhibitors, metformin, propofol, isoniazid, linezolid)	• Renal tubular acidosis • Diarrhea • Aldosterone deficiency, such as congenital adrenal hyperplasia • Small bowel fistulas • Excess chloride administration (iatrogenic from intravenous fluids or total parenteral nutrition) • Renal failure • Urinary tract diversions through intestinal lumen • Ammonia chloride ingestion • Posthypocapnia • Medications, such as topiramate trimethoprim-sulfamethoxazole, spironolactone, acetazolamide, and cyclosporine

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with viral AGE and dehydration?

Most patients with AGE and dehydration can be safely managed as an outpatient; however, hospitalization should be considered in the following scenarios:

- The child's caregivers are unable to provide appropriate care at home, obtain timely follow-up, or return to care in the event of worsening symptoms.
- The child has intractable vomiting, refuses ORS, or is not able to consume sufficient ORS volumes to keep up with ongoing fluid losses.

Box 1.2. Infectious Causes of Acute Gastroenteritis in Children

Viral	Bacterial	Parasitic
Noroviruses (Norwalk-like viruses) Rotaviruses Enteroviruses Enteric adenoviruses Sapovirus Astroviruses Hepatitis A	Nontyphoid *Salmonella* spp *Campylobacter jejuni*[a,b] *Shigella* spp *Yersinia enterocolitica*[a] Shiga toxin–producing *Escherichia coli* (also known as enterohemorrhagic *E coli*)[c] *Salmonella* Typhi and *Salmonella* Paratyphi *Clostridioides difficile* Enteropathogenic *E coli* Enterotoxigenic *E coli* Enteroaggregative *E coli* Enteroinvasive *E coli* *Vibrio cholerae* Foodborne, highly emetogenic: *Bacillus cereus, Clostridium perfringens, Staphylococcus aureus* Other foodborne etiologies: *Listeria monocytogenes, Clostridium botulinum,* noncholera *Vibrio* spp	*Cryptosporidium* spp[d] *Giardia lamblia* (also known as *Giardia intestinalis*) *Cyclospora cayetanensis* *Entamoeba histolytica* *Cystoisospora belli* *Blastocystis hominis*[e,f] *Balantidium coli*[e,g] Helminths, such as *Strongyloides stercoralis* or *Trichinella* spp[e]

[a] These organisms are known to cause a pseudoappendicitis from mesenteric adenitis.

[b] Other species are less common.

[c] O157:H7 is one of many serotypes.

[d] *Cryptosporidium hominis* is the most common species.

[e] Infections are usually asymptomatic.

[f] Organism's role in causing diarrhea is controversial.

[g] Infection is rare in the United States.

- Severe dehydration or anuria exists (see Table A.2 in the Appendix).
- Significant electrolyte abnormalities are present.
- The child is unusually drowsy or irritable.
- Uncertainty about the diagnosis or illness severity exists, especially in an infant or young child.

You feel that Emma meets the criteria for hospitalization based on her inability to keep up with her fluid losses at home.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Emma is a 16-month-old otherwise healthy girl who is in the ED with mild to moderate dehydration, hypokalemia, AKI, and metabolic acidosis from suspected viral AGE. She is not currently tolerating oral fluids and therefore requires hospitalization for ongoing treatment and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Emma's symptoms, you review the literature to remind yourself about the treatment of dehydration and AGE in children. You decide to divide treatment considerations into the following components:

1. **Rehydration:** The goal of rehydration therapy is to replace the patient's fluid deficit within 3 to 4 hours. The manner of rehydration depends on the severity of the patient's dehydration as follows:
   - Minimal or no dehydration: No rehydration therapy is needed.
   - Mild to moderate dehydration: Correct the fluid deficit over a period of 3 to 4 hours. If the patient is tolerating oral fluids, start with oral rehydration therapy by spoon or syringe feeding. Infants and young children with ongoing vomiting can better tolerate a slow drip of ORS via a nasogastric tube (NGT), if needed. For persistent vomiting or parental preference, IV fluids can be used instead. There is no significant difference in outcomes among oral, NGT, and IV fluid rehydration. While there may be a risk of increased vomiting with oral rehydration, it has fewer side effects when compared with use of IV fluids.
   - Severe dehydration: Severe dehydration is a medical emergency that requires rapid administration of IV fluids in the form of isotonic crystalloid at volumes of 20 mL/kg until pulses, perfusion, and mental status return to normal based on frequent reassessment. For infants who are malnourished, consider providing smaller fluid blouses of 10 mL/kg so as not to cause cardiac compromise. Once perfusion is improved, administer 100 mL/kg ORS over 4 hours or IV fluids at twice the child's maintenance fluid rate.
2. **Maintenance of hydration:** To maintain hydration, patients need their maintenance fluid requirements met *plus* replacement of ongoing losses.

BACK TO BASICS

The Holliday-Segar Method for Calculating Maintenance Fluid Requirements in Children

While a patient's fluid requirements should be individualized based on any underlying conditions as well as needs related to their acute illness, the Holliday-Segar method helps determine a patient's maintenance fluid requirements assuming normal physiology. This method was derived from energy expenditure and estimates daily or hourly fluid requirements based on the patient's weight. The formula for calculation of the hourly rate is frequently simplified as the "4, 2, 1 rule."

To use this method, the hourly rate is calculated by adding the following values:

- 4 mL/kg/h for the first 10 kg of the patient's weight
- 2 mL/kg/h for every kilogram between 10 and 20 kg of weight
- 1 mL/kg/h for every kilogram of weight above 20 kg

The maximum maintenance fluid rate is generally considered to be 100 mL/h, although some patients may require more, depending on their individual circumstances. The daily and hourly maintenance fluid calculations, as well as an example calculation, can be found in Table A.4 of the Appendix.

- Rate: For Emma, using an estimated preillness weight of 11.4 kg, the Holliday-Segar method yields an hourly rate of approximately 43 mL/h ([4 mL/kg × 10 kg] + [2 mL/kg × 1.4 kg]).
- Electrolyte composition of fluids.
  - Sodium: There is a growing body of evidence that administration of hypotonic IV fluids places children at risk of iatrogenic hyponatremia, which can cause symptoms such as nausea, vomiting, headache, confusion, or lethargy. In certain disease states, particularly pulmonary diseases, central nervous system (CNS) diseases, nausea, pain, and postoperatively, the body secretes excess arginine vasopressin, leading to the retention of free water. For otherwise healthy children who have nausea and vomiting, routine use of an isotonic electrolyte solution is now recommended. Exceptions to this are patients with voluminous watery diarrhea, neurosurgical disorders, traumatic brain injury, cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, severe burns, or adrenal disorders; neonates younger than 28 days or in the neonatal intensive care unit; and patients older than 18 years, for whom an individualized approach is recommended.
  - Potassium: For most pediatric patients with normal renal function but poor oral intake, 10 to 20 mEq/L (10–20 mmol/L) of potassium is added to their maintenance fluids to meet the body's potassium requirements, although this may need to be adjusted based on the serum potassium level when known. To avoid iatrogenic hyperkalemia, most sources recommended waiting to add potassium until the patient has been rehydrated with evidence of adequate urine output.
  - Dextrose: Most children without diabetes mellitus or significant hyperglycemia should receive 5 g/dL (278 mmol/L) of dextrose ("D5") in their maintenance fluids to prevent catabolism.
  - Other electrolytes: For children receiving IV fluid for only a few days, electrolytes such as calcium, phosphorous, and bicarbonate are generally not added to their IV fluid; however, patients with significant bicarbonate losses, such as is common in diarrhea, may benefit from the addition of acetate to their IV fluid.
  - Refer to Table A.3 in the Appendix for a comparison of the electrolyte composition of commonly prescribed IV fluid to human plasma.
- To replace ongoing losses, accurate measurement of the child's losses must be obtained. When there is difficulty ensuring accuracy of stool volumes and urine output, frequent patient weights may be helpful to ensure the patient remains above admission (dehydrated) weight. The composition of replacement fluids is highly variable and decisions should take into consideration the electrolyte composition of the fluids that are being replaced (eg, gastric, urine, ileostomy, diarrhea).
  - To estimate stool output, it is common to use weighed diapers in the hospital setting, subtracting the dry weight of the diaper.
  - Distinguishing between liquid stool and urine can be challenging. When necessary, attempts may be made to collect urine separately, either by placing a collection bag over the child's urethra or by temporarily placing a urinary catheter.
    - If the child's losses can be accurately measured, the CDC recommends administering 1 mL of replacement fluid for each gram of stool or vomitus. In the hospital setting, replacement fluid is commonly administered intravenously but can be administered enterally with ORS given orally or via NGT.
    - If losses cannot be measured, the CDC offers 2 different methods to determine replacement volumes.
      - Method 1: For each watery stool, administer 10 mL/kg of body weight in ORS; for each episode of emesis, administer 2 mL/kg of body weight in ORS.
      - Method 2: For patients weighing less than 10 kg, administer 60 to 120 mL ORS for each diarrheal stool or vomiting episode (maximum daily volume of approximately 500 mL); for patients weighing more than 10 kg, administer 120 to 240 mL ORS for each diarrheal stool or vomiting episode (maximum daily volume of approximately 1 L).

3. Correction of and monitoring for electrolyte derangements

- Because hypokalemia contributes to intestinal ileus, it can be helpful to correct this. Correction of hypokalemia enterally is preferred to avoid the risk of arrhythmias with IV infusions.

- Given the risks of electrolyte abnormalities, especially in patients with large volume losses or who have continued need for IV fluid therapy, ongoing monitoring of serum electrolytes may be needed.

4. **Antiemetics:** In children, ondansetron is now the antiemetic of choice given its relatively benign side effect profile, although its use should be avoided in patients with long QT syndrome, and it should be used with caution in patients taking other QT-prolonging agents or serotonergic drugs. Studies indicate that use of antiemetics (ondansetron, in particular) is associated with a shorter duration of vomiting and a decreased incidence of hospitalization when given in the ED. Use of antiemetics such as prochlorperazine, promethazine, and metoclopramide should be avoided in infants and young children given the risk of sedation and extrapyramidal symptoms, such as acute dystonic reactions.
5. **Anti-infectives:** Because viral AGE and self-limited bacterial enteritis are the most common causes of vomiting and diarrhea in otherwise healthy children, routine use of anti-infectives is not recommended, even in the setting of bloody diarrhea.
   - Empiric antibiotics may be considered in the following scenarios:
     - Patients younger than 3 months who are ill appearing or when a bacterial etiology is suspected
     - Ill-appearing patients with a high clinical suspicion for *Shigella* spp (fever, scant bloody stools, abdominal cramps, and tenesmus)
     - Patients with sepsis and suspected enteric fever, after blood and stool cultures have been obtained
     - Immunocompromised patients
   - For treatment of specific pathogens, refer to the most recent edition of the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases.*
6. **Antidiarrheal agents:** Given the concern about side effects with the use of antimotility agents (including drowsiness, ileus with associated abdominal distension, and nausea) and bismuth subsalicylate agents (salicylate toxicity and risk of Reye syndrome) in children, routine use of these agents is not recommended in patients younger than 18 years.
7. **Diet:** Allowing an unrestricted normal diet, including breastfeeding if applicable, is recommended.
   - Dietary restrictions and the practice of gut rest are rarely indicated.
   - Only a small percentage of children with AGE experience carbohydrate malabsorption during illness, resulting in an increase in stool output after drinking fluids or consuming foods high in simple sugars, including some forms of ORS. If there is concern for carbohydrate malabsorption, offering ORS and foods with fewer simple sugars is indicated.
     - Lactose avoidance is usually unnecessary but may be helpful in some infants and children, especially in those with severe dehydration or those with a clear worsening of diarrhea after consuming lactose-containing foods or beverages. Restricting human (breast) milk intake is generally not recommended.
8. **Antipyretics and analgesics**
   - Acetaminophen: Acetaminophen is safe in the setting of dehydration and can be helpful for both pain and fever.
   - Nonsteroidal anti-inflammatory drugs: Nonsteroidal anti-inflammatory drugs such as ibuprofen should be avoided in the setting of gastritis or gastrointestinal bleeding and until dehydration has resolved (to prevent renal injury).
   - Antispasmodics (anticholinergics): While some patients with abdominal cramping may find relief from occasional use of hyoscyamine or dicyclomine, routine use of these medications is not recommended.
   - Opiates: Although it is ideal to avoid opiates in patients with infectious or inflammatory gastroenteritis because of their effects on intestinal motility, opiates can be helpful in patients experiencing significant pain. Care should be taken when using opiates in patients with AKI, as decreased renal clearance can lead to poor clearance of metabolites, increasing the risk of respiratory depression and somnolence.
9. **Supplemental therapies**
   - Probiotics: *Lactobacillus* spp appear to be safe and may be effective in the treatment of acute infectious diarrhea and antibiotic-associated diarrhea in children.

- Zinc: Although studies have demonstrated that zinc supplementation is useful for the treatment and prevention of diarrheal diseases in developing countries, it has limited utility in developed nations and is therefore not recommended for routine use in the United States.

10. **Skin care:** Generous application of barrier creams to the buttocks and perineum can help protect the skin from breakdown or allow already irritated skin to heal.

CASE FOCUS

Plan for Treatment and Monitoring

- **Rehydration therapy:** Based on Emma's examination findings during your admission assessment and knowing that she is not yet tolerating oral fluids, you decide to provide additional IV fluid to improve her peripheral perfusion. Given that part of her fluid deficits were replaced in the ED, you decide to replace another 500 mL, which will be infused over 3 hours.
- **Maintenance therapy:** Given Emma's poor oral intake, you decide to start maintenance fluids and replace her ongoing losses. Her parents decline the option of NGT placement, so you decide to provide IV fluid instead. Based on your Holliday-Segar calculations, you estimate that Emma requires 43 mL/h of 5% dextrose in normal saline adding 20 mEq/L (20 mmol/L) of potassium chloride once adequate urine output is established. For her ongoing losses, you decide to provide stool replacements with IV normal saline every 6 hours. Once she is tolerating oral intake, stool replacements can be provided as ORS.
- **Antiemetics:** You order ondansetron as needed to treat nausea and vomiting.
- **Anti-infectives:** None are indicated, as a viral etiology is suspected.
- **Correction of electrolyte derangements:** Given Emma's mild hypokalemia and continued poor oral intake, you decide to provide a small dose of oral potassium. If her vomiting and diarrhea are not improving throughout the day, you will obtain a set of repeat electrolytes in 12 to 24 hours, depending on the amount of her fluid losses.
- **Monitoring:** You order strict monitoring of intake and output, vital signs every 4 hours, and daily or twice daily weights.
- **Probiotics:** Based on the available evidence, you start *Lactobacillus rhamnosus* twice daily.
- **Diet:** You allow an unrestricted diet and encourage Emma's family to continue offering her food and beverages as tolerated.
- **Antipyretics and analgesics:** You order acetaminophen as needed for pain or fever.
- **Skin care:** You order 40% zinc oxide cream to be applied generously to the buttocks and perineum with diaper changes.

Case Resolution

Over the next 2 days, Emma's vomiting resolves, her oral intake slowly improves, her activity level returns toward baseline, and her diarrhea significantly slows. She requires stool replacements for the first 12 hours of her stay, and her follow-up electrolyte panel the morning after admission shows resolution of her acidosis, hypokalemia, and AKI. Her clinical course supports the presumptive diagnosis of viral AGE, so no further evaluation is required.

Discharge Criteria

Q: How do you know when Emma is ready to go home?

You can feel comfortable discharging your patient with dehydration due to AGE when the following criteria are met:

- The patient is tolerating enough oral intake to account for losses from vomiting or diarrhea.
- The patient's caregivers are educated about oral rehydration and the signs of dehydration.
- You have no concerns for an acute abdominal process or a CNS process.
- Adequate follow-up is ensured.

Anticipatory Guidance

Q: What instructions should you provide to Emma's caregivers on discharge?

- Provide additional oral fluids for each episode of vomiting or diarrhea at home.
- Continue to monitor the amount and color of her urine to ensure adequate hydration.
- Emma should remain home from child care until her fever, vomiting, and diarrhea have resolved.
- Emma should return to care for diarrhea lasting longer than 7 days; lethargy; inability to tolerate oral fluids; new blood in her stool; a lack of urine for more than 8 hours; worsening abdominal pain; the development of jaundice, severe headache, or neck pain; or any new symptoms.

Clinical Pearls

- Dehydration scales are imperfect but can be useful in guiding decisions about fluid resuscitation.
- The most common etiology of vomiting and diarrhea in childhood is viral AGE, which generally requires no diagnostic evaluation apart from a history and physical examination.
- ORSs are the mainstay of dehydration treatment.

Documentation Tips

- Document signs of dehydration present on examination (eg, absent tears, delayed capillary refill, dry mucous membranes, lethargy). It is important to document signs that were present at the time of initial evaluation in the ED and not just at the time of admission.
- Specify the percentage of weight loss, if known.
- Document oliguria if urine output is less than 1 mL/kg/h.
- Document any associated medical complexity or comorbid medical conditions.
- On daily progress notes, document if there is ongoing need for IV fluid or the presence of feeding intolerance.

Suggested Readings

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CASE 2

Anita, a 4-Month-Old Girl With Respiratory Distress

CASE PRESENTATION

You are called to the emergency department (ED) to examine Anita, a 4-month-old girl, who presented 1 hour ago with increased work of breathing. You have been told by the ED physician that on arrival, Anita was noted to have subcostal retractions and a respiratory rate between 70 and 79 breaths/min. She was found to have crackles and wheezes on auscultation of her lungs and was given 5 mg of albuterol through a nebulizer without significant improvement. The ED physician is concerned that Anita will need further respiratory support because she continues to have significantly increased work of breathing, and, thus, she asks you to evaluate Anita for admission to the inpatient unit.

Patient History and Review of Systems

Q: What information should you collect from Anita's caregivers?

- History of present illness
  - Onset and duration of symptoms
  - Home treatments (eg, nasal saline, suctioning, humidifiers)
  - Recent dietary history and any signs of dehydration, including decreased number of wet diapers compared to normal, dry mouth, absence of tears, refusal to feed, or coughing or choking with feeds
- Associated symptoms such as cough, congestion, fever, or vomiting
- Medical history
  - Birth history and prenatal history, specifically whether the infant was born full term and whether there were any respiratory complications after birth
  - Respiratory history, including previous hospitalizations or respiratory infections
  - History of atopy
  - Immunization status
- Medications, including use of bronchodilators, steroids, or antibiotics
- Family history, especially noting history of atopy, and first-degree relatives with asthma
- Exposure history, including travel, sick contacts, child care attendance, or exposure to smoke or smokers

CASE FOCUS

History and Review of Systems

Once you arrive in the ED, you learn that Anita has been sick for 3 days. Her illness started with clear rhinorrhea and a wet-sounding cough. The cough has become more frequent today. Her mother noticed that she seemed to be short of breath starting this morning, and her breathing has progressively worsened through the day. Anita's mother reports fever as high as 38.6 °C (101.5 °F; obtained temporally) on the first day of illness, but Anita has not been febrile since. Anita's mother has been using nasal saline with a nasal aspirator at home and obtaining large volumes of clear mucus from Anita's nose, which provides some temporary relief. Anita is exclusively breastfed and continues to breastfeed but must take frequent breaks due to nasal congestion. She has had 4 wet diapers since yesterday, which is significantly decreased from her baseline of approximately 8 wet diapers per day.

Anita was born full term, without complications, and she has never had previous respiratory problems. She takes no regular medications at home but did take 1 dose of acetaminophen 2 days ago for her fever. She has not traveled recently. She does have an older sibling who attends child care and had a cough and congestion earlier this week. Anita has no history of coughing or choking with feeds. She is up to date on her vaccinations and does not have any known food allergies, eczema, or prior wheezing episodes. There is no smoke exposure at home, and no one in the immediate family has asthma.

Physical Examination

Q: What parts of the physical examination should you focus on for Anita?

- Compete set of vital signs
- Level of consciousness and ability to arouse normally
- Fontanelle (sunken, flat, or full)
- Mucous membranes (moist, tacky, or dry)
- Nares (patency, nasal turbinate swelling)
- Ears, with visualization of bilateral tympanic membranes (bulging, erythema, mobility, purulence)
- Respiratory, including work of breathing, auscultation of lungs for crackles, wheezes, rhonchi, quality of air entry, and symmetry between left and right sides

BACK TO BASICS

Evaluating for Work of Breathing

Indications of work of breathing in a patient include the following:

- Asymmetry of chest or chest expansion.
- Use of accessory muscles of breathing (muscles outside of the diaphragm) recruited to apply more force to inhalation and exhalation, with contractions manifesting externally as a retraction of the skin at various areas of the chest wall: between the ribs (intercostal), below the rib cage (subcostal), and immediately superior to the sternum (suprasternal).
- Other signs of difficulty breathing such as head bobbing, nasal flaring, or grunting sounds made during exhalation.
- Work of breathing is generally classified as mild, moderate, or severe. An example of how to use these classifications follows:
  - Mild: retractions in 1 area
  - Moderate: retractions in 2 or more areas
  - Severe: pronounced retractions, paradoxical breathing, head bobbing, grunting

- Cardiovascular
  - Auscultation of heart sounds: rate, rhythm, first and second heart sounds (S_1 and S_2), any extra heart sounds such as murmurs or gallops, or a fixed splitting of S_2
  - Palpation of the precordium to assess for a displaced point of maximal impulse (PMI) or a hyperdynamic precordium
  - Central cyanosis: coloration of lips and tongue (but visual identification of cyanosis is highly variable and should not replace oxygen saturation measurement with a pulse oximeter)
  - Peripheral perfusion: capillary refill time, temperature of extremities, quality of peripheral and femoral pulses (eg, diminished, thready, normal)

CASE FOCUS

Physical Examination

Anita's vital signs show that she is afebrile. Her respiratory rate is elevated at 72 breaths/min with an oxygen saturation of 89% on room air. She has a heart rate of 132 beats/min and a blood pressure of 91/62 mm Hg.

On your examination, you find that Anita is alert and interactive but in obvious respiratory distress. Her anterior fontanelle is open, soft, and flat. Her mucous membranes are tacky. You note some dried crusting around both nares and mild bilateral nasal turbinate swelling. Her tympanic membranes are pearly gray with clear bony landmarks. On the respiratory examination, you note moderate subcostal and intercostal retractions. On auscultation of the lungs, she has bilateral rhonchi and crackles with diffuse end-expiratory wheezes. Her cardiovascular examination shows normal S_1 and S_2 without murmurs, extra heart sounds, or displaced PMI. She is appropriately warm and well perfused with normal peripheral and femoral pulses, and her capillary refill time is less than 3 seconds. There is no evidence of cyanosis. The ED physician has ordered for Anita to receive oxygen via nasal cannula, which the respiratory therapist initiates while you are in the room. With this intervention, Anita's oxygen saturation improves to 95%, but her work of breathing remains prominent.

CASE FOCUS

Urgent Intervention

Because Anita continues to have significant work of breathing, you and the ED physician decide to start oxygen via high-flow nasal cannula (HFNC) before proceeding.

While attaching the HFNC, you notice worsening tachypnea and deeper subcostal retractions while Anita is crying. A few minutes later, she calms and you note that her tachypnea improves and her retractions are significantly reduced on oxygen flow of 6 L/min with a fraction of inspired oxygen (FIO_2) of 0.4 to maintain her oxygen saturations at approximately 95%.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an infant with respiratory distress?

The differential diagnosis for an infant with respiratory distress is shown in Table 2.1 and is divided into causes that seem more and less likely based on Anita's presentation.

Table 2.1. Differential Diagnosis for an Infant With Respiratory Distress

Diagnoses of highest suspicion	• Asthma/reactive airway disease • Bronchiolitis[a] • Pneumonia (viral or bacterial, including aspiration)
Other diagnoses to consider	• Airway malacia (eg, bronchomalacia, tracheomalacia) • Anaphylaxis • Bronchitis (particularly for patients with cystic fibrosis, immunodeficiency, or impaired ciliary clearance) • Chronic lung disease • Croup • Foreign body aspiration • Heart failure (eg, congenital heart disease, cardiomyopathy, or myocarditis) • Masses within the airway (eg, airway hemangiomas, cysts, papillomas) • Mediastinal mass • Metabolic acidosis (most commonly indicated by tachypnea or deep respirations without retractions) • Pertussis • Pneumonitis (aspiration or chemical) • Pulmonary hypertension • Tracheitis/epiglottitis • Vascular rings or slings • Viral upper respiratory infection

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with acute-onset respiratory distress?

- While many diagnoses can cause acute-onset respiratory distress in young children, viral bronchiolitis is one of the most common causes, especially in patients experiencing rhinorrhea, cough, and fever. As such, it is reasonable to begin the diagnostic evaluation with this is mind. The diagnosis of bronchiolitis is typically based on history and physical examination findings. In general, routine laboratory and radiographic testing are not recommended.
- Classically, bronchiolitis occurs in children younger than 2 years and presents with a prodrome of nasal congestion, rhinorrhea, and cough. Clinical symptoms consist of tachypnea, diffuse wheezing, crackles, and rhonchi, with or without increased work of breathing.
- Viral polymerase chain reaction (PCR) testing is expensive and generally does not alter treatment, which is largely supportive; therefore, it is not routinely recommended. However, viral testing may be considered to help the physician decide between viral bronchiolitis and bacterial pneumonia or to identify influenza, if these results would alter management (ie, treatment with oseltamivir or antibiotics). It should be noted, however, that the presence of a viral infection identified by nasal PCR testing does not rule out concomitant bacterial infection. Likewise, the absence of an identifiable virus by nasal PCR testing does not imply that the patient has a bacterial process. Viral testing may also be considered for infectious surveillance, as in the case of contact tracing for SARS-CoV-2.
- Although most causes of respiratory distress can be determined on the basis of history and physical examination alone, in some cases the diagnosis is not immediately clear and further diagnostics may be necessary. Refer to Table 2.2 for a list of clinical scenarios that may prompt further evaluation.

Table 2.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Respiratory Distress

Diagnosis	Possible clinical features	Diagnostic evaluation to consider
Foreign body aspiration	Younger children with acute-onset respiratory distress without typical preceding symptoms of nasal congestion, rhinorrhea, or cough. May have localized monophonic wheezing.	Use chest radiographs to evaluate for a radiopaque foreign body. Bilateral lateral decubitus radiographs can also be helpful when evaluating for evidence of air trapping. Consider bronchoscopy for removal.
Superimposed bacterial infection	Worsening fever or signs and symptoms of respiratory distress	Although classic pneumonia can often be diagnosed based on history and physical examination alone, if the diagnosis is unclear, a chest radiograph can be used to evaluate for consolidation or effusion.
Underlying cardiac etiology	History of sweating with feeds, murmur, central or peripheral cyanosis, or known cardiac history	Consider using chest radiographs to evaluate for pulmonary edema and cardiac silhouette. Echocardiogram can be useful in assessing heart structure and function. BNP can be helpful in assessing overall heart strain in fluid overload state. Troponins can be useful in assessing myocardial ischemia. ECG can be useful in assessing for left or right heart enlargement and potential ischemia.

(continued)

Table 2.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Respiratory Distress *(continued)*

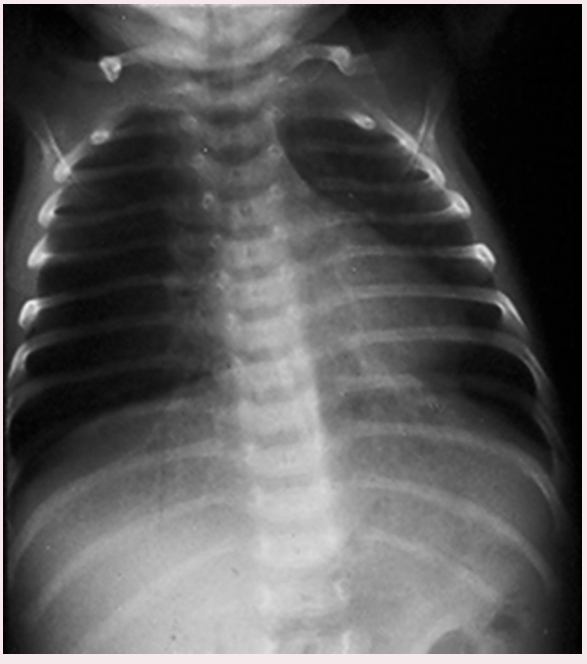
Diagnosis	Possible clinical features	Diagnostic evaluation to consider
Aspiration	Infant with chronic coughing or choking with feedings	Consider using chest radiographs to evaluate for signs of chronic aspiration or aspiration pneumonia, although the appearance of evidence of aspiration pneumonia on chest imaging can be delayed following an acute aspiration event. Depending on persistence of symptoms, a modified barium swallow study may be indicated to evaluate for aspiration events with feeds. Due to the potential for falsely abnormal results, this test should not be performed during an acute illness.

Abbreviations: BNP, B-type natriuretic peptide; ECG, electrocardiogram.

CASE FOCUS

Diagnostic Evaluation

The physician in the ED obtained a chest radiograph, which looks like this:



Reprinted with permission from Hall CB. Bronchiolitis. *Pediatric Care Online*. Updated 2016. Accessed May 16, 2022. https://publications.aap.org/pediatriccare/book/348/chapter/5777235/Bronchiolitis. Courtesy of Edgar O. Ledbetter, MD, FAAP.

At the time of your evaluation, a radiologist has not yet interpreted Anita's chest radiograph.

Arriving at a Diagnosis

Q: How do you develop an assessment for Anita?

1. **Assess Anita's airway, breathing, and circulation:** Anita's airway is intact, but her breathing is significantly labored, and her oxygen saturations are low. Fortunately, her breathing and oxygenation are improved following initiation of HFNC. While Anita does not have any vital signs or examination findings concerning for circulatory compromise, she does appear to have mild dehydration based on her history of decreased urine output and tacky mucous membranes on examination.
2. **Interpret key findings on history, examination, and diagnostic evaluation:** In thinking through Anita's case, you first consider pertinent clues from her history and physical examination.
   - History: When obtaining Anita's history, you learned she developed cough, congestion, and fever within the last 3 days with a progressively worsening course. She was exposed to a sibling at home with similar symptoms. Her symptoms were not improved with administration of albuterol in the ED. This history is consistent with a viral etiology.
   - Physical examination: On initial examination, Anita has an oxygen saturation of 89% with moderately increased work of breathing as evidenced by her subcostal and intercostal retractions. Her oxygen saturation improves with oxygen via nasal cannula, but her work of breathing does not improve. She is escalated to HFNC with some improvement of respiratory status. On auscultation, you note diffuse crackles and expiratory wheezes. She appears mildly dehydrated with an otherwise normal examination. These examination findings are consistent with bronchiolitis.
   - Diagnostic evaluation: While a radiologist has yet to review Anita's chest radiograph, you believe that her radiograph shows an age-appropriate cardiothymic silhouette and no focal opacities other than some bilateral perihilar thickening of her bronchioles. There are no radiopaque foreign bodies or signs of pneumothorax, pneumomediastinum, or pleural effusion. Although a chest radiograph is not needed (or recommended) to diagnose bronchiolitis, when obtained, bilateral perihilar thickening of the bronchioles and hyperexpansion are common findings. Refer to Section III of the Appendix for more information on interpreting chest radiographs.

Q: How do you determine whether Anita is in acute respiratory failure?

In general, there are 2 types of respiratory failure.

- Type 1, hypoxemic respiratory failure: This type of respiratory failure is characterized by Pa_{O_2} less than 60 mm Hg with a low or normal arterial Pa_{CO_2} between 38 and 42 mm Hg.
- Type 2, hypercapnic respiratory failure: This type of respiratory failure is characterized by Pa_{CO_2} greater than 50 mm Hg.

Without blood gas test results, many clinicians tend to define acute respiratory failure based on a patient's clinical status. While there is some variation in the clinical definition of acute respiratory failure, some general principles are outlined in Box 2.1.

Box 2.1. Clinical Definition of Acute Respiratory Failure in Infants and Children Beyond the Neonatal Period

Infants and children requiring respiratory support at or above the following levels may be considered to have acute respiratory failure:

- ≥4 L/min and/or 30% of F_{IO_2} by nasal cannula
- Use of mechanical ventilation, CPAP, or BiPAP

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen.

- *Chronic respiratory failure* may be defined by chronic hypoxemia, hypercapnia, and compensatory metabolic alkalosis for a period of 28 days or longer. These patients generally require supplemental home oxygen therapy.
- *Acute on chronic respiratory failure* describes ongoing chronic respiratory failure that acutely requires an increase from baseline F_{IO_2} or pressure support.

Q: How do you determine if the patient has hypoxemia?

The most accurate way to determine if a patient is adequately oxygenated is by measuring Pa_{O_2}; therefore, a low Pa_{O_2} (<60 mm Hg) would indicate hypoxemia or low oxygen content of the blood. In general, it is not recommended to check a blood gas for most patients with bronchiolitis because the saturation of oxygen (Sa_{O_2}) is a fairly reliable proxy for determining hypoxemic states. The Sa_{O_2} represents the percentage of hemoglobin that is saturated with oxygen. Because about 97% of oxygen carried by blood is transported attached to hemoglobin, Sa_{O_2} is a rough estimate of oxygenation status. Generally, a patient who is awake with an Sa_{O_2} less than 90% can be considered hypoxemic, although institutional definitions may vary slightly.

3. **Develop the list of findings.**

Q: What major findings have you identified for Anita?

- Cough
- Rhinorrhea
- Fever (resolved)
- Moderately increased work of breathing
- Hypoxemia
- Acute respiratory failure
- Mild dehydration

4. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Anita's presentation?

- Acute viral bronchiolitis is the most likely cause of Anita's symptoms based on her history, the presence of crackles and expiratory wheezes appreciated bilaterally on physical examination, and the results of her diagnostic evaluation.
- There is no evidence of bacterial pneumonia based on a lack of focality on examination and lack of obvious consolidations on chest imaging. Anita's lack of personal or family history of atopy and the bilateral crackles present on auscultation make you less suspicious of reactive airways disease or asthma. Additionally, her history, examination, and imaging are less concerning for a cardiac etiology.

Q: What are common viral infectious etiologies of bronchiolitis in childhood?

- The most common cause of bronchiolitis in childhood is respiratory syncytial virus, with the highest level of illness prevalence in the fall, winter, and spring, according to geographic season ranges.
- In general, the constellation of signs and symptoms is similar with all viral etiologies. Other commonly seen etiologies include human rhinovirus, influenza, human metapneumovirus, coronavirus, and parainfluenza viruses.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with viral bronchiolitis?

- The patient's work of breathing is indicative of impending respiratory failure and need for escalation to HFNC, positive pressure ventilation, or intubation to maintain adequate ventilation.
- The patient has persistent hypoxemia requiring oxygen therapy.
- The patient is dehydrated, or there is concern for inability to maintain adequate hydration.
- The patient is unable to feed without aspiration due to respiratory distress.

- The child's caregivers are unable to provide appropriate care at home, obtain timely follow-up, or return to care in the event of worsening symptoms.

You classify Anita as hypoxemic based on her Sa_{O_2} of 89% on room air and decide that she will require admission for supplementary oxygen. Furthermore, she has been escalated to HFNC for her increased work of breathing, which classifies her as being in acute respiratory failure and requires hospital admission.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Anita is a 4-month-old otherwise healthy girl born full term who is here with acute respiratory failure with hypoxemia secondary to suspected viral bronchiolitis. She will require hospital admission for respiratory support and supplemental oxygen.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Anita's symptoms, you review the literature to remind yourself about the management and treatment of viral bronchiolitis in children. Although there have been numerous trials of various therapeutic interventions over the years, most have not been found to be significantly beneficial. You consider the following interventions:

1. **Supplemental oxygen:** Supplemental oxygen may be administered to any patients who have oxyhemoglobin saturation less than 92%. There are multiple methods of oxygen delivery that are briefly summarized in the following sections:
   - Nasal cannula
     - Oxygen administered via nasal cannula is 100% oxygen, but the F_{IO_2} that the patient experiences is much less than 100% due to the oxygen blending with the patient's expired air and inhaled room air during breathing.
     - The F_{IO_2} provided to the patient via nasal cannula is shown in Table 2.3.

Table 2.3. Amount of Oxygen Delivered to Patients via Nasal Cannula Based on Different Flow Rates

Oxygen flow rate (L/min)	FIO_2 (%)
1	24
2	28
3	32
4	36
5	40

Abbreviation: FIO_2, fraction of inspired oxygen.

- Simple face mask
  - As with a nasal cannula, the oxygen delivered via simple face mask is 100% oxygen, but it mixes with the patient's expired air and inhaled room air. The FIO_2 provided by a simple face mask is shown in Table 2.4.
  - Of note, 5 L/min is the required minimum flow rate to adequately flush or wash out carbon dioxide from the mask.

Table 2.4. Amount of Oxygen Delivered to Patients via Simple Face Mask Based on Different Flow Rates

Oxygen flow rate (L/min)	FIO_2 (%)
5	35
6	39
7	43
8	47
9	51
10	55

Abbreviation: FIO_2, fraction of inspired oxygen.

- Nonrebreather face mask
  - A nonrebreather face mask is a low-flow mask device that uses a reservoir to deliver a higher FIO_2 to the patient. This is accomplished with a one-way valve that prevents reinhalation of expired air.
  - The flow of oxygen can be set between 10 and 15 L/min and delivers FIO_2 ranging from 80% to 95%.

- HFNC
  - HFNC is a humidified and heated form of oxygen delivery. The F_{IO_2} delivered with HFNC can be easily titrated ranging from 21% to 100%. Studies have shown that in clinical practice, HFNC use has the potential to prevent the need for intubation in patients with viral bronchiolitis. There are multiple proposed mechanisms as to why this may be the case.
    - Some studies show a modest amount of positive airway pressure can be generated with HFNC when used at higher flow rates.
    - It has been suggested that HFNC provides a more oxygen-rich supply of air by washing out carbon dioxide from the anatomic dead space (eg, the nasopharynx).
    - HFNC provides flow rates that can match or exceed the patient's inspiratory flow rates generated with each breath, thereby theoretically decreasing the respiratory effort needed for inhalation.
  - Although clinical data appear promising, the lack of randomized trials focusing on HFNC efficacy precludes specific recommendations for its use by the American Academy of Pediatrics at this time.
- Escalated care options: Occasionally, patients may have symptoms of respiratory failure that do not improve or even worsen despite the use of nasal cannula oxygen supplementation. These patients may require an increase in their respiratory support to bilevel positive airway pressure, continuous positive airway pressure, mechanical ventilation, and even extracorporeal membrane oxygenation. In general, use of noninvasive positive pressure ventilation requires admission to an intensive care setting where there is the ability to perform increased monitoring under the supervision of appropriately trained staff.

2. **Monitoring:** Transient hypoxemia is a normal phenomenon in up to 60% of healthy infants and children. Studies have shown that use of continuous pulse oximetry in bronchiolitis frequently leads to prolonged hospitalization for perceived need for oxygen, even without the presence of other symptoms, with no evidence of benefit. Studies have also shown that pulse oximetry is sometimes mistakenly used as a surrogate measure of clinical status and can ultimately lead to less effective surveillance of a patient's illness severity. For these reasons, a pediatric hospitalist may choose not to use continuous pulse oximetry to monitor an infant or child with bronchiolitis but instead use intermittent measurements. However, when a patient is actively being provided with supplemental oxygen, it is appropriate to monitor oxygen saturations with continuous pulse oximetry.
3. **Additional therapies**
   - Nasal suction: Intermittent nasal suctioning is an important and recommended component of supportive care in viral respiratory illnesses including bronchiolitis. Studies have shown that lapses of longer than 4 hours in noninvasive suctioning of the nares have led to longer length of hospital stay. Therefore, the recommendation is to provide noninvasive, intermittent nasal suctioning. Deeper suctioning is generally not recommended.
   - Diet/hydration: Clinicians should provide adequate hydration for those infants who are unable to maintain adequate hydration independently or for those who show evidence of aspiration (coughing or choking) with feeds while on respiratory support. Large-scale studies have shown no significant difference between intravenous hydration and nasogastric hydration in terms of length of hospital stay or other meaningful outcomes. Either method can be selected depending on clinician comfort or parental preference. If the infant is breastfed and unable to tolerate direct breastfeeding due to significant respiratory distress, encourage the breastfeeding parent to express breast milk to maintain milk supply and provide the expressed milk for gavage feeding.
   - Antipyretics and analgesics: Acetaminophen may be used for infants with fever or pain. In infants older than 6 months, ibuprofen may also be considered.
   - Chest physiotherapy: Subsegmental atelectasis seen on chest radiographs in bronchiolitis has led to the clinical use of chest physiotherapy in the past; however, studies have shown that chest physiotherapy does not affect hospital length of stay or duration of illness, and therefore it is generally not recommended.

- Medications and breathing treatments
  - Nebulized hypertonic saline: Some studies have shown that using hypertonic saline while children are admitted to the hospital decreases the total hospital length of stay; however, this benefit was only observed in patients with longer hospital stays for bronchiolitis (>3 days). If the average hospital stay for bronchiolitis is fewer than 3 days, this therapy would likely not be beneficial. Additionally, administration of nebulized hypertonic saline is not without side effects, and higher concentrations can lead to worsening bronchospasm in some patients.
  - Albuterol: In general, short-acting β_2-agonists such as albuterol are not recommended for the treatment of acute viral bronchiolitis. Several randomized control trials and systematic reviews have demonstrated that albuterol may subjectively improve clinical symptoms temporarily, but there is no proven benefit in meaningful measures such as resolution of disease, need for hospital admission, or length of hospital admission.
  - Epinephrine: Studies have looked at systemic as well as nebulized forms of epinephrine and have demonstrated no improvement in meaningful outcomes. Thus, the recommendation is that epinephrine should not be administered to infants and children with bronchiolitis.
  - Corticosteroids: A comprehensive systematic review and large multicenter randomized control trials have shown corticosteroids provide no significant benefit.
  - Anti-infectives: In general, studies have shown that a febrile infant without an identifiable source of infection has a risk of bacteremia as high as 7%; however, febrile infants with a suspected viral syndrome have a much lower risk of concurrent bacteremia (<1%). Because of this, it is not recommended that infants with bronchiolitis receive empiric antibiotics. In febrile neonates younger than 28 days, antibiotics can still be considered as part of febrile neonate protocols.
    - Oseltamivir, an antiviral agent used in treatment of influenza, is recommended for hospitalized patients with known influenza. Studies have recommended initiation of treatment within 48 hours of symptom onset, as it can shorten the overall duration of hospital stay. About 15% of children treated with oseltamivir will have gastrointestinal side effects, most commonly vomiting. If not well tolerated, treatment with oseltamivir can be discontinued.

CASE FOCUS

Plan for Treatment and Monitoring

- **Supplemental oxygen therapy:** Based on Anita's examination findings of increased work of breathing and tachypnea you decide to continue 6 L/min HFNC at 40% oxygen for respiratory support. You will monitor her hypoxemia with a continuous pulse oximeter while she needs respiratory support. As Anita begins to look more comfortable and her oxygen saturations stabilize, you will wean the flow of oxygen and FIO_2 as tolerated.
- **Additional therapies:** You order nasal suctioning as needed. You will not administer albuterol or hypertonic saline, as these therapies will not be beneficial in Anita's case.
- **Anti-infectives:** None are indicated for Anita's case because a viral etiology is suspected.
- **Diet:** You decide to allow Anita to breastfeed per her normal home routine. If you notice that she is coughing or choking with feeds while on HFNC, you will consider nasogastric tube placement for administration of feeds, preferably expressed human (breast) milk.
- **Monitoring:** You order strict monitoring of intake and output and vital signs every 4 hours.
- **Antipyretics and analgesics:** You order acetaminophen as needed for pain or fever.

Case Resolution

Over the course of the next 36 hours, Anita's increased work of breathing gradually improves, her oxygen saturation remains stable, and she is slowly weaned off of the HFNC. She continues to feed well throughout her admission. On auscultation of her lungs prior to discharge, there are still fine crackles heard throughout both lungs, but reassurance is provided to the family that although Anita will likely continue to cough for several more days, she will continue to improve on her own. Her clinical course supports the presumptive diagnosis of viral bronchiolitis, so no further workup is required.

Discharge Criteria

Q: How do you know when Anita is ready to go home?

You can feel comfortable discharging your patient with bronchiolitis when the following criteria are met:

- The patient's work of breathing has improved without need for respiratory support.
- Any oxygen requirement above the patient's baseline has resolved.
- No concerns exist regarding potential for untreated bacterial infection such as pneumonia.
- The patient can feed orally and maintain adequate nutrition and hydration without intravenous or nasogastric support.
- Caregivers have been educated on signs and symptoms that would be concerning and merit return to care.

Anticipatory Guidance

Q: What instructions should you provide to Anita's caregivers on discharge?

- It is normal for there to be viral symptoms (eg, cough, congestion) that continue after discharge. These symptoms may wax and wane, but there is research to suggest that approximately 75% of coughs associated with viral illnesses abate by 10 to 14 days.
- High fevers that are unresponsive to antipyretics or signs of increased work of breathing (eg, retractions, head bobbing) are indications that Anita should return to care for reevaluation.

Clinical Pearls

- Bronchiolitis is a diagnosis that is made based on history and physical examination findings alone. It does not typically require additional diagnostic workup.
- Symptomatic support is the mainstay of treatment of viral bronchiolitis.
- Supplemental oxygen should be used when a patient demonstrates hypoxemia, and the oxygen delivery method should be the minimum required to correct the patient's hypoxemia.

Documentation Tips

- Document presence of acute respiratory failure and/or hypoxia.
- Include history of preterm birth when applicable, especially if the patient is younger than 12 months.
- Document associated medical complexity or comorbid medical conditions (eg, chronic lung disease, technology dependence) when applicable.
- Include a detailed description of work of breathing, including tachypnea and severity of retractions.
- Discuss need for continuous versus intermittent respiratory monitoring.

Suggested Reading

Silver AH, Nazif JM. Bronchiolitis. *Pediatr Rev*. 2019;40(11):568–576 PMID: 31676530 https://doi.org/10.1542/pir.2018-0260

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CASE 3

Baby Girl Smith, a Newborn With Respiratory Distress

CASE PRESENTATION

You are covering the newborn nursery when you are called to assess Baby Girl Smith for respiratory distress. The nurse reports that the neonate was born approximately 10 minutes ago via precipitous vaginal delivery. She cried at birth and thus was immediately placed skin to skin on her mother's abdomen. Umbilical cord clamping was delayed for 1 minute while the neonate was being suctioned and dried. She then appeared to have grunting during the nursing assessment and was immediately brought to the radiant warmer. The nurse reports that the newborn's heart rate is above 100 beats/min with a respiratory rate of 70 breaths/min and an oxygen saturation of 81%. After finishing your call with the nurse, you quickly head to the delivery room.

Patient History and Review of Systems

Q: What information should you collect from Baby Girl Smith's parents, her nurse, and her mother's medical record?

- Gestational age
- Amniotic fluid quality (clear, meconium-stained, sanguineous, malodorous)
- Complications during pregnancy, labor, and delivery
- Medications during pregnancy and labor
- Prenatal care, including results of genetic screening and ultrasound examinations
- Results of infectious screening (HIV, rapid plasma reagin, hepatitis, rubella, group B streptococcal [GBS] colonization, herpes simplex virus, tuberculosis, gonococcal and/or chlamydial infection)
- Presence of maternal intrapartum fever
- Duration of rupture of membranes
- Apgar scores

CASE FOCUS

History and Review of Systems

From reviewing the medical record and speaking with the nurse and mother, you learn that Ms Smith is a 31-year-old gravida 3, now para 3 mother who has a history of mild gestational hypertension, obesity, and diet-controlled gestational diabetes. She had 2 prior uncomplicated vaginal deliveries. Prenatal care began when she was 6 weeks pregnant, and she received adequate care with her obstetric provider. Serology testing during the first and third trimesters was normal. Genetic screening tests and ultrasound examination results were normal. Her blood type is O Rh+ with negative antibody screening results, and her GBS screening result was negative. Her medications included prenatal vitamins. She lives with her husband and 2 other children. There is no history of neonatal complications reported for her other children. They are healthy and fully vaccinated and were breastfed for approximately 1 year.

She presented in labor at 37 weeks' estimated gestational age and quickly progressed to spontaneous vaginal delivery. She had rupture of membranes 6 hours prior to delivery and the fluid was clear; she has been afebrile and received epidural anesthesia. Apgar scores were 7 and 8 at 1 and 5 minutes after birth, respectively.

Physical Examination

Q: What parts of the physical examination should you focus on for Baby Girl Smith?

- Complete set of vital signs
- Ballard score
- Anthropometric measurements: weight, length, frontal-occipital circumference (FOC)
- General: level of alertness, response to stimulus, dysmorphic features
- Skin: color (eg, cyanosis, pallor), rashes, lesions
- Head: shape, molding, caput succedaneum, evidence of scalp injury
- Oropharynx: cleft lip and/or palate, ankyloglossia
- Cardiac: precordium, heart rate, rhythm, murmur, peripheral pulses, perfusion
- Lungs: adventitious sounds, respiratory rate, work of breathing (retractions, grunting, nasal flaring)
- Abdomen: appearance, bowel sounds, organomegaly, umbilical cord abnormalities
- Genitourinary: appearance of genitalia
- Anus: placement, patency
- Extremities: hypoplasia, polydactyly, syndactyly
- Musculoskeletal: Ortolani and Barlow tests
- Back: spine appearance, lumbosacral abnormalities
- Neurology/reflexes: symmetric Moro, grasp, and suck reflexes; muscle tone

CASE FOCUS

Physical Examination

Baby Girl Smith's heart rate is normal at 130 beats/min. She is tachypneic with a respiratory rate of 70 breaths/min, and her oxygen saturation is 80% to 85% on room air. Her temperature and blood pressure are normal.

Her nurse reports to you that Baby Girl Smith's birth weight is 3,900 g (89th percentile), head circumference/FOC is 35 cm (75th percentile), and length is 52 cm (79th percentile).

On initial physical examination, she appears term and has no dysmorphic features. She has good muscle tone, but she is cyanotic and grunting and has subcostal retractions and nasal flaring. You auscultate her chest and hear equal breath sounds bilaterally with good air entry. There is no inspiratory stridor. No cardiac murmur is appreciated, and she has strong peripheral pulses. You place a gloved finger in her mouth, and she begins to suck vigorously. Her skin is pink and appears normal, with vernix in some areas and no birthmarks. Her anterior and posterior fontanelles are open, soft, and flat. Her head is normocephalic and has molding; the sutures are overriding and no scalp swelling is noted. Her ears are normally set with no anomalies noted. She has a strong sucking reflex, her palate is intact, and there is no evidence of ankyloglossia. Examination of her neck reveals no abnormalities, and her clavicles are intact bilaterally. She has normal bowel sounds, and her abdomen is soft and nondistended without organomegaly. The umbilical cord appears normal with 3 vessels noted. Her external genitalia appear normal. Her hips are stable with negative Ortolani and Barlow test results. Her Ballard score is consistent with 37 weeks' estimated gestational age.

BACK TO BASICS

Neonatal Oxygen Saturations

In utero, fetal oxyhemoglobin concentration is approximately 50%, with higher saturations in the preductal areas. Several physiological cardiorespiratory changes begin to occur during the transition to extrauterine life. When evaluating a newborn with respiratory symptoms during this period of transition from fetal to neonatal circulation, it is important to know the values of normal preductal oxygen saturation.

Q: What are the target oxygen saturations for the first 10 minutes after birth?

Oxygen saturation increases with each minute after birth, as shown in the table.

Minutes after birth	Target oxygen saturation
1	60%–65%
2	65%–70%
3	70%–75%
4	75%–80%
5	80%–85%
10	85%–95%

CASE FOCUS

Urgent Intervention

Because Baby Girl Smith's oxygen saturation is below the targeted preductal saturation for 10 minutes after birth, you begin administering free-flow supplemental oxygen at 21% to 30% fraction of inspired oxygen. Her oxygen saturation steadily increases to 90%, and her work of breathing improves slightly.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a term newborn with respiratory distress and hypoxemia?

There are relatively few causes of respiratory distress and hypoxemia in a term newborn. The etiologies can be further narrowed based on a complete history and thorough physical examination. Table 3.1 demonstrates a differential diagnosis for these symptoms and is separated into diagnoses that appear more or less likely for Baby Girl Smith.

Table 3.1. Differential Diagnosis for a Term Newborn With Respiratory Distress and Hypoxemia

Diagnoses of highest suspicion	• EOS • Neonatal pneumonia • Retained fetal lung fluid (TTN)[a]
Other diagnoses to consider	• Cyanotic CHD (eg, transposition of the great arteries) • Lung malformations or pulmonary hypoplasia (eg, CDH) • MAS • Pneumothorax or pneumomediastinum • PPHN • RDS

Abbreviations: CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; EOS, early-onset sepsis; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is required for a term newborn with respiratory distress and hypoxemia?

- For newborns who have respiratory distress and hypoxemia at birth, the Neonatal Resuscitation Program® algorithm should be followed. For term newborns who respond well to the initial steps of the algorithm and do not require ongoing respiratory support, no further immediate evaluation is necessary, but close monitoring should be provided.

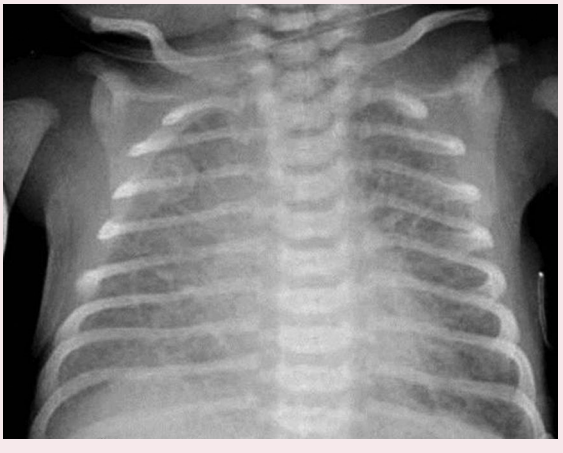
- For term newborns with persistent respiratory distress and/or hypoxemia, a chest radiograph is a useful tool to evaluate abnormalities in the lung fields (eg, pneumonia, abnormal pulmonary vascular markings, pneumothorax) and to identify gross anatomic abnormalities (eg, congenital diaphragmatic hernia [CDH], tracheoesophageal fistula, abnormal cardiac silhouette). Blood gas testing may also be useful to evaluate for acidosis.
- For hypoxemia disproportionate to the degree of respiratory distress or chest radiograph findings, clinicians should consider cardiac etiologies, specifically cyanotic congenital heart disease (CHD).
  - The initial step to evaluate for cyanotic CHD is to perform the hyperoxia test. This test is performed by measuring the preductal Pa_{O_2} after administering 100% oxygen. A Pa_{O_2} level of less than 150 mm Hg indicates the presence of cyanotic CHD.
  - For neonates with a concerning hyperoxia test or other findings suspicious for CHD or persistent pulmonary hypertension of the newborn (PPHN), an echocardiogram should be obtained.
- When sepsis is suspected, clinicians should perform additional testing, such as a complete blood cell count and blood culture. Neonatal sepsis calculators can be useful to assess a newborn's risk of early-onset sepsis (EOS). Initiation of empiric antibiotic therapy may be indicated. Risk factors for EOS include maternal GBS colonization at delivery, preterm labor, prolonged rupture of membranes, maternal intrapartum fever, and a history of a previous child with invasive GBS disease.

CASE FOCUS

Diagnostic Evaluation

You continue to closely monitor Baby Girl Smith. Thirty minutes after birth, her grunting has become intermittent. She continues to have retractions and requires supplemental oxygen to maintain oxygen saturation greater than 90%. You order a portable chest radiograph to evaluate her lung fields and to assess for relevant anatomic abnormalities.

Her chest radiograph shows prominent bilateral perihilar peribronchial markings, a normal cardiothymic silhouette, and fluid in the right horizontal lung fissure. You see no evidence of pneumothorax or pneumomediastinum. (Refer to Section III of the Appendix for a primer on chest radiograph interpretation.)



Reprinted with permission from Reuter S, Moser C, Baack M. Respiratory distress in the newborn. *Pediatr Rev*. 2014;35(10):417–429.

Arriving at a Diagnosis

Q: How do you develop an assessment for Baby Girl Smith?

You decide to first interpret the findings from Baby Girl Smith's history, examination, and diagnostic evaluation to develop a list of findings that narrows your differential diagnosis to the most likely etiology. You can then determine how to triage her to the appropriate level of care based on her diagnosis.

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - Baby Girl Smith is an early term infant of a diabetic mother and developed grunting, hypoxemia, tachypnea, and retractions within minutes of a precipitous vaginal birth. She has no significant risk factors for EOS, and her amniotic fluid was not stained with meconium. Her growth parameters are consistent with an appropriate-for-gestational-age (AGA) neonate, and she has no dysmorphic features or evidence of congenital anomalies. Although she has hypoxemia and respiratory distress on examination, she has good respiratory effort and muscle tone. Her cardiac examination and peripheral pulses are normal.
   - Her respiratory status and oxygen saturation improved during 30 minutes on oxygen. Clinical improvement, as opposed to further worsening, can help rule out some etiologies of her symptoms. Additionally, her chest radiograph shows findings consistent with retained fetal lung fluid, which helps to further eliminate many other etiologies.
2. **Develop the list of findings.**

Q: What major findings have you identified for Baby Girl Smith?

- Early term (37 weeks) AGA neonate without risk factors for sepsis
- Infant of a diabetic mother
- Precipitous vaginal delivery
- Acute respiratory distress
- Hypoxemia
- Improvement with temporary supplemental oxygen
- Chest radiograph showing perihilar markings and fluid in the right horizontal fissure

3. **Revisit the differential diagnosis.**

Q: Based on the differential diagnosis and list of findings, are you able to choose one diagnosis to explain Baby Girl Smith's symptoms?

Based on her history, examination, clinical course, and chest radiograph findings, you determine that transient tachypnea of the newborn (TTN) (ie, retained fetal lung fluid) is the most likely diagnosis. Her history of a precipitous labor and delivery supports the diagnosis of TTN, which causes respiratory distress at birth. As the fluid gradually clears from the alveoli, the symptoms begin to improve. These neonates seldom have high oxygen requirements and generally do not appear very ill. Risk factors for TTN include cesarean delivery, precipitous vaginal delivery, and weak respiratory efforts at birth.

Q: How do you know that more serious etiologies can be excluded?

- EOS and neonatal pneumonia should be considered in the differential diagnosis of any newborn who presents with respiratory distress at birth. As GBS infection is the most common etiology of EOS and neonatal pneumonia, it is imperative that maternal risk factors be assessed carefully. These include maternal GBS colonization at delivery, preterm labor, prolonged rupture of membranes (≥ 18 hours), maternal intrapartum fever, and history of a previous child with invasive GBS disease. Primary strategies for prevention of neonatal GBS disease include universal GBS screening of pregnant women at 36 to 37 weeks' gestation and administration of appropriate

antibiotic prophylaxis in labor, if indicated. Newborns with EOS are usually symptomatic at or shortly after birth and deteriorate rapidly if untreated. A sepsis calculator can be used to assess the risk of EOS. Based on minimal risk factors, Baby Girl Smith has relatively low risk for EOS and neonatal pneumonia, and a review of her chest radiograph does not demonstrate findings concerning for pneumonia.

- Pulmonary vascular resistance begins to decrease immediately after birth in response to increasing Pa_{O_2} concentration. PPHN can occur when right-sided pressures do not decrease and blood is shunted from right to left across the patent foramen ovale and patent ductus arteriosus. Neonates with PPHN will have persistent hypoxemia without rapid improvement.
- Meconium aspiration syndrome (MAS) is caused by aspiration of meconium-contaminated amniotic fluid during labor or delivery and results in alveolar hyperinflation, inflammatory pneumonitis, significant pulmonary hypertension, and secondary surfactant deficiency. Neonates with MAS have meconium-stained amniotic fluid, may be depressed at birth, and exhibit progressively worsening respiratory distress and hypoxemia. Baby Girl Smith did not have meconium-stained amniotic fluid and her status improved with minimal intervention, rather than worsened.
- Spontaneous pneumothorax or pneumomediastinum is uncommon in term neonates and usually occurs when there is underlying lung pathology or when mechanical ventilation is required. Findings on the chest radiograph are diagnostic in these cases. Baby Girl Smith's chest radiograph rules out these diagnoses.
- Hypoxemia disproportional to the severity of respiratory distress should raise suspicion for cyanotic congenital heart defects. Newborns with cyanotic congenital heart defects demonstrate only minimal response to supplemental oxygen. Baby Girl Smith's oxygen saturations improved with a small amount of oxygen supplementation, making this diagnosis unlikely. Additionally, her cardiac examination results and cardiac silhouette on chest radiograph are normal.
- CDH is most commonly diagnosed by prenatal ultrasonography. Neonates with CDH exhibit marked respiratory distress with minimal improvement with oxygen because of coexisting pulmonary hypoplasia. Baby Girl Smith's chest radiograph findings decrease your suspicion for many pulmonary anomalies and rule out CDH.
- Baby Girl Smith's clinical picture and chest radiograph findings are characteristic of TTN or retained fetal lung fluid.

4. **Determine the appropriate level of care.**
   - Newborns who continue to require respiratory support or have other risk factors should be triaged to the neonatal care unit appropriate for their ongoing needs (eg, neonatal intensive care unit).
   - If Baby Girl Smith continues to transition well and recover from her respiratory distress and hypoxemia, she can be allowed to room-in with her mother.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Baby Girl Smith is a term AGA female neonate born 1 hour ago at 37 weeks' gestation via precipitous, spontaneous vaginal delivery. Her 31-year-old gravida 3, now para 3 mother has a history of gestational diabetes, obesity, and hypertension. The newborn developed respiratory distress and hypoxemia shortly after birth and required supplemental oxygen support. Her respiratory status improved quickly, and she has become clinically stable. Additionally, she is at low risk of EOS but is at risk of hypoglycemia due to maternal gestational diabetes. Based on her response to respiratory support with supplemental oxygen, clinical examination status, and associated chest radiograph findings, TTN is the most likely etiology of her respiratory symptoms.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

With the diagnosis of TTN and given that Baby Girl Smith is an infant of a diabetic mother, her care plan includes close monitoring of her respiratory status and glucose homeostasis while providing routine newborn care. You decide to divide her treatment considerations into the following components:

1. **Treatment and monitoring of TTN**
   - Newborns with TTN require close monitoring of vital signs and respiratory status until the tachypnea resolves.
   - Any further respiratory distress, cyanotic episodes, or inability to quickly wean off supplemental oxygen should prompt a reevaluation of the diagnosis and further investigation.
2. **Monitoring for hypoglycemia**
   - Infants of diabetic mothers are at risk of developing hypoglycemia and need to be closely monitored with glucose screening algorithms to ensure adequate glucose homeostasis.
   - Prefeeding glucose levels are the most reliable indicator of postnatal glucose homeostasis.
   - Current evidence recommends glucose screening for newborns who are infants of diabetic mothers; those who are large or small for gestational age, have a low birth weight (<2,500 g), or are preterm (<37 weeks' gestation); those with poor feeding or midline defects; and those who develop symptoms of hypoglycemia.
   - Symptomatic and/or severe hypoglycemia requires timely initiation of intravenous (IV) dextrose therapy to prevent neuronal injury and adverse neurodevelopmental outcomes. For severe, persistent, or symptomatic hypoglycemia, a continuous infusion of IV dextrose and transfer to the neonatal intensive care unit may be indicated. Breastfeeding should be supported during IV therapy if the newborn is stable.
   - Most newborns with transient asymptomatic hypoglycemia will respond to an appropriate oral feeding regimen (eg, breastfeeding, expressed colostrum, pasteurized donor milk, infant formula with or without glucose gel).
3. **Routine newborn care:** Clinicians need to ensure that all newborns, including those with respiratory distress, receive appropriate newborn care. This care includes the following elements:
   - Feeding assessment
     - Breastfeeding should be initiated within 1 hour of birth when possible, and the neonate's positioning, latch, vigor, and milk transfer should be assessed. Initiation of breastfeeding should be delayed in newborns with respiratory distress until tachypnea and respiratory distress improve. Occasionally, use of IV fluids or insertion of a feeding tube is needed for newborns with prolonged respiratory distress.
     - Breastfeeding provides health benefits to the newborn and mother. The mother's decision to breastfeed should be supported and lactation preserved.
     - Rates of breastfeeding initiation, exclusivity, and continuation improve when the health care team provides maternal education and guidance.
     - The routine use of artificial nipples and pacifiers should be avoided until breastfeeding is established.
     - Rooming-in will help mothers identify feeding cues and encourage exclusive breastfeeding on demand. Supplemental feeds are generally not needed unless medically indicated.
     - In the first days after birth, newborns experience physiologic weight loss. Weight loss that is greater than 7% of birth weight requires close supervision. Excessive weight loss (>10%–12% of birth weight) is concerning and warrants further evaluation. Most breastfed neonates regain their birth weight by 2 weeks of age.
     - A newborn's elimination pattern, including changes in the consistency and color of stools, should be monitored to aid in the assessment of feeding adequacy.
   - Medications and vaccinations
     - Erythromycin eye ointment provides prophylaxis against ophthalmia neonatorum from *Neisseria gonorrhoeae.*

- Intramuscular vitamin K decreases the risk of bleeding from vitamin K deficiency (previously known as hemorrhagic disease of the newborn).
- Hepatitis B vaccine prevents transmission of the virus from mother to newborn.
- Hepatitis B immune globulin is recommended, in addition to the vaccine, for neonates born to mothers with a positive hepatitis B surface antigen test result.

- Monitoring
  - Routine newborn monitoring includes assessment of the newborn's vital signs; weight trend; feeding, voiding, and stooling; and physical assessments, including for any visible jaundice.
  - A newborn should urinate within the first 24 hours after birth and pass their first meconium within the first 48 hours after birth. Further evaluation is required if meconium passage is delayed.
- Evaluating the risk for severe hyperbilirubinemia
  - Cord blood testing is indicated when maternal blood type is O and/or Rh negative. If a maternal antibody screening result is positive, or if the newborn's blood type is A, B, or AB, a direct antigen test (DAT) should be conducted to screen for the presence of maternal antibodies.
  - All newborns should be assessed for their risk of developing severe hyperbilirubinemia by obtaining a predischarge bilirubin level.
    - This bilirubin level should then be plotted on the Bhutani nomogram (Figure 3.1) for stratification of the neonate's risk. Treatment and follow-up planning should be based on this risk stratification and the assessment of other risk factors (Box 3.1).

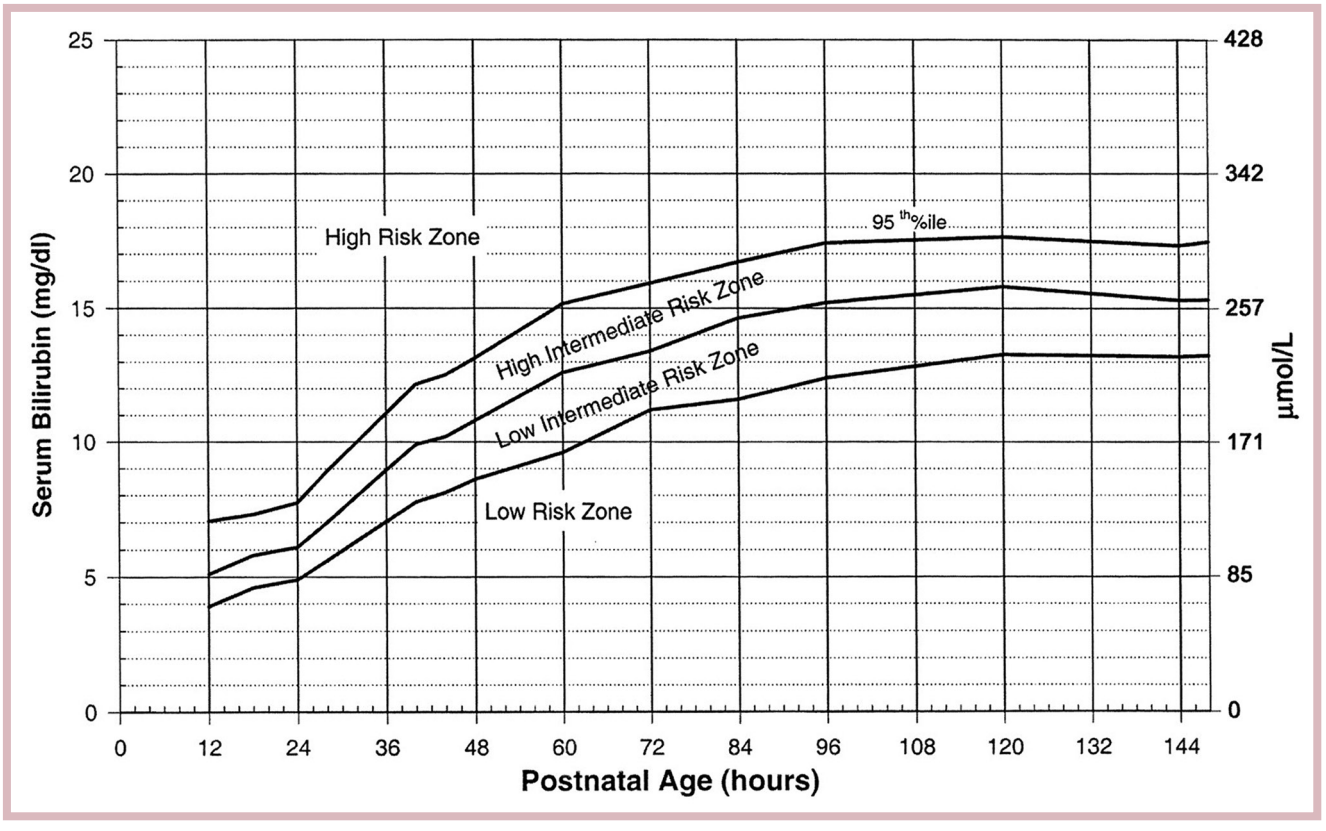


Figure 3.1. Hour-specific nomogram for assessing the risk of developing severe hyperbilirubinemia based on total serum bilirubin level.

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Box 3.1. Risk Factors for the Development of Severe Hyperbilirubinemia

Major risk factors	Minor risk factors
• Gestational age 35–36 weeks • Total bilirubin level in the high-risk zone • Jaundice in the first 24 hours after birth • ABO incompatibility with positive DAT • Other known hemolytic disease (eg, G6PD deficiency) • Elevated $ETCO_c$ • Previous sibling requiring phototherapy • Cephalohematoma or significant bruising • Exclusive breastfeeding with poor feeding or excessive weight loss • East Asian race	• Gestational age 37–38 weeks • Total bilirubin level in the high-intermediate risk zone • Jaundice noted before discharge • Previous sibling with jaundice • Macrosomic infant of a diabetic mother • Maternal age >25 years • Male sex

Abbreviations: DAT, direct antigen test; $ETCO_c$, end-tidal carbon monoxide, corrected for ambient carbon monoxide; G6PD, glucose-6-phosphate dehydrogenase.

Adapted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.

    - The bilirubin level should also be plotted on the phototherapy treatment curve (see Figure 5.1 in Case 5), which correlates to the newborn's gestational age and other neurotoxicity risk factors. These neurotoxicity risk factors include isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, and hypoalbuminemia. If Baby Girl Smith remains well without any neurotoxicity risk factors, her phototherapy treatment threshold is determined by the medium risk curve, based on her gestational age of 37 weeks.
- Newborn screening
  - Metabolic: The exact disorders tested for vary by state, but they include certain metabolic disorders and endocrinopathies, hemoglobinopathies, and other genetic conditions. The preferred time of collection is between 24 and 48 hours after birth.
  - Critical congenital heart disease (CCHD): CCHD screening is used to detect cyanotic CHD. Testing is conducted after 24 hours of age.
    - CCHD screening is performed by placing a pulse oximeter probe on the neonate's right hand (preductal) and foot (postductal) to evaluate oxygen saturation and any difference in values.
    - If the pulse oximeter readings are at least 95% with 3% or less absolute difference between them, it is considered a passing result.
    - If any reading is less than 90%, the neonate's screening result is considered positive.
    - If any reading is 90% to less than 95%, or if there is greater than 3% absolute difference in the oxygen saturation between the right hand and foot, the screening can be repeated hourly up to 3 times. If abnormal findings persist after 3 successive measurements, the screening result is considered positive.
    - Newborns with a positive screening result should be evaluated with an echocardiogram.
  - Hearing: Hearing screening should be performed prior to discharge. Newborns who do not pass their hearing screen should be referred for audiologic evaluation. Additionally, clinicians should consider testing these newborns for congenital cytomegalovirus infection.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment and monitoring of TTN:** You plan to wean Baby Girl Smith's oxygen as indicated by her clinical status until she is stable on room air. You will continue to closely monitor her respiratory rate and for any signs of distress.
- **Monitoring for hypoglycemia:** You will monitor Baby Girl Smith for hypoglycemia based on institutional protocol.
- **Routine newborn care**
  - Feeding assessment: Given the improvement in Baby Girl Smith's respiratory status, you plan for Ms Smith to directly breastfeed on demand and at least 8 to 12 times per day. You also order a lactation consultation.
  - Medications and vaccinations: You order erythromycin eye ointment, a vitamin K injection, and a hepatitis B vaccine.
  - Monitoring: Baby Girl Smith's vital signs will be monitored. The nursing staff will also assess her feeding, weight change, and urine and stool output. You will perform serial physical examinations and monitor family bonding.
  - Risk evaluation for severe hyperbilirubinemia: You order cord blood testing because Ms Smith's blood type is O Rh+. The timing of the bilirubin check depends on Baby Girl Smith's blood type and DAT result.
  - Newborn screening: Baby Girl Smith will undergo metabolic, CCHD, and hearing screening tests prior to discharge.

Case Resolution

In the first hour after birth, Baby Girl Smith is weaned off oxygen and has no further respiratory distress. She receives erythromycin ophthalmic ointment, a hepatitis B vaccine, and a vitamin K intramuscular injection. She remains with her mother after delivery and breastfeeds well, which continues after Ms Smith works with the lactation consultant. Her initial blood glucose level (at approximately 1 hour after birth) is 47 mg/dL (2.61 mmol/L), and all subsequent blood glucose screening results are above 50 mg/dL (2.77 mmol/L).

Cord blood testing determines that Baby Girl Smith's blood type is O Rh+. CCHD and hearing screens are performed at 36 hours after birth, and both have passing results. Her newborn metabolic screen and total bilirubin level are also obtained at this time.

Baby Girl Smith's total bilirubin level at 36 hours after birth is 10 mg/dL (171.04 µmol/L). Applying this to the bilirubin risk stratification nomogram (Figure 3.1) places her in the high-intermediate risk zone with a phototherapy threshold of 11.7 mg/dL (200.12 µmol/L; see Figure 5.1 in Case 5). Based on this result and her lack of neurotoxicity risk factors, she is discharged with a plan to see her primary care physician within 48 hours. At discharge, she is breastfeeding well, has lost 5% of her birth weight, has passed 3 stools, and has voided 9 times.

Discharge Criteria

Q: How do you know when Baby Girl Smith is ready for discharge?

You can feel comfortable discharging a term neonate, including a neonate with TTN, when the following conditions are met:

- The newborn's clinical course and physical examination have improved and reveal no abnormalities, or abnormalities have been addressed.
- The newborn has normal vital signs for at least 12 hours on room air.
- The newborn has had consistent successful feedings with an appropriate weight trend, and a home feeding plan has been established. If breastfeeding, the mother has received information about community lactation support and has been taught how to perform hand expression of her breast milk.
- The newborn has urinated regularly and has passed at least 1 spontaneous stool.
- The clinician has reviewed maternal laboratory results, including syphilis, hepatitis B, GBS, and HIV status.
- The clinician has reviewed the neonate's laboratory results, including blood type and DAT, if applicable.
- The neonate's risk for severe hyperbilirubinemia has been assessed, and follow-up has been planned.
- The neonate has been adequately evaluated for sepsis.
- Vaccination status of the newborn, parents, and close family members has been discussed.
- The newborn has consistently stable glucose levels, if applicable.
- All routine screenings are normal or have been addressed if abnormal.
- Home safety has been discussed.
- A medical home is identified and a follow-up appointment has been made for 24 to 48 hours after discharge.
- The parents are comfortable with newborn care, and all concerns and questions have been answered.
- The parents have a car safety seat that meets federal standards, and appropriate use has been demonstrated.

Anticipatory Guidance

Q: What instructions should you provide to Baby Girl Smith's caregivers on discharge?

- Return to care if Baby Girl Smith experiences any difficulty breathing, trouble feeding, or less than the expected output of urine and stool.
- Continue to feed Baby Girl Smith on demand and at least 8 to 12 times per 24-hour period.
- Baby Girl Smith should receive 400 IU/day of supplemental vitamin D.
- Always place Baby Girl Smith on her back to sleep, on a firm surface with a fitted sheet, and without other bedding or soft objects.
- Avoid smoke exposure.
- Seek medical attention if Baby Girl Smith appears increasingly jaundiced.
- Newborn fever is defined as 38 °C (100.4 °F) or higher and requires evaluation in the emergency department.
- Keep the umbilical cord dry, and avoid submersion baths until the umbilical cord detaches.
- Recognize signs of postpartum depression, and seek evaluation and support if needed.

Clinical Pearls

- Respiratory distress and hypoxemia in a term newborn has a limited differential diagnosis that includes EOS, neonatal pneumonia, TTN, cyanotic CHD, PPHN, MAS, pneumothorax or pneumomediastinum, and pulmonary abnormalities such as hypoplasia.
- Relevant maternal, prenatal, and delivery histories and physical examination can help to narrow this differential diagnosis.
- A chest radiograph has a high sensitivity for detecting anatomic or pulmonary abnormalities affecting breathing, and it is an appropriate tool to aid in evaluating a newborn with respiratory distress.
- TTN has a characteristic clinical picture and chest radiograph findings, and it self-resolves as fluid clears from the alveoli.
- GBS infection is the most common cause of neonatal EOS and neonatal pneumonia. Risk calculators can aid in determining an individual newborn's risk of EOS and decisions about empiric antibiotics.
- Infants of diabetic mothers are at risk for hypoglycemia and require close monitoring of glucose levels. Severe, persistent, and/or symptomatic hypoglycemia in a newborn requires continuous IV dextrose and transfer to a higher level of care.
- The 2004 American Academy of Pediatrics clinical practice guidelines should be used to determine the newborn's risk for developing severe hyperbilirubinemia. Treatment and follow-up are based on total bilirubin level, risk factors, and age.

Documentation Tips

- For the first year after birth, document in the medical history the infant's gestational age and birth weight.
- Link the infant's respiratory distress to the final diagnosis, if known, or to a suspected diagnosis if the final diagnosis is still unclear.
- Document the diagnosis of hypoxemia, if present, instead of only listing low oxygen saturations.
- Document acute respiratory failure, if present. In the neonatal period, this is generally considered when infants are requiring greater than or equal to 2 L/min of supplemental oxygen via nasal cannula, as this provides continuous positive airway pressure. Clarify whether the acute respiratory failure is hypoxemic or hypercapneic, if known.
- Document if the infant is being treated for sepsis. Be sure to document if sepsis has been ruled out (the infant is no longer thought to have sepsis) or resolved (the infant was diagnosed with sepsis, and treatment is complete).

Suggested Readings

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CASE 4

Parker, a 3-Year-Old Boy With Difficulty Breathing

CASE PRESENTATION

While on an overnight shift, you are called by the emergency department (ED) physician with a request to evaluate a new patient for admission. The ED physician tells you about Parker, a 3-year-old boy who presented tonight with difficulty breathing. Parker is healthy despite being born at 31 weeks' gestation. He has had coughing and rhinitis for 2 days and a fever up to 38.2 °C (100.8 °F). Tonight, he was breathing louder and harder, so his parents brought him to the ED. He had significant respiratory distress in the ED, where he was given oral dexamethasone and a nebulized racemic epinephrine treatment with subsequent improvement. While he was being monitored in the ED, his symptoms returned 2 hours later, and he was treated again with racemic epinephrine. The ED physician is requesting admission for continued monitoring.

Patient History and Review of Systems

Q: What information should you collect from Parker's parents?

- History of present illness
  - Detailed description of loud and labored breathing, cough, fever, and runny nose
  - Any alteration of voice or cry
  - Any witnessed choking episodes or placing of nonfood objects in mouth
  - Presence of drooling
  - Exacerbating or relieving factors (eg, whether symptoms worsen when he is upset)
  - Sick contacts, including child care attendance
  - Potential dehydration symptoms, such as decreased urine output, sunken appearance of eyes, malaise, lethargy, irritability, and absence of tears
- Associated symptoms, such as nasal congestion, vomiting, difficulty swallowing, or rash
- Medical history, including immunization status, especially seasonal influenza vaccine; any history of similar symptoms; prior airway surgery; reflux; and any respiratory support in the neonatal intensive care unit, including intubation

CASE FOCUS

History and Review of Systems

From his history, you learn that Parker spent 4 weeks in the neonatal intensive care unit but was never intubated. He briefly required nasal continuous positive airway pressure but otherwise had an uneventful hospitalization. He is fully immunized, including his seasonal influenza vaccine, and has overall been healthy and developing typically. He has had what his parents characterize as occasional colds, but his parents report he has never had symptoms like this. Parker's parents think his cough sounds different. When you prompt them, they agree that his cough sounds barky and note that he also has been making a funny sound when breathing in. His parents had not considered it until you asked, but they note that he seems to have more difficulty breathing when he becomes upset. He has multiple sick classmates at child care. He does not typically put toys or other objects in his mouth; nor has he had any choking episodes. Although he has been drinking less than usual, he is still urinating well and does not seem to have any difficulty swallowing. He is not drooling, has not been vomiting, and has not had any rashes.

Physical Examination

Q: What parts of the physical examination should you focus on for Parker?

- Complete set of vital signs
- Level of consciousness; amount of distress, with attention to reducing the patient's distress and prioritizing the patient's comfort
- Position of comfort, such as tripod position or neck extension
- Presence or absence of tears with crying
- Mucous membranes: moist, sticky, or dry; presence of drooling or pseudomembrane
- Oropharyngeal: trismus, intraoral swelling, tonsillar size and color, exudate, uvula size and position
- Vocal sounds: hoarse, muffled
- Nose: foreign body, drainage or discharge
- Neck: adenopathy, meningismus, torticollis, range of motion, tenderness
- Respiratory
  - Indications of work of breathing, including presence and location of retractions, and presence of nasal flaring or grunting
  - Auscultation, including any inspiratory or expiratory noises and symmetry of airflow
  - Quality of cough
- Any cyanosis around the mouth, of the lips and/or tongue, or the extremities (note that visual identification of cyanosis is highly variable and should not replace oxygen saturation measurement with a pulse oximeter)
- Peripheral perfusion: capillary refill time, pulse quality, and temperature of distal extremities
- Skin: rashes or other lesions

CASE FOCUS

Physical Examination

At the time of your examination, Parker is febrile with a temperature of 38.3 °C (100.9 °F). He has a respiratory rate of 30 breaths/min and an oxygen saturation of 96% on room air. He is tachycardic with a heart rate of 150 beats/min.

Parker is awake, sitting on his mother's lap comfortably, and looking at a book. He sounds hoarse, with an occasional barking cough. When he becomes nervous about your examination, he develops mild stridor, but it goes away after you reassure him that there will be "no pokes." He has clear rhinorrhea, moist mucous membranes, and can fully open his mouth. He has no drooling or swelling of his lips, tongue, or uvula. His tonsils appear normal-sized and symmetric, and he has no posterior oropharyngeal erythema or exudates. His neck is supple with full range of motion. You palpate small, scattered, nontender lymph nodes, indicating anterior cervical lymphadenopathy. Parker is mildly tachypneic but has no nasal flaring, grunting, or retractions when calm, and his lungs are clear with normal air entry. His cardiac examination shows tachycardia with a regular rhythm and no murmurs. His peripheral perfusion is normal without cyanosis, and you do not note any rashes or other skin lesions.

After the examination, you consult the ED physician to learn more specifics about Parker's respiratory findings on initial presentation. You learn that he had a respiratory rate of 50 breaths/min and an oxygen saturation of 96% on room air. He had stridor at rest along with suprasternal, supraclavicular, and subcostal retractions as well as nasal flaring. On auscultation, his lungs were clear but breath sounds were decreased bilaterally. Based on this information and the results of your examination, you decide he is improving after the treatments he received in the ED.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with stridor?

In forming your differential diagnosis, it can be helpful to remember that the presence of stridor indicates narrowing of the upper airway, glottis, or subglottis. This is usually due to diffuse or regional edema but can also be caused by masses in or external compression of those areas. Causes of stridor can include those listed in Table 4.1.

Table 4.1. Differential Diagnosis for a Young Child With Stridor

Diagnoses of highest suspicion	• Croup[a] • Foreign body aspiration • Parapharyngeal or retropharyngeal abscess • Peritonsillar abscess
Other diagnoses to consider	• Allergic reaction (eg, acute angioneurotic edema) • Anatomic etiologies (more commonly present in infancy, but possible in young children) — Airway hemangiomas — Congenital causes (eg, laryngeal webs, vallecular cysts, neurofibromas) — Laryngomalacia (most common) — Papillomatosis — Tracheobronchomalacia — Vascular rings or slings — Vocal cord paralysis • Aspiration pneumonia or pneumonitis • Bacterial tracheitis (a potential complication of croup) • Caustic ingestion • Epiglottitis • Hereditary angioedema • Inhalational injury • Subglottic stenosis • Trauma (eg, from intubation)

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with stridor?

- Although stridor has a large differential diagnosis, croup is the most common cause in toddlers and young children. The term *croup* refers to a group of conditions causing upper airway obstruction via inflammation and/or edema, and *croup* may be used to describe laryngotracheitis, laryngotracheobronchitis, laryngotracheobronchopneumonitis, and spasmodic croup. Croup is primarily diagnosed clinically when there is evidence of infectious symptoms (eg, fever, rhinorrhea, coryza, congestion) coupled with inspiratory stridor, characteristic barking cough, and/or hoarseness.
- Occasionally, diagnostic testing can be helpful.
  - Two-view neck and chest radiographs (frontal and lateral views).
    - With croup, 50% of neck radiographs will show the characteristic steeple sign (subglottic narrowing with smooth tracheal contour on posteroanterior view).
    - Irregularity of the tracheal contour may suggest viral or bacterial tracheitis.
    - The finding of a thumbprint sign (thickening of the free edge of the epiglottis) on a lateral neck film suggests epiglottitis.
    - Radiopaque foreign bodies may be visible on the neck or chest radiographs (eg, coins, batteries, magnets), whereas radiolucent foreign bodies are not visible (eg, small toys, food particles, plant material, plastic). Foreign body aspiration may present as a sudden onset of symptoms without any preceding upper respiratory infection (URI) symptoms or fever. Air trapping may also be seen on chest radiograph due to obstruction of expired airflow.

  - If lower respiratory symptoms (eg, cough, wheeze, rapid breathing) are present, a chest radiograph may help depict signs of disease, such as pneumonia.
  - Retropharyngeal abscesses usually cause widening of the retropharyngeal space on lateral neck radiographs. Confirmation with a computed tomography (CT) scan may be needed.
- Complete blood cell count (CBC): A CBC is usually not indicated for suspected croup. However, in cases in which there is suspicion for a bacterial infection of the airway, a CBC may demonstrate markedly elevated white blood cell count. Peritonsillar abscesses and deep neck infections may cause leukocytosis.
- Respiratory pathogen panel: Although generally not indicated, a respiratory pathogen panel can confirm a viral etiology. This test should only be performed if the presence or absence of an identifiable virus would alter management significantly. The presence of a virus is usually assumed based on clinical presentation.
- Bacterial throat culture: Although rarely indicated in the evaluation of stridor, a throat culture can be considered for an unvaccinated patient with a stable airway or a patient with a suspected peritonsillar abscess.
- Contrast-enhanced CT imaging.
  - Contrast-enhanced CT scan of the neck may be needed if there are clinical symptoms of dysphagia, neck stiffness/pain, or swelling, which could indicate a deep neck infection such as an abscess.
  - Contrast-enhanced CT scan of the neck is also indicated if a tumor or other anatomic concerns are suspected.
  - Contrast-enhanced CT angiogram of the chest may be needed to evaluate for vascular rings or slings, which could cause tracheal compression.
- Laryngoscopy or bronchoscopy.
  - Laryngoscopy can be useful in cases of severe, persistent, or recurrent symptoms with no clear explanation.
  - Laryngoscopy is indicated in children with concern for an anatomic anomaly. Bronchoscopy is indicated if there is a need for visualization of the airway below the vocal cords or any concern for intrinsic airway anomalies.

CASE FOCUS

Diagnostic Evaluation

Parker's medical record indicates that the ED physician did not perform any diagnostic testing. You initially consider ordering a respiratory pathogen panel and neck radiograph to confirm your suspected diagnosis of viral laryngotracheitis (or croup). However, you conclude that no further diagnostic imaging or laboratory testing is indicated, as it is not needed for diagnosis and would not change your management.

Arriving at a Diagnosis

Q: How do you develop an assessment for Parker?

First, you decide to review his history, physical examination, and diagnostic studies for their most pertinent information, and then you will develop a finding list to help narrow your differential diagnosis.

1. **Interpret key findings from the history and examination.**
   - History: Parker developed stridor, difficulty breathing, a barking cough, and rhinitis in the setting of multiple sick contacts. He had an initial response to dexamethasone and racemic epinephrine with subsequent rebound of his symptoms. At the time of your evaluation, he seems to have responded well to his second dose of racemic epinephrine.

- Physical examination: Parker is well appearing on your examination. He has rhinorrhea and stridor that is apparent when he is anxious. He is well hydrated, and his examination is otherwise nonfocal.

2. **Develop the list of findings.**

Q: What major findings have you have identified for Parker?

- Stridor (improving)
- Respiratory distress (resolved)
- Barking cough
- Rhinorrhea
- Fever

3. **Revisit the differential diagnosis.**

Q: Based on Parker's history, examination, and list of findings, are you able to choose one diagnosis to explain his presentation?

- Parker developed inspiratory stridor in the setting of upper respiratory symptoms and multiple sick contacts; therefore, you suspect that he likely has viral croup. His physical examination further supports a diagnosis of viral croup, not only because he has inspiratory stridor, a barking cough, and rhinorrhea, but also because he overall is well appearing. Given that an infection in the lower respiratory tract should cause crackles, rales, or rhonchi—all of which are absent in Parker's case—his illness is likely laryngotracheitis rather than laryngotracheobronchitis or another lower respiratory infection.
- Parker is unlikely to have epiglottitis or bacterial tracheitis because he appears nontoxic. He has no neck swelling, which is reassuring against a neck abscess or mass. His neck also shows full range of motion, which makes a deep neck infection unlikely. Finally, he has no history of allergy exposure and no rash on physical examination, which makes anaphylaxis unlikely.
- Parker's stridor improved with racemic epinephrine. While this is not diagnostic, it further supports the diagnosis of viral croup, because generally the stridor caused by a foreign body or fixed anatomical obstruction does not improve significantly with racemic epinephrine.

Q: What are the most common infectious etiologies of croup?

- Acute viral infection is by far the most common cause of croup. However, occasionally, bacteria and other atypical agents are identified.
- Laryngotracheitis is typically caused by viral agents. Occasionally, bacteria and other atypical agents may cause laryngotracheitis.
- Disease lower in the respiratory tract can be caused by both viral and bacterial agents.
- Refer to Box 4.1 for a list of most common infectious etiologies of croup.

Box 4.1. Infectious Etiologies of Croup

Viral (common)	Bacterial (rare)
Parainfluenza viruses (most frequent)	*Staphylococcus aureus*
Influenza viruses A and B (somewhat frequent)	*Streptococcus pyogenes*
RSV	*Streptococcus pneumoniae*
Rhinovirus	*Haemophilus influenzae*
Enterovirus	*Moraxella catarrhalis*
Adenovirus	*Corynebacterium diphtheriae*
Measles[a]	*Mycoplasma pneumoniae*

Abbreviation: RSV, respiratory syncytial virus.

[a] This etiology is rare in highly immunized populations.

4. **Assess the severity of Parker's croup.**

Q: Are there objective ways to assess the severity of Parker's presentation?

- There are multiple scoring systems that can be used to help objectively qualify croup severity. These scoring systems utilize clinical features, including a patient's mental status, work of breathing, air entry, and presence of cyanosis, and/or stridor (particularly stridor at rest).
- Parker's clinical features on arrival to the ED, including increased work of breathing, stridor at rest, and decreased air entry, indicate croup of moderate severity. Following initial interventions, he is currently having mild symptoms.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with croup?

- The patient required 2 to 3 doses of nebulized epinephrine in the ED (depending on hospital policy and resources).
- Ongoing stridor is present at rest.
- The patient has a level of respiratory distress necessitating further monitoring or treatment.
- The patient is agitated, restless, or ill appearing.
- The patient has hypoxemia requiring supplemental oxygen or has sufficient respiratory distress to require other forms of respiratory support.
- The patient is dehydrated, or there is concern for ability to maintain adequate hydration.
- There is uncertainty about the diagnosis or the severity of illness, especially in an infant or young child.

Given that Parker required 2 doses of racemic epinephrine in the ED, he warrants admission for ongoing monitoring and treatment as needed.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Parker is a 3-year-old otherwise healthy boy who presented to the ED with mild respiratory distress, stridor, runny nose, and a barking cough secondary to viral croup (laryngotracheitis). He meets admission criteria for croup because he required multiple doses of nebulized epinephrine in the ED.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Croup is generally a self-limited illness; thus, management and interventions for children hospitalized with croup are primarily supportive.

1. **Maintain a calm environment and limit the child's pain or anxiety:** In children with stridor, symptoms often worsen when the child is agitated. In some causes of stridor, such as epiglottitis, pain and anxiety can result in acute decompensation and the need for intubation. Because of this, it is important to consider the child's tolerance of the interventions when deciding on treatment and monitoring. Painful or anxiety-provoking procedures, such as placement of an intravenous (IV) line or administration of intramuscular medications, are generally not

recommended until the child's breathing has been stabilized. This may also include postponing uncomfortable portions of the physical examination until the child is stable from a respiratory standpoint.

2. **Steroids:** All children hospitalized with suspected croup should be given steroids, because early administration of steroids has been shown to shorten hospital stays. Oral dexamethasone is the most commonly used steroid in the ED or inpatient setting. Alternatively, inhaled budesonide is also effective in the treatment of croup. There is no benefit to IV steroids over oral steroids; thus, placement of an IV should be avoided in the initial management of croup but may be considered in children who are lethargic, ill appearing, or unable to tolerate oral intake secondary to posttussive emesis. Parker received a dose of oral dexamethasone in the ED; repeated doses of steroids are not routinely recommended.
3. **Nebulized epinephrine:** While the mechanism of nebulized epinephrine is not definitively known, it is thought that activation of the β-adrenergic receptors causes constriction of precapillary arterioles, which subsequently decreases edema in the laryngeal mucosa. Use of nebulized epinephrine decreases stridor and improves work of breathing in children with moderate to severe croup. Parker received 2 doses of nebulized epinephrine in the ED, which improved his symptoms. Nebulized epinephrine may be redosed if the child continues to have stridor at rest along with other concerning signs such as respiratory distress, restlessness or agitation, or decreased alertness. Improvement in croup symptoms should be seen within 30 minutes of administration of each dose and last for 2 hours. While racemic epinephrine is commonly used, there is no difference between l-epinephrine and racemic (D and l) epinephrine. Historically, epinephrine was given via positive pressure ventilation, but this was not shown to improve outcomes.
4. **Antibiotics:** In the era of widespread *Haemophilus influenzae* type b vaccination, most stridor in young children is caused by viral infections. Because of this, routine use of antibiotics is not indicated unless there is significant suspicion for a bacterial etiology.
5. **Other supportive therapies**
   - Oxygen supplementation: By definition, laryngotracheitis affects primarily the upper airway; therefore, alveolar gas exchange is typically normal and hypoxemia is rare. In some cases of severe obstructive disease or when the infection extends to the lower respiratory tract, hypoxemia may be present. In these cases, supportive care may include oxygen as needed to maintain saturation above 92% (or according to institution protocols). Although rare, some patients with severe croup require intubation. Intubation may be required when there is prolonged increased work of breathing and concern for respiratory failure secondary to fatigue or in the setting of hypoxic respiratory failure.
   - Heliox: Some studies have shown heliox to be as effective as nebulized epinephrine in reducing symptoms of croup. Heliox may not be available at all institutions, but when available, it can be used alone or in combination with nebulized epinephrine.
   - Hydration: Patients should be encouraged to maintain hydration orally, if able. In cases of severe respiratory distress, oral hydration may not be possible and IV fluids should be considered.
6. **Antipyretics and analgesics:** Acetaminophen or ibuprofen may be considered as needed for symptoms of pain or fever.
7. **Monitoring:** Children who require multiple doses of racemic epinephrine, more frequently than every 2 hours, should be placed on cardiac monitoring due to the possibility of rare cardiac complications. Additionally, the child with stridor should have frequent clinical reassessments, as some children may experience worsening symptoms or begin to demonstrate findings consistent with another etiology.

CASE FOCUS

Plan for Treatment and Monitoring

- **Reducing anxiety:** You plan to admit Parker to a private room and minimize interventions so as to not cause unnecessary agitation that could worsen his symptoms.
- **Steroids:** Parker has received an adequate dose of systemic steroids in the ED. Unless he has an atypical or prolonged course, you do not anticipate that he will require further doses.
- **Nebulized epinephrine:** At this time, Parker does not require any further doses. If he has a return of stridor at rest associated with signs of distress, you may need to provide another dose.
- **Supportive care:** At this time Parker does not need oxygen support; however, you plan to administer oxygen as needed to maintain a saturation above 92%. You also encourage oral hydration.
- **Antibiotics:** No antibiotics are indicated in this case.
- **Monitoring:** You order strict monitoring of intake and output and vital signs to be checked every 4 hours. You order continuous pulse oximeter monitoring, if tolerated. Additionally, you plan to reassess Parker's clinical status in a few hours. Cardiac monitoring may be needed if multiple doses of nebulized epinephrine are required more frequently than every 2 hours.
- **Diet:** Regular diet is allowed for Parker.
- **Antipyretics and analgesics:** Acetaminophen or ibuprofen may be administered as needed for pain or fever.

Case Resolution

Parker's respiratory symptoms continue to improve following admission. He does not require any additional doses of racemic epinephrine, but you do give him a dose of acetaminophen for low-grade fever. The morning following his admission, Parker is breathing comfortably, afebrile, and tolerating food and liquids by mouth. You decide he is clinically stable for discharge home and recommend he follow up with his primary care pediatrician in the next few days.

Discharge Criteria

Q: How do you know when Parker is ready to go home?

You can feel comfortable discharging your patient with croup when the following criteria are met:

- The patient clinically appears well and has no signs of respiratory distress.
- The patient has gone more than 4 hours without requiring nebulized epinephrine.
- The patient does not require oxygen.
- The patient is drinking enough to maintain hydration.
- You are confident that other etiologies of stridor have been ruled out.

Anticipatory Guidance

Q: What instructions should you provide to Parker's caregivers on discharge?

- Monitor Parker's work of breathing. Watch for worsening stridor, change in mental status, poor oral intake, or decreased urine output. Parker should return to the ED with any worsening symptoms or other new concerns.
- The symptoms of croup generally peak on days 2 or 3 of illness.
- Cold mist (humidified air) may be helpful in improving croup symptoms at home.

Clinical Pearls

- The typical presentation for croup is a patient aged 6 months to 3 years with 1 to 2 days of mild viral URI symptoms (cough, congestion, and/or fever) who then develops a barking cough, stridor, and difficulty breathing at night. Croup is most common in the fall or winter.
- All children hospitalized with croup should be given systemic steroids.
- If the child has no preceding URI, has not had a typical course of illness, or seems sicker than expected, consider alternative diagnoses (eg, aspirated foreign body, bacterial tracheitis).

Documentation Tips

- Document any continued signs of respiratory distress (grunting, flaring, retractions, or persistent stridor at rest) despite steroids and racemic epinephrine.
- When applicable, include the need for previous steroids or repeated clinic or ED visits prior to admission.
- Document any associated medical complexity or comorbid medical conditions.

Suggested Reading

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CASE 5

John, a 4-Day-Old Boy With Hyperbilirubinemia

CASE PRESENTATION

John is a 4-day-old boy who presents as a direct admission from his pediatrician's office for hyperbilirubinemia. He was born at an estimated gestational age (EGA) of 37 weeks. His pediatrician does not have access to the maternal records, and John's mother does not recall her blood type. Today, following the pediatrician visit, John was found to have an elevated bilirubin level of 17.9 mg/dL (306.16 µmol/L) with a direct bilirubin of 0.8 mg/dL (13.68 µmol/L), and he is noted to have lost nearly 13% of his birth weight. Based on these findings, his pediatrician asked John's family to take him directly to the inpatient unit.

Patient History and Review of Systems

Q: After placing John under phototherapy lights, what information should you collect from John's caregivers and his newborn records?

- Prenatal history: pregnancy complications, maternal serologies, maternal blood type and antibody screen, maternal group B streptococcus status, antepartum complications
- Delivery history, including EGA at birth, delivery date and time, mode of delivery (vaginal or cesarean) including assisted delivery (forceps or vacuum), delivery complications, length of rupture of membranes (prolonged rupture of membranes is defined as rupture of membranes >18 hours prior to delivery), need for resuscitation, and Apgar scores
- Postnatal course: need for neonatal intensive care, complications in the newborn period, evidence of birth trauma (bruising, cephalohematoma, subgaleal hemorrhage), jaundice in the first 24 hours after birth, need for phototherapy, total serum bilirubin (TSB) or transcutaneous bilirubin level prior to discharge, direct bilirubin (if available), newborn screen results (if available)
- Growth and feeding history
  - Birth weight with classification of birth weight relative to gestational age (eg, small for gestational age, appropriate for gestational age, large for gestational age)
  - If breastfeeding: frequency and duration of breastfeeding, including daytime and nighttime patterns; presence of breast fullness or changes in breasts since delivery; adequacy of latch; maternal pain or discomfort with breastfeeding; presence of neonate's audible gulps and swallows during breastfeeding; neonate's vigor with breastfeeding; feeling of breast emptiness after breastfeeding; pumping history; consultation with lactation consultant; and maternal history of prior breastfeeding success

  - If formula feeding: type of formula used; amount and frequency of feeds, including daytime and nighttime pattern; total amount of formula taken per 24-hour period; and method of formula preparation (ie, ratio of powdered formula to water)
  - Frequency of voiding and stooling, including heaviness of wet diapers, color (eg, black or dark green, green, yellow, pale) and consistency of stools
- Parental health: physical and mental health, maternal hydration and nutrition status (if breastfeeding), and parental support system
- Family history: sibling with jaundice or phototherapy; anemia (specifically glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency, elliptocytosis, or spherocytosis); Gilbert syndrome; liver disease, cholecystectomy, or splenectomy; or East Asian heritage, as there is an increased incidence of Gilbert syndrome in persons of East Asian heritage
- Signs of acute bilirubin encephalopathy (ABE): irritability, lethargy, high-pitched cry, opisthotonos, retrocollis
- Other associated symptoms: fever, cough, difficulty breathing, rash, poor feeding, vomiting, diarrhea

CASE FOCUS

History and Review of Systems

From your conversation with John's family and your review of his newborn records, you learn that John was born at 37 weeks 0/7 days EGA to a 22-year-old gravida 2, para 1 mother via vacuum-assisted vaginal delivery. He was born in the afternoon and is approximately 96 hours of age at the time of your evaluation. Pregnancy was complicated by maternal blood type of O Rh-negative, necessitating treatment with Rho(D) immune globulin during pregnancy and at delivery. Maternal serologies were negative, her group B streptococcus testing was positive, and she received 2 doses of ampicillin prior to delivery. Rupture of membranes occurred 5 hours prior to delivery. The remainder of the antepartum course was uncomplicated.

John was vigorous at birth and did not require any resuscitation. His Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. His umbilical cord clamping was delayed for 60 seconds, and he was immediately placed skin-to-skin with his mother. His birth weight was 3,250 g. His newborn course was notable for ankyloglossia and maternal discomfort with breastfeeding, which prompted a lactation evaluation. Subsequently, his mother reports improvement in latch and comfort with breastfeeding. Jaundice was not noted in the first 24 hours after birth, but due to his blood type of A Rh-negative and direct antiglobulin test (DAT) positive, a TSB level was obtained at 12 hours after birth and was 4.2 mg/dL (71.84 µmol/L). A repeat TSB level was obtained prior to discharge at 42 hours after birth and was 8.6 mg/dL (147.09 µmol/L), placing him in the low intermediate risk category on the designation of risk nomogram. A direct bilirubin level was not obtained. He was discharged home at less than 48 hours of age. In the setting of his early term gestational age and ABO isoimmunization, his mother was asked to follow up with a pediatrician in 24 hours for a bilirubin recheck.

John's mother had difficulty with transportation and was unable to present to the pediatrician's office until the following day. Since discharge from John's newborn hospitalization, his mother has been exclusively breastfeeding John, but this is her first time breastfeeding, as her older son was fed formula. His mother reports that John seems to be feeding less in the past day, specifically 7 times in the past 24 hours. He stays latched for 10 to 15 minutes each breastfeeding session and does not feed vigorously, as he falls asleep quickly during feeding. In the past 24 hours, John has had 1 wet diaper and 1 stool, which was dark brown and pasty.

His mother states that John's older brother had jaundice after birth, but he did not require phototherapy. John's parents do not have East Asian heritage. John does not have any swelling on his head, and he has not had fever, irritability, vomiting, diarrhea, or rash. John's mother reports adequate access to nutrition, does not currently take any medications, and denies dehydration. She is exhausted and concerned about his feeding, but otherwise she feels healthy and is well supported by her family and friends. John's initial newborn screen results are unknown at the time of his readmission.

Physical Examination

Q: What parts of the physical examination should you focus on for John?

- Complete set of vital signs
- Current weight and percentage of weight loss
- General: activity level, appearance (eg, ill appearing), presence of dysmorphic features
- Head, eyes, ears, nose, and throat: fontanelle, sclera, mucous membranes, cleft palate or oral anomalies
- Cardiovascular: murmur, quality of pulses, capillary refill time
- Respiratory: work of breathing, noisy breathing
- Abdomen: distension, tenderness, organomegaly
- Genitalia: any abnormalities
- Neurologic: muscle tone, irritability, lethargy, suck, quality of cry
- Skin: color (pallor, jaundice, and/or plethora), bruising, rashes, cephalohematoma
- Visualization of stool

CASE FOCUS

Physical Examination

John is normothermic, with a rectal temperature of 36.7 °C (98.1 °F). He is mildly tachycardic with a heart rate of 170 beats/min, and his blood pressure is normal at 70/45 mm Hg. His respiratory rate is normal at 48 breaths/min, and his oxygen saturation is 99% on room air. John's birth weight was 3,250 g, and his current weight is 2,830 g, indicating a 12.9% weight loss.

John appears comfortable sleeping under the phototherapy lights. He is mildly fussy but consolable when examined. His anterior fontanelle is slightly sunken, and he has no swelling or bogginess of his scalp. His sclera are icteric, and his mucous membranes are icteric and dry. His palate is intact, and he has ankyloglossia. His breath sounds are clear and equal, and his breathing is comfortable. He is slightly tachycardic but has a regular rhythm without a murmur, and his pulses are normal and equal. His perfusion is normal. His abdomen is not distended or tender, his bowel sounds are normal, and there is no hepatosplenomegaly. His genitalia are normal for age, and he is uncircumcised. He responds to examination but quickly falls back asleep and has mild hypotonia. His reflexes are normal for age. His skin is jaundiced from his head to his abdomen, but when blanched with pressure, neither the palms of his hands nor the soles of his feet are jaundiced. No rash is present. His diaper is dry with a smear of brown-green stool. On completion of the examination, his mother asks to breastfeed him before restarting phototherapy. He latches briefly and then falls asleep. After a few minutes of attempting to breastfeed, his mother places him back under the phototherapy lights.

Differential Diagnosis

Q: What is the differential diagnosis for jaundice in a newborn?

Understanding bilirubin metabolism is important when formulating a differential diagnosis for jaundice. Bilirubin metabolism involves the production, transport, conjugation, excretion, and recirculation of bilirubin products. There are many etiologies of hyperbilirubinemia, and it is helpful to categorize them based on whether the bilirubin is unconjugated or conjugated, although some etiologies may cause both types. Conjugated hyperbilirubinemia is always considered pathologic; for the purposes of this chapter, it will not be discussed here. Table 5.1 shows the various causes of unconjugated hyperbilirubinemia. For any neonate, there can be multiple underlying factors that contribute to an elevated bilirubin level. The most likely cause of John's severe hyperbilirubinemia is a combination of physiologic processes, including inadequate intake, reduced intestinal motility, and his early term gestational age (which is associated with lower bilirubin uridine diphosphate-glucuronosyl transferase [B-UGT] activity compared to full-term infants). The possibility of hemolysis due to ABO blood group incompatibility must also be considered.

Table 5.1. Causes of Unconjugated Hyperbilirubinemia in a Newborn

	Physiologic processes[a]	Pathologic processes
Increased production of bilirubin	• Greater amounts produced from other hemoproteins • Higher RBC turnover (shorter life span) • Larger RBC mass	• Extravasation of blood (eg, cephalohematoma, pulmonary hemorrhage, intracranial hemorrhage) • Hemolysis due to ABO/Rh/minor blood group incompatibilities[b] • Inherited RBC disorders — Erythrocyte membrane defects (eg, spherocytosis, elliptocytosis) — Enzyme defects (eg, G6PD, pyruvate kinase deficiency) • Polycythemia
Altered transport	• Lower albumin • Lower capacity and affinity of albumin for bilirubin	• Acidosis • Drugs (eg, rapid infusion of ampicillin, sulfa drugs, ceftriaxone) • Hypothermia • Hypoxia • Malnutrition
Altered conjugation	• Decreased hepatic uptake • Lower B-UGT activity[b]	• Decreased activity of B-UGT (eg, Gilbert syndrome, Crigler Najjar syndrome) • Liver failure
Altered excretion and increased enterohepatic recirculation	• Decreased intestinal flora • Decreased intestinal motility[b] • Inadequate nutritional intake[b] • Increased β-glucuronidase activity	• Biliary obstruction (may cause both unconjugated and conjugated hyperbilirubinemia) • GI obstruction (eg, Hirschsprung disease, bowel atresia/stenosis, meconium plug, meconium ileus)

Table 5.1. Causes of Unconjugated Hyperbilirubinemia in a Newborn *(continued)*

	Physiologic processes[a]	Pathologic processes
Multifactorial/other	NA	• Hypopituitarism • Hypothyroidism • Metabolic disorders • Prematurity • Sepsis/infection

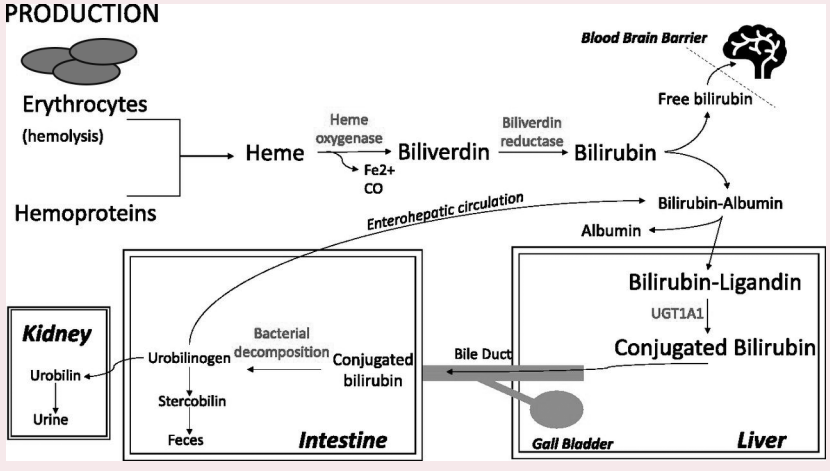
Abbreviations: B-UGT, bilirubin uridine diphosphate-glucuronosyl transferase; GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase; NA, not applicable; RBC, red blood cell.

[a] When compared with older children and adults.

[b] Diagnoses that seem most likely based on your patient's presentation.

BACK TO BASICS

Bilirubin Metabolism and Excretion



Bilirubin production, metabolism, and excretion.

Abbreviations: Fe2+, ferrous iron; CO, carbon monoxide.

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Unconjugated bilirubin is a breakdown product of heme (from hemoglobin and other hemoproteins). It is a lipophilic molecule that must be bound to a carrier, such as albumin, for transport through the blood. Unconjugated bilirubin is transported to the liver, where it is conjugated by B-UGT. Conjugated bilirubin then moves into the intestine via the hepatic canaliculi and bile ducts, where it is further metabolized by intestinal flora into urobilinogen and excreted in feces.

Enterohepatic circulation is the process by which intestinal bilirubin is unconjugated by β-glucuronidase, which resides in the brush border of the intestine. This unconjugated bilirubin is then reabsorbed into the bloodstream, further increasing TSB levels. Enterohepatic circulation of bilirubin is high in newborns because of a paucity of intestinal bacteria, a high concentration of bilirubin in meconium, and high intestinal β-glucuronidase activity. Reduced intestinal motility further increases enterohepatic circulation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for newborns who present with jaundice?

For a newborn who presents to the hospital for evaluation of jaundice, a diagnostic evaluation will help determine the need for phototherapy and elucidate the underlying cause of the hyperbilirubinemia.

- All newborns should undergo testing of both TSB level and direct bilirubin level to evaluate for the presence of unconjugated or conjugated hyperbilirubinemia.
- Additionally, most newborns readmitted to the hospital with significant hyperbilirubinemia should undergo screening for hemolysis with a complete blood cell count (CBC), reticulocyte count, peripheral smear, and a DAT (formerly known as a *Coombs test*).
- Further testing may be indicated based on different clinical scenarios, as illustrated in Table 5.2.

Table 5.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Neonates with Jaundice

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Hemolysis	Early-onset jaundice Bilirubin rate of rise of >0.2 mg/dL/h (3.42 µmol/L/h) Risk factors include maternal-fetal blood type incompatibility, family history of RBC disorders	CBC, peripheral smear, reticulocyte count, blood type, DAT, crossmatch (if near exchange transfusion threshold), albumin, G6PD testing; consider consultation with a hematologist.
Decreased nutritional intake (caloric and fluid volume)	Excessive weight loss (consider utilizing newborn weight loss curves) or loss of >10% from birth weight, lethargy, dry mucous membranes, sunken fontanelle, decreased urine and stool output	Serum electrolytes and formal feeding evaluation
Infection	Fever or hypothermia, lethargy, ill appearance, tachycardia, hypotension, tachypnea or apnea, hypotonia Risk factors may include maternal chorioamnionitis, maternal GBS positivity, prolonged rupture of membranes, infection exposure.	Blood culture, CBC with differential, UA with urine culture, LP (if indicated), consider inflammatory markers (eg, CRP or procalcitonin)

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; DAT, direct antiglobulin test; G6PD, glucose-6-phosphate dehydrogenase; GBS, group B streptococcus; LP, lumbar puncture; RBC, red blood cell; UA, urinalysis.

CASE FOCUS

Diagnostic Evaluation

You order an initial set of laboratory tests to confirm John's total bilirubin level, evaluate his direct bilirubin, rule out hemolysis, and check for sequelae of significant dehydration. The results of these tests are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	148 mEq/L (148 mmol/L)	135–146 mEq/L (135–146 mmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)	3.2–5.7 mEq/L (3.2–5.7 mmol/L)
Chloride	108 mEq/L (108 mmol/L)	97–108 mEq/L (97–108 mmol/L)
Carbon dioxide	22 mEq/L (22 mmol/L)	17–24 mEq/L (17–24 mmol/L)
BUN	20 mg/dL (7.14 mmol/L)	2–19 mg/dL (0.71–6.78 mmol/L)
Creatinine	0.5 mg/dL (44.2 μmol/L)	0.3–0.9 mg/dL (26.5–79.6 μmol/L)
Total bilirubin	18.2 mg/dL (311.29 μmol/L)	Refer to Figure 5.1
Direct bilirubin	0.9 mg/dL (15.39 μmol/L)	≤ 0.6 mg/dL (10.26 μmol/L)
CBC		
WBC count	13,200/μL (13.2 × 10^9/L)	5,000–15,000/μL (5–15 × 10^9/L)
Hemoglobin	14.1 g/dL (141 g/L)	15–24 g/dL (150–240 g/L)
Hematocrit	42% (0.42)	44%–70% (0.44–0.70)
CBC		
MCV	108 μm^3 (108 fL)	99–115 μm^3 (99–115 fL)
MCHC	33 g/dL (330 g/L)	32–36 g/dL (320–360 g/L)
Other hematologic studies		
DAT	Positive for anti-A IgG antibodies	Negative
Blood type	A Rh-negative	NA
Reticulocyte count	5.6% (0.06)	0.4–2.7% (0–0.03)
Peripheral smear	Fragmented cells, microspherocytes	NA

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; DAT, direct antiglobulin test; IgG, immunoglobulin G; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NA, not applicable; WBC, white blood cell.

Arriving at a Diagnosis

Q: How do you develop an assessment for John?

Your steps in formulating an assessment for John will begin with interpretation of his history, vital signs, examination, and diagnostic studies. Next, you will determine John's risk of bilirubin neurotoxicity (low, medium, or high) to identify at what bilirubin level phototherapy and exchange transfusion are recommended. From there, you can develop a list of findings and assign an underlying etiology to his symptoms.

1. **Interpret key findings from the history, vital signs, physical examination, and diagnostic evaluation.**
   - History: John's history reveals that he is an early-term neonate, having been born at 37 weeks EGA. His maternal blood type is O Rh-negative. Additionally, there is concern for poor feeding based on his excessive weight loss (> 10%), low urine and stool output, and stools that have not transitioned. He has not had any fevers, rash, or vomiting.
   - Physical examination: John's admission weight demonstrates a weight loss of 12.9% since birth. On examination, John is found to have tachycardia, ankyloglossia, somnolence, a weak suck, and visible jaundice. His examination and history are suggestive of poor intake (based on his percentage weight loss, lethargy, tachycardia, dry mucous membranes, and sunken anterior fontanelle).
   - Laboratory tests: John is found to have severe unconjugated hyperbilirubinemia with an elevated total bilirubin level of 18.2 mg/dL (311.29 µmol/L) and a normal direct bilirubin level of 0.9 mg/dL (15.39 µmol/L). His laboratory test results also demonstrate evidence of hemolysis, with low hemoglobin (mild anemia), increased reticulocyte count, and fragmented cells on the peripheral smear. John's blood type and antibody screen are consistent with ABO incompatibility: he has a positive DAT with evidence of maternal anti-A immunoglobulin G antibodies on his red blood cells (RBCs). His laboratory test results also show an elevated sodium level.
2. **Develop the list of findings.**

Q: What major findings have you identified for John?

- Severe unconjugated hyperbilirubinemia
- Isoimmune hemolytic disease
- Excessive weight loss
- Breastfeeding difficulties with suboptimal human (breast) milk intake
- Concern for ankyloglossia
- Low hemoglobin and hematocrit

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and the list of findings, are you able to choose one diagnosis to explain John's presentation?

It appears that John's unconjugated hyperbilirubinemia is multifactorial. Analysis of John's previously listed findings can help narrow the potential causes of his unconjugated hyperbilirubinemia to the following:

- ABO isoimmunization (ABO isoimmune hemolytic disease): ABO isoimmunization may occur when maternal antibodies to A and/or B antigens on the fetal RBCs (which are not present on maternal RBCs) are transferred to the fetus and lead to destruction of the newborn's RBCs. Findings include early onset of jaundice within hours to a few days after birth, ABO incompatibility with maternal blood type O and baby blood type A/B/AB, DAT positive (although may be negative in severe cases), decreased hemoglobin and hematocrit, elevated reticulocyte count, and a peripheral smear with microspherocytosis.
- Feeding difficulty: Feeding difficulties may result in decreased caloric intake and thus increased enterohepatic circulation. Dehydration may also occur in this setting; when present, it supports the diagnosis of decreased intake. Factors that are frequently seen in the setting of feeding difficulties include exclusive breastfeeding with suboptimal intake, parent's first time breastfeeding, reports of poor latch and increased sleepiness of the newborn, maternal discomfort with breastfeeding, and a decreased number of daily breastfeeding sessions. The neonate may present with weight loss, decreased urine and/or stool output, mild lethargy, and electrolyte abnormalities (typically mild).
- Contribution of physiologic "normal" mechanisms of newborn jaundice: Physiologic mechanisms alone may cause jaundice that appears after 24 hours of age. For term neonates, the TSB generally peaks at less than 12 mg/dL (205.25 µmol/L) within 3 to 5 days after birth. Refer to Table 5.1 for mechanisms of physiologic jaundice.

Q: On the American Academy of Pediatrics (AAP) phototherapy treatment guidelines (Figure 5.1), which risk curve should be used for John? At what TSB level would you start his phototherapy? At what TSB level would an exchange transfusion be a consideration (Figure 5.2)?

- The phototherapy treatment curves shown in Figure 5.1 provide thresholds for phototherapy initiation based on different neurotoxicity risk factors. These risk factors include the gestational age at birth, isoimmune hemolytic disease, G6PD deficiency, asphyxia, lethargy, temperature instability, acidosis, or albumin level lower than 3.0 g/dL (30 g/L).
- Because John was born at 37 weeks EGA with evidence of isoimmune hemolytic disease, he belongs on the higher risk curve (ie, the bottom curve). At approximately 96 hours of age, his bilirubin is above this curve, and thus phototherapy should be initiated.
- Based on the AAP exchange transfusion thresholds (Figure 5.2), John is likewise on the higher risk curve and has an exchange transfusion threshold of 19 mg/dL (324.98 µmol/L).

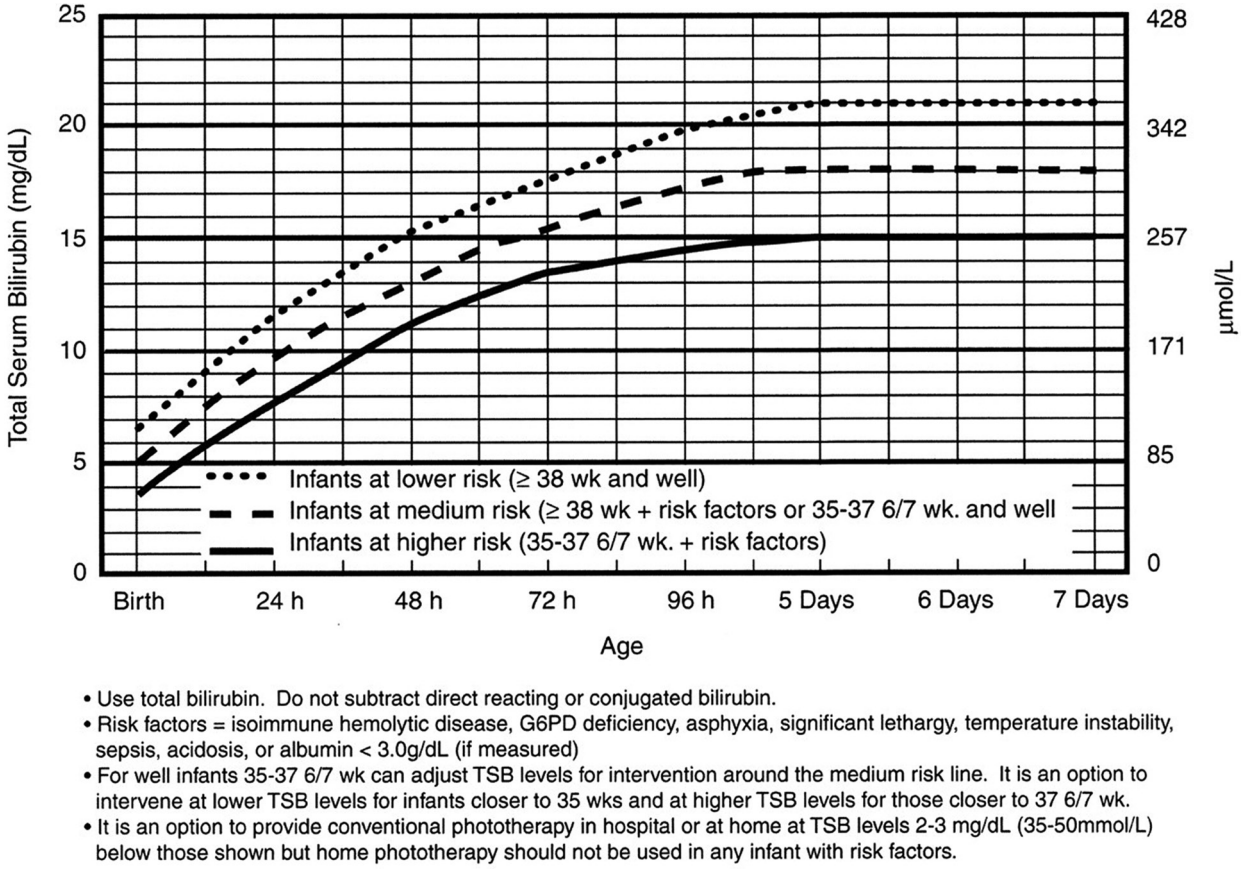

Figure 5.1. AAP 2004 phototherapy treatment guidelines.

Reprinted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.

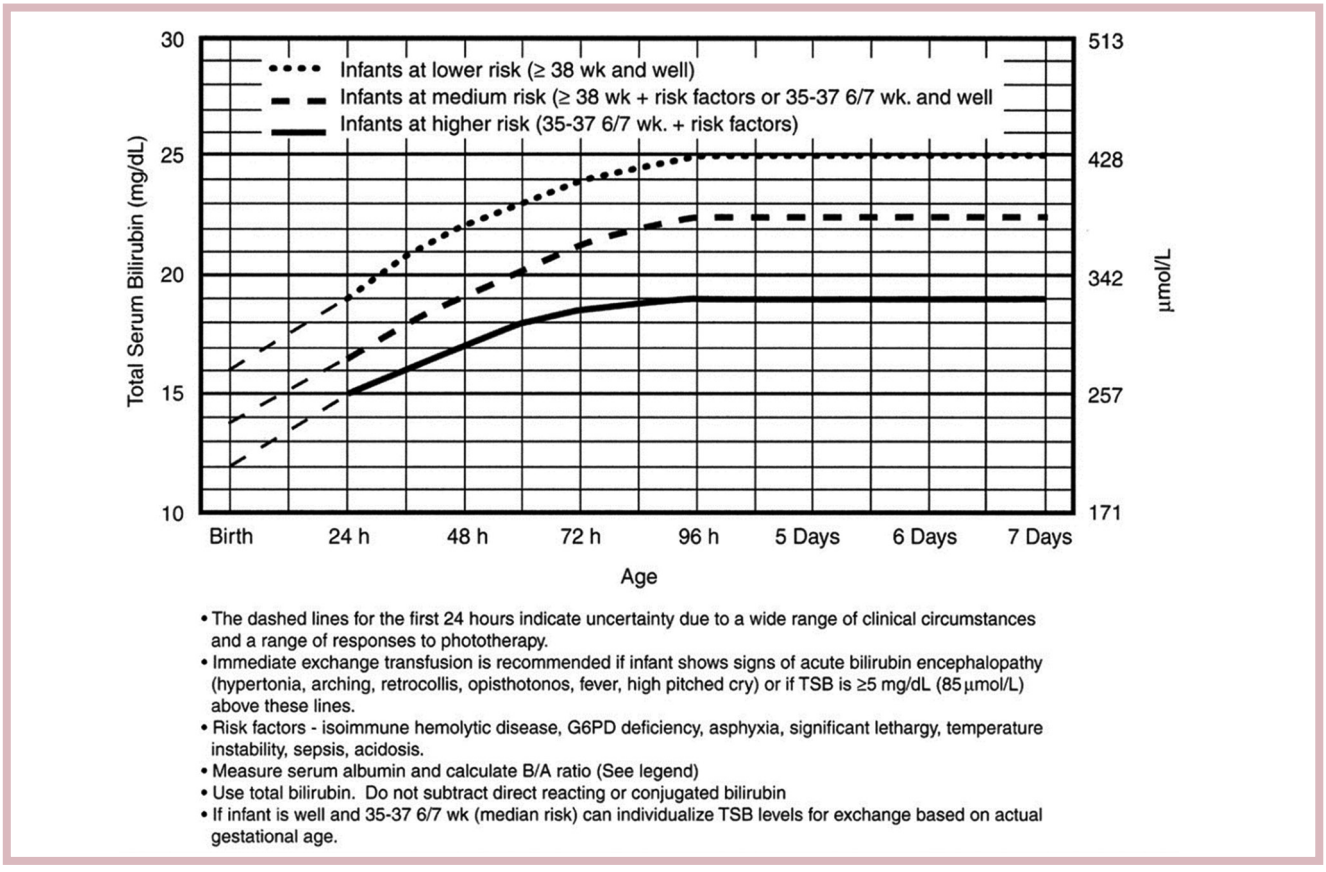

Figure 5.2. AAP exchange transfusion guidelines.

Reprinted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.

Q: What is John's risk of ABE?

- ABE refers to the acute direct effects of bilirubin on the brain.
  - Early reversible signs include lethargy, hypotonia, and poor suck.
  - Intermediate signs that are possibly reversible with immediate exchange transfusion include hypertonia, arching, retrocollis, opisthotonos, fever, and high-pitched cry.
  - Severe signs that likely indicate irreversible brain injury include pronounced retrocollis, opisthotonos, deep stupor to coma, seizures, apnea, fever, and lack of feeding.
- Kernicterus traditionally refers to the neuropathology that is a consequence of bilirubin neurotoxicity and is the yellow staining pattern of brainstem nuclei and the cerebellum. Chronic bilirubin encephalopathy is manifested by choreoathetoid cerebral palsy, an upward gaze, sensorineural hearing loss, and dental dysplasia of deciduous teeth.

John currently exhibits signs of early ABE, which are typically reversible with prompt aggressive phototherapy. Because he does not demonstrate signs of intermediate or advanced ABE, immediate exchange transfusion is not indicated.

4. Consider admission criteria.

Q: What are reasonable admission criteria for a neonate with unconjugated hyperbilirubinemia?

- The neonate's TSB level is nearing or above the level at which phototherapy is recommended.
- The neonate has signs of ABE.

- The neonate has dehydration with poor ability for oral intake.
- Concern exists for a diagnosis that requires urgent evaluation and treatment.

John requires hospitalization for urgent treatment of his hyperbilirubinemia and evaluation and management of his feeding difficulty.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

John is a 4-day-old former 37-week 0/7-day EGA neonate who presents with dehydration and unconjugated hyperbilirubinemia from isoimmune hemolytic disease and inadequate breast milk intake. He meets criteria for inpatient initiation of phototherapy and treatment of his dehydration. He does not have any findings of irreversible ABE. Additionally, John is noted to have anemia and findings of ankyloglossia, which may impede his ability to nurse effectively.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

When considering a plan for John's treatment and monitoring, you decide to focus initially on the following 2 components:

1. **Treatment of poor intake:** Although providing expressed breast milk, donor milk, or formula orally for rehydration is an option for neonates who can safely drink, you decide to administer an intravenous (IV) normal saline bolus of 20 mL/kg because of John's somnolence and poor suck. Afterward, you will reassess his heart rate, blood pressure, and perfusion and consider additional fluids if signs of dehydration persist.
2. **Treatment and monitoring of indirect hyperbilirubinemia**
   - Initiation of intensive phototherapy: Intensive phototherapy is indicated when the TSB level exceeds the line/curve indicated for each risk category. Intensive phototherapy implies irradiance in the blue-green spectrum (wavelengths of 460–490 nm) of at least 30 uW/cm^2/nm (measured at the neonate's skin directly below the center of the phototherapy unit) and delivered to as much body surface area as possible. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system. Additionally, a light-emitting diode blanket or pad (ie, biliblanket) is used to provide phototherapy to additional surface area.
   - Monitoring TSB levels.
     - For neonates who are readmitted for hyperbilirubinemia and receiving intensive phototherapy, a repeat TSB level should be obtained at the following intervals, with TSB values adjusted downward as needed for neonates at medium or higher risk of neurotoxicity as illustrated by Figure 5.1:
       - If the TSB level is greater than 25 mg/dL (427.60 µmol/L), repeat the TSB test within 2 to 3 hours.
       - If the TSB level is 20 to 25 mg/dL (342.08–427.60 µmol/L), repeat the TSB test within 3 to 4 hours.
       - If the TSB level is less than 20 mg/dL (342.08 µmol/L), repeat the TSB test within 4 to 6 hours.
       - If the TSB level continues to fall, repeat the TSB test in 8 to 12 hours.
     - Based on this guidance and John's higher neurotoxicity risk, you decide to obtain a repeat TSB level in 2 hours.

- There is no standard for when to discontinue phototherapy, as this decision should take into account multiple factors, such as the patient's age and the underlying etiology.
  - John's phototherapy may be discontinued when his TSB level is well below his phototherapy threshold, such as when it is less than 13 mg/dL (222.35 µmol/L), although you may consider a lower threshold given his underlying diagnosis of ABO isoimmune disease.
- In general, obtaining a rebound TSB level after discontinuation of phototherapy is not necessary; however, in the setting of hemolytic disease or in neonates younger than 3 to 4 days, a follow-up bilirubin measurement within 24 hours of discharge is recommended. Additionally, clinical follow-up within 24 hours of discharge should be considered for all neonates requiring readmission for phototherapy.

3. **Continuation of the management plan after reassessment**

Q: When should you consider IV immunoglobulin (IVIG) or exchange transfusion?

- For isoimmune hemolytic disease, consider administering IVIG if one of the following is true:
  - The TSB level is rising despite intensive phototherapy.
  - The TSB level is within 2 to 3 mg/dL (34.21–51.31 µmol/L) of the exchange transfusion level.
- A dose of IVIG can be repeated in 12 hours if needed.
- For neonates who are readmitted to the hospital with hyperbilirubinemia, an exchange transfusion is recommended if the neonate's TSB level (repeated every 2–3 hours) remains above the level at which an exchange transfusion is recommended despite receiving intensive phototherapy for 6 hours or if the neonate demonstrates progressive signs of ABE. Exchange transfusions should be performed in a neonatal intensive care unit setting.

Q: What is your plan for feeding and monitoring of hydration status?

- It is important to continue breastfeeding as the primary source of nutrition. Breastfeeding will also stimulate the mother's milk supply. If there is insufficient breast milk supply, consider supplementation with donor breast milk or formula, but only after there have been attempts at breastfeeding and/or expressing maternal breast milk. If the breast milk supply is adequate but the neonate's feeding quality is poor, consultation with a neonatal feeding specialist should be sought.
- When the feeding quality is inadequate or when significant dehydration is evident, IV fluid may be considered. There is no evidence, however, that excessive fluid administration affects the serum bilirubin concentration; therefore, once adequate hydration and feeding quality are achieved, IV fluid should be discontinued.

4. **Transportation assistance:** For patients without access to reliable transportation, there are programs to assist with transportation to medical appointments. Hospital social workers can be helpful to identify these services for families in need who qualify.

CASE FOCUS

Intervention and Reassessment

After administering the IV normal saline bolus and continuing intensive phototherapy, you reevaluate John.

- **His heart rate is improved at 150 beats/min, and his other vital signs are relatively unchanged. On examination, he is now vigorous, awake, alert, and rooting. His anterior fontanelle is soft and flat. His capillary refill is less than 2 seconds. Jaundice and icterus are again noted. His examination is otherwise within normal limits.**
- **Two hours after starting phototherapy, John's repeat TSB level is 18.4 mg/dL (314.71 µmol/L), slightly higher than his value on admission.**

HEALTH EQUITY FOCUS

Transportation Insecurity

Reliable transportation is an important aspect of health care access. Studies have shown that transportation insecurity can interfere with a patient's ability to access preventive care in their medical home, obtain outpatient testing and/or treatments, or attend hospital follow-up appointments. This barrier to access leads to worse health outcomes and disproportionately disadvantages nonwhite patients, patients with lower socioeconomic status, and those who may have higher burdens of disease.

Physicians should familiarize themselves with local transportation resources. Screening patients for transportation insecurity and providing these resources may alleviate this important barrier to health care access.

CASE FOCUS

Plan for Treatment and Monitoring

- **Therapy for hyperbilirubinemia:** Because John's TSB level is 18.4 mg/dL (314.71 µmol/L) despite phototherapy (with an exchange transfusion threshold of 19 mg/dL [324.98 µmol/L]), you decide to administer IVIG at a dose of 1 g/kg over 2 hours and recheck the bilirubin afterward. You do not think that an exchange transfusion is indicated at this time because John remains otherwise asymptomatic, so you continue intensive phototherapy and monitor his TSB level closely. Once his TSB level is less than 13 mg/dL (222.35 µmol/L), you decide you can safely discontinue his phototherapy with plans to recheck his bilirubin level within 24 hours.
- **Feeding:** Because John is awake and shows hunger cues, you decide to provide him with expressed breast milk and/or formula until his bilirubin level is decreasing. You provide his mother a breast pump, and she is able to express 1 oz (30 mL) of breast milk. Once John's bilirubin is decreasing, you plan to observe a breastfeeding session to assess his nursing. Because of John's initial poor milk intake, possibly related to ankyloglossia, you request a lactation consultation. Because John is now awake, able to feed by mouth, and no longer tachycardic, you discontinue his IV fluids.
- **Monitoring:** During his hospitalization, you will monitor John's intake and output and daily weights prior to feeding to ensure he is receiving sufficient calories and fluids. You also order monitoring of his vital signs every 4 hours. Until John's TSB level is downtrending, you will perform frequent neurologic assessments for signs that would indicate a need for exchange transfusion.
- **Transportation assistance:** You will place a request for social work consultation to determine whether the family qualifies for transportation assistance programs.

Case Resolution

John's repeat TSB level after the IVIG is complete is 15.8 mg/dL (270.24 µmol/L). You decide to continue intensive phototherapy and obtain a repeat TSB level in 6 hours. You do not administer a repeat dose of IVIG because John's bilirubin is now more than 3 mg/dL (51.31 µmol/L) below exchange transfusion level. You watch John breastfeed and note that he has a shallow latch, there is no audible swallowing, and his mother has engorged breasts with bruised nipples. You call the lactation consultant and ask that John's mother continue to pump frequently and feed expressed breast milk until John has improved transference of milk.

Discharge Criteria

Q: How do you know when John is ready to go home?

You can feel comfortable discharging your newborn patient with hyperbilirubinemia when the following criteria are met:

- The newborn's TSB level is less than 13 mg/dL (222.35 µmol/L).
- The newborn demonstrates good oral intake with resolution of dehydration.
- Close follow-up is ensured. For newborns with hemolytic disease or in newborns who are younger than 3 to 4 days, a follow-up TSB test is recommended within 24 hours after discharge.

Anticipatory Guidance

Q: What instructions should you provide to John's caregivers on discharge?

- Sunlight exposure is not recommended, because it is not a reliable method of decreasing John's bilirubin and has the risk of causing sunburn or overheating.
- Feed John at least every 2 to 3 hours and on demand (8–12 times in a 24-hour period). Monitor stool frequency and urine output to ensure he is receiving adequate breast milk/formula.
- Follow up with John's pediatrician within 24 hours of discharge for a repeat TSB test.
- Return to care for poor feeding, lethargy, vomiting, worsening jaundice, fever (rectal temperature of 38 °C [100.4 °F] or higher), or any other concerns.

Clinical Pearls

- There are multiple concurrent etiologies for jaundice in a newborn. A thorough history, physical examination, and screening laboratory tests can help to narrow the differential diagnosis.
- Mothers of babies readmitted for phototherapy may be experiencing breastfeeding difficulties. A detailed history should be obtained and a feeding session should be observed.
- If a newborn's direct bilirubin level has not been checked prior to admission, it is important to check both direct bilirubin and total bilirubin levels on admission.

- A negative DAT result does not exclude the possibility of hemolysis.
- Decisions about initiating phototherapy should take into account the newborn's gestational age, postnatal age in hours, and certain neurotoxicity risk factors as illustrated by Figure 5.1.
- There is usually no need to check a rebound TSB level in the hospital after discontinuation of phototherapy as long as close outpatient follow-up is ensured. A rebound bilirubin check prior to discharge should be considered for patients with hemolysis, especially for patients with difficulty obtaining timely follow-up.
- In neonates without severe dehydration, use of IV fluids does not have any advantages over oral feeds.
- Use of IVIG may reduce the need for exchange transfusion in babies experiencing hemolysis related to isoimmunization.

Documentation Tips

- Document if conventional phototherapy is not effective in your patient's case (ie, if bilirubin levels increase or do not decrease after 6 hours of phototherapy).
- Include risk factors that may require a more prolonged course of phototherapy (eg, isoimmune hemolytic disease).
- Document whether the patient is approaching or has passed the exchange transfusion level, or if there is concern for encephalopathy.
- Include the degree of weight loss from birth and whether there is associated dehydration or electrolyte abnormalities.

Suggested Readings

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CASE 6

Isaiah, an 8-Year-Old Boy With Shortness of Breath

CASE PRESENTATION

Isaiah is an 8-year-old boy with intermittent asthma who presents to the emergency department (ED) with shortness of breath and audible wheezing that has worsened over the last day. At home, he has used his albuterol metered-dose inhaler (MDI) with spacer multiple times during the last 24 hours without improvement. In the ED, Isaiah is given multiple albuterol treatments using an MDI and spacer, ipratropium bromide, and oral dexamethasone. These treatments have improved his symptoms, but he continues to have shortness of breath, wheezing, and increased work of breathing. His oxygen saturation is 97% on room air. The pediatric emergency medicine fellow is concerned that Isaiah continues to have symptoms and calls to ask that you evaluate him for admission to the pediatric inpatient unit.

Patient History and Review of Systems

Q: What information should you collect from Isaiah and his caregivers?

- History of present illness
  - Symptoms associated with this exacerbation (eg, cough, wheezing, shortness of breath, chest tightness, sputum production), their onset and responsiveness to short-acting β_2-agonist (SABA)
  - Recent activity, to determine potential triggers for current symptoms (eg, allergic response, environmental exposures, exercise)
  - Exposure to sick contacts
  - Number and timing of interventions used at home, including dosages and administration method of albuterol treatments
  - Presence of additional associated symptoms (eg, fever, headache, dry or wet cough, nasal congestion, rash)
- History pertaining to underlying asthma diagnosis, severity, and control, including the following:
  - Age of asthma onset and disease progression over time
  - Assessment of asthma severity, including risk and level of impairment
    - Frequency and characteristics of asthma symptoms over the preceding month, including nighttime symptoms, daytime symptoms, and frequency of SABA use each week
    - Frequency of exacerbations requiring systemic steroids, particularly the number of steroid courses in the past year; usual prodromal symptoms; and rapidity of symptom onset during exacerbations

  - Number of lifetime hospitalizations for asthma exacerbations
  - Highest level of respiratory support required (ie, bilevel positive airway pressure, continuous positive airway pressure, or intubation)
  - Adherence to controller medications, including inhaled corticosteroids (ICS) or montelukast
- Method and technique of medication use (ie, MDI with spacer vs nebulizer)
- Recent or ongoing exposure to known or potential triggers for exacerbations, including viral illness, weather conditions, exercise, seasonal or environmental allergens, primary or secondary cigarette/smoke exposure

- Other important considerations
  - Medical history, including immunization status, specifically the influenza vaccine; other underlying medical conditions; history of poor growth or recurrent bacterial infections; presence of food allergies; seasonal allergic rhinitis; and eczema
  - Social determinants of health (SDOH) (eg, home environment, ability to refill medications)

CASE FOCUS

History and Review of Systems

In the ED, Isaiah's mother tells you Isaiah has had 2 days of dry cough, nasal congestion, and intermittent fever to 38.8 °C (101.8 °F). Today, he developed shortness of breath, worsening cough, chest tightness, and wheezing. He has used 6 puffs of his albuterol MDI with a spacer almost every 4 hours for the last 2 days. Isaiah's review of systems is otherwise negative. His 5-year-old sister is also sick with fever and cough. Isaiah is up to date on his immunizations, including the seasonal influenza vaccine.

His mother shares that over the last month, Isaiah has been using his albuterol multiple times a week but not daily, and he occasionally has difficulties keeping up with his friends when they play soccer. He wakes up at night coughing 1 to 2 times per month. His only hospitalization for an asthma exacerbation was 2 years ago, and he did not require intubation or admission to the intensive care unit (ICU) at that time. His last course of systemic steroid treatment was 5 months ago for an exacerbation triggered by a viral illness, and he had not had any steroids in the year prior to that exacerbation. His first episode of wheezing occurred at age 3 years, and he has never been prescribed a controller medication. His typical asthma triggers include viral illnesses, seasonal allergies, and cold weather. Isaiah's mother states that when he was an infant, he had eczema, but he has never shown symptoms of a food allergy. He takes an antihistamine as needed for seasonal allergies. Isaiah was born at term and had no perinatal complications. He has been growing and developing well and does not have a history of recurrent bacterial infections. Isaiah's mother had asthma as a child. The family lives in an apartment complex near a busy highway, and they rely on public transportation. His father smokes cigarettes.

Physical Examination

Q: What parts of the physical examination should you focus on for Isaiah?

- Complete set of vital signs
- Level of respiratory distress: ability to speak in full sentences, accessory muscle use, nasal flaring, cyanosis
- Lung examination
  - Air entry throughout lungs as demonstrated by audible breath sounds in all lung fields
  - Presence, location, and characteristics of wheezing, including whether wheezing is inspiratory, expiratory, or biphasic, and mono- or polyphonic
  - Inspiratory to expiratory ratio, specifically noting the presence of a prolonged expiratory phase

- Signs of atopy, including periorbital eye swelling or darkening, fluid behind the tympanic membrane, swollen nasal turbinates, eczematous rashes
- Signs of chronic disease, such as digital clubbing or hepatomegaly
- Signs of dehydration, such as sunken appearance of eyes, malaise, lethargy, irritability, and absence of tears

CASE FOCUS

Physical Examination

You examine Isaiah after his initial albuterol treatments in the ED. His mother states his work of breathing has improved after receiving the treatments. Isaiah's most recent vital signs indicate tachycardia with a heart rate of 125 beats/min, tachypnea with a respiratory rate of 28 breaths/min, and an oxygen saturation of 97% on room air. He is afebrile with a temperature of 37 °C (98.6 °F). His blood pressure is normal. When you enter the room, Isaiah appears to be in respiratory distress, and he is only able to speak in partial sentences due to shortness of breath. He has no cyanosis. You see that he has moderately increased work of breathing and is using his intercostal and substernal muscles to breathe. You auscultate his lungs and hear diffuse polyphonic, biphasic inspiratory and expiratory wheezes. The expiratory phase is prolonged. His peripheral perfusion is normal, and the remainder of his examination is unremarkable except for tachycardia.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child presenting with respiratory distress and wheezing?

When thinking through your differential diagnosis, it is helpful to remember that wheezing is a high-pitched adventitious lung sound produced when air flows through an abnormally narrowed or compressed airway anywhere from the larynx to the small bronchi. The differential diagnosis for a child presenting with respiratory distress and wheezing is shown in Table 6.1 and is divided into causes that seem more and less likely based on Isaiah's presentation.

Table 6.1. Differential Diagnosis for a Child With Wheezing and Respiratory Distress

Diagnoses of highest suspicion	• Anaphylaxis • Asthma exacerbation[a] • LRTI viral or bacterial (including atypical pneumonia)
Other diagnoses to consider	• Allergic bronchopulmonary aspergillosis • Bronchiectasis • Bronchopulmonary dysplasia • Cardiac dysfunction/heart failure • Chronic aspiration • CF/primary ciliary dyskinesia • Dysphagia with aspiration • Extrinsic airway compression (ie, masses, vascular rings or slings) • Foreign body aspiration • Inducible laryngeal obstruction • Tracheomalacia/bronchomalacia • Underlying immunodeficiency • Viral-induced bronchospasm

Abbreviation: CF, cystic fibrosis; LRTI, lower respiratory tract infection.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with increased work of breathing and wheezing?

- While there is a large differential diagnosis for wheezing, many of the illnesses on the differential are clinical diagnoses and do not require laboratory or imaging tests.
- Asthma is largely a clinical diagnosis based on recurring symptoms including chest tightness, cough, difficulty breathing, or wheezing. The objective resolution or improvement of symptoms with β_2-agonist therapy suggests a diagnosis of asthma. For older children and adolescents, pulmonary function tests can be used to confirm a suspected asthma diagnosis and monitor a patient's degree of lung impairment; however, these tests are generally not performed in the acute setting. Given Isaiah's clinical presentation and known history of asthma, his wheezing and respiratory symptoms are most likely caused by an asthma exacerbation. While the diagnostic evaluation of asthma in the acute setting is limited and generally not indicated, in certain scenarios, clinicians may consider the following evaluation:
  - A blood gas analysis in patients who have severe respiratory distress, when there is concern for impending respiratory failure, or in patients with suspected hypercapnia.
  - An upright chest radiograph when a patient's symptoms are not responsive to treatment, there is suspicion for an alternative diagnosis, there are focal examination findings, or there is concern for a complication from asthma (eg, pneumomediastinum or pneumothorax).
  - A peak expiratory flow measurement or bedside spirometry. It should be noted that the use of peak expiratory flow meters in the acute setting may be limited by the lack of a baseline measurement for comparison, variability between different devices, and the inability of many children to provide a reliable value.

CASE FOCUS

Diagnostic Evaluation

Based on Isaiah's suspected diagnosis and his current clinical status, you decide that no laboratory or imaging tests are indicated at this time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Isaiah?

1. **Assess airway, breathing, and circulation.**
   - Isaiah is experiencing respiratory distress; however, he is maintaining his oxygen saturation on room air and has adequate air movement on examination. Signs of impending respiratory failure may include altered mental status, physical fatigue (which may be evidenced by an inappropriately low respiratory rate), and cyanosis. If a patient is exhibiting these signs, they may require noninvasive positive pressure ventilation or endotracheal intubation. Isaiah does not demonstrate any features concerning for impending respiratory failure.
   - Whenever possible, endotracheal intubation and mechanical ventilation should be avoided in patients with severe asthma. This is because intubation can exacerbate the hyperinflation present in patients experiencing an asthma exacerbation and lead to increased morbidity. Additionally, manipulation of the airway may increase bronchial reactivity, and the patient's clinical status may acutely worsen.
2. **Interpret key findings from the history and physical examination.**
   - History: Isaiah has a history of asthma and is presenting with acute onset of shortness of breath and wheezing. His symptoms have improved with albuterol administration; however, he continues to have wheezing and shortness of breath. He has other symptoms, including intermittent fever at home, cough, and nasal congestion with known sick contacts. His asthma has been labeled as intermittent in the past. This is his second exacerbation requiring systemic steroids in the past year, and he has asthma symptoms multiple days a week, but not daily, with at least 1 nighttime awakening each month. His social history demonstrates proximity to a busy highway and secondhand smoke exposure.
   - Physical examination: On examination, Isaiah is mildly dyspneic and tachypneic and has increased work of breathing as evidenced by intercostal and substernal retractions. Inspiratory and expiratory wheezing is present with a prolonged expiratory phase. His work of breathing has improved slightly after albuterol administration, indicating a responsiveness to β_2-agonists. Otherwise, there are no focal findings on examination.
3. **Develop the list of findings.**

Q: What major findings have you identified for Isaiah?

- Previous diagnosis of asthma
- Shortness of breath
- Moderately increased work of breathing
- Wheezing
- History of fever
- Cough and congestion
- Secondary smoke exposure
- Housing located in an area with increased air pollution

4. **Revisit the differential diagnosis.**

Q: Based on Isaiah's history, examination, and list of findings, are you able to choose one diagnosis to explain his presentation?

- Isaiah's current shortness of breath associated with wheezing and cough, and his history of asthma, are most consistent with acute asthma, also known as an asthma exacerbation or asthma attack. On physical examination, his diffuse polyphonic and biphasic wheezing combined with a prolonged expiratory phase is consistent with asthma. Of note, the terms *acute asthma, asthma exacerbation,* and *asthma attack* are equivalent. *Acute severe asthma*, also known as *status asthmaticus*, is defined as severe asthma not fully responsive to β_2-agonists.
- Anaphylaxis, while on your differential diagnosis, is less likely given the slower time course of Isaiah's illness and the lack of a trigger. Additionally, many, though not all, patients with anaphylaxis demonstrate cutaneous, gastrointestinal, or mucosal involvement.
- Isaiah's recent fever and known sick contact are consistent with a concomitant infection such as a viral upper respiratory infection, which is likely the trigger for his exacerbation. There are no findings on examination to suggest a lower respiratory tract infection such as pneumonia.

Q: How is the severity of an acute asthma exacerbation determined?

Clinical scoring systems are effective in assessing acute asthma exacerbation severity and response to treatment. The most widely used scoring system is the Pediatric Asthma Score (PAS) outlined in Table 6.2.

Table 6.2. Pediatric Asthma Score

	Score[a]		
Clinical feature	**0**	**1**	**2**
Respiratory rate (breaths/min) 6–12 years of age	≤ 26	27–30	≤ 31
Oxygen saturations	> 95% on room air	90%–95% on room air	< 90% on room air or requiring any amount of supplemental oxygen
Auscultation	Range from normal breath sounds to end-expiratory wheezing only	Expiratory wheezing	Inspiratory and expiratory wheezing or diminished breath sounds
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences	Speaks in partial sentences	Speaks in single words/short phrases/grunting

[a] Mild = 0–2; moderate = 3–6; severe = 7–10.

Adapted with permission from Kelly CS, Andersen CL, Pestian JP, et al. Improved outcomes for hospitalized asthmatic children using a clinical pathway. *Ann Allergy Asthma Immunol.* 2000;84(5):509–516.

- After receiving treatments in the ED, Isaiah has a PAS of 5 based on a respiratory rate of 28 breaths/min (1 point), pulse oxygenation of 97% on room air (0 points), inspiratory and expiratory wheezing (2 points), intercostal and substernal retractions (1 point), and ability to speak only in partial sentences (1 point).

Q: How is a patient's overall asthma severity and/or level of control classified?

- A patient's asthma severity is based on their symptoms (degree of impairment) and an assessment of their risk (frequency and severity of exacerbations). The classifications are divided into intermittent, mild persistent, moderate persistent, and severe persistent. These classifications are most commonly applied to patients who are not currently on any controller medications.
  - Isaiah is currently having asthma symptoms multiple days a week, but not daily, with at least 1 nighttime awakening each month. His last exacerbation requiring steroids was 5 months ago. Although he previously had been diagnosed with intermittent asthma according to the guidelines, based on Table 6.3, you reclassify Isaiah's asthma as mild persistent asthma.

Table 6.3. Classification of Asthma Severity in Children Aged 5 to 11 Years

Components of severity		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/mo	3–4x/mo	>1x/wk but not nightly	Often 7x/wk
	SABA use for symptom control	≤2 d/wk	>2 d/wk 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 (predicted) or peak flow (personal best)	>80%	>80%	75%–80%	<75%
Risk	Exacerbations requiring oral systemic corticosteroids (consider severity and interval since last exacerbation)	0–1/y (see notes)	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes in 1 year lasting >1 day AND risk factors for persistent asthma	≥2x/y (see notes) Relative annual risk may be related to FEV_1.	≥2x/y (see notes) Relative annual risk may be related to FEV_1.

Abbreviations: FEV_1, forced expiratory volume in first second of expiration; SABA, short-term β_2-agonist.

Notes

Level of severity is determined by both impairment and risk. Assess impairment domain by caregiver's recall of previous 2 to 4 weeks. Assign severity to the most severe category in which any feature occurs.

Frequency and severity of exacerbations may fluctuate over time for patients in any severity category. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and severe exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate greater underlying disease severity. For treatment purposes, patients with ≥2 exacerbations described above may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94–138. Published correction appears in *J Allergy Clin Immunol*. 2008;121(6):1330.

- For patients who use controller medications, the level of control is assessed by evaluating asthma symptoms (level of impairment) and risk (frequency and severity of exacerbations). Classifications for levels of control are well controlled, not well controlled, or very poorly controlled. Refer to the National Heart, Lung, and Blood Institute guidelines (included in the Suggested Readings section) for demonstration of these criteria.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with an asthma exacerbation?

- The patient demonstrates a lack of significant improvement after multiple respiratory treatments, either at home, in the pediatrician's office, or in the ED. For example, a patient with a PAS of 3 or higher despite optimal treatment in the outpatient or ED setting may benefit from hospitalization.
- The patient requires supplemental oxygen.
- The patient is unable to maintain their hydration.

You decide Isaiah meets criteria for admission given his persistent symptoms, as demonstrated by a PAS of 5, despite initial treatment at home and in the ED.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Isaiah is an 8-year-old boy with mild persistent asthma presenting with an acute moderately severe asthma exacerbation likely triggered by a viral upper respiratory infection. Based on his continued symptoms with a PAS of 5, he requires admission for frequent albuterol treatments and monitoring until his exacerbation improves.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In the acute setting, management of an asthma exacerbation is focused primarily on stabilization of the patient's respiratory status, identification of modifiable triggers and risk factors, and development of a management plan for home.

1. **Stabilization of airway, breathing, and circulation and adequate oxygenation:** It is important to assess initial oxygen saturation, as patients with severe asthma exacerbations are at higher risk for hypoxemia. Patients with hypoxemia should be placed on a continuous pulse oximeter and provided supplemental oxygen as needed to maintain oxygen saturation greater than 92% (or according to institutional policy).
2. **Inhaled β_2-agonists:** All patients experiencing an asthma exacerbation should receive repetitive or continuous β_2-agonists. Albuterol is the most commonly used β_2-agonist in the emergency or hospital setting. Levalbuterol is an alternative. Intravenous (IV)/intramuscular β_2-agonists do not improve clinical outcomes, and children may experience side effects; therefore, they are not recommended. Inhaled β_2-agonists can be administered via a nebulizer with face mask or MDI with spacer, as both methods are effective at administering the medication.

3. **Systemic oral corticosteroids:** Systemic steroids should be given to all patients experiencing moderate to severe asthma exacerbations or mild asthma exacerbations unresponsive to inhaled β_2-agonists. Patients who receive steroids require less inhaled β_2-agonists, have decreased admission rates, and fewer relapses. There is no evidence that longer or higher-dose regimens are superior to shorter or lower-dose regimens. Dexamethasone, prednisone, and prednisolone are equivalent in efficacy with similar adverse effect profiles. Some studies indicate a 2-dose course of dexamethasone, the steroid that Isaiah received in the ED, may increase patient ability to complete treatment and improve cost-effectiveness in patients with mild to moderate asthma.
4. **Inhaled anticholinergics:** For patients experiencing severe asthma exacerbations, the use of inhaled anticholinergics decreases admission rates when given in combination with SABAs. Ipratropium bromide is the most commonly used anticholinergic. There is no evidence that continued use has any clinical benefit after a patient has been admitted to the inpatient unit.
5. **Adjunctive therapies:** Adjunctive therapies may be considered in severe or refractory exacerbations; however, there is limited data supporting their efficacy. IV magnesium sulfate use has limited evidence supporting reduced rates of admission and hospital length of stay. When infused quickly (in <20 minutes), it is associated with hypotension; however, it is otherwise safe and recommended for use in patients with severe or persistent asthma exacerbations.
6. **Supportive therapies:** Depending on the level of respiratory distress, it may be difficult for patients to maintain adequate hydration. The use of IV hydration should be considered in patients who are clinically dehydrated or unable to tolerate fluids by mouth.
7. **Monitoring:** It is important to frequently assess patient response to albuterol treatments. Many institutions utilize objective asthma exacerbation scoring systems (such as the PAS outlined in Table 6.2) and clinical pathways to monitor and manage patients with asthma exacerbations in the inpatient setting. Clinical pathways have been found to decrease hospital length of stay, reduce unnecessary treatments or imaging, and improve quality of asthma care. It is also important to monitor patients for tachycardia and diastolic hypotension while they are receiving recurrent/continuous SABA treatments. Albuterol targets β_2 receptors in the smooth muscle of the lung. β_2 receptors are also present in the vasculature causing vasodilation, which may appear as diastolic hypotension, and reflexive tachycardia. Administration of a fluid bolus should be considered for initial treatment of diastolic hypotension. If hypotension persists, ICU consultation should be considered.
8. **Asthma education:** An asthma action plan is a written document that outlines specific instructions for caregivers to use at home. It can be a useful tool for families, detailing when and what medications to administer when a child begins to experience asthma symptoms. Each family of a child with a diagnosis of asthma should receive an asthma action plan to keep at home and to leave at school. Every family should also receive education on how to administer asthma medication, as improper technique can result in inadequate treatment. Emphasizing the daily use of controller medications, even when the child is feeling well, may also be beneficial.
9. **Influenza vaccine:** All children with asthma should receive the seasonal influenza vaccine due to risk of increased morbidity and mortality in children with asthma who contract influenza.
10. **Stepping up asthma therapy:** For patients newly diagnosed with persistent asthma, their asthma severity classification (mild, moderate, severe persistent) will determine what type of controller therapy to initiate. Table 6.4 outlines the recommended stepwise therapy options for improved asthma control in 5- to 11-year-olds. For Isaiah, based on Table 6.3, his diagnosis is mild persistent asthma. Table 6.4 indicates that he should be started on a low-dose ICS at the time of discharge.

Table 6.4. Stepwise Therapy Options for Improved Asthma Control in Children Aged 5 to 11 Years

Intermittent asthma	Persistent asthma Consult with an asthma specialist if step 4 or higher is required. Consider consultation at step 3.				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
SABA as needed	Daily low-dose ICS and SABA as needed	Daily and as needed low-dose ICS-formoterol OR medium-dose ICS + SABA as needed	Daily and as needed medium-dose ICS-formoterol OR daily medium dose ICS-LABA and SABA as needed	Daily high-dose ICS-LABA and SABA as needed	Daily high-dose ICS-LABA + oral corticosteroid and SABA as needed

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94–S138. Published correction appears in *J Allergy Clin Immunol*. 2008;121(6):1330.

11. Addressing modifiable triggers

- Secondhand smoke exposure is associated with increased risk of asthma exacerbations. Families should be counseled on the benefits of smoking cessation and provided with national and/or community resources to aid with smoking cessation. The Centers for Disease Control and Prevention hotline (1-800-QUIT-NOW) provides free national smoking cessation services.
- Many children with asthma are affected by indoor and outdoor allergens. An important component of their asthma control is to reduce their exposure to these allergens when possible. Common indoor allergens include dust mites, cockroaches, animal dander, and mold. Strategies to minimize indoor allergens can include the use of dust mite–proof pillow and mattress covers, frequent washing of bedsheets in hot water, keeping pets outdoors (or at least out of the child's bedroom and off fabric furniture), treating for cockroach infestations, and cleaning moldy surfaces. Common outdoor allergens include mold and pollen. Many children need to remain indoors during certain seasons or times of the day (midday and afternoon) when pollen and mold counts are highest.
- Children with asthma should be encouraged to exercise regularly; however, for many children, exercise can be a trigger. Use of a β_2-agonist prior to planned exercise can help alleviate exercise-induced symptoms.

12. SDOH: Asthma disproportionately affects children of color, especially Black children, and those in lower socioeconomic classes. Asthma exacerbation is the leading cause of ED visits and among the top 3 reasons children are hospitalized. Black children are twice as likely to visit the ED for asthma and 9 times as likely to die from asthma compared with white children. Research has found that SDOH, including low household income, substandard housing, exposure to pollution, living in poor communities, and high levels of stress, play a large role in asthma control. These disparities emphasize the importance of optimizing asthma control whenever possible and addressing SDOH.

HEALTH EQUITY FOCUS

Housing

Housing instability can be defined in several ways and may include high housing cost relative to income, homelessness, overcrowding, poor housing quality, and/or unsafe neighborhoods. Housing instability is linked to a variety of adverse health outcomes for children.

Children with housing insecurity may be less likely to have a medical home and disproportionately receive medical care in an acute setting (ED or hospital). Therefore, screening for housing insecurity and providing resources for families is a critical element of care for the hospitalized child.

A recent quality improvement study showed promising outcomes when the families of hospitalized children were provided resources for housing insecurity identified using the following 4 screening questions:

- "During the last 12 months, was there a time when you were not able to pay the mortgage or rent on time?"
- "In the past 12 months, in how many places has the child lived?"
- "What type of housing does the child live in?"
- "Since birth, has the child ever been homeless or lived in a shelter?"

CASE FOCUS

Plan for Treatment and Monitoring

- **Oxygenation:** Isaiah is maintaining oxygen saturations above 92%. He does not require continuous monitoring on pulse oximetry. He requires pulse oxygenation checks every 4 hours, with supplemental oxygen as needed.
- **Inhaled ß$_2$-agonists:** Isaiah has received multiple continuous albuterol treatments but continues to be symptomatic. He requires frequent or continuous albuterol treatments until his exacerbation improves.
- **Systemic oral steroids:** Isaiah received his first dose of dexamethasone in the ED. He will require his second (final) dose 24 to 48 hours after the first dose.
- **Inhaled anticholinergics:** After receiving nebulized anticholinergics in the ED, Isaiah does not require further treatments while admitted.
- **Adjunctive therapies:** No IV magnesium is required at this time.
- **Monitoring:** You order strict monitoring of intake and output and vital signs every 4 hours. You plan to reassess Isaiah's clinical status before his next albuterol treatment.
- **Diet:** You order a regular diet.
- **Asthma education:** You write an updated asthma action plan, including all daily preventive medications and abortive medications. Prior to discharge, the respiratory therapist will review the proper technique of each inhaler with Isaiah and his family.
- **Stepping up asthma therapy:** Your order that Isaiah start low-dose fluticasone twice daily on discharge.
- **Addressing modifiable triggers:** You discuss the risk of increased asthma exacerbations due to secondhand smoke exposure in a nonjudgmental way with Isaiah's family and provide free community resources on smoking cessation.
- **SDOH:** You consult case management for referral to community resources, home environment assessment, and for possible equipment, including a high-efficiency particulate air filter vacuum cleaner.

Case Resolution

On admission, Isaiah continues to receive scheduled albuterol treatments every 2 hours. As his PAS improves over the course of the day and overnight, his treatments are gradually spaced out to every 4 hours. The following morning, Isaiah and his mother receive education on common asthma triggers, the proper use of his inhaled albuterol and ICS, and his personalized asthma action plan. Isaiah is discharged home on hospital day 2 with a prescription for an albuterol inhaler, inhaled fluticasone, and a second dose of oral dexamethasone.

Discharge Criteria

Q: How do you know when Isaiah is ready to go home?

You can feel comfortable discharging your patient with an asthma exacerbation when the following criteria are met:

- The patient does not require oxygen supplementation.
- Symptoms are well controlled using albuterol every 3 to 4 hours.
- The patient has prescriptions for all required medications at the time of discharge.
- Asthma education has been provided and the patient's asthma action plan has been reviewed with the patient and caregivers. This plan can also be shared with the patient's school in case an exacerbation occurs while at school.
- Inhaler techniques have been reviewed with the patient by a trained provider, which may include a respiratory therapist, physician, advanced practice provider, or nurse.
- The annual seasonal influenza vaccine has been administered if needed and if there are no contraindications.
- Smoking cessation education and resources have been provided to parents, as applicable.

Anticipatory Guidance

Q: What instructions would you provide to Isaiah's caregivers on discharge?

- Continue administering albuterol as needed until Isaiah's respiratory status is at baseline. As Isaiah's condition improves, the frequency of albuterol treatments will decrease.
- Complete the oral steroid course as prescribed to decrease the risk of symptom recurrence.
- Continue using the controller medications (eg, ICS) recommended by Isaiah's physician. Inhaled steroids can take several weeks of regular use to become effective.
- Continue to obtain annual seasonal influenza vaccines each year.
- Follow up with Isaiah's pediatrician for long-term asthma management in 1 to 3 days.

Clinical Pearls

- Asthma is a common reason for hospitalization in children.
- Children presenting with an asthma exacerbation should be assessed for the following:
  - The severity of their asthma as indicated by their level of impairment and risk. Asthma severity is defined as intermittent, mild persistent, moderate persistent, or severe persistent. Patients with persistent asthma benefit from initiation of controller medications, such as an ICS.
  - The level of asthma control for patients receiving asthma controller medications. Categories of asthma control include well controlled, not well controlled, and very poorly controlled. Patients whose asthma is not well controlled or very poorly controlled should have their asthma controller medications stepped up.
  - The severity of their current exacerbation. A common tool for this is the PAS. This score can also be used to assess the patient's response to asthma treatment and help inform decisions about admission and discharge.
- Treatment of an acute asthma exacerbation primarily involves administration of inhaled β_2-agonists (eg, albuterol) and systemic corticosteroids. The addition of inhaled ipratropium is shown to decrease admission rates when administered in the outpatient or ED setting. IV magnesium sulfate should be considered for patients who are not demonstrating significant improvement after multiple treatments with inhaled β_2-agonists.
- Children with asthma should be assessed for possible asthma triggers, including exercise, infections, smoke exposure, and indoor and outdoor allergens. Education should be provided to patients and families about reducing exposure to triggers.
- All patients who are hospitalized with a suspected asthma exacerbation should receive asthma education and a personalized asthma action plan prior to discharge.

Documentation Tips

- Document the number or frequency of β_2-agonist doses given prior to admission, including those at home and in the ED.
- Document recent steroid use (failed outpatient treatment).
- Specify the degree of respiratory distress (mild, moderate, severe). Use of a standardized PAS is helpful if used in your institution.
- Specify history of pediatric ICU admission or co-occurring conditions (eg, prematurity, chronic lung disease).
- Characterize asthma classification (intermittent, mild/moderate/severe persistent).
- Specify acute respiratory failure if the patient requires back-to-back continuous bronchodilator treatments.

Suggested Readings

Cloutier MM, Baptist AP, Blake KV, et al; Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 focused updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217–1270 PMID: 33280709 https://doi.org/10.1016/j.jaci.2020.10.003

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CASE 7

Rose, a 3-Week-Old Girl With Fever

CASE PRESENTATION

Rose, a 3-week-old previously healthy girl, is being admitted to the general pediatrics unit from the emergency department (ED) where she was seen for fever and decreased oral intake. In the ED, she had a rectal temperature of 39.5 °C (103.1 °F), an intravenous (IV) line was placed, blood was drawn for laboratory tests, a urine specimen was collected for analysis, and a lumbar puncture (LP) was performed. Additionally, Rose was given an IV fluid bolus of normal saline (0.9%) at 20 mL/kg and received IV antibiotics. You were called with a request for admission.

After speaking to the physician caring for Rose in the ED, you begin your evaluation to start the admission process.

Patient History and Review of Systems

Q: What information should you collect from Rose's caregivers?

- History of present illness
  - Onset and duration of fever, including maximum temperature during illness and method of measurement (eg, axillary, rectal, oral)
  - Signs of dehydration, such as decreased urine output, sunken appearance to the eyes, lethargy, irritability, and absence of tears
  - Nasal congestion or drainage, including duration of symptoms, methods for extracting mucus, and frequency and timing of suctioning in relation to feeding
  - Presence of residual umbilical cord and any redness, swelling, or warmth around or drainage from the umbilicus
  - Dietary intake, specifically any change in the amount or frequency of feeding, any changes in energy to latch if breastfeeding, and details about formula preparation if formula feeding
  - Associated symptoms, such as somnolence, fussiness, coughing, difficulty breathing, cyanosis, vomiting, diarrhea, rashes, or pain/redness/swelling of an extremity
- Medical history
  - Birth history, including mode of delivery, complications during delivery (eg, maternal fever, prolonged rupture of membranes), gestational age at delivery, birth weight, abnormalities in nursery stay, or admission to the neonatal intensive care unit

    - Routine newborn care, such as vitamin K, erythromycin eye ointment, and hepatitis B vaccine
    - Mother's prenatal history, including group B streptococcus (GBS) status and prophylaxis (with *adequate prophylaxis* defined as appropriate antibiotics administered 4 hours prior to delivery), if indicated; herpes simplex virus (HSV), HIV, hepatitis, and syphilis status; any infections during pregnancy, such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, toxoplasmosis, varicella zoster, parvovirus B19, and cytomegalovirus; and tuberculosis risk factors
  - Newborn screen results
  - Surgical history
  - Immunization status
- Medications, including any vitamins or supplements
- Social history
  - Household contacts and any animal or smoke exposure
  - Sick contacts, including recent HSV "cold sores" in parents, siblings, and/or visitors
  - Attendance to child care

CASE FOCUS

History and Review of Systems

From her history, you learn that Rose has had 2 days of mild nasal congestion, fussiness, decreased oral intake, and decreased urination. Today, she felt warm, and her parents found she had a rectal temperature of 39.4 °C (102.9 °F), which is what prompted their visit to the ED. To alleviate Rose's nasal congestion, her mother has been using a bulb suction with saline prior to feedings. Rose has not had any recent cough or difficulty breathing.

Rose normally feeds every 2 to 3 hours. She mostly breastfeeds but will occasionally receive 1 to 2 oz (30–60 mL) of formula, which is properly mixed. Today, however, she has not been nursing well and is only taking 1 oz of formula every few hours. Normally, she has 6 wet diapers daily, but she has only had 1 wet diaper today. Her last stool was yesterday and is described as yellow/brown and paste-like in consistency. Rose has not had any vomiting.

Today, Rose has been more fussy than usual but is consolable. She has not had any rash. Her umbilical stump fell off prior to her 2-week checkup, and her family denies any redness or drainage from the area. Her review of systems is otherwise negative.

Rose was born at 39 weeks' gestation via induced vaginal delivery related to maternal hypertension, and she received a hepatitis B vaccine, vitamin K, and erythromycin eye ointment in the newborn period. Her mother was GBS positive and received a dose of penicillin more than 4 hours prior to delivery. She denies any other relevant prenatal history, including any history of HSV infection. Rose's family reports no other complications during Rose's delivery, and her newborn course was unremarkable. Her birth weight was 3.7 kg with a discharge weight of 3.5 kg at 48 hours after birth. Rose does not attend child care. Her family reports that she had appropriate weight gain at her 1- and 2-week checkups and that her newborn screen result was normal. Rose's family denies any known sick contacts, they do not have any pets, and no one smokes in the home.

Physical Examination

Q: What parts of the physical examination should you focus on for Rose?

- Complete set of vital signs
- Current weight and evaluation of growth trends since birth
- General appearance: level of consciousness, irritability, ability to arouse normally
- Fontanelle depth (sunken, flat, or bulging)
- Appearance of eyes (presence of icterus, drainage, or conjunctival injection)
- Oral mucosa, including redness, ulcers or lesions, and moisture level (moist, sticky, or dry)
- Tympanic membranes (bulging, erythema, purulence)
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Cardiac: heart rate, rhythm, presence of murmurs, quality of femoral pulse
- Pulmonary: tachypnea/depth of respirations, signs of increased work of breathing (eg, nasal flaring, tracheal tugging, retractions, belly breathing, head bobbing), auscultation of the lungs (eg, areas of diminished air entry, crackles, rhonchi, wheezing)
- Abdomen: quantity and quality of bowel sounds, tenderness, guarding, presence of a mass
- Anogenital: abnormalities of the external genitalia, appearance of anus
- Musculoskeletal: areas of limited movement, redness, tenderness, or edema
- Neurologic: muscle tone, reflexes, symmetric movement of extremities
- Skin: rashes or other lesions, signs of mastitis, redness/tenderness/drainage of umbilicus

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Physical Examination

Rose's vital signs show that she is febrile with a temperature of 39.5 °C (103.1 °F). She is tachycardic with a heart rate of 180 beats/min, and she has mild tachypnea with a respiratory rate of 66 breaths/min, even after a fluid bolus. She has normal blood pressure for age and normal oxygen saturation. Her weight on arrival to the ED was 4.1 kg (60th percentile for age).

On examination, Rose is initially fussy but is easily consoled in her mother's arms. Her fontanelle is mildly sunken. She has no tear production, and her oral mucosa is dry but without lesions. No scleral icterus or conjunctival injection is present. Her tympanic membranes are normal in appearance. She appears to have mildly increased work of breathing with belly breathing, mild tachypnea, and mild subcostal retractions. No tracheal tugging, nasal flaring, or grunting is present. She has good air movement through all lung bases without focal findings. Her heart rate is tachycardic but with a regular rhythm. No murmurs, rubs, or gallops are heard. Her capillary refill time is prolonged at 4 seconds, and her peripheral pulses are normal. Her abdomen is soft, nontender, and nondistended, without masses or organomegaly. Her umbilicus does not have any drainage or surrounding erythema. Her genitourinary examination is normal. There are no areas of swelling, tenderness, or decreased range of motion on her musculoskeletal examination. Her skin is warm and dry, with no rashes. She has normal muscle tone and no focal neurologic deficits.

Differential Diagnosis

Q: What is the differential diagnosis for an infant (<60 days of age) who presents with fever (defined as a rectal temperature of 38 °C [100.4 °F] or higher)?

There are multiple causes of fever in newborns and young infants; however, these etiologies can be narrowed based on a complete history and thorough physical examination. Table 7.1 demonstrates a differential diagnosis for fever in this age group and has been separated into diagnoses that appear more or less likely for Rose.

Table 7.1. Differential Diagnosis for an Infant Younger Than 60 Days With Fever

Diagnoses of highest suspicion	• Bacteremia[a] • CNS infections,[a] most commonly meningitis or encephalitis • HSV infection, of which there are 3 neonatal manifestations (with overlap among types common): skin, eyes, and mouth disease; CNS disease; and disseminated disease • LRTI: bronchiolitis, viral pneumonia, or bacterial pneumonia (including *Chlamydia trachomatis* pneumonia) • UTI[a] • Viral syndromes (including severe enteroviral disease in neonates)
Other diagnoses to consider	• Acute infectious gastroenteritis • AOM • KD • Osteomyelitis or septic arthritis • Skin and soft tissue infections: abscess, cellulitis, mastitis, or omphalitis • Viral URTI

Abbreviations: AOM, acute otitis media; CNS, central nervous system; HSV, herpes simplex virus; KD, Kawasaki disease; LRTI, lower respiratory tract infection; URTI: upper respiratory tract infection; UTI, urinary tract infection.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for neonates and young infants presenting with fever?

- The most common cause of fever in neonates is viral infection; however, up to 10% of neonates presenting with fever will be diagnosed with a bacterial infection. Bacteremia, bacterial meningitis, and urinary tract infections (UTIs) are among the most common sources of bacterial infection, although other bacterial infections are possible, as illustrated by the differential diagnosis.
- Historically, the diagnostic evaluation in a well-appearing febrile neonate varied at different institutions but generally included a complete blood cell count (CBC), blood culture, urinalysis (UA), urine culture, and cerebrospinal fluid (CSF) analysis, including Gram stain and culture. Testing for viral pathogens was likewise variable, with some institutions testing and empirically treating all neonates for HSV infection, and others stratifying neonates by risk of HSV. For infants 29 days and older, many institutions utilized prediction algorithms to make decisions about evaluation and treatment. These algorithms employed a combination of history, examination, and laboratory findings but yielded differing sensitivities, specificities, and negative predictive values. No algorithm was universally adopted.

- In 2021, the American Academy of Pediatrics (AAP) published a clinical practice guideline pertaining to the evaluation and management of well-appearing febrile infants 8 to 60 days of age. This guideline recommends a tailored approach based on the infant's age, certain risk factors, and the results of initial laboratory tests and can be accessed online at https://doi.org/10.1542/peds.2021-052228.
  - It is important to note that the AAP clinical practice guideline only applies to well-appearing, term, febrile infants 8 to 60 days of age who are home following their birth hospitalization (or were born at home). As such, a thorough diagnostic evaluation should be considered for febrile infants who do not meet these criteria, including those who have had a complicated perinatal course, and for any ill-appearing infant, regardless of age.
  - Given lower rates of meningitis and bacteremia, neonates with clinical bronchiolitis are excluded from the AAP clinical practice guideline. Clinicians must use their clinical judgement to make decisions about testing for bacterial coinfection in these patients.
  - Febrile ill-appearing neonates and febrile neonates younger than 8 days of age are also excluded from the AAP clinical practice guideline. For these patients, clinicians should perform thorough diagnostic testing which may include, but is not limited to, blood culture, UA, urine culture, HSV studies, CSF studies, and chest radiographs.
- Evaluation for bacterial infection.
  - Well-appearing febrile neonates 8 to 21 days of age should undergo testing with a blood culture, UA, urine culture, and CSF analysis, including Gram stain and culture. Clinicians may consider also obtaining a CBC, procalcitonin level (if available), and C-reactive protein level. Refer to Figure 1 of the AAP clinical practice guideline for the diagnostic algorithm for this age group. The evaluation of febrile neonates in this age group who have a positive viral test result or a focal source of infection (eg, mastitis, acute otitis media) is controversial. Although some studies indicate there is a decreased risk of concomitant bacterial infection in this population, the AAP clinical practice guideline recommends a complete evaluation for bacterial coinfection in this age group, including an LP.
  - Febrile infants 22 to 60 days of age are at lower risk of meningitis when compared with younger infants, so an LP is not uniformly recommended for well-appearing infants in this age group. Instead, clinicians can utilize the results of clinical or laboratory-based inflammatory markers to guide decisions about LP. Of note, the AAP clinical practice guideline defines an elevated inflammatory marker as any of the following:
    - Documented temperature of 38.5 °C (101.3 °F) or higher.
    - Procalcitonin (when available) greater than 0.5 ng/mL.
    - Absolute neutrophil count (ANC) greater than 4,000 cells/mm^3.
    - C-reactive protein (CRP) greater than 2 mg/dL.
  - At any age, the patient's symptoms and examination findings should help guide further evaluation for bacterial infection. Examples of further testing may include the following:
    - Stool culture when diarrhea is present.
    - Eye cultures for any purulent eye drainage.
    - Chest radiograph for respiratory symptoms.
    - Bone or joint imaging for musculoskeletal tenderness or decreased range of motion.
- Testing for viral infection.
  - Routine viral testing of the nasopharynx is generally not indicated; however, influenza testing should be considered during influenza season as it may alter management.
  - For ill-appearing neonates with a suspected viral infection, testing for the following organisms should be considered:
    - HSV: HSV testing and empiric treatment should be considered for neonates who are ill appearing. Additionally, HSV testing should be considered for neonates who have a relevant exposure history, including maternal fever 48 hours before or following delivery, or have seizure, hypothermia, leukopenia, thrombocytopenia, transaminitis, CSF pleocytosis, or a concerning rash (specifically, vesicles or mucous membrane ulcers). It should be noted that many neonates with HSV have no maternal history of HSV. HSV infection is less common in infants 29 days of age and older but still should be considered in this age group. Testing for HSV most often includes liver enzymes and HSV polymerase chain reaction (PCR) from the blood, conjunctiva, mouth, anus, CSF, and any skin lesions. HSV cultures are an option for mucosal surfaces and skin lesions when PCR testing is not available.

- Enteroviruses: Neonatal enteroviral disease can present with a wide range of clinical manifestations. Although most neonates develop a self-limited nonspecific febrile illness, others, particularly those younger than 21 days of age, can present with severe enteroviral sepsis, hepatitis, meningoencephalitis, pneumonitis, or myocarditis. For neonates with suspected severe enteroviral disease, studies to detect the virus may include reverse-transcriptase PCR (RT-PCR) testing on CSF, nasopharynx, stool, blood, or other sites, depending on the patient's clinical manifestations.
- Human parechovirus (HPeV): Neonatal infections caused by HPeV commonly present with symptoms ranging from a nonspecific febrile illness to central nervous system disease, hepatitis, myocarditis, or a sepsis-like syndrome. When needed, specific testing can include RT-PCR on the CSF, stool, blood, or respiratory secretions.

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Diagnostic Evaluation

You note the results of Rose's laboratory tests obtained in the ED, which are as follows:

Laboratory test	Results	Reference range
Serum chemistries		
Sodium	141 mEq/L (141 mmol/L)	135–146 mEq/L (135–146 mmol/L)
Potassium	4.6 mEq/L (4.6 mmol/L)	3.4–6.2 mEq/L (3.4–6.2 mmol/L)
Chloride	111 mEq/L (111 mmol/L)	97–108 mEq/L (97–108 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)	17–23 mEq/L (17–23 mmol/L)
Anion gap	7 mEq/L (7 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	23 mg/dL (8.2 mmol/L)	2–19 mg/dL (0.7–6.8 mmol/L)
Creatinine	0.28 mg/dL (24.8 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	82 mg/dL (4.55 mmol/L)	50–90 mg/dL (2.78–5.0 mmol/L)
Calcium	8.5 mg/dL (2.13 mmol/L)	8.5–11 mg/dL (2.13–2.75 mmol/L)
AST	23 U/L (0.38 µkat/L)	9–80 U/L (0.15–1.34 µkat/L)
ALT	32 U/L (0.53 µkat/L)	13–45 U/L (0.22–0.75 µkat/L)
ALP	400 U/L (6.68 µkat/L)	150–420 U/L (2.51–7.01 µkat/L)
Total bilirubin	0.8 mg/dL (13.68 µmol/L)	< 12 mg/dL (205.25 µmol/L)
CBC with differential		
WBC count	20,300/µL (20.3×10^9/L)	5,000–15,000/µL ($5–15 \times 10^9$/L)
Hemoglobin	17 g/dL (170 g/L)	15–24 g/dL (150–240 g/L)
Hematocrit	45% (0.45)	44%–70% (0.44–0.70)
Platelet count	280×10^3/µL (280×10^9/L)	$150–400 \times 10^3$/µL ($150–400 \times 10^9$/L)
Neutrophils	75% (0.75)	20%–50% (0.20–0.50)
Lymphocytes	22% (0.22)	10%–60% (0.10–0.60)
Monocytes	2% (0.02)	5%–20% (0.05–0.20)
Eosinophils	1% (0.01)	2%–5% (0.02–0.05)

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Diagnostic Evaluation *(continued)*

Laboratory test	Results	Reference range
Inflammatory markers		
Procalcitonin	1.25 ng/mL (1.25 µg/L)	< 0.5 ng/mL (< 0.5 µg/L)
Urinalysis		
Specific gravity	1.02	1.005–1.03
Leukocyte esterase	Negative	Negative
Nitrites	Negative	Negative
WBC count	None	0–5/HPF
RBC count	10–20/HPF	0–2/HPF
CSF studies		
RBC count	0 cells/µL	0–5 cells/µL
WBC count	3 cells/µL	0–12 cells/µL
Protein	35 mg/dL	20–100 mg/dL
Glucose	50 mg/dL (2.77 mmol/L)	40-80 mg/dL (2.2-4.4 mmol/L)
CSF Gram stain	Occasional WBC, no organisms	No organisms
Respiratory panel by PCR		
Negative for the presence of influenza A/B, parainfluenza 1/2/3, RSV, rhinovirus, enterovirus, coronaviruses (including SARS-CoV-2), *Bordetella pertussis*, adenovirus, human metapneumovirus, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*		
Bacterial cultures		
Blood culture	Pending	Negative
Urine culture	Pending	Negative
CSF culture	Pending	Negative
Imaging		
Chest radiograph (1 view)	No focalities	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CSF, cerebrospinal fluid; HPF, high-power field; PCR, polymerase chain reaction; RBC, red blood cell; RSV, respiratory syncytial virus; WBC, white blood cell.

Rose is considered higher risk for invasive bacterial infection based on the height of her fever, her elevated ANC count, and her high procalcitonin level. She appropriately underwent a full diagnostic evaluation, including an LP and chest radiograph, based on these findings. You do not think that further diagnostic testing is needed at this time.

Arriving at a Diagnosis

Q: How do you develop your assessment for Rose?

In thinking through Rose's case, you start by interpreting her history, vital signs, examination findings, and diagnostic evaluation to develop a list of findings that helps narrow your differential diagnosis to the most likely etiologies. Afterward, you can generate admission criteria for your specific diagnosis.

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Rose is a 3-week-old full-term healthy girl with nasal congestion, decreased oral intake and urine output for 3 days, and fever for 1 day. Her birth history is significant for her mother being GBS positive. Rose's mother received adequate prophylactic treatment. However, although appropriate GBS prophylaxis decreases the risk of early-onset GBS disease, it does not decrease the risk of late-onset GBS disease.
   - Vital signs: For her age, Rose is tachycardic and tachypneic. This can be a sign of dehydration, acute respiratory distress, or systemic inflammatory response syndrome. Also notable is that Rose had a rectal temperature of 39.5 °C (103.1 °F) in the ED. Literature supports that the presence of fever of 38.5 °C (101.3 °F) or higher stratifies a neonate as higher risk of bacterial infection.
   - Physical examination: Based on Rose's physical examination findings of sunken fontanelle, dry mucous membranes, and slow capillary refill, there are concerns for mild to moderate dehydration. Her lungs do not show adventitious sounds or decreased air entry, making a lower respiratory tract infection less likely. Her tachypnea and mild increased respiratory effort may relate to the presence of fever and dehydration. Her physical examination is otherwise nonfocal for a source of her fever.
   - Laboratory tests.
     - Rose's laboratory studies show leukocytosis and an elevated procalcitonin. The ANC is calculated by multiplying the total white blood cell (WBC) count by the percentage of neutrophils. Rose's ANC is elevated at 15,225/μL (15.22×10^9/L). According to the AAP clinical practice guideline, her ANC and procalcitonin values show that she is at a higher risk of an invasive bacterial infection.
     - Her complete metabolic panel is normal with no signs of transaminitis.
     - An abnormal UA is defined as the presence of any leukocyte esterase on dipstick, greater than 5 WBCs per high-power field (HPF) in centrifuged urine, or greater than 10 WBCs/mm^3 in uncentrifuged urine on microscopic UA using a hemocytometer. Rose's UA shows no WBCs, leukocyte esterase, or nitrites and is therefore not suggestive of a UTI. It should be noted that nitrates do not convert to nitrites as commonly in infants with a UTI because they urinate frequently, and thus there is not sufficient time for this process to occur. For this reason, the absence of nitrites is not as sensitive of an indicator for UTIs in infants. Red blood cells (RBCs) are present on her UA, likely as a result of the method of urine collection (catheterization).
     - Rose's CSF results are normal, with only 3 WBCs/HPF and normal protein and glucose. It should be noted that CSF glucose values should be interpreted in relation to the serum glucose value. For neonates, a normal CSF glucose is at least 50% of the serum value. Although Rose's CSF results are reassuring against bacterial infection, the CSF Gram stain and culture results are needed to rule out bacterial meningitis.
     - Her respiratory pathogen panel is negative. This does not eliminate the possibility of a viral infection, however, because an inadequate sample collection or an infection caused by a pathogen not included on the panel is possible. Despite this, you determine that a viral infection seems less likely to be the cause of her symptoms based on her laboratory evidence of systemic inflammation, as noted previously.
     - Blood, urine, and CSF cultures are pending. An incubation period of 24 hours is sufficient to detect between 87% and 91% of pathogens in blood cultures; at 36 hours, between 92% and 96% of pathogens can be detected; and at 48 hours, between 95% and 99% of pathogens can be detected, depending on the study. In a well-appearing neonate, negative bacterial culture results by 36 to 48 hours can exclude the vast majority of bloodstream infections.

- Imaging: Rose's chest radiograph does not show signs of pneumonia or other acute findings.
- Assessment for sepsis: Given that Rose is suspected to have an infection, she meets the definition of sepsis because of the presence of fever, tachypnea, and an elevated WBC count. She does not have any findings concerning for severe sepsis or septic shock. Refer to Section IV of the Appendix for age-based systemic inflammatory response syndrome and sepsis criteria and definitions of severe sepsis and septic shock.

2. **Develop the list of findings.**

Q: What major findings have you identified for Rose?

- Poor oral intake with mild to moderate dehydration
- Fever from unknown source
- Tachypnea and increased respiratory effort
- Elevated procalcitonin and ANC
- Presumed sepsis (fever, tachypnea, and leukocytosis in the setting of a suspected infection)

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Rose's presentation?

Although you are not yet able to choose one diagnosis for Rose, you are able to develop a more prioritized differential diagnosis and eliminate several etiologies. Rose's normal UA and CSF indices make UTI and meningitis seem unlikely, respectively, but you will need negative bacterial culture results to eliminate these as possibilities. Likewise, neonatal pneumonia is less likely in the setting of a normal chest radiograph. Rose's lack of specific examination findings also makes acute otitis media, skin and soft tissue infection, osteomyelitis, and septic arthritis unlikely. HSV infection seems unlikely given that she is well appearing and has a negative maternal history, normal liver enzymes, a lack of CSF pleocytosis, and no rash. Bacteremia is possible based on Rose's history of maternal GBS, the absence of focal findings on examination, and her leukocytosis and elevated procalcitonin. Given that viruses are the most common cause of neonatal fever, a viral syndrome is also possible.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a newborn or young infant with fever?

Clinicians should consider hospitalization for febrile newborns or young infants with any of the following features:

- Age 21 days or younger
- Age 22 to 28 days when the UA is abnormal, inflammatory markers are abnormal, no CSF is obtained, CSF pleocytosis is present, or CSF results are uninterpretable
- Age 29 to 60 days when inflammatory markers are abnormal or CSF results are concerning for bacterial meningitis (if obtained)
- Ill appearance
- Any neonate or young infant with an identified source of infection which requires treatment with IV antimicrobials
- HSV risk factors are present
- Inability to maintain adequate oral intake
- Social concerns or an inability to obtain timely follow-up

You decide that Rose meets the criteria for hospital admission because she has abnormal inflammatory markers and poor oral intake.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Rose is a 3-week-old, full-term baby girl who was born to a GBS-positive mother and is in the ED with presumed sepsis (fever, leukocytosis, and tachypnea in the presence of a suspected infection) and mild to moderate dehydration. Although you cannot eliminate the possibility of a viral syndrome, her combination of high fever and elevated ANC and procalcitonin are concerning for a bacterial infection, with bacteremia being the most likely. Given her young age and higher risk of bacterial infection, she requires hospitalization for ongoing monitoring and continuation of empiric antibiotics while the results from her blood, urine, and CSF cultures are pending.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Rose's symptoms, you review the literature to remind yourself about the empiric treatment recommendations for a neonate with a fever.

1. **Antibiotics**
   - Before deciding about empiric antibiotic options, you first consider the most common organisms causing bacterial infection in term neonates and young infants. These organisms differ by age and site of infection (Table 7.2 and Box 7.1).

Table 7.2. Common Organisms to Cause Bacteremia and Meningitis in Term Neonates and Young Infants

Infection onset	Age	Source/risk factor	Pathogen(s)
Early-onset infection	0–7 d	Usually vertical transmission via the maternal genital tract	*Escherichia coli* and other gram-negative enteric pathogens Group B streptococcus *Enterococcus* spp Group A streptococcus and other *Streptococcus* spp *Listeria monocytogenes*[a]
Late-onset infection	>7 d	Can be vertical or horizontal transmission[b]	*E coli* and other gram-negative enteric pathogens Group B streptococcus *Haemophilus influenzae* type b *Staphylococcus aureus* *Streptococcus pneumoniae* *Neisseria meningitidis* *L monocytogenes*[a] Coagulase-negative *Staphylococcus*[c]

[a] Many recent studies have not detected any infections caused by *L monocytogenes* in term neonates and young infants.

[b] Horizontal transmission occurs when infectious organisms are transmitted from care providers or the environment.

[c] Coagulase-negative *Staphylococcus* is usually considered a contaminant in term neonates and young infants without central venous access.

Box 7.1. Common Organisms to Cause Urinary Tract Infections in the Neonatal Period

Gram-negative bacteria	Gram-positive bacteria
Escherichia coli[a]	*Enterococcus* spp
Klebsiella spp[a]	Group B streptococcus
Citrobacter spp	*Staphylococcus aureus*
Pseudomonas aeruginosa	

[a] These organisms are the 2 most common causes of urinary tract infections in neonates.

- Empiric antibiotics should be given to febrile neonates 21 days or younger until blood, urine, and CSF culture results are negative for 24 to 36 hours. For this age group, based on the most common organisms, the AAP clinical practice guideline recommends empiric use of ampicillin *plus* either ceftazidime or gentamicin. Gentamicin should only be used if there is no concern for bacterial meningitis based on results of CSF analysis.
- For febrile neonates from 22 to 28 days of age, the AAP clinical practice guideline recommends that empiric antibiotics should be provided if CSF analysis is suggestive of bacterial meningitis, if the UA is abnormal, or for any well-appearing neonate who will be monitored at home. It should be noted that home monitoring is only an option when CSF analysis, UA, and inflammatory markers are normal. Empiric antibiotics can also be given to any neonate in this age range regardless of the results of their preliminary laboratory studies. When empiric antibiotics are given, the AAP clinical practice guideline recommends use of ceftriaxone, or when there is suspicion of bacterial meningitis, ampicillin *plus* ceftazidime.
- Empiric antibiotic therapy for infants 29 to 60 days of age is usually limited to ceftriaxone alone, although oral cephalosporins can be provided for well-appearing febrile infants with a suspected UTI if inflammatory markers are normal. If the infant's CSF analysis is suggestive of bacterial meningitis, empiric vancomycin should be given, in addition to either ceftriaxone or ceftazidime. Clinicians may opt to withhold antibiotics in this age range if the infant is well appearing and has a normal UA, normal inflammatory markers, and if CSF is obtained, CSF analysis is normal or positive for enterovirus.
- If blood, urine, or CSF culture results are positive, antibiotics will need to be tailored based on the organism, site of infection, and the organism's antibiotic sensitivities.
- If the neonate has focal findings of a bacterial infection on examination, such as acute otitis media, mastitis, or omphalitis, antibiotics should be tailored to treat the most common organisms known to cause this type of infection.
- Empiric antibiotics may be discontinued when bacterial cultures are negative for 24 to 36 hours, provided that the infant is well appearing, is clinically improving, does not have other reasons for ongoing hospitalization, and does not have an identified infection that requires ongoing treatment (eg, acute otitis media, cellulitis).

2. **Antivirals**
   - If there is concern for neonatal HSV infection, empiric acyclovir is recommended until HSV testing is negative. If HSV testing is positive, the duration of treatment will depend on the manifestation of illness. Consultation with a pediatric infectious disease expert is recommended.
   - For severe neonatal infections (eg, myocarditis) related to enteroviruses or HPeV, early consultation with a pediatric infectious disease specialist is indicated. Some studies on the use of IV immunoglobulin have shown promise.
   - For Rose, HSV or severe enteroviral or HPeV disease is unlikely, and thus antiviral therapy is not indicated.
3. **Antipyretics**
   - Acetaminophen may be given orally or rectally for fever or pain.
   - Nonsteroidal anti-inflammatory drugs should be avoided in infants younger than 6 months.

4. **Diet and hydration**
   - Regular diet (human [breast] milk or formula) should be continued unless the neonate is unable to drink safely. Breastfeeding parents should be encouraged to express and appropriately store their breast milk until the neonate resumes normal nursing patterns. Lactation consultants can be helpful to optimize breastfeeding and breast milk expression.
   - IV fluids or nasogastric tube feedings can be considered for neonates with hypovolemia or for neonates who are unable to maintain hydration through oral intake. IV fluids are also indicated for neonates receiving acyclovir to decrease the risk of renal injury.
   - For Rose, you will start maintenance IV fluids until her oral intake improves.
5. **Ongoing monitoring:** The level of monitoring required will depend on the neonate's individual status and suspected diagnosis. Neonates who are at higher risk of invasive bacterial infection and/or findings consistent with sepsis should be monitored with frequent vital sign checks and reassessment of their clinical status. For neonates with dehydration or concern for sepsis, monitoring of their intake and output and weight is warranted. Additionally, the use of continuous pulse oximetry is reasonable for neonates with respiratory symptoms.

CASE FOCUS

Plan for Treatment and Monitoring

- **Empiric antibiotics:** You order ampicillin and cefepime to be continued until Rose's bacterial culture results are negative for 36 hours, based on your institution's protocol.
- **Empiric antiviral:** No antiviral medications are indicated.
- **Diet and hydration:** You allow an unrestricted diet as tolerated, but you also start dextrose-containing IV fluids at 16 mL/h until Rose is demonstrating adequate oral intake.
- **Antipyretics and analgesics:** You order acetaminophen as needed for pain or fever.
- **Monitoring:** You order monitoring of intake and output, vital signs every 4 hours, daily weights, and frequent reassessments of clinical status.

Case Resolution

Rose's blood culture is positive for gram-positive cocci at 16 hours. Her blood culture ultimately grows GBS, and thus she is diagnosed with late-onset GBS bacteremia. Subsequent repeat blood cultures are negative. Once her urine and CSF cultures are negative at 36 hours, her antibiotics are narrowed to penicillin G, based on the universal susceptibility of GBS to penicillin, and Rose receives the medication in the hospital for a total of 10 days.

Discharge Criteria

Q: How do you know when Rose is ready to go home?

You can feel comfortable discharging your patient home when the following criteria are met:

- The newborn is well appearing with improving temperature. Although not every newborn needs to be afebrile prior to discharge, some clinicians prefer to monitor newborns and young infants in the hospital until they are afebrile. If a newborn is discharged without complete resolution of fevers, strict return precautions should be discussed with the family.
- Blood, urine, and CSF cultures are negative for 24 to 36 hours. If cultures are positive, the newborn will need to complete the appropriate course of IV antibiotic treatment.
- The newborn is able to maintain hydration through oral intake.
- Adequate follow-up is ensured.

Anticipatory Guidance

Q: What instructions should you provide to Rose's caregivers on discharge?

- Rose should be seen by her pediatrician for follow-up within 1 to 3 days of discharge.
- Check Rose's temperature only if there is concern that she is not well or is warm.
  - Temperature is best taken rectally.
  - Fever is considered to be a temperature of at least 38 °C (100.4 °F), taken rectally.
  - If temperature is taken in a location other than the rectum, the temperature might be falsely low.
- Rose should return to the ED for any fever, difficulty breathing, lethargy, or signs of dehydration (eg, not making any urine for >6 hours).
- The most common source for a fever in a neonate is viral infection, and the best way to prevent infection is appropriate handwashing by caregivers.

Clinical Pearls

- The most common cause of a fever in a neonate is a self-limited viral infection.
- Clinical manifestations of neonatal bacterial infection can be subtle and nonspecific.
- *Escherichia coli* and GBS are the most common bacteria to cause neonatal infections.
- Most neonates 21 days or younger should undergo a full evaluation to determine the presence of invasive bacterial infection and should be admitted to the hospital for empiric antibiotic treatment while cultures are pending. Clinicians should consider an evaluation for HSV, enterovirus, or HPeV for neonates who are ill appearing or have CSF pleocytosis or transaminitis.
- For infants 22 to 60 days of age, an LP may be avoided if the infant is considered low risk based on their inflammatory markers. If the infant is considered higher risk, an LP is recommended. The infant may also require admission for empiric antibiotics and observation.

Documentation Tips

- When applicable, document whether sepsis is present on admission. Refer to Section IV in the Appendix and Case 9 for discussions of sepsis in children.
- When indicated, use strong language to support the need for admission (eg, "presumed," "likely," "suspected," or "probable sepsis/bacterial infection") and avoid terms such as "rule out," "suspicious for," "consistent with," "consider," "possible," "concern for," or "meets criteria for."

Suggested Reading

Pantell RH, Roberts KB, Adams WG, et al; Subcommittee on Febrile Infants. Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics*. 2021;148(2):e2021052228 PMID: 34281996 https://doi/org/10.1542/peds.2021-052228

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CASE 8

Austin, an 8-Month-Old Boy With Fever and Vomiting

CASE PRESENTATION

Prior to morning rounds, you are preparing to see a new patient named Austin, an 8-month-old boy with no significant medical history who was admitted yesterday afternoon after presenting to the emergency department (ED) with fever and vomiting for 2 days. Austin had further vomiting after an oral challenge in the ED, and thus he was hospitalized for supportive care. His admitting diagnosis was mild to moderate dehydration and oliguria from suspected acute gastroenteritis (AGE).

In the ED, a blood culture was drawn, a peripheral intravenous (IV) line was placed, and Austin was given a 20 mL/kg bolus of normal saline. Overnight, he received maintenance IV fluids, ondansetron, and acetaminophen for his symptoms. In reviewing his medical record, you note that his vomiting has resolved, he has not had any bowel movements documented, and his fevers have persisted, with a maximum temperature of 39.6 °C (103.3 °F). His urine output overnight is documented as 0.8 mL/kg/h. Given his lack of diarrhea and worsening fevers, you are concerned that Austin's prior diagnosis of AGE may be incorrect.

Patient History and Review of Systems

Q: What information should you collect from Austin's caregivers?

- History of present illness
  - Duration of illness
  - Symptoms at illness onset and symptom progression over time
  - Height of fever at home and method of temperature measurement
  - Change in level of alertness or somnolence
  - Fussiness and ability to console
  - Recent oral intake and hydration status
  - Characteristics of vomiting episodes, including color and any associated triggers
  - Detailed description of urine, including volume and frequency, change in urine output since receiving IV fluids, urine stream (strong vs dribble), odor or color change, and normal versus current voiding habits
  - Associated symptoms, including weight loss, cough, nasal congestion/drainage, oral lesions, difficulty breathing, signs of abdominal pain, constipation, diarrhea, and presence of rashes

- Medical history and underlying health status, including prenatal history, birth history, chronic medical conditions, and immunization status
  - History of urinary tract infections (UTIs), ear infections, or pneumonia
  - Presence of genitourinary anomalies and circumcision status
- Medications taken at home
- Dietary history, focused on risk factors for foodborne illness
- Social history, including recent travel history and possible sick contacts, including attendance to child care

CASE FOCUS

History and Review of Systems

In reviewing Austin's history with his family, you confirm that his illness started 3 days ago with decreased oral intake. He then developed nonbilious vomiting and fevers up to 38.7 °C (101.7 °F). On the day of hospital admission, he had been fussy throughout the day and had become more listless before arrival to the ED. Austin's diet normally consists of formula (appropriately mixed) and jars of pureed cereals, fruits, and vegetables. For the past 2 days, he had not been taking his bottle as well as he normally does and has had no interest in purees. His parents estimate that he had about 5 episodes of nonbloody, nonbilious emesis yesterday and only 1 wet diaper. The emesis did not have a clear trigger.

Overnight, Austin's vomiting has resolved with ondansetron, but he continues to drink less than is normal for him. He has received IV fluids since admission, and his parents report that his urine output has improved since his presentation but remains below his baseline. He has not developed any diarrhea. His last bowel movement was yesterday prior to admission and was normal in consistency. He has remained fussy but consolable, and he has been febrile with a maximum temperature of 39.6 °C (103.3 °F). He has also been napping more than normal.

His parents state there have been no sick contacts at home, and Austin has not had any runny nose, congestion, cough, rash, or recent travel. Austin does not attend child care, is generally healthy, and has not had any surgeries. He has received all of his immunizations according to the Centers for Disease Control and Prevention schedule, and he has never had any infections that required antibiotics. Austin was born full term and was adopted by his parents at the age of 2 months. His birth mother reportedly had limited prenatal care. Austin is uncircumcised; his parents cannot recall ever seeing him void, and thus they are unable to describe his urine stream. They deny any history of constipation. With this illness, Austin's parents have been treating his fever at home with acetaminophen and ibuprofen. A recent preillness weight at his pediatrician's office was 7.9 kg (approximately 20th percentile for age).

Physical Examination

Q: What parts of the physical examination should you focus on for Austin?

- Complete set of vital signs
- Weights (current compared with presentation)
- Level of consciousness and ability to arouse normally
- Fontanelle (closed, sunken, flat, or full)
- Head, eyes, ears, nose, and throat: tympanic membranes, conjunctiva, lymph nodes, nares, oropharynx, mucous membranes (moist, sticky, or dry)
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Respiratory: work of breathing, adventitious sounds, signs of focality

- Abdomen: distension, bowel sounds, tenderness, masses
- Genitourinary: circumcision status, phimosis, hypospadias, meatal stenosis, testicles (for positioning)
- Costovertebral angle tenderness, if possible
- Musculoskeletal system and extremities: tenderness, erythema, edema (including hands and feet)
- Skin: turgor, presence of rashes
- Neurologic: bulging fontanelle, widened cranial sutures, altered level of consciousness, focal neurologic deficits

CASE FOCUS

Physical Examination

Austin's vital signs show that he has been febrile with a maximum recorded temperature of 39.6 °C (103.3 °F) and has had mild tachycardia (heart rate: 150–170 beats/min). He has had normal blood pressure for age and normal oxygen saturations. His weight on arrival to the ED was 7.5 kg, and his current weight is 7.7 kg. His length is recorded as 69 cm (25th percentile).

On examination, Austin appears fussy but is consolable in his mother's arms. His anterior fontanelle is open, soft, and flat, and his cranial sutures feel well approximated. You notice very few tears when he is crying, and his oral mucosa is sticky but without any lesions. No conjunctival erythema, nasal discharge, or nasal congestion is noted. His tympanic membranes are pearly gray with clear bony landmarks. His cardiac examination is normal, aside from his tachycardia, and he has a normal respiratory examination. His peripheral pulses are normal with a capillary refill time of less than 2 seconds. His abdomen is soft and nontender. You are able to feel the top of his bladder approximately 2 to 3 cm below the umbilicus. His genitourinary examination shows an uncircumcised penis with both testes in his scrotum. You are able to gently retract his foreskin just enough to visualize the opening of the urethra at the tip of the penis. As you are examining him, Austin spontaneously voids, and you notice that his urine stream is weak. There is stool in his diaper during the examination, which is brown and soft. He does not have any appreciable costovertebral angle tenderness, sacral dimples, or other abnormalities of his lower spine. His lower extremity sensation is intact, and his patellar and ankle reflexes are normal. He has no rashes or any other abnormalities on examination.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an infant or young child with acute onset of fever, fussiness, and emesis?

There are many illnesses that could cause fever, emesis, and fussiness in infants and young children, with self-limited infectious etiologies predominating. Table 8.1 shows a differential diagnosis for these symptoms and has been prioritized based on features of Austin's illness.

Table 8.1. Differential Diagnosis for Fever, Fussiness, and Vomiting in an Infant or Young Child

Diagnoses of highest suspicion	• Acute infectious gastroenteritis • Intussusception • Systemic viral infections • UTI, specifically pyelonephritis[a]
Other diagnoses to consider	• Acute otitis media • Appendicitis • Bacteremia • CNS infection • Group A streptococcal pharyngitis • KD • Pancreatitis • Peritonitis • Pneumonia • Sepsis

Abbreviations: CNS, central nervous system; KD, Kawasaki disease; UTI, urinary tract infection.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for an infant or young child who presents with fever and emesis?

- The diagnostic evaluation of an infant or young child with fever and vomiting should be individualized based on the patient's unique factors (including age) and the patient's history and examination. For example, these symptoms in a newborn generally warrant a full evaluation for serious bacterial infections. (Refer to Case 7 for a discussion of the evaluation of febrile neonates.) In an older infant or young child who is clinically stable, clinicians should use assessment of the patient's general well-being, pertinent positives and negatives on the history of present illness and review of systems, the patient's vital signs, and examination findings to determine what diagnostic evaluation should be performed, if any.
- For infants and young children with a reassuring history and examination, clinicians may opt for watchful waiting and not perform any immediate testing.
- For infants and young children with vomiting and concern for significant dehydration and oliguria, serum electrolytes, blood urea nitrogen, and creatinine laboratory studies may be indicated.
- For infants and young children in whom there is concern for a UTI, a urine sample should be obtained for urinalysis and culture.

Q: What are the risk factors for UTI in infants and young children?

For febrile infants without an obvious source of fever, the prevalence of UTI is approximately 5% to 7%; however, not all infants and young children are at the same risk. Factors that place an infant or young child at higher risk for a UTI include the following:

- Sex: Throughout most of childhood, girls are much more likely to have a UTI compared with boys; however, in the first 3 months after birth, the prevalence of febrile UTI is highest in uncircumcised boys.
- Circumcision status: For boys aged 2 to 24 months, circumcision status is an important risk factor. Circumcised male infants have a significant reduction in their odds of UTI compared with uncircumcised boys.

- Age: Infants younger than 1 year are at a higher risk of febrile UTI than older children.
- Characteristics of fever.
  - Height of fever: Infants who have temperatures of 39 °C (102.2 °F) or higher have at least twice the risk of UTI compared with infants who have lower temperatures.
  - Duration of fever: Higher risk is associated with a longer duration of fever (>24 hours for male infants and > 48 hours for female infants).
- No other identifiable source of fever: The presence of another clinically apparent source of infection reduces the likelihood of UTI by one-half but does not eliminate the risk.
- Prior UTI: Infants younger than 1 year who experience a febrile UTI have a 12% to 30% risk of recurrence.
- Other risk factors: The presence of bowel and bladder dysfunction; constipation; in-process toilet training; neurogenic bladder; genitourinary anomaly, including labial adhesions, vesicoureteral reflux, or urinary tract obstruction; or urologic instrumentation, including recent catheterization, are all additional risk factors for UTI.
- Factors associated with an increased risk of recurrent UTI include high-grade vesicoureteral reflux, bladder and bowel dysfunction, and baseline renal scarring.

Q: How should a urine sample be collected when there is concern for a UTI in an infant or young child?

If an infant or young child is deemed to be at risk for UTI by the clinician's judgment, a urine sample may be collected in one of the following ways:

- Catheterization or suprapubic aspiration (SPA). Refer to Section V of the Appendix for a list of indications, contraindications, and risks of bladder catheterization.
- Midstream clean catch, after cleansing of the perineum and gentle retraction of the foreskin, when present.
- Collection of a bag specimen after cleaning and rinsing of the perineum.

If the results of a urinalysis obtained by bag specimen are suggestive of a UTI, then a catheterized or SPA sample must be obtained for culture. In general, urine collected from a bag specimen is highly susceptible to contamination and should not be submitted for culture. When the results of a urinalysis obtained by bag specimen are normal, a UTI can generally be ruled out.

CASE FOCUS

Diagnostic Evaluation

Although Austin was previously diagnosed with AGE, the presence of vomiting and fever are nonspecific symptoms. Because Austin is uncircumcised and has had a fever for more than 24 hours, with a maximum temperature greater than 39.6 °C (103.3 °F) and no clear etiology, you determine he is at risk for a UTI and will proceed with obtaining a urine sample via catheterization for testing. Given his bladder enlargement and weak urinary stream, you also would like to assess Austin's electrolytes and renal function. The results of his evaluation are as follows:

Laboratory test	Result	Reference range
Basic metabolic profile		
Sodium	139 mEq/L (139 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.4 mEq/L (4.4 mmol/L)	3.5–6.3 mEq/L (3.5–6.3 mmol/L)
Chloride	107 mEq/L (107 mmol/L)	97–106 mEq/L (97–106 mmol/L)
Bicarbonate	19 mEq/L (19 mmol/L)	19–24 mEq/L (19–24 mmol/L)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Basic metabolic profile *(continued)*		
Anion gap	13 mEq/L (13 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	14 mg/dL (5 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.6 mg/dL (53 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	109 mg/dL (6.05 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Urinalysis		
Color	Dark yellow	Light yellow
Appearance	Slightly cloudy	Clear
Glucose	Negative	Negative
Bilirubin	Negative	Negative
Ketones	Negative	Negative
Specific gravity	1.030	1.005–1.030
pH	6.5	4.5–8
Nitrite	Positive	Negative
Blood	Small	Negative
Leukocyte esterase	Large	Negative
RBCs (microscopic)	5–10/HPF	Occasional
WBCs (microscopic)	21–50/HPF	0–2/HPF
Bacteria (microscopic)	Moderate	None
Epithelial cells	0–2/HPF	Occasional
Casts	None	None
Microbiology		
Blood culture	No growth for 18 hours	Negative
Urine culture	Pending	Negative

Abbreviations: BUN, blood urea nitrogen; HPF, high-power field; RBC, red blood cell; WBC, white blood cell.

Given the presence of pyuria, bacteriuria, and nitrites on urinalysis, you decide to order a urine culture. A catheter was placed to obtain a sterile urine sample, and then the catheter was removed. Because the urinalysis was obtained by catheterization, you are able to send a specimen from the sample already obtained.

Arriving at a Diagnosis

Q: How do you develop an assessment for Austin?

In thinking through Austin's case, you first interpret his history, vital signs, examination findings, and diagnostic evaluation to develop a list of findings that helps narrow your differential diagnosis to the most likely etiology or etiologies.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Austin is an 8-month-old boy who is currently hospitalized for mild to moderate dehydration related to a febrile illness featuring poor intake, fussiness, decreased urination, and vomiting. His vomiting has resolved overnight, but he continues to be fussy and is now on his third day of fever.
   - Physical examination: On examination, Austin is fussy with fever and tachycardia. He is noted to be uncircumcised and to have a weak urinary stream and an enlarged bladder.
   - Laboratory tests: Austin's basic metabolic profile shows an elevated creatinine level, which could represent acute kidney injury (AKI) or chronic kidney disease (CKD). His urinalysis shows pyuria, nitrites, bacteriuria, and large leukocyte esterase, which is concerning for a UTI. His elevated urinary specific gravity is consistent with his continued dehydration.
   - On admission, Austin was approximately 5% below his preillness weight, which is consistent with mild to moderate dehydration. His weight has increased 0.2 kg today; however, he continues to have poor oral intake and decreased urine output, and he is approximately 3% below his preillness weight. Based on this, you conclude that Austin continues to have mild dehydration that is improving. (Refer to Table A.2 in the Appendix for the Centers for Disease Control and Prevention dehydration assessment.)
   - Assessment for sepsis: Austin's fever and tachycardia are concerning for sepsis; however, there are no findings to suggest severe sepsis or septic shock. Refer to Section IV in the Appendix for the age-based systemic inflammatory response syndrome and sepsis criteria.

BACK TO BASICS

Elevated Serum Creatinine in Infants and Children

Acute etiologies: The etiologies of acute rises in serum creatinine level (reflecting an acute decrease in the glomerular filtration rate [GFR]) are divided into 3 categories: (1) prerenal AKI (related to decreased renal perfusion; generally resolves once renal hypoperfusion is reversed); (2) intrinsic AKI (related to glomerular, tubular, interstitial, or vascular damage or nephrotoxin exposure; sustained hypoperfusion can lead to intrinsic AKI by ischemia/hypoxic injury leading to acute tubular necrosis); or (3) postrenal, such as urinary tract obstruction. Although there are different definitions, AKI in children is commonly defined as an acute rise in the serum creatinine level from baseline by 50% or 0.3 mg/dL (26.5 µmol/L). Oliguric AKI is defined as AKI in a patient with a urine output of less than 1 mL/kg/h. Complications of AKI can include electrolyte disturbances, metabolic acidosis, and fluid overload.

Chronic etiologies: CKD is defined as renal damage or renal abnormality that is present for at least 3 months. This renal damage may be evidenced by either functional or structural abnormalities of the kidney or a GFR of less than 60 mL/min/1.73 m^2. Many pediatric GFR calculators can be found online. In infants and children, common causes of CKD include glomerulopathies, congenital anomalies of the kidneys and urinary tract, infection, hereditary nephropathies, and vascular disorders. Complications of CKD can include hypertension, cardiovascular disease, poor growth, anemia, electrolyte disturbances, cognitive impairment, malnutrition, and metabolic bone disease.

Oftentimes, the etiology of an elevated creatinine level in hospitalized infants or young children may be apparent based on the patient's history (eg, in the setting of dehydration, nephrotoxic medications) and examination. Renal bladder ultrasonography (RBUS) can be useful to rule out structural or postrenal etiologies. When the cause of an elevated creatinine level is unknown, the evaluation into the etiology may include obtaining a urinalysis with microscopy (assessing the urine color, specific gravity, hematuria, proteinuria, casts, etc), urine protein to creatinine ratio, urine sodium, and urine osmolality. Unfortunately, these studies are inaccurate if the patient has received IV fluids or diuretics, so their use for hospitalized children is oftentimes limited. Laboratory test results suggestive of a prerenal etiology include concentrated urine (specific gravity > 1.020, urine osmolality > 500 mOsm/kg [500 mmol/kg]), low urine sodium (< 20 mEq/L [20 mmol/L]), and a fractional excretion of sodium (FE_{Na}) less than 1%. A low urine specific gravity (< 1.010), low urine osmolality (< 350 mOsm/kg [350 mmol/kg]), high urine sodium level (> 40 mEq/L [40 mmol/L]), and an FE_{Na} of greater than 2% are suggestive of intrinsic renal pathology such as acute tubular necrosis. The presence of urinary white blood cell (WBC) or red blood cell casts on urine microscopy also suggests intrinsic renal pathology. A renal biopsy should be considered in cases concerning for intrinsic pathology or in the setting of rapidly progressive loss of renal function.

2. **Develop the list of findings.**

Q: What major findings you have identified for Austin?

- Possible sepsis (based on the presence of fever and tachycardia in the setting of a suspected infection)
- Mild dehydration (improving)
- Vomiting (improving)
- Fever for 3 days
- Elevated serum creatinine level
- Weak urinary stream with bladder distension
- Pyuria, nitrites, and large leukocyte esterase present on urinalysis

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Austin's fever and vomiting?

- To determine the underlying etiology of Austin's symptoms and findings, you first need to consider the cause of his elevated serum creatinine level and interpret his urinalysis findings.
- For Austin's increased serum creatinine level, there are 2 etiologic categories to consider: AKI and CKD.
  - AKI: Austin's increased creatinine level may be prerenal from the combination of his dehydration and home use of nonsteroidal anti-inflammatory drugs (NSAIDs), both of which lead to renal hypoperfusion. Given his enlarged bladder, acute bladder dysfunction or obstruction of his bladder outlet are both other possible etiologies of his increased creatinine level.
  - CKD: For Austin, the 2 possible etiologies that relate to his examination findings of an enlarged bladder and weak urinary stream would be a congenital anomaly of the urinary tract (eg, posterior urethral valves [PUVs]) or chronic bladder dysfunction (eg, neurogenic bladder).
- Interpretation of his urine sample.

Q: How do findings on a dipstick urinalysis and urine microscopy help predict the presence of a UTI in infants and young children?

- Dipstick urine testing
  - Positive leukocyte esterase test result indicates that WBCs are present in the urine and is 83% sensitive for UTI in children with symptoms. In addition to UTI, leukocyte esterase can be present in infants and young children with other febrile illnesses.
  - Positive result for nitrites on urinalysis has a sensitivity of 53% for UTI but specificity of nearly 100%. The conversion of nitrates to nitrites by gram-negative bacteria requires 4 hours in the bladder; therefore, this test can be negative despite the presence of a UTI in patients with urinary frequency, especially infants, and in patients who have infections caused by yeast or gram-positive bacteria.
  - Combined positive nitrite and leukocyte esterase on dipstick analysis is 80% to 90% sensitive and 60% to 98% specific for a UTI.
- Microscopy
  - WBCs: Most commonly, microscopy is performed on the urinary sediment of a centrifuged urine sample and is suggestive of infection when there are at least 5 WBC/high-power field (HPF).
  - Bacteria: Urine microscopy can also be suggestive of infection when bacteria are noted on the Gram stain of a fresh uncentrifuged specimen.

Austin's urinalysis, obtained from catheterization, is suggestive of a UTI because of the presence of 21 to 50 WBC/HPF and bacteria on microscopic evaluation as well as positive nitrites and large leukocyte esterase on dipstick. Findings of blood and epithelial cells are likely secondary to the minor trauma associated with catheterization.

Q: How is a UTI definitively diagnosed in infants and young children?

In general, the diagnosis of a UTI in children is made by the presence of *both* of the following criteria: evidence of pyuria and/or bacteriuria *and* growth of at least 50,000 CFU/mL of a uropathogen on urine culture.

- Evidence of pyuria and/or bacteriuria
  - Pyuria is defined differently for centrifuged and uncentrifuged urine specimens.
    - Pyuria in a centrifuged specimen is defined as at least 5 WBC/HPF.
    - When an uncentrifuged specimen is analyzed in a counting chamber (ie, a hemocytometer), pyuria is defined as at least 10 WBC/mcL.
    - The presence of leukocyte esterase on dipstick should be considered as consistent with pyuria, particularly when urine microscopy is not readily available.
  - Bacteriuria is defined as the presence of bacteria on the Gram stain of a fresh, uncentrifuged urine specimen.
- Growth of at least 50,000 CFU/mL of a uropathogen on culture of a catheterized urine sample
  - For a catheterized specimen, clinically significant growth is generally defined as at least 50,000 CFU/mL of a single urinary pathogen; however, recent studies have suggested that clinicians should also consider the growth of 10,000 CFU/mL or more as significant in catheterized specimens from infants who are at risk for UTI and have both fever and pyuria.
  - Outside of the neonatal intensive care unit, SPA is not commonly performed. If this method is used, however, growth on culture of at least 1,000 CFU/mL of a uropathogen is considered significant.
  - In toilet-trained children (or when feasible in infants and toddlers), a midstream clean-catch sample is usually a satisfactory specimen. For clean-catch urine specimens, growth of more than 100,000 CFU/mL of a single urinary pathogen is considered significant.
  - If multiple organisms are present, there should be a high suspicion for sample contamination with perineal or prepuce skin flora.

In general, a positive culture result in the absence of pyuria and/or bacteriuria is suggestive of sample contamination or asymptomatic bacteriuria.

Q: In infants and toddlers, how are upper tract UTIs (eg, pyelonephritis) differentiated from lower tract UTIs (eg, cystitis)?

- Although older children are able to verbalize distinguishing symptoms, such as dysuria for cystitis/urethritis or back pain for pyelonephritis, clinicians must rely on other clinical indicators in infants and young children. For these patients, the presence of temperature of at least 38.5 °C (101.3 °F), elevated C-reactive protein level (≥4 mg/dL [40 mg/L]), or leukocytosis generally indicates an upper UTI.
- It should be noted that the absence of fever does not rule out an upper tract UTI, especially for newborns and young infants.

Q: What is the significance of Austin's weak urinary stream and bladder distension?

- Weak urine stream and bladder distension could be indicative of neurogenic bladder, but this would be unlikely in Austin who is a neurotypical infant boy with no signs of spinal cord abnormalities.
- More likely for Austin, bladder outlet obstruction, such as seen with PUVs, should be suspected in a male infant when there is a palpable bladder on examination and the urinary stream is weak. If the bladder outlet obstruction is severe and goes unrecognized during the neonatal period, infants can present with failure to thrive, sepsis from UTI, and end-stage renal disease. With lesser degrees of obstruction, children present later in life with difficulty in achieving diurnal urinary continence or with a UTI.

Based on all of these considerations, you decide that a diagnosis of an upper UTI (ie, pyelonephritis) is the most likely cause of Austin's symptoms; however, the results of his urine culture are necessary to confirm this diagnosis. Additionally, you are concerned for the possibility of an outflow tract obstruction, specifically PUV, based on his examination findings.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for an infant or child with a UTI?

Although Austin is currently hospitalized, you consider what would be reasonable admission criteria for an infant or child with a UTI:

- The patient is ill appearing (including concern for sepsis).
- The patient is unable to tolerate sufficient oral intake and is dehydrated, requiring IV or nasogastric fluids.
- The patient has persistent vomiting or is unable to tolerate oral antibiotics.
- Outpatient treatment has failed, and the child needs IV therapy.

It should be noted that fewer than 1% of patients diagnosed with UTI require admission.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Austin is an 8-month-old healthy boy who presented yesterday with acute onset of fever and vomiting. His fever continued overnight and today's evaluation shows findings consistent with mild dehydration, possible sepsis, suspected oliguric AKI, and presumed acute pyelonephritis. His examination findings of a distended bladder and weak urine stream are concerning for bladder outlet obstruction. He requires ongoing hospitalization for treatment of his UTI and further evaluation of his urinary tract.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Prompt treatment of suspected upper tract UTIs is important to prevent renal scarring in infants and children. Renal scarring may contribute to an increased lifetime incidence of hypertension and CKD. To be thorough in your treatment of Austin, you divide his plan for treatment and monitoring into the following categories:

1. **Antibiotic therapy:** Empiric antibiotic therapy should be guided by local sensitivity patterns to the most common uropathogens.

Q: What are the common uropathogens in infancy and childhood?

- The most common bacterial organism responsible for UTIs in infants and children is Escherichia coli (present in 54% to 67% of cultures).
- Other possible organisms include *Klebsiella* spp, *Proteus* spp, *Enterococcus* spp, *Enterobacter* spp, Staphylococcus saprophyticus (in adolescents), group B streptococcus (in neonates and young infants), and *Pseudomonas aeruginosa*.

Q. While the urine culture is pending, what are options for empiric antibiotic therapy?

- Empiric treatment of UTIs should be based on local resistance patterns from published antibiograms when available. If an antibiogram is unavailable, it is reasonable to start empiric therapy with a first-, second-, or third-generation cephalosporin. Nitrofurantoin has poor renal tissue penetration and thus should not be used for febrile UTI/pyelonephritis.
- In children with a suspected UTI and whose urinalysis is negative for nitrites, the addition of empiric coverage for gram-positive organisms such as *Enterococcus* should be considered.

- In general, use of fourth-generation cephalosporins and fluoroquinolones should be limited to treatment of resistant uropathogens.
- In many areas, use of trimethoprim-sulfamethoxazole is a poor empiric choice due to high resistance rates.
- Antibiotic therapy should later be adjusted or discontinued based on urine culture results and sensitivities. The use of narrow-spectrum antibiotics is preferred, when possible, to decrease the risk of emerging antibiotic resistance. Total duration of antibiotic therapy in infants and young children should be 7 to 14 days.

2. **Imaging of the urinary tract**
   - For children aged 2 to 24 months with their first febrile UTI, the American Academy of Pediatrics recommends that RBUS be performed to evaluate for anatomic abnormalities or signs of severe vesicoureteral reflux such as hydroureteronephrosis. For a well-appearing child, RBUS should be deferred until after 48 hours of antibiotic therapy to ensure the ultrasound better represents the patient's baseline. Renal ultrasounds obtained during an acute infection can be misleading because the infection itself may cause changes that can be visualized on ultrasound.
   - For children aged 2 to 24 months, voiding cystourethrogram (VCUG) should be reserved for patients with abnormalities on RBUS or recurrent febrile UTIs (Box 8.1).

Box 8.1. Indications for Voiding Cystourethrogram in Infants and Children Aged 2 to 24 Months

- The patient has had a second febrile UTI.
- The following abnormal findings are present on RBUS after the patient's first UTI:
  - Hydronephrosis
  - Scarring
  - Dilated ureter
- The test has been recommended by the reviewing pediatric radiologist.

Abbreviations: RBUS, renal bladder ultrasonography; UTI, urinary tract infection.

3. **Monitoring**
   - Except for patients in whom there is concern for sepsis or severe dehydration, routine monitoring should be ordered, including vital signs every 4 hours, tracking of the patient's intake and output, and daily weights. Repeat testing of the urine or follow-up serum laboratory studies are not necessary for most patients.
   - When there is concern for sepsis, more frequent monitoring and clinical reassessments are indicated until there is improvement in the patient's vital signs and clinical status.
4. **Supportive care and symptomatic treatment**
   - Acetaminophen and ibuprofen can be used for fever, pain, and dysuria. The use of ibuprofen should be limited in the setting of dehydration or AKI and avoided in infants younger than 6 months.
   - Ondansetron can be administered for nausea and vomiting.
   - IV fluids can be used to improve hydration status, when indicated. In the setting of AKI, clinicians should be mindful of the electrolyte composition of IV fluids (eg, avoid adding potassium).

CASE FOCUS

Plan for Treatment and Monitoring

- **Antibiotic therapy:** You start IV cefazolin according to your hospital's urinary antibiogram.
- **Imaging:** Given Austin's findings of a weak urinary stream and bladder distension, you decide to obtain an RBUS immediately.
- **Monitoring:** You order frequent clinical reassessments, strict monitoring of intake and output, vital signs every 4 hours, and daily weights. You plan to obtain a repeat basic metabolic panel in 24 hours to reevaluate Austin's elevated creatinine level.
- **Supportive care and symptomatic treatment:** You allow Austin to continue with his age-appropriate, unrestricted diet as tolerated. Given his elevated creatinine level, you remove potassium from his IV fluids to avoid the risk of hyperkalemia. You order acetaminophen as needed for pain or fever. You plan to avoid NSAIDs for the time being given Austin's elevated creatinine level and continued dehydration. You order ondansetron as needed for emesis.

Case Resolution

Austin's RBUS shows bilateral mild to moderate hydronephrosis with a mildly enlarged, trabeculated bladder. Because of these findings, a urology specialist is consulted and inserts a urinary catheter to relieve Austin's obstruction. Over the following days, Austin is monitored closely for the possibility of a postobstructive diuresis and any electrolyte abnormalities. His urine culture ultimately grows more than 100,000 CFU/mL of *Escherichia coli*, sensitive to cefazolin. As his fever resolves, a VCUG is obtained and confirms the diagnosis of PUV. Because of this, Austin undergoes PUV repair via cystoscopy. Prior to discharge, Austin is voiding spontaneously and has no evidence of hypertension, and his creatinine level has stabilized at 0.4 mg/dL (35.4 µmol/L).

Discharge Criteria

Q: How do you know when Austin is ready to go home?

You can feel comfortable discharging your patient with a febrile UTI when the following criteria are met:

- This patient's clinical status is improving.
- Dehydration is resolving, and the patient is able to tolerate oral antibiotics.
- Any electrolyte abnormalities or AKI has resolved.
- If the urine culture and sensitivities are pending, a reliable method of contacting the family has been ensured.
- If RBUS was performed during the hospitalization, results have been reviewed to determine if further imaging (eg, VCUG) is needed prior to the completion of antibiotic therapy.
- Pediatrician follow-up is available. If the patient has an abnormal imaging of the urinary tract or recurrent UTIs, referrals to urology and/or nephrology may be indicated.

Anticipatory Guidance

Q: What instructions should you provide to Austin's caregivers on discharge?

- It is important that Austin drink plenty of fluids to ensure he stays hydrated.
- Most children with UTIs will feel better within 2 to 3 days, but it is important to complete the entire course of antibiotics as prescribed to make sure the infection does not return.
- Approximately 12% to 30% of infants and children with a UTI will have a recurrence. In the future, Austin should be seen by his pediatrician if he has fever (temperature of 38 °C [100.4 °F] or higher) so that the possibility of a UTI can be evaluated.
  - Regular use of cranberry-containing products or probiotics does not appear to reduce the risk of a recurrent UTI.
  - For infants and young children with constipation, treatment of constipation can help to decrease the risk of recurrent UTI.
- Many patients with PUVs have bladder problems and/or CKD. It is important for Austin to follow up closely with his urologist and/or nephrologist to monitor for any ongoing abnormalities.
- Austin should return to care for any weakness in his urinary stream, persistent vomiting, fever, or any new concerns.

Clinical Pearls

- In cases of suspected UTI in a child younger than 24 months, a urine specimen should be obtained through catheterization or SPA. For toilet-trained children, a midstream clean-catch sample is also acceptable.
- The diagnosis of a UTI depends on 2 criteria: (1) the presence of pyuria and/or bacteriuria and (2) growth of at least 50,000 CFU/mL of a uropathogen on a catheterized specimen. For voided specimens, growth of more than 100,000 CFU/mL of a uropathogen is generally considered significant.
- Empiric treatment of UTI should be based on local resistance patterns from published antibiograms when available.
- Antibiotic therapy should be tailored based on urine culture results. Narrow-spectrum agents should be used preferentially.
- Total duration of antibiotic therapy in infants and young children should be 7 to 14 days.
- For infants and children aged 2 to 24 months with their first febrile UTI, an ultrasound of the urinary system should be obtained. Except in cases with suspicion for significant urologic abnormalities or perinephric abscess, the timing of RBUS should be delayed until after 48 hours of antibiotic therapy.
- Most infants and children do not have any long-term sequelae from a single UTI, but renal scarring is observed in 2.8% of infants and children after their first febrile UTI.

Documentation Tips

- Include history of significant uropathy (eg, obstructive defects, moderate to severe vesicoureteral reflux) when appropriate.
- Document whether outpatient treatment has failed.
- Include the presence of dehydration or AKI and the need for IV fluid rehydration.
- Include need for further evaluation, including RBUS or VCUG.
- Mention whether the identified organism has extended antibiotic resistance requiring IV treatment.

Suggested Reading

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CASE 9

Holly, a 5-Year-Old Girl With Fever, Vomiting, and Thigh Swelling

CASE PRESENTATION

Holly is a 5-year-old previously healthy girl who presents to the emergency department (ED) with fever, vomiting, and right thigh swelling. In the ED, she is lethargic (Glasgow Coma Scale [GCS] score: 11), febrile with a temperature of 38.9 °C (102.0 °F), tachycardic with a heart rate of 160 beats/min, and she is noted to have a rash. The ED physician caring for her obtains intravenous (IV) line access, orders a blood culture and laboratory tests, and gives Holly a dose of IV clindamycin for suspected thigh cellulitis. Holly is also given 40 mL/kg of normal saline boluses with subsequent improvement in her tachycardia. After Holly's stabilization, the ED physician contacts you with a request for admission. Holly arrives to the inpatient unit before you have an opportunity to evaluate her in the ED. Her nurse calls you and asks that you immediately come to her bedside to assess her.

Patient History and Review of Systems

Q: What information should you collect from Holly's caregivers?

- History of present illness
  - Onset, pattern, and duration of fever, including maximum temperature
  - Onset and progression of thigh swelling and any associated pain or redness; any known inciting event for thigh swelling, such as insect bites or trauma
  - Onset and characterization of rash, including the location of rash origin and associated pruritis
  - Number of vomiting episodes, description of vomitus, and any associated abdominal pain or diarrhea
  - Associated symptoms, such as decreased oral intake, headache, malaise, myalgias, upper respiratory symptoms, joint pain, chest pain, dyspnea, decreased urination, and mucous membrane changes or conjunctival injection
- Personal or family history of recurrent skin infections
- Medical history, including underlying health status and chronic medical conditions
- Immunization history, especially meningococcal, pneumococcal, and measles-mumps-rubella vaccines

- Medication history, such as any current or recent medications (including over-the-counter medications), and the possibility of any unwitnessed ingestions
- Allergy history, particularly to food or medications, and any recent allergen exposures
- Social history, particularly possible exposures to sick contacts, arthropods, or animals, and recent travel and activity history

CASE FOCUS

History and Review of Systems

From your conversation with Holly's parents, you learn that Holly was in her usual state of health up until 4 days ago. On that day, she was playing in the backyard and was noted to have a bump on her right thigh, which was assumed to be a mosquito bite. The following day, the surrounding area was erythematous and swollen, and her parents applied over-the-counter topical antibiotics and ice to the area. The next day (the day prior to arrival), though she was still playful and at her behavioral baseline, her parents did notice that the area was increasingly erythematous, swollen, and tender to the touch.

On the day of presentation, Holly woke up with a rash on her trunk, fever of 39.4 °C (102.9 °F), and body aches. She then had some abdominal discomfort and several episodes of nonbloody, nonbilious emesis and nonbloody loose stools. She was drinking well until this morning but has not been able to tolerate any fluids today. She has urinated only once since waking up today and has not urinated after receiving IV fluids in the ED. Her rash has been spreading since arrival to the ED and does not itch. Her parents have not noticed any redness of her eyes or lips. Holly did have a cough and some nasal congestion last week, but these symptoms have been improving without the use of any medications. Her parents deny sore throat. They also deny any sick contacts, ingestions, recent travel, freshwater exposure, or interactions with animals apart from their family cat. There is no personal or family history of recurrent skin infections. Holly does not have any chronic medical conditions, does not regularly take any medications, and has received all of her routine childhood vaccines according to the Centers for Disease Control and Prevention (CDC) immunization schedule.

Physical Examination

Q: What parts of the physical examination should you focus on for Holly?

- Complete set of vital signs
- General appearance: level of consciousness (GCS score), pallor, any obvious distress
- Perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses, presence of mottling
- Neck: meningismus, jugular venous distension (JVD), adenopathy
- Mucosal surfaces: mucous membranes, including conjunctivae, to evaluate for erythema or lesions
- Cardiac: murmurs, gallops, rubs
- Respiratory: breath sounds, air movement, work of breathing
- Abdomen: organomegaly, masses, tenderness or peritoneal signs

- Musculoskeletal: particularly the right lower extremity for areas of tenderness, crepitus, or edema
- Lymph nodes: any enlargement
- Neurologic: focal deficits, alertness, ability to follow commands
- Skin: appearance and distribution of rash, including thorough evaluation of the trunk and extremities (including the palms and soles); abrasions or wounds

CASE FOCUS

Physical Examination

On reviewing Holly's vital signs, you note that she is tachycardic with a heart rate of 140 beats/min, and she is ill appearing and lethargic with poor mentation (GCS score: 11). She opens her eyes when you greet her but then closes them again. You review the rest of her vital signs, which show that she is febrile with a temperature of 38.9 °C (102.0 °F), normotensive with a blood pressure of 85/50 mm Hg, mildly tachypneic with a respiratory rate of 30 breaths/min, and she has normal oxygen saturations on room air.

On examination, Holly is breathing comfortably, with clear lungs. Her neck is supple with full range of motion. No JVD is noted. Other than her tachycardia and a hyperdynamic precordium, her cardiac examination is normal, with no murmurs or gallops and a normal point of maximal impulse (PMI); however, her capillary refill time is 4 to 5 seconds, her extremities are cool to the touch, and her peripheral pulses are weak. You note a diffuse macular erythematous rash on her face, trunk, and extremities that resembles a sunburn and is present on her palms and soles as well. The rash blanches with pressure. No skin peeling or blistering is noted, and Nikolsky sign is negative. Additionally, she has a localized right upper thigh lesion with a central eschar, surrounding induration, and erythema, but there is no fluctuance, purulence, or involvement of the joints. She moans and withdraws her leg when you palpate the area. Examination of her head, ears, eyes, nose, and throat is significant for hyperemia of the palpebral conjunctiva and mild audible nasal congestion but is otherwise unremarkable. No lymphadenopathy or abnormalities are noted on the respiratory or abdominal examination.

Differential Diagnosis

Q: What is the differential diagnosis for an ill-appearing child with fever and rash?

Holly's parents brought her to the ED for fever, vomiting, and right thigh swelling, redness, tenderness. You have additionally noted that she has recent vomiting/diarrhea, myalgias, a low GCS, tachycardia, tachypnea, poor perfusion, and a rash that involves her skin, mucosa, and palms and soles. Because many of these symptoms are nonspecific, you would first like to think through the different causes of fever and rash in an ill-appearing child. Table 9.1 shows a differential diagnosis for these symptoms, prioritized based on Holly's presentation.

Table 9.1. Differential Diagnosis for an Ill-Appearing Child With Fever and Rash

Diagnoses of highest suspicion	• Encephalitis, such as enteroviruses or West Nile virus • Meningococcemia • MIS-C • Rickettsial diseases, such as Rocky Mountain spotted fever or murine typhus[a] • Sepsis related to an underlying infection[a] • SJS or toxic epidermal necrolysis • Staphylococcal scalded skin syndrome • TSS[a] • Viral syndromes, including enteroviruses, adenovirus, measles, EBV, parvovirus, varicella, and influenza
Other diagnoses to consider	• DRESS syndrome • Infective endocarditis • KD • Meningitis • *Mycoplasma pneumoniae* • Necrotizing fasciitis • Rheumatic fever • Scarlet fever • SLE • Systemic JIA

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; SJS, Stevens-Johnson syndrome; SLE, systemic lupus erythematosus; TSS, toxic shock syndrome.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is required for an ill-appearing child with fever and rash?

- The diagnostic evaluation for patients who present with these symptoms should be individualized based on underlying host factors and specific findings from their history and examination.
- If a patient's symptoms are attributable to a benign viral etiology, diagnostic testing may not be required. This is particularly true for patients who have a reassuring examination and vital signs and tachycardia responsive to fluid resuscitation; however, a benign viral etiology appears less likely for Holly, so a broad diagnostic evaluation is important.
- Holly's prioritized differential diagnosis and associated diagnostic evaluation are listed in Table 9.2.

Table 9.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Ill-Appearing Children With Fever and Rash

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Sepsis (including meningococcemia and TSS)	Some combination of fever, tachycardia, tachypnea, leukocytosis, and/or hypotension in the setting of a suspected or proven infection; rash may or may not be present, depending on the underlying etiology.	Blood and urine cultures; serum electrolytes, renal function, liver function tests, CBC, lactate level, and ESR/CRP; other bodily fluid cultures as relevant (eg, wound, indwelling line, CSF) Consider other diagnostic testing as indicated by history and physical examination.
Rickettsial illnesses	Fever, lethargy, headache, myalgias; rash is commonly present (but not invariably) and may involve palms and soles. Risk factors include exposure to ticks/fleas/mites/lice, high-prevalence region, and symptoms occurring in the typical season for transmission.	CBC, serum electrolytes, renal function, and liver function tests; rickettsial titers
MIS-C	Fever, laboratory evidence of inflammation, and multisystem organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); no alternative plausible diagnoses; and positive for current or recent SARS-CoV-2 infection or recent exposure to a suspected or confirmed COVID-19 case	CBC, serum electrolytes, renal function, liver function tests, coagulation studies, inflammatory markers (eg, CRP, ESR), SARS-CoV-2 serologies, and infectious studies as indicated by history and physical examination
Staphylococcal scalded skin syndrome	Skin pain, erythematous rash, and desquamation, which usually develops in association with a localized *Staphylococcus aureus* skin infection (such as impetigo); desquamation of the flexural areas is most prominent but can be diffuse. Positive Nikolsky sign	Diagnosis is clinical and skin biopsies are generally not required. Culture of site of bacterial infection (such as impetigo) can be helpful.
Scarlet fever	Fever; pharyngitis; cervical adenopathy; confluent, erythematous, blanching sandpaper-like rash; headache; abdominal pain; and emesis are not uncommon in children with streptococcal pharyngitis.	Rapid strep test with or without throat culture; ASO titers if diagnosis is uncertain
SJS/TEN	Fever, myalgias, malaise, and blistering rash with cutaneous and mucosal involvement Most often develops days or weeks after exposure to a high-risk medication but can also be triggered by infection, particularly *Mycoplasma pneumoniae*	Diagnosis is clinical and skin biopsy is not generally required. Consider diagnostic testing for infection when no causative etiology is identified. Consider CBC, serum electrolytes, renal function, and liver function tests to evaluate for complications.

Abbreviations: ASO, antistreptolysin O; CBC, complete blood cell count; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TSS, toxic shock syndrome.

CASE FOCUS

Diagnostic Evaluation

You review the laboratory test results from Holly's evaluation in the ED, which are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	136 mEq/L (136 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.6 mEq/L (3.6 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	102 mEq/L (102 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	18 mEq/L (18 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	24 mg/dL (8.57 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.8 mg/dL (70.7 μmol/L)	0.3–0.6 mg/dL (26.5–53.0 μmol/L)
Glucose	93 mg/dL (5.16 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
AST	73 U/L (1.22 μkat/L)	13–35 U/L (0.22–0.58 μkat/L)
ALT	80 U/L (1.34 μkat/L)	5–45 U/L (0.08–0.75 μkat/L)
Total bilirubin	0.8 mg/dL (13.7 μmol/L)	<1.2 mg/dL (20.5 μmol/L)
Lactate	4.2 mmol/L	<2.4 mmol/L
CBC		
WBC count	16,600/μL (16.6×10^9/L)	4,000–13,000/μL ($4–13 \times 10^9$/L)
Hemoglobin	13.2 g/dL (132 g/L)	11.5–14.5 g/dL (115–145 g/L)
Hematocrit	37.1% (0.371)	33%–43% (0.33–0.43)
Platelet count	95×10^3/μL (95×10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	86.8% (0.868)	54%–62% (0.54–0.62)
Inflammatory markers		
ESR	85 mm/h	<10 mm/h
CRP	12 mg/dL (120 mg/L)	<1 mg/dL (10 mg/L)
Microbiology		
Blood culture	Pending	Negative
Urine culture	Pending	Negative

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Additionally, Holly's urinalysis has a specific gravity of 1.030 but is otherwise negative.

Based on your suspicions about the etiology of Holly's symptoms, you decide to obtain a culture of any drainage that develops from her right thigh lesion. Because of her myalgias, you order a creatine kinase (CK) level to be obtained from her blood sample drawn in the ED, and the result shows that her CK level is twice the upper limit of normal.

You do not order any immediate laboratory testing at this time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Holly?

To arrive at Holly's diagnosis, you will need to think through the key findings from her history, examination, and diagnostic evaluation to develop a list of findings that will help narrow the differential diagnosis. Given Holly's ill appearance, however, you will start with assessing her airway, breathing, and circulation.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Airway, breathing, and circulation: Holly's airway is intact, she is tachypneic but breathing comfortably, and she is oxygenating normally on room air; however, her circulation is impaired as evidenced by her prolonged capillary refill time, decreased mentation, decreased urination, and weak pulses. Despite her poor perfusion, she does not have pulmonary rales, hepatomegaly, or JVD, and therefore you believe she has distributive shock and not cardiogenic shock. You decide to immediately intervene and provide a third isotonic fluid bolus of 20 mL/kg.

CASE FOCUS

Urgent Intervention

You order a lactated Ringer solution bolus of 20 mL/kg to be given immediately using the push-pull method. You note that Holly received a dose of clindamycin in the ED. To provide broad-spectrum coverage, you order doses of vancomycin and ceftriaxone to be given immediately as well.

As the fluid bolus is being administered, Holly's perfusion and mentation do not significantly improve. You remain at her bedside and continue your assessment.

- While the bolus is finishing, you continue to think through the other findings from Holly's history, vital signs, physical examination, and diagnostic evaluation.
  - History: From her history, you note that Holly had a possible bug bite to her right thigh that has subsequently developed erythema, tenderness, and induration suggestive of a skin infection. Her illness has quickly progressed to include systemic symptoms such as fever, vomiting, diarrhea, myalgias, and rash.
  - Vital signs and physical examination: Holly's vital signs and physical examination show an ill-appearing young girl with decreased mentation who has tachycardia with normal blood pressure but poor peripheral perfusion. She has findings on her right thigh consistent with cellulitis and a whole-body macular rash consistent with erythroderma. Her conjunctiva is hyperemic. Her examination does not have any other localizing findings.
  - Laboratory tests: Holly's laboratory tests show an anion gap metabolic acidosis (low bicarbonate with an elevated anion gap) and elevated lactate levels (contributing to her metabolic acidosis). There is evidence of leukocytosis with a neutrophil predominance, concerning for an infection/inflammation. Additionally, she has evidence of an acute kidney injury (AKI) given her elevated creatinine and blood urea nitrogen (BUN) levels, which could be secondary to her dehydration and poor perfusion. Her liver enzymes are slightly elevated, consistent with mild transaminitis. Her elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) further point to a state of acute systemic inflammation. Her complete blood cell count (CBC) is notable for thrombocytopenia, and her CK is mildly elevated, consistent with a mild myositis.

2. **Assess for the presence of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, or septic shock:** In patients who are acutely ill, it is helpful to recognize the presence of sepsis. Early recognition of severe sepsis and septic shock paired with appropriate resuscitation and management can lead to improved outcomes.
   - SIRS criteria: Refer to Table A.5 in the Appendix for age-based white blood cell (WBC) count and vital sign criteria.
     - WBC count above or below age-specific cutoffs or greater than 10% immature neutrophils, or a core temperature of above 38.5 °C (101.3 °F) or below 36 °C (96.8 °F)

       and at least 1 of the following:
     - Abnormal heart rate: a heart rate that is 2 SDs above normal for age (or bradycardia for children < 1 year)
     - Tachypnea: a respiratory rate that is 2 SDs above normal for age
   - Sepsis: Sepsis is defined as meeting SIRS criteria with a known or suspected infection. Sepsis is a common and well-defined illness; however, the causes are broad and wide-ranging.
     - Sepsis results in approximately 8% of all pediatric intensive care unit (PICU) admissions throughout most of the world and has mortality rates as high as 50%, depending on individual factors.
     - In the United States, 75,000 children annually are hospitalized with severe sepsis, with an incidence of 1:1,000.
     - Respiratory and bloodstream infections result in two-thirds of cases of severe sepsis worldwide, with a significantly higher risk of severe sepsis for unvaccinated children.
   - Severe sepsis: Sepsis is severe when the previously listed sepsis criteria are met and 1 of the following features are present (refer to Table A.5 in the Appendix for full criteria):
     - Cardiovascular dysfunction as characterized by hypotension, the need for vasoactive treatment, or 2 signs of hypoperfusion.
     - Respiratory dysfunction is defined as the presence of acute respiratory distress syndrome (ARDS). ARDS is caused by an acute and severe inflammatory response that results in increased permeability of pulmonary vasculature and noncardiogenic pulmonary edema. These pathologic changes can result in profound hypoxemia. The degree of hypoxemia, based on a calculated value called the *oxygenation index*, determines the severity of ARDS as mild, moderate, or severe.
     - Sepsis-associated organ dysfunction, which is characterized by dysfunction of 2 or more of the following organ systems.
       - Neurologic: Neurologic dysfunction is defined as a change in the patient's mentation. Decreased level of consciousness can be the first sign of hypoperfusion in children. This is because extensive vasodilation causes poor cerebral perfusion and oxygenation, resulting in poor cerebral function.
       - Hematologic: Hematologic dysfunction is defined as the presence of thrombocytopenia, an elevated international normalized ratio, disseminated intravascular coagulation (DIC), or fibrinolysis.
       - Renal: Renal dysfunction is defined as a significant elevation of the patient's serum creatinine. This can occur for many reasons, including inflammation-mediated vasodilation, hypovolemia, decreased cardiac output, and/or shunting of blood to preserve perfusion to vital organs, such as the heart and brain.
       - Hepatic: Hepatic dysfunction is defined as an elevated total bilirubin or alanine aminotransferase level.

- Septic shock: Septic shock is a subset of severe sepsis with signs of cardiovascular dysfunction, as previously listed, that does not respond to appropriate fluid resuscitation (fluid boluses of up to 60 mL/kg over 1 hour).
  - Children can be in shock long before their blood pressure decreases. *Compensated shock* is defined as the maintenance of blood pressure and organ perfusion by increasing heart rate and systemic vascular resistance in a state of low blood volume. This results in tachycardia, cool extremities, delayed capillary refill, and weak pulses as early signs of shock. Hypotension is not a necessary criterion for septic shock in pediatrics. Instead, septic shock may be indicated by other signs of hypoperfusion, such as a prolonged capillary refill time, oliguria, acidosis, or an elevated lactate level.
  - Risk factors for septic shock are
    - Age younger than 1 month.
    - Severe injury, such as trauma, burns, or penetrating wounds.
    - Immunocompromised state or underlying health conditions, including transplant recipients, patients receiving chemotherapy or chronic steroid therapy, and those with underlying immunodeficiency.
    - Patients with foreign indwelling objects, such as vascular catheters, Foley catheters, or endotracheal tubes.
    - Asplenic patients (eg, sickle cell disease, postsplenectomy, and some patients with complex congenital heart disease) who are at risk for infection with encapsulated organisms.
    - Patients with recent history of surgery requiring large surgical incisions.

Despite her lack of hypotension, Holly meets the criteria for septic shock based on the presence of sepsis (fever/leukocytosis and tachycardia in the setting of a suspected infection), signs of organ dysfunction (renal and neurologic), and findings indicative of cardiac dysfunction (lactic acidosis and poor peripheral perfusion).

3. **Develop the list of findings.**

Q: What major findings have you identified for Holly?

- Septic shock as evidenced by sepsis, organ dysfunction, and cardiac dysfunction
- Erythroderma
- Right thigh cellulitis
- Vomiting and diarrhea
- Myalgias
- Conjunctival injection

4. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Holly's presentation?

In thinking through Holly's case, it is helpful to first ask yourself an important question about her list of findings to determine how the findings relate to one another.

Q: How do Holly's rash, conjunctival injection, vomiting, and diarrhea relate to her thigh cellulitis and septic shock?

- These findings are consistent with toxic shock syndrome (TSS), a severe illness characterized by multisystem organ involvement.
- Although relatively rare, TSS is a major cause of pediatric septic shock (causing up to 18% of cases) and should therefore be considered for all patients presenting with sepsis, especially those with a rash similar to Holly's.
  - TSS is an acute systemic illness caused by toxin-producing *Staphylococcus aureus* or *Streptococcus pyogenes* strains. In general, the abbreviation *TSS* is used to denote *S aureus* TSS, and *STSS* is used to denote streptococcal TSS. TSS is much more common than STSS.
  - Holly's clinical features are highly concerning for TSS related to her right thigh cellulitis. As demonstrated by the following diagnostic criteria, TSS would explain the presence of her vomiting, diarrhea, thrombocytopenia, conjunctival hyperemia, and erythroderma.

Q. What are the diagnostic criteria for TSS?

- TSS is diagnosed by a constellation of clinical findings and can be considered probable when 4 of the 5 clinical criteria are present. For patients who survive their illness, subsequent desquamation confirms the diagnosis. As defined by the CDC, the criteria to diagnose TSS include the following:
  - Fever: For TSS, fever is defined as a temperature of 38.9 °C (102 °F) or higher.
  - Rash: The rash associated with TSS is diffuse macular erythroderma, similar to the appearance of a sunburn.
  - Desquamation: The onset of desquamation is 1 to 2 weeks after the appearance of the rash. Desquamation is usually not present at the time the patient presents to medical care.
  - Hypotension: Hypotension is defined as a systolic blood pressure of 90 mm Hg or lower for patients 16 years or older or below the 5th percentile by age for patients younger than 16 years.
  - Evidence of multisystem involvement (≥3 of the following organ systems):
    - Gastrointestinal: the presence of vomiting or diarrhea at illness onset
    - Muscular: severe myalgias or CK level more than 2 times the upper limit of normal
    - Mucous membranes: presence of vaginal, oropharyngeal, or conjunctival hyperemia
    - Renal: BUN or creatinine level more than 2 times the upper limit of normal, or urinary sediment with pyuria (≥5 WBC/high-power field) in the absence of urinary tract infection
    - Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal
    - Hematologic: platelet count less than 100,000/mm^3
    - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
  - Detection of *S aureus* from the blood or spinal fluid is supportive of this diagnosis but is not required; however, the isolation of other pathogens from the blood or spinal fluid rules out this diagnosis.
- The diagnosis of STSS requires isolation of group A streptococcus from a sterile site (*confirmed case*) or nonsterile site (*suspected case*), and mortality is much higher in cases of STSS than in cases of TSS. The diagnostic criteria for STSS are slightly different from those for TSS and can be found in the most recent edition of the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases* and on the CDC website.

5. Consider admission and PICU criteria.

Q: What are reasonable admission criteria for patients in whom there is concern for severe sepsis or septic shock?

- All patients in whom there is concern for severe sepsis or septic shock should be hospitalized for close monitoring and treatment.
- Clinicians should maintain a low threshold for transferring patients with severe sepsis and septic shock to the PICU, where they can undergo closer monitoring and further interventions can be quickly implemented. Clear indications for transfer to the PICU include
  - Fluid-refractory hypotension: low blood pressure despite adequate fluid resuscitation (up to 60 mL/kg).
  - Worsening lactic acidosis.
  - Severe hypoxemia (definition varies as per hospital guidelines).
  - Concern for developing acute respiratory failure.
  - Need for nursing interventions or patient monitoring that exceeds what can safely be done on the acute care unit.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Holly is a 5-year-old previously healthy girl with septic shock secondary to suspected TSS related to right thigh cellulitis. She has signs of cardiovascular and other end-organ dysfunction, including neurologic and renal impairment. She has a normal blood pressure but has received the maximum recommended fluid resuscitation of 60 mL/kg of isotonic crystalloid. She requires hospitalization for hemodynamic stabilization, antimicrobial treatment, and intensive monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Regardless of the etiology of a patient's underlying sepsis, which for Holly is suspected to be TSS, many of the elements of sepsis management are similar. Initial treatment priorities include the rapid administration of volume expansion and broad-spectrum antibiotics. The following are the most recent recommendations for sepsis management based on the 2020 Surviving Sepsis Campaign international guidelines:

1. **Basic principles: Rapid recognition and resuscitation.**
   - Most pediatric sepsis-related deaths occur due to refractory shock and end-organ damage, with a large percentage of those patients dying within the first 72 hours of treatment. Hence, rapid recognition of severe sepsis and septic shock is crucial to decrease morbidity and mortality.
   - Protocols to improve the speed of care for children with septic shock have been shown to improve outcomes, such as mortality, length of stay, and organ dysfunction; therefore, pediatric institutions should have protocols in place to trigger the recognition of severe sepsis and minimize the time to resuscitation and initiation of treatment.
   - The goal is for IV access, fluid resuscitation, laboratory testing, and broad-spectrum antibiotic therapy to be completed within the first hour after sepsis recognition.
   - Fluid resuscitation.
     - In healthcare facilities with a PICU, clinicians should provide IV fluid boluses of 20 mL/kg of isotonic fluids over 5 minutes (lactated Ringer solution preferred). Fluid boluses can be repeated until there are signs of increased end-organ perfusion, up to a total volume of 60 mL/kg; however, boluses should be discontinued if signs of fluid overload develop.
     - In healthcare settings without ICUs, the recommendations for fluid resuscitation are as follows:
       - When a patient does not have hypotension, fluid boluses are not recommended; maintenance fluids should be initiated instead.
       - When a patient has hypotension, clinicians should give 10 to 20 mL/kg in fluid boluses up to 40 mL/kg total, after which clinicians should consider the addition of vasoactive medications.

2. **Antimicrobial therapy.**
   - Empiric broad-spectrum IV antimicrobial therapy should be given within 1 hour of septic shock recognition, ideally after collecting blood cultures. Urine cultures and other bodily fluid cultures, as indicated based on history and physical examination, should also be collected as soon as feasible.
   - The initial choice of antibiotics should be based on local antibiograms and adjusted according to suspected sources of infection, culture speciation and sensitivities, and known risk factors. In most instances, a third- or fourth-generation cephalosporin with or without vancomycin is appropriate empiric coverage, but choices should be individualized based on patient susceptibilities and risk factors.
   - The empiric antibiotic management of TSS may include vancomycin (methicillin-resistant *S aureus* coverage) or oxacillin (methicillin-susceptible *S aureus*) and clindamycin. Because TSS is largely a toxin-mediated disease process, the adjunctive use of clindamycin should be strongly considered as it has been shown to reduce toxin production by staphylococcal and streptococcal species. Occasionally, IV immunoglobulin is used for refractory cases of TSS, although studies have not confirmed the benefit of its use.
   - In children with sepsis-associated organ dysfunction but without septic shock, antibiotics should be administered as soon as possible, within 3 hours of recognition of sepsis, after proper diagnostic workup.
   - If no organism is identified in cultures and the patient's infection does not have an identifiable etiology, clinicians may narrow or discontinue antimicrobial coverage based on the patient's presentation, risk factors, laboratory test result trends, and/or discussion with infectious disease experts.
3. **Source control:** Source control is the physical removal of the source of infection or actions taken to control or prevent systemic spread of local infection. If reasonable to do so, source control should be achieved within 6 to 12 hours and must not be delayed while waiting for the patient to clinically stabilize. Source control may include
   - Percutaneous or deep abscess drainage.
   - Drainage of empyema, septic joint, or subperiosteal abscess.
   - Removal of confirmed infected hardware or intravascular access devices.
4. **Monitoring and goals of treatment:** Septic shock compromises vital perfusion to multiple organ systems that must be monitored closely. The goal is to maintain tissue and organ perfusion as evidenced by
   - Strong pulses, stable heart rate, and stable/normal blood pressure.
   - Warm skin with a normal capillary refill time (<2 seconds).
   - Baseline mental status.
   - Adequate urine output (>1 mL/kg/h) and resolution of AKI with normalization of creatinine and BUN levels.
   - If obtained, serum lactate within normal limits (<2 mmol/L).
   - If obtained and from central access, mixed venous saturations greater than 70%.
   - Additional laboratory values to trend for improvement may include inflammatory markers and WBC counts.
5. **Care escalation for fluid-refractory septic shock:** If there are persistent signs of end-organ hypoperfusion or increasing lactic acidosis despite appropriate fluid resuscitation, such as 40 to 60 mL/kg of isotonic crystalloid (or less, if signs of fluid overload exist), further treatment measures are necessary. Vasoactive medications and ventilatory support should be administered in an intensive care setting by appropriately trained staff.
   - Vasoactive medications
     - In cases of fluid-refractory shock, treatment with vasoactive medications may be required to ensure adequate organ perfusion. Initial treatment includes epinephrine or norepinephrine, with the addition of vasopressin if these medications cannot adequately maintain end-organ perfusion.
     - Central venous access is the preferred route of administration for vasoactive medications; however, if this is not possible, a dilute vasoactive medication can be administered temporarily through a large-bore peripheral IV line or intraosseous access.

  - In cases of refractory shock not responsive to fluid and vasopressors, adrenal crisis should be considered. Adrenal crisis may occur as a complication of the patient's critical illness, or it may exist as an additional underlying diagnosis that is contributing to the patient's shock. Adrenal crisis, regardless of the etiology, typically presents with refractory hypotension and other signs of shock and may be associated with hyperkalemia and hyponatremia related to mineralocorticoid deficiency. The treatment for adrenal crisis is IV hydrocortisone.
- Ventilation
  - Early intubation for children with fluid-refractory septic shock is no longer strongly recommended; therefore, decisions about intubation should be based on the patient's presentation and clinical status. Signs of poor oxygenation, such as worsening lactic acidosis, end-organ dysfunction, and increased work of breathing, should prompt consideration of mechanical ventilation.
  - The decision to initiate mechanical ventilation should not be based solely on chest radiographs, which can lag behind the patient's clinical symptoms. Even normal chest radiographs can quickly progress to ARDS.
  - If no end-organ dysfunction is evident, noninvasive mechanical ventilation, such as continuous positive airway pressure, bilevel positive airway pressure, and/or high-flow nasal cannula, can be trialed before intubation.
- Treatment of metabolic and hematologic derangements
  - Lactic acidosis: Elevated lactate levels can indicate hypoperfusion; therefore, lactate should be frequently monitored as a marker of oxygenation and perfusion of organs and tissue. Uncontrolled lactic acidosis, especially in the setting of signs of renal failure (elevated creatinine or BUN), may be an indication for continuous renal replacement therapy.
  - Blood glucose: Hypo- or hyperglycemia can occur. Insulin therapy is no longer recommended to target specific blood glucose levels. Blood glucose should be carefully monitored and treated on an individual basis.
  - Antipyretic therapy can be considered to decrease metabolic demand caused by the physiological stress of sepsis.
  - Nutritional status should be individualized and optimized based on the patient's clinical and laboratory evaluation. It is preferred to initiate enteral nutrition within 48 hours.
  - Treatment of anemia, thrombocytopenia, and DIC may require blood product transfusions, such as packed red blood cells, platelets, cryoprecipitate, or fresh frozen plasma, depending on the severity.

CASE FOCUS

Plan for Treatment and Monitoring

- **Recognition and fluid resuscitation:** After administration of the additional fluid bolus, Holly has received fluid resuscitation of 60 mL/kg of isotonic fluids. You decide to start maintenance IV fluids while care escalation is pending.
- **Antimicrobial therapy:** You order empiric broad-spectrum antimicrobial therapy with cefepime, vancomycin, and clindamycin.
- **Source control:** You order ultrasonography of Holly's right thigh to evaluate for an underlying abscess.
- **Monitoring:** You order repeat laboratory testing, including CBC, serum electrolytes, BUN level, creatinine level, and serum lactate. You also plan to obtain coagulation studies and fibrinogen to assess for DIC.
- **Care escalation:** Given Holly's continued poor perfusion, altered mental status, oliguria, and tachycardia despite 60 mL/kg in fluid boluses, you plan to contact the ICU for evaluation.

Case Resolution

While awaiting PICU consultation, Holly's blood pressure trends downward, and she is determined to be in fluid-refractory shock. She is promptly transferred to the PICU for a higher level of care. On arrival to the PICU, she is started on epinephrine and has a central venous line placed. Her coagulation studies are mildly abnormal but do not require transfusion of blood products. Ultrasonography of her right thigh reveals an abscess, which undergoes incision and drainage. She is continued on empiric broad-spectrum antibiotics. Her wound culture ultimately grows methicillin-susceptible *S aureus*, and her blood culture is negative. With appropriate antibiotics, source control, and reversal of her shock, her mental status normalizes, and she has improvement in her tachycardia and perfusion. She is able to wean off epinephrine within 24 hours. Her laboratory test results show subsequent improvement in her CBC, AKI, and lactate levels. She is discharged home on hospital day 5 to complete a 10-day total course of antibiotics.

Discharge Criteria

Q: How do you know when Holly is ready to go home?

You can feel comfortable discharging your patient with septic shock when the following criteria are met:

- The patient is hemodynamically stable off of pressors, has a downtrending fever curve, and has been stable on room air for at least 24 hours.
- The patient is tolerating oral intake and able to transition from IV antibiotics to oral antibiotics with continued clinical improvement.
- Source control (eg, incision and drainage) has been achieved as an adjunct to antimicrobial therapy, with resolution of signs and symptoms of disease.

Anticipatory Guidance

Q: What instructions should you provide to Holly's caregivers upon discharge?

- Complete the entire course of oral antibiotics as prescribed.
- Keep surgical wound sites clean and dry, and monitor for purulent discharge, redness, swelling, or fever.
- Encourage plenty of oral fluids to ensure adequate hydration.
- Monitor for the return of fever, rash, tachycardia, dizziness, lethargy, or decreased urination. Contact Holly's pediatrician or return to care for any of these symptoms.

Clinical Pearls

- TSS is a common cause of septic shock and presents with high fever, hypotension, rash, and multisystem involvement.
- Hypotension is a late sign of septic shock in children. To recognize septic shock in children, other signs of hypoperfusion should be considered, such as prolonged capillary refill time, oliguria, acidosis, or elevated lactate level.

- Rapid recognition of shock and provision of adequate resuscitation is the mainstay of sepsis management. Administer up to 40 to 60 mL/kg of balanced/buffered crystalloids (preferred over normal saline) over the first hour. Discontinue use if signs of fluid overload develop.
- Broad-spectrum empiric antibiotic therapy should be initiated within the first hour of sepsis recognition. Antibiotics can be narrowed later based on the patient's progress and culture results.
- Ideally, cultures should be obtained prior to the initiation of antimicrobial therapy.
- Source control is an important part of sepsis management.
- Escalation to a higher level of care is needed in cases of fluid-refractory shock or when the patient's respiratory support requirements are beyond the level that can be safely provided in the acute care setting.

Documentation Tips

- If known, document the underlying etiology or causal organism.
- Clarify the presence of SIRS, sepsis, or severe sepsis.
- When the patient has severe sepsis, the documentation must state "severe" or show evidence of acute organ dysfunction.
- If the patient has circulatory failure and sepsis that are related, document septic shock.
- Document sepsis onset (ie, present on admission or developed during the hospital stay).

Suggested Reading

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CASE 10

Ilyas, a 6-Year-Old Boy With Acute Abdominal Pain

CASE PRESENTATION

Ilyas, a 6-year-old boy with no significant medical history, presents to the emergency department (ED) with acute abdominal pain. In the ED, he undergoes laboratory and imaging studies, and a pediatric surgery consultant determines that his abdominal pain does not require surgical intervention. Ilyas' pain is severe but improved with a small dose of morphine, and his parents are unsure whether they will be able to manage his pain at home. The ED physician agrees with their concerns and requests evaluation for admission by the pediatric team. You are called to the ED to evaluate Ilyas.

Patient History and Review of Systems

Q: What information should you collect from Ilyas and his caregivers?

In developing your questions, you are mindful that the patient's age frequently drives the differential diagnosis.

- History of present illness
  - Timing, including onset, whether onset was sudden or gradual, progression of pain over time, whether pain is constant or intermittent, and duration of pain when present
  - Location and radiation of pain, including whether pain is localized or diffuse
  - Intensity of pain, commonly rated on a scale of 0 to 10 or by use of the Wong-Baker FACES Pain Rating Scale for young patients
  - Quality of pain (eg, vague, aching, sharp, twisting, squeezing, burning)
  - Aggravating and alleviating factors, including whether there is any change in pain with eating, movement/position, bowel movements, urination, or breathing
  - Associated symptoms, such as vomiting, diarrhea, constipation, hematemesis, hematochezia or melena, cough, fever, weight loss, anorexia, rash, change in urine quality, dysuria, testicular pain/swelling/redness, inability to tolerate oral intake, sore throat, or symptoms of dehydration
  - Trauma to the chest, abdomen, or testes
  - Recent unusual or strenuous activity
  - Sick contacts
  - Intentional or accidental ingestions, including alcohol, prescription medications, illicit drugs, household products, or foreign bodies

- Medical history, including previous similar symptoms, chronic medical disorders, and surgical history, especially previous abdominal surgery
- Medications, including dosages and frequency, especially nonsteroidal anti-inflammatory drugs (NSAIDs)
- Family history, especially of gallstones, kidney stones, or inflammatory bowel disease

CASE FOCUS

History and Review of Systems

From your conversation with Ilyas and his parents, you learn that Ilyas' abdominal pain began about 12 hours ago, and the pain has been diffuse, severe, colicky, and intermittent. There have not been any identifiable aggravating or alleviating factors. During the past few hours, he has had several episodes of nonbloody, nonbilious emesis. Ilyas' parents also report he has been drinking and urinating less than normal today. In the ED, he had additional episodes of vomiting after drinking an oral electrolyte solution. His parents deny any history of similar abdominal pain. When asked about the severity of his pain, Ilyas points to the Wong-Baker FACES Pain Rating Scale face that corresponds to pain at a level of 7 on a scale of 10.

On further questioning, you discover that Ilyas has had a rash on his legs and buttocks that was first noticed a few days ago. For the past few days, he has intermittently complained of knee and ankle pain but continued to be active until the abdominal pain started. He has not had any fevers, diarrhea, constipation, hematochezia, sick contacts, trauma, strenuous activity, or recent travel.

Ilyas is otherwise healthy, growing, and developing well and is fully immunized according to the Centers for Disease Control and Prevention schedule. He has never had any abdominal surgeries. There is no family history of intestinal, biliary, or urinary disease. The family has been treating him at home with appropriately dosed acetaminophen, which has been administered for the past 48 hours. His parents deny the possibility of an ingestion of a harmful substance.

Physical Examination

Q: What parts of the physical examination should you focus on for Ilyas?

- Complete set of vital signs
- Level of consciousness and ability to arouse normally
- Head, eyes, ears, nose, and throat examination: appearance of eyes (eg, sunken, icteric, injected), presence or absence of tears with crying, mucous membranes (moist, sticky, or dry), pharyngeal appearance (erythema/exudates)
- Peripheral perfusion: capillary refill time, temperature of extremities, quality of peripheral pulses
- Abdomen: appearance (bruising, lacerations, distention), auscultation (quantity and quality of bowel sounds), palpation (tenderness, guarding, rebound tenderness)
- Costovertebral angle tenderness
- Skin: turgor, presence of rashes (refer to Section VI of the Appendix for characterization of rashes)
- Genitourinary: inspection and palpation of testes, presence of cremasteric reflex, as appropriate
- Visual examination of the stool, if possible

BACK TO BASICS

Abdominal Examination

There are specific signs to note on the abdominal examination that may help provide important diagnostic clues in patients with abdominal pain:

- **Murphy sign:** This examination technique is performed by the examiner placing their fingers under the right costal margin and having the patient inspire. Pain that causes the patient to halt inspiration indicates a positive test and is suggestive of cholecystitis.
- **Psoas sign:** To perform this technique, the examiner has the patient lie on their back while actively flexing their right hip against the resistance of the examiner. Alternatively, the patient can lie on their left side with their right leg held straight. The examiner then passively extends the patient's right hip. Pain with this maneuver may suggest appendicitis.
- **Obturator sign:** The patient lies on their back with their right knee and hip flexed 90 degrees. The examiner internally rotates the patient's hip while pushing the patient's ankle laterally. Pain with this technique may suggest appendicitis.
- **Rovsing sign:** Palpation of the left lower quadrant causes pain in the right lower quadrant. A positive Rovsing sign may suggest appendicitis.
- **McBurney point tenderness:** The McBurney point is located two-thirds of the distance between the umbilicus and the right anterior superior iliac spine. Pain on palpation at this location may suggest appendicitis.
- **Cullen sign:** The presence of superficial ecchymosis and edema around the umbilicus may suggest acute pancreatitis.

CASE FOCUS

Physical Examination

Ilyas' vital signs show that he is afebrile, with a temperature of 37 °C (98.6 °F). His heart rate (105 beats/min) and respiratory rate (20 breaths/min) are within normal limits. He has a normal blood pressure for age and height (100/65 mm Hg) and a normal oxygen saturation on room air (99%).

On examination, Ilyas appears uncomfortable. He moves on the bed trying to find a position of comfort, but he is interactive and answers your questions. While speaking to Ilyas and his family, you observe Ilyas to have several episodes of non-bloody, nonbilious vomiting. On oropharyngeal examination, his oral mucosa is sticky but otherwise unremarkable, without erythema, exudates, or lesions. He has a normal cardiac and respiratory examination. His peripheral pulses are normal with brisk capillary refill.

Ilyas is reluctant to let you examine his abdomen. On auscultation, his bowel sounds are present and normoactive. His abdomen is soft with light palpation, and no masses or organomegaly are noted. With deep palpation, he has tenderness throughout his abdomen, but there is no rebound tenderness, guarding, or increased tenderness at the McBurney point. Additionally, Murphy, Rovsing, psoas, obturator, and Cullen signs are all negative. There is no appreciable costovertebral angle tenderness.

On musculoskeletal examination, Ilyas has tenderness and slight limitation of passive flexion in both knees, but no effusion, erythema, or warmth of the joints is noted. His skin examination reveals a few palpable purpuric lesions in clusters on his legs and buttocks. On genitourinary examination, Ilyas is noted to be Tanner Stage 1 and circumcised. His testicles are descended bilaterally without swelling or tenderness, and cremasteric reflex is present bilaterally.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a young child with acute abdominal pain and vomiting?

The differential diagnosis for a young child with acute abdominal pain and vomiting is shown in Table 10.1 and is divided into causes that seem more and less likely based on Ilyas' presentation.

Table 10.1. Differential Diagnosis for a Young Child With Acute Abdominal Pain and Vomiting

Diagnoses of highest suspicion	• Acute infectious gastroenteritis (viral, bacterial, parasitic) • Appendicitis • IgA vasculitis[a] • Intussusception • Mesenteric lymphadenitis
Other diagnoses to consider	• Abdominal migraine • Abdominal trauma • Allergic reaction, including a delayed hypersensitivity reaction (eg, FPIES) • Biliary tree dysfunction, including cholecystitis, cholelithiasis, or choledocholithiasis • Constipation • DKA • Foreign body ingestion • Gastritis • IBD • Intestinal obstruction • Malrotation (with or without volvulus) • Myocarditis • Nephrolithiasis • Pancreatitis • PUD • Peritonitis • Pneumonia • Small-bowel obstruction • Streptococcal pharyngitis • Testicular torsion • UTI or pyelonephritis • Rare causes, such as lead toxicity, black widow spider bite, porphyria, familial Mediterranean fever

Abbreviations: DKA, diabetic ketoacidosis; IBD, inflammatory bowel disease; FPIES, food protein–induced enterocolitis syndrome; IgA, immunoglobulin A; PUD, peptic ulcer disease; UTI, urinary tract infection.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for children who present with acute abdominal pain and vomiting?

- As outlined previously, the differential diagnosis for acute abdominal pain is broad. The diagnostic evaluation should be directed by the patient's history and physical examination.
- Clinicians should be mindful to consider and exclude diagnoses that would require emergent evaluation and treatment. These diagnoses may be suggested by bilious emesis, shock, or the presence of peritoneal signs, such as abdominal guarding or rebound tenderness. Peritoneal signs suggest irritation of the peritoneal lining and are usually seen with more severe disease processes such as necrotic or perforated bowel.
- Refer to Table 10.2 for a list of clinical scenarios associated with acute abdominal pain that may prompt further diagnostic evaluation.

Table 10.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Abdominal Pain

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Abdominal trauma	Abdominal tenderness, bruising	CBC, AST, ALT, UA, amylase and lipase levels, FAST ultrasonography or CT scan of the abdomen
Acute infectious gastroenteritis	Vomiting and/or diarrhea, with or without fever; sick contacts	Testing is usually not needed; see Case 1 for further discussion of acute gastroenteritis
Appendicitis	Right lower quadrant pain, abdominal pain with cough/percussion/hopping, anorexia, fever, nausea/vomiting	CBC, CRP level, UA, right lower quadrant ultrasonography or CT scan
Biliary tree dysfunction	Right upper quadrant abdominal pain, anorexia, jaundice, pruritis	Ultrasonography of right upper quadrant, liver function tests, lipase level
Intestinal obstruction	Severe abdominal pain, abdominal distention, vomiting, inability to pass stool and/or flatus	Two-view abdominal radiographs, limited abdominal ultrasonography (if there is concern for intussusception or pyloric stenosis), upper GI series (to rule out malrotation, volvulus, or other obstruction/luminal narrowing), CT scan of the abdomen
Intussusception	Episodic abdominal pain, with or without stool mixed with blood and mucus	Abdominal ultrasonography
Nephrolithiasis	Intermittent sharp pain that radiates to lower abdomen or groin, urinary urgency, hematuria	UA, noncontrast abdominal CT scan
Pancreatitis	Upper abdominal pain, pain radiating to the back, pain worse after eating, fever	Lipase level; abdominal ultrasonography, MRI, or CT scan of the abdomen if there is concern for necrosis, pseudocyst, or obstruction of common bile duct
Testicular torsion	Pain or swelling of the scrotum, testicle positioned higher than normal	Scrotal ultrasonography with Doppler to evaluate testes, or pelvic ultrasonography with Doppler to evaluate ovaries/adnexa

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood cell count; CRP, C-reactive protein; CT, computed tomography; FAST, focused assessment with sonography for trauma; GI, gastrointestinal; MRI, magnetic resonance imaging; UA, urinalysis.

Q: What diagnostic evaluation is needed for patients who present with a purpuric rash?

Broadly, purpuric rashes can be divided into thrombocytopenic and nonthrombocytopenic purpura. Thrombocytopenic purpura can be caused by decreased platelet production (eg, marrow suppression from viruses, malignancy, drugs), platelet destruction (eg, disseminated intravascular coagulation, hemolytic uremic syndrome, autoimmune disease, idiopathic thrombocytopenic purpura), or platelet sequestration. Nonthrombocytopenic purpura can have many causes, including severe infections, vasculitides, drugs, trauma, and hereditary hemorrhagic telangiectasia. Patients with a purpuric rash should have a complete blood cell count (CBC) to determine whether the patient is thrombocytopenic. The CBC may provide additional pertinent information, such as whether the patient has reactive lymphocytosis, anemia, or bone marrow suppression. Prothrombin time and activated partial thromboplastin time may also be of utility in determining the underlying cause of purpura. Additionally, when a vasculitis is a consideration, obtaining serum renal studies and a urinalysis (UA) is an important part of the initial diagnostic evaluation.

CASE FOCUS

Diagnostic Evaluation

In the ED, Ilyas' CBC, UA, prothrombin time, activated partial thromboplastin time, and comprehensive metabolic panel are within normal reference ranges for his age.

A 2-view abdominal plain film does not reveal any free air. There are mildly dilated bowel loops, with no air fluid levels. No significant stool burden is apparent.

Given Ilyas' history of intermittent, colicky abdominal pain, you order limited abdominal ultrasonography to be performed immediately, looking for intussusception, and the ultrasonography is negative.

You decide no further diagnostic laboratory testing is indicated at this time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Ilyas?

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Ilyas' history is significant for the recent onset of colicky abdominal pain, joint pain, and a rash without the presence of fever. More recently, he has developed nonbloody, nonbilious vomiting with decreased oral intake and decreased urination.
   - Physical examination: Ilyas' examination does not demonstrate findings concerning for peritonitis, and you note that his rash appears consistent with palpable purpura. Additionally, although he does have pain and limited movement of his knees, there are no findings of septic arthritis. His dry oral mucosa is consistent with mild dehydration.
   - Laboratory tests: Ilyas' CBC with a normal platelet count, in conjunction with normal coagulation studies, greatly narrows the differential diagnosis for a purpuric rash. With a coagulopathy excluded, a vasculitis is the most likely etiology of the rash.

2. **Develop the list of findings.**

Q: What major findings have you identified for Ilyas?

- Mild dehydration
- Vomiting
- Abdominal pain
- Arthralgias
- Palpable purpura

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Ilyas' presentation?

- The presence of a purpuric rash, abdominal pain, and arthralgias strongly suggest that Ilyas has immunoglobulin A (IgA) vasculitis. IgA vasculitis, formerly called *Henoch-Schönlein purpura*, is the most common vasculitis in children. The condition is characterized by inflammation of small blood vessels with IgA deposition on histopathology. Although the exact cause of the disease has not been fully established, it is associated with preceding infections, in particular group A streptococcus. IgA vasculitis most commonly affects children ages 2 to 6 years, but cases can occur at any age. Clinically, this vasculitis produces a spectrum of findings that may include purpuric rash, abdominal pain, polyarthralgia, proteinuria, hematuria, vomiting, or gastrointestinal bleeding.
- The diagnosis of IgA vasculitis can be made based upon the 2008 European League Against Rheumatism/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society Henoch-Schönlein purpura criteria:

  The presence of purpura or petechiae not related to thrombocytopenia with lower limb predominance and at least 1 of the following 4 criteria:

  - Abdominal pain
  - Histopathology, typically a biopsy of the skin showing vasculitis with IgA deposit or a renal biopsy showing glomerulonephritis with IgA deposit
  - Arthritis or arthralgia
  - Renal involvement (proteinuria or hematuria)
- Early in the course, the rash appears macular, papular, or petechial before evolving into the more classic palpable purpura. In more severe cases, bullae can develop. The rash has a symmetric distribution with predilection for gravity-dependent areas. Peripheral, periorbital, and scrotal edema is also common.
- Although the characteristic rash of IgA vasculitis frequently suggests the diagnosis, all clinical features are not present in every case. Joint pain is present in up to 82% of cases, whereas gastrointestinal symptoms are present in 50% to 75% of cases and renal manifestations occur in 20% to 60% of cases.
- Further complicating the diagnosis, the sequence of symptoms can vary. Joint and/or abdominal pain can proceed the appearance of the rash in 30% to 43% of cases.
- In the vast majority of cases, a biopsy is not necessary to make the diagnosis. Occasionally, however, the clinical characteristics do not satisfy the diagnostic criteria, or there is uncertainty about the diagnosis. In these cases, a skin or renal biopsy can be helpful to confirm the diagnosis by fulfilling the histopathologic criteria.

Q: What are possible complications of IgA vasculitis?

IgA vasculitis is usually a mild, self-limited illness that resolves within 6 to 8 weeks; however, some patients do experience a more severe course that requires hospitalization, often due to severity of gastrointestinal symptoms. Possible complications are numerous but can include gastrointestinal problems (bleeding, intestinal perforation, intussusception), renal disorders (glomerulonephritis, hypertension, chronic kidney disease, end-stage renal disease, nephrotic-range proteinuria), testicular pain, and central nervous system involvement. Additionally, some patients can develop relapses, usually within a year of their initial diagnosis.

At this time, there are no signs to suggest that Ilyas has developed any of these more serious complications.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with IgA vasculitis?

- The patient's pain is unable to be controlled at home with over-the-counter medications.
- The patient has intractable vomiting, is refusing oral intake, or is unable to maintain hydration.
- There is significant renal pathology, such as elevated creatinine, nephrotic syndrome, or hypertension.
- The patient has significant gastrointestinal bleeding.

Ilyas meets criteria for hospitalization based on his persistent vomiting in the ED and his poorly controlled abdominal pain.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Ilyas is a 6-year-old otherwise healthy boy who is in the ED with abdominal pain, joint pain, and a rash from suspected IgA vasculitis. His pain was not controlled at home with over-the-counter medications, and he has had multiple episodes of emesis in the ED; therefore, he requires hospitalization for ongoing management and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The treatment of IgA vasculitis is usually focused on providing supportive care and monitoring for potential complications.

1. **Pain management:** Mild to moderate arthralgias and gastrointestinal pain from IgA vasculitis can be managed with NSAIDs. However, NSAIDs should be avoided in patients with evidence of renal dysfunction. In patients with severe abdominal or joint pain, opioids may be needed, and the use of glucocorticoids should be considered. Studies assessing the effectiveness of glucocorticoids for treating IgA vasculitis-related abdominal pain have had mixed results, although one study showed that initiation of steroids reduced the duration of abdominal pain from 2.7 days to 1.5 days. Steroids can also be helpful for severe joint pain. When used, corticosteroids should be tapered slowly to prevent a recurrence of symptoms.
2. **Management of hydration:** Although most children with IgA vasculitis are able to maintain hydration orally at home, Ilyas has developed multiple episodes of vomiting and is at risk of worsening dehydration. Although you will allow him a clear liquid diet as tolerated, you also decide to provide him with maintenance intravenous (IV) fluids until he is able to demonstrate tolerance of oral intake.
3. **Monitoring for gastrointestinal complications:** The most common gastrointestinal complication of IgA vasculitis is small bowel to small bowel intussusception, which has been reported in up to 3.5% of patients. Signs and symptoms of intussusception may include episodic bouts of intense abdominal pain that may cause patients to draw their knees to their chest, a palpable mass on abdominal examination, vomiting, or currant jelly stools. The preferred diagnostic modality for detecting intussusception in children is abdominal ultrasonography. The classic finding on ultrasonography is a target sign, where the telescoped bowel has the appearance of a target or donut when viewed in cross section. Intussusception without evidence of bowel perforation can usually be managed

with nonoperative reduction by pneumatic or hydrostatic enema, though these small bowel to small bowel intussusceptions may be more resistant to therapy than the more typical ileocolic intussusceptions. It is important to note that intussuscepted bowel may spontaneously reduce without interventions. For this reason, it is most useful to obtain ultrasonography during an acute episode of pain whenever possible. Other intestinal complications to monitor for include melena or hematochezia, bowel obstruction related to bowel wall hemorrhage or edema, and peritonitis related to bowel necrosis or perforation. Patients with significant gastrointestinal manifestations may benefit from IV glucocorticoids.

4. **Monitoring for signs of renal disease:** About 2% of patients with IgA vasculitis will develop long-term renal complications. Although nephritis may develop within days of the initial symptoms, renal manifestations can develop up to 6 months later. For this reason, urine and blood pressure should be measured not only upon presentation but also at regular intervals for 6 months after diagnosis. Proteinuria should prompt consultation with pediatric nephrology. Unfortunately, empiric use of glucocorticoids in a child without findings suggestive of nephritis does not appear to decrease the risk of developing renal involvement. Glucocorticoids are, however, frequently administered when there is evidence of nephritis in an attempt to decrease the severity. Some studies have suggested that steroids may be effective when used in this manner, but further research is needed.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment of pain: Based on your examination findings and history indicating that Ilyas' pain has not been controlled with acetaminophen at home, you schedule naproxen for the next 3 days to provide symptomatic relief throughout the day and will order acetaminophen and opioids to be available if needed. You would like to monitor Ilyas' symptoms for improvement before starting any glucocorticoids.**
- **Hydration and vomiting: You order a clear liquid diet to be advanced as tolerated, maintenance IV fluids, and ondansetron as needed.**
- **Monitoring: You plan to perform serial examinations of Ilyas' abdomen and obtain a UA to evaluate for hematuria and proteinuria.**

Case Resolution

Fortunately, Ilyas' UA does not show any hematuria or proteinuria; however, he does continue to have significant abdominal pain and vomiting despite the use of ondansetron and pain medications. Because of this, you initiate a course of glucocorticoids after discussions with his family. The next day, Ilyas' pain starts to improve, and you are able to advance his diet. On hospital day 3, he is discharged home with a 2-week prescription for steroids, including a taper, gastric prophylaxis with a histamine-2 receptor antagonist, and instructions to follow up with his pediatrician for repeat blood pressure measurements and serial UAs.

Discharge Criteria

Q: How do you know when Ilyas is ready to go home?

Children admitted to the hospital due to IgA vasculitis do not typically require prolonged hospitalization. One large multicenter study reported a median stay of 3 days for initial hospitalizations. You can feel comfortable discharging your patient with IgA vasculitis when the following criteria are met:

- The patient is tolerating adequate oral intake.
- Pain is controlled with oral medications.
- There is no significant gastrointestinal bleeding.
- There is no evidence of significant renal disease.

Anticipatory Guidance

Q: What instructions should you provide to Ilyas' caregivers upon discharge?

- Pain can be treated at home with NSAIDs. Return to the hospital for pain that cannot be controlled with properly dosed NSAIDs.
- Return to care for persistent vomiting, signs of dehydration, or significant amounts of blood in the stool.
- Follow up with Ilyas' primary care pediatrician or a nephrologist for repeat blood pressure measurement and urine studies within 1 week. Ilyas will need frequent monitoring for signs of renal disease for the next 6 months.

Clinical Pearls

- The etiology of abdominal pain in children is broad. Assessing the cardinal features of a child's pain and performing a thorough abdominal examination can help with narrowing the differential diagnosis.
- A thorough, full-body assessment for purpuric rash is important when examining any child with acute abdominal pain or arthralgia.
- The classic clinical manifestations of IgA vasculitis (palpable purpura, arthritis/arthralgia, abdominal pain, and renal disease) are not all always present in the same sequence. These symptoms may develop over days to weeks.
- IgA vasculitis is generally a self-limited condition, and supportive care is the mainstay of treatment. Some patients with more severe gastrointestinal or joint involvement may benefit from a course of corticosteroids followed by a taper.
- Ongoing renal monitoring is required for several months after an episode of IgA vasculitis. Several algorithms have been proposed for the frequency of monitoring. Commonly, a UA is performed weekly for at least the first month after diagnosis. Patients require ongoing monitoring with UA and blood pressure measurement for 6 months, as 97% of individuals who develop renal involvement do so within 6 months of the initial diagnosis.

Documentation Tips

- Document the reason for admission (eg, ongoing pain management, need for IV fluids, further imaging, or care coordination).
- If the patient requires IV fluids, document whether dehydration is present.
- Document when there is need for IV pain medications. This can include the patient's pain scale if available.

Suggested Readings

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CASE 11

Judah, a 2-Year-Old Boy With Buttock Pain and Redness

CASE PRESENTATION

Judah is a 2-year-old boy who presents to the emergency department (ED) with 4 days of worsening redness, pain, and swelling to his left buttock. He saw his pediatrician 2 days ago and was prescribed cephalexin for a presumed skin infection. His symptoms have continued to worsen despite taking the cephalexin as prescribed. Over the last day, he has also had poor oral intake, decreased urine output, and fever. In the ED, he is started on intravenous (IV) clindamycin and fluids. The ED physician requests that you evaluate Judah for admission given that his symptoms have not responded to outpatient antibiotic treatment.

Patient History and Review of Systems

Q: What information should you collect from Judah's caregivers?

- History of present illness
  - Appearance of the affected area at symptom onset and progression over time
  - Presence of pustules, vesicles/blisters, or drainage from the site
  - Insect bites or other traumatic skin injury, including burns or possible foreign material at the site of involvement
  - Amount of pain and home pain control measures
  - Amount of recent oral intake and number of wet diapers in the past 24 hours
  - Onset, duration, and height of fever
  - Dose and frequency of cephalexin
  - Associated symptoms, such as vomiting, diarrhea, or other skin rashes
- Medical history, including underlying health status, any history of similar episodes, and immunization status
- Medications, including any over-the-counter medications
- Social history, especially travel history, water-related activities, and animal contact
  - Sick contacts, including attendance to child care
  - History of contact/exposure with individuals who work in health care facilities, child care, the housekeeping industry, correctional facilities, livestock settings, and veterinary clinics
- Family history of skin or soft tissue infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) infections

CASE  FOCUS

History and Review of Systems

From your conversation with Judah's parents, you learn that they first noticed something was wrong when he started to fuss and say "ouchie" during diaper changes. They initially noticed a quarter-sized red bump on his left buttock, to which they began to apply a topical antibiotic. However, the redness continued to enlarge, and Judah developed several other small, pimple-like lesions on his buttocks. At that time, his parents took him to the pediatrician where he was given cephalexin, which he has now been taking for 48 hours as prescribed. Unfortunately, the redness has continued to progress, and Judah has been refusing to sit on his left buttock due to pain. Over the last day, his parents have noticed that he has not been eating or drinking well, and his morning diaper was not as full as usual. This morning, he woke up with a fever of 38.5 °C (101.3 °F), which prompted their visit to the ED. In the ED, Judah has remained fussy and pushes away any fluids that are offered. Judah has had no other associated symptoms.

A few months ago, Judah was treated in another ED for a similar episode and was found to have an abscess on his right buttock. At that time, he underwent incision and drainage in the ED and was sent home with antibiotics. He recovered well, but his parents cannot recall the name of that antibiotic.

Other than the current prescription for cephalexin and the use of topical antibiotics, Judah does not take any medications regularly. The family has been giving him acetaminophen and ibuprofen for pain. His immunizations are up to date, and he has no chronic medical conditions.

Judah has not traveled recently. His parents have not noticed any insect bites and deny the possibility of a burn or foreign material. He does take swim lessons once a week, and his family owns 1 dog that lives indoors, but the dog does not have fleas. He has not had any recent sick contacts but does attend child care. His mother and older sister have a history of skin abscesses, but they are unsure if they were tested for MRSA. No one in the household has any of the occupations that you mention during your conversation.

Physical Examination

Q: What parts of the physical examination should you focus on for Judah?

- Complete set of vital signs
- Mental status: level of consciousness and ability to arouse normally
- Skin: erythema, tenderness, warmth, induration, edema, drainage, fluctuance, rash, pustules, streaking
- Eyes: sunken, erythematous, presence or absence of tears with crying
- Oral mucosa: moist, sticky, or dry
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses

CASE  FOCUS

Physical Examination

Before starting your examination, you note Judah's vital signs in the ED, which include a low-grade fever of 38 °C (100.4 °F), mild tachycardia with a heart rate of 149 beats/min, a respiratory rate of 25 breaths/min, and a normal blood pressure of 90/55 mm Hg.

CASE FOCUS

Physical Examination *(continued)*

Judah is alert but fearful and hesitant to let you examine him. He is wearing only a diaper, and you observe that his head, trunk, and extremities are without rashes or skin changes. His eyes appear normal, and he is producing tears when crying. His oral mucosa is sticky, but his peripheral pulses and capillary refill time are normal. His extremities are warm to the touch. On his buttocks, he has multiple small pustules bilaterally. On his left buttock, he has a circular area of erythema and induration that is approximately 4 cm × 4 cm. In the center of this lesion there is a 2 cm × 2 cm circular nodule, which is fluctuant and exquisitely tender to touch. It is at least 5 cm from his anal verge. There is no skin breakdown or bullae, and the Nikolsky sign is negative. He stands and ambulates normally without a limp. He appears neurologically intact without focal deficits. His cardiac, pulmonary, and abdominal examinations are normal.

Differential Diagnosis

Q: What is the differential diagnosis for a child with acute onset of localized skin erythema and tenderness?

There are many causes of localized skin erythema and tenderness; however, the etiologies can be narrowed based on a complete history and thorough physical examination. Table 11.1 demonstrates a differential diagnosis for these symptoms and has been separated into diagnoses that appear more or less likely for Judah.

Table 11.1. Differential Diagnosis for a Child With Acute Onset of Localized Skin Erythema and Tenderness

Diagnoses of highest suspicion	• Cellulitis • Erysipelas • Folliculitis, furuncles, and carbuncles • Skin and soft tissue abscess[a]
Other diagnoses to consider	• Candidal or bacterial intertrigo • Contact or irritant dermatitis • Drug eruptions, particularly a fixed drug eruption • Eczema with bacterial or viral superinfection • Erythema migrans (from *Borrelia burgdorferi*) • Erythema nodosum • Herpes simplex infection • Herpes zoster • Impetigo or ecthyma • Lymphadenitis • Necrotizing fasciitis • Osteoarticular infections • Reaction to Hymenoptera sting, spider bite, or vaccination • Septic bursitis • Thermal injuries

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with acute onset of localized erythema and tenderness?

- The diagnostic evaluation will vary by patient presentation; however, often the diagnosis can be made clinically, and testing is not needed.
- Judah has skin redness, tenderness, fluctuance, and fever, and therefore a bacterial skin and soft tissue infection (SSTI) appears most likely.
- For any patient with an SSTI, when purulent material or drainage is present, obtaining a culture of the material is important to inform antibiotic therapy.
- In general, serum laboratory testing for patients with SSTI in not indicated; however, the following scenarios may warrant blood cultures and serum electrolytes, renal function, and liver function tests. Clinicians may also consider obtaining inflammatory markers and coagulation studies for some patients as follows:
  - Patients with complicated SSTIs, which are defined as surgical site infections, traumatic wound infections, infections that require advanced surgical intervention, infected ulcers, or infected burns.
  - Patients in whom there is concern for severe sepsis or septic shock.
  - Patients who are immunocompromised.
  - Patients with a suspected necrotizing skin or soft tissue infection. Signs may include rapidly worsening erythema, edema extending beyond the erythema, severe pain, fever, crepitus, skin bullae, necrosis, or ecchymosis.
- Most patients with SSTIs do not require diagnostic imaging. Indications for imaging may include the following:
  - Soft tissue ultrasonography can be helpful to assess abscess formation or to determine the size and location of an abscess prior to a drainage procedure.
  - Radiography or ultrasonography can be useful to look for underlying radiopaque and nonradiopaque foreign bodies, respectively.
  - Contrast-enhanced computed tomography or magnetic resonance imaging of the soft tissue may be considered in cases of suspected necrotizing infection but should not delay prompt surgical evaluation and broad-spectrum antimicrobial therapy. Magnetic resonance imaging with contrast can also be used to evaluate for osteomyelitis when there is clinical concern.

CASE FOCUS

Diagnostic Evaluation

Given that Judah's left buttock lesion is fluctuant, your suspicion for a well-defined abscess is high, and you do not think any imaging is needed. Additionally, because he is immunocompetent and his infection appears uncomplicated, you decide to continue your assessment without ordering any immediate diagnostic testing.

Arriving at a Diagnosis

Q: How do you develop an assessment for Judah?

In developing Judah's assessment, you would like to interpret the key findings from his history and examination, evaluate his hydration status, and apply his age-based sepsis criteria. From there, you will generate a list of his findings, narrow the differential diagnosis, and consider admission criteria.

1. **Interpret key findings from the history and examination.**
   - History and examination: Judah is an immunocompetent patient with a history of an abscess requiring drainage and a family history of SSTI. Outpatient antibiotic therapy failed to improve his symptoms. His examination shows folliculitis and a clearly defined abscess without drainage and with surrounding erythema and induration.
   - Hydration status: You determine Judah has mild to moderate dehydration based on his history and physical examination. Refer to Table A.2 in the Appendix for the Centers for Disease Control and Prevention dehydration assessment.
   - Assessment for sepsis: Judah meets his age-based criteria for sepsis based on the presence of fever greater than 38.5 °C (101.3 °F), tachycardia, and tachypnea in the setting of a suspected infection. He does not have any features of severe sepsis or septic shock. Refer to Section IV in the Appendix for the age-based criteria for systemic inflammatory response syndrome and sepsis.
2. **Develop the list of findings.**

Q: What are the major findings you have identified for Judah?

- Probable sepsis (fever, tachycardia, and tachypnea in the setting of a suspected infection)
- Left buttock abscess with surrounding cellulitis and areas of folliculitis
- Mild to moderate dehydration
- History of right buttock abscess requiring incision and drainage

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Judah's presentation?

Judah appears to have an SSTI. SSTIs are generally divided into purulent and nonpurulent categories because the etiologies and empiric treatment options differ between the two.

- Purulent SSTIs generally present as painful, fluctuant, and erythematous nodules with or without surrounding cellulitis. Purulent SSTIs include abscesses, furuncles (involving a hair follicle), and carbuncles (involving multiple hair follicles). Incision and drainage is the treatment of all 3 purulent SSTIs.
- Nonpurulent SSTIs present as an area of skin erythema, edema, and warmth without a focus of purulence. Patients may have fever and other systemic findings. Nonpurulent SSTIs include cellulitis, erysipelas, and necrotizing infections.
  - Cellulitis and erysipelas develop as a result of bacteria entering the skin. Cellulitis involves the deeper dermis and subcutaneous fat, whereas erysipelas involves the upper dermis and superficial lymphatics. In erysipelas, there is clear demarcation bordering involved and uninvolved tissue, resulting in what is sometimes referred to as a *butterfly pattern*. Cellulitis and erysipelas commonly involve the extremities and are nearly always unilateral. Bilateral involvement should prompt workup for other diagnoses.
  - Necrotizing SSTIs are severe, life-threatening infections involving necrosis of the fascia, muscle, or skin. These infections are rare in children and may manifest with altered mentation, soft-tissue edema, erythema, severe pain, fever, crepitus, and skin bullae or necrosis. Accurate diagnosis and treatment must include early surgical intervention and antibiotic therapy.
  - Factors that may help differentiate necrotizing SSTI from cellulitis/erysipelas are recent surgery, pain out of proportion to clinical signs, hypotension, severe edema, skin necrosis, and hemorrhagic bullae.

Given that Judah's skin findings are localized, have worsened over the course of several days, and he has no blisters or bullae, you are confident that he has an underlying abscess with surrounding cellulitis. Other diagnoses such as nonpurulent cellulitis or necrotizing fasciitis are unlikely.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with an SSTI?

The majority of patients with SSTIs can be managed as outpatients; however, clinicians should consider hospitalization for patients with SSTIs in the following scenarios:

- There has been no improvement after 48 hours of appropriate outpatient antibiotics.
- There is rapid expansion of the lesion or a lesion more than 3 cm in diameter.
- The patient is unable to tolerate oral intake, including oral antibiotics.
- The patient has systemic symptoms, such as fever or meeting sepsis criteria.
- There is significant pain or wound care needs.
- The patient has immunocompromised status.
- There is concern for a deeper or necrotizing infection.

You determine that Judah meets the criteria for hospitalization based on his systemic symptoms (sepsis), inadequate oral intake, and lack of improvement despite outpatient antibiotic therapy.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Judah is a 2-year-old boy with a prior right buttock abscess who presented with a suspected left buttock abscess with surrounding cellulitis, probable sepsis, and mild to moderate dehydration. He requires incision and drainage and hospitalization for rehydration with IV fluids and IV antibiotics to treat his infection.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goals of treatment for purulent SSTIs are to perform drainage of the lesion and determine if antimicrobial therapy is indicated. For Judah, you will also need to develop a plan to address his dehydration.

1. **Incision and drainage:** Given the evidence of a subcutaneous abscess, you determine that incision and drainage of Judah's lesion is necessary. Because incision and drainage is a painful procedure, you first review your options for procedural sedation and the technique for incision and loop drainage.
   - Procedural sedation: Sedating children for procedures creates a safe and humane environment for conducting appropriate medical care. Sedation that does not require general anesthesia can occur in the ED, intensive care unit, hospital ward, and other clinical settings. The goal of procedural sedation can be pain relief, anxiolysis, or both. The provider conducting the sedation must have the appropriate training and hospital privileges and be able to manage possible complications, including hemodynamic instability, respiratory depression, and airway compromise. Patients with underlying respiratory, upper airway, neurologic, or cardiac conditions may be poor candidates for procedural sedation without the presence of an anesthesiologist.
     - Fasting: The practice of fasting prior to sedation (nil per os [nothing by mouth] status) was developed to reduce the risk of pulmonary aspiration of gastric contents. Recommendations by the American Society of Anesthesiologists suggest nil per os status for 2 hours after clear liquids; 4 hours after human (breast) milk; 6 hours after nonhuman milk, formula, or light meals; and 8 hours after fatty meals.

- Equipment and monitoring
  - Equipment must be age- and size-appropriate and include oxygen, suction, medications, a bag-mask ventilation device, and intubation equipment. Necessary monitors include pulse oximetry, capnography, and cardiac monitors. Blood pressure should be determined before sedation begins and at 5-minute intervals during sedation.
  - The most common serious side effect of procedural sedation is respiratory depression; therefore, monitoring of respiratory status (chest rise, auscultation, oxygenation, and capnography) is important.
- Medication choices
  - There are many options for oral, intranasal, and IV medications to achieve sedation and pain relief. Table 11.2 lists some common medications, their indications, contraindications, and common side effects.
  - If opioids or benzodiazepines are used, it is important to have quick access to the reversal agents naloxone or flumazenil, respectively.

- Abscess drainage: Although there are different methods of performing incision and drainage procedures, you decide to perform the loop drainage method. With this method, no packing material is used in the abscess cavity. The loop drain can be removed in 7 to 10 days once drainage has stopped and cellulitis has improved. For a list of indications, contraindications, and risks of incision and drainage, refer to Section V of the Appendix.

2. **Further testing:** During incision and drainage, it is important that purulent material be collected and sent for Gram stain and culture.

Table 11.2. Common Medications for Procedural Sedation in Pediatrics

Drug (class)	Indications	Absolute contraindications[a]	Relative contraindications	Side effects
Morphine or fentanyl (opioids)	Analgesia; may cause sedation at higher dosages	—	—	Respiratory depression, hypotension, nausea, pruritus
Midazolam (benzodiazepine)	Anxiolysis, sedation, anterograde amnesia	Hypotension or potential for cardiovascular collapse, narrow-angle glaucoma	Renal failure, CHF	Respiratory depression, hypotension, disinhibition with paradoxical excitement
Ketamine (dissociative agent and analgesic)	Dissociative state and analgesia	Age ≤3 months, psychosis	Elevated ICP or IOP, age ≤12 months, laryngeal stimulation, laryngospasm, URTI, active asthma, cardiac disease, porphyria, thyroid disease, seizure disorder	Unpleasant emergent reaction, nausea, hypersalivation, laryngospasm; random movements may occur, so not ideal for CT or MRI sedation
Diphenhydramine (antihistamine)	Sedation, adjunct to opioids to prevent histamine release	Nonreversible; do not use in neonates, premature infants, or if a child's neurologic status needs to be followed	—	May cause hallucination in overdose

Abbreviations: CHF, congestive heart failure; CT, computed tomography; ICP, intracranial pressure; IOP, intraocular pressure; MRI, magnetic resonance imaging; URTI, upper respiratory tract infection.

[a] In addition to hypersensitivity.

3. **Antimicrobial therapy**
   - For simple abscesses without significant surrounding cellulitis, the potential risks and benefits of antibiotics after incision and drainage should be discussed with the patient and/or their guardian.
     - Possible benefits: Evidence suggests that use of antibiotics after incision and drainage (when compared to incision and drainage alone) leads to a mild improvement in pain, decreased risk of treatment failure, and decreased risk of abscess recurrence.
     - Possible risks: Antibiotics may have unwanted side effects, including nausea and diarrhea, and may lead to the development of antibiotic resistance.
   - If starting antibiotic therapy, antibiotics should be tailored toward the most common etiology and local resistance patterns. Duration of therapy is generally 5 to 14 days, depending on the severity of the infection and the response to treatment.

Q: What are common infectious etiologies of uncomplicated SSTI in childhood?

- Table 11.3 lists various SSTIs with their most common etiologic organisms and examples of empiric treatment options. As demonstrated, group A streptococcus (GAS) and *S aureus* are the most common organisms causing uncomplicated SSTI; however, their prevalence varies based on the type of infection.
- Local antibiograms are useful in treatment decisions, especially in cases of suspected *S aureus*. Different geographic regions encounter MRSA more frequently than others, so empiric treatment of MRSA may be warranted for certain patients. An additional consideration for empiric coverage of *S aureus* is the rising prevalence of clindamycin resistance, which limits the utility of this antibiotic in many regions.
  - For suspected MRSA, empiric options include clindamycin, trimethoprim-sulfamethoxazole, a tetracycline (doxycycline or minocycline), and linezolid.

Table 11.3. Etiology, Diagnostic Evaluation, and Treatment of Different SSTIs

Suspected diagnosis	Causative organisms	Empiric treatment
Impetigo Ecthyma	GAS and *Staphylococcus aureus* (MSSA is more common than MRSA)	Empiric systemic options: cephalexin, clindamycin, or amoxicillin-clavulanate Empiric topical options: mupirocin or retapamulin Impetigo: topical if localized; systemic if numerous Ecthyma: systemic antibiotics for 7 days
Purulent infections Cutaneous abscesses Furuncles Carbuncles Inflamed epidermoid cysts	*S aureus* (most common) GAS (less common)	Incision and drainage Systemic antibiotics when fever or sepsis is present Coverage for MRSA recommended if prior treatment failure, severe sepsis, abnormal host defenses
Nonpurulent infections Cellulitis Erysipelas	Streptococci (mostly GAS, which is the most common cause of nonpurulent infections) *S aureus* (less common)	For mild infections (ie, no systemic symptoms/sepsis), empiric coverage for GAS and MSSA is reasonable

Table 11.3. Etiology, Diagnostic Evaluation, and Treatment of Different SSTIs *(continued)*

Suspected diagnosis	Causative organisms	Empiric treatment
Surgical site infections	MSSA, MRSA, gram-negative bacteria and anaerobes	Incision and drainage with suture removal Systemic antibiotics when SIRS/sepsis is present First-generation cephalosporin or antistaphylococcal penicillin for MSSA Coverage for MRSA recommended if nasal colonization, prior MRSA infection, recent hospitalization, or recent antibiotic use Coverage for gram-negative bacteria and anaerobes following operations on the axilla, GI tract, perineum, or female GU tract
Necrotizing infections	Mixed infections, *S aureus*, *Streptococcus pyogenes*, *Clostridium* spp, *Aeromonas hydrophila*, *Vibrio vulnificus*	Prompt surgical evaluation and treatment Broad empiric antibiotics as infection may be polymicrobial or monomicrobial Penicillin + clindamycin for documented GAS necrotizing fasciitis
Human bites	Mixed infections, *Eikenella corrodens*, *S aureus*,[a] *S pyogenes*, and *Corynebacterium* spp	Antibiotic prophylaxis, which should include empiric coverage of human oral and skin flora First-line choice: amoxicillin-clavulanate
Animal bites	*S aureus*, *S pyogenes*, *Pasteurella*, *Capnocytophaga*, *Moraxella*, *Corynebacterium*, *Neisseria*, and anaerobic bacteria	Prophylactic antibiotics are not indicated for all bites but are warranted for any of the following types of wounds: ● Wounds that have undergone primary closure ● Moderate or severe bite wounds or puncture wounds (especially if there is penetration of bone, tendon sheath, or joint) ● Bites to the face, hands, feet, or genital area ● Wounds sustained by victims who are immunocompromised or asplenic First-line choice: amoxicillin-clavulanate Appropriate tetanus and rabies prophylaxis as indicated

Abbreviations: GAS, group A streptococcus; GI, gastrointestinal; GU, genitourinary; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; SIRS, systemic inflammatory response syndrome.

[a] *S aureus* is isolated in 30% of human bite wounds and is associated with more severe infection.

- Although GAS is generally sensitive to penicillins, cephalosporins, and clindamycin, treatment of methicillin-susceptible *S aureus* (MSSA) requires use of penicillinase-resistant penicillins such as dicloxacillin, nafcillin, oxacillin, and amoxicillin-clavulanate. Cephalosporins (preferably first- or second-generation) and doxycycline are other options for empiric treatment of suspected MSSA. For some regions, use of clindamycin is an option as well.
- In many geographic regions, trimethoprim-sulfamethoxazole provides good coverage for MSSA and MRSA; however, its use for GAS is limited based on a lack of data.

4. **Dehydration:** For patients with dehydration, rehydration and maintenance of hydration can be done orally or via nasogastric tube, if tolerated. Refer to Case 1 for more information on the treatment of dehydration and maintenance of hydration. Given Judah's dehydration, inability to tolerate fluids, and your plan for incision and drainage, you decide to perform rehydration and maintenance hydration via IV fluids. After the procedure, you will encourage him to start taking fluids by mouth.
5. **Monitoring:** During procedural sedation, patients should be monitored on continuous pulse oximetry. The use of capnography should also be considered. A sedation-trained nurse is needed to monitor the patient's airway and vital signs. Afterward, frequent reassessments are needed to monitor for improvement of infection, monitor intake and output, and to ensure stabilization of vital signs.
6. **Indications for consultation**
   - Surgery: For patients who experience worsening pain or erythema, persistent fevers, or when there are concerns for a necrotizing infection, a surgical specialist should be consulted.
   - Infectious disease: If the infection is atypical in appearance, growing uncommon or resistant pathogens, or not improving with antibiotics, involvement of an infectious disease specialist should be considered.
7. **Discharge planning:** Patient caregivers should be educated about how to care for the site of the incision and drainage, such as keeping the wound site clean and covered at home. Patients and families should be provided return precautions for signs of reinfection, sepsis, and dehydration.

CASE FOCUS

Plan for Treatment and Monitoring

- **Incision and drainage:** You decide to perform incision and drainage of the lesion with loop drainage technique prior to Judah's admission to the inpatient unit, and the attending ED physician has agreed to provide procedural sedation using ketamine. A nurse will provide close monitoring during the procedure.
- **Further testing:** You plan to collect a sample of the exudate from the lesion and have ordered a Gram stain and bacterial culture. No other laboratory tests are needed at this time.
- **Antimicrobial therapy:** You discuss with Judah's family the risks and benefits of treating him with antibiotics, and together you decide to start empiric IV antibiotics. You order both cefazolin and clindamycin to provide coverage for MSSA, GAS, and MRSA.
- **Diet and dehydration:** Judah will remain nil per os for the procedure. You order a 20 mL/kg normal saline bolus and start maintenance IV fluids. After the procedure, you will advance Judah's diet.
- **Monitoring:** Judah requires continuous monitoring during the procedure and recovery period. Given the presence of sepsis criteria, you will initially perform frequent reassessments to monitor for progression to severe sepsis or septic shock. As his vital signs stabilize, you will transition to monitoring Judah's vital signs every 4 hours and routine monitoring of his intake and output.
- **Discharge planning:** Education about home wound care will be provided to Judah's family, and follow-up with the primary care physician (PCP) for reassessment and drain removal should be established.

Case Resolution

Judah tolerates the incision and drainage procedure well, and a sample of the lesion's exudate is collected for Gram stain and culture. Afterward, Judah is admitted to the inpatient unit on maintenance IV fluids and empiric IV antibiotics. His vital signs stabilize after his normal saline bolus. The following day, the area of erythema surrounding the abscess site has improved and regressed from the lines you drew around the site. Judah's oral intake starts to increase and his tachycardia resolves, and thus you are able to discontinue his IV fluids. The next day, his wound culture grows clindamycin-sensitive MRSA, and you therefore discontinue cefazolin but continue clindamycin. Judah is afebrile and shows continued improvement in his erythema and pain. His oral intake is near baseline, and his parents express comfort with his wound care at home. He is discharged home on hospital day 3 with plans to follow up with his PCP in the coming days for reevaluation and eventual drain removal.

Discharge Criteria

Q: How do you know when Judah is ready to go home?

You can feel comfortable discharging your patient with an SSTI when the following criteria are met:

- The lesion is significantly improved and any abscess has been drained.
- The patient's fever curve is improving.
- The patient is tolerating oral intake.
- Pain is controlled with oral medications.
- The patient demonstrates the ability to bear weight or use the involved extremity.
- Follow-up with the PCP is assured.

Anticipatory Guidance

Q: What instructions should you provide to Judah's caregivers upon discharge?

- Complete the entire course of antibiotics as prescribed.
- Follow up with Judah's PCP within 48 hours.
- Recurrent *S aureus* SSTI is common in children within 1 year, and *S aureus* infections tend to cluster within households (likely due to colonization of family members and household environmental surfaces). As such, the family should discuss home decolonization measures with their PCP.

Clinical Pearls

- SSTIs are common in pediatric populations.
- Most SSTIs do not require additional workup unless the patient is toxic in appearance, has signs of systemic infection, or has additional risk factors (such as young age or immunocompromised status), or when the physical examination is equivocal for an abscess.

- Purulent infections are most commonly caused by *S aureus*, and the mainstay of treatment is drainage with or without antibiotic therapy.
- Nonpurulent infections are most commonly caused by GAS, and the mainstay of treatment is antibiotics.
- Acute worsening in skin and systemic findings should prompt consideration of a necrotizing infection and immediate involvement of the surgical team.

Documentation Tips

- Document sepsis, if present.
- Document failure of outpatient treatment, when appropriate.
- Include a detailed description of the infection, presence of abscess, need for surgical drainage, and results of wound or blood cultures, if available.

Suggested Readings

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CASE 12

Maryam, a 4-Year-Old Girl With Fever and Cough

CASE PRESENTATION

Maryam is a 4-year-old girl with no significant medical diagnoses who presents to the emergency department (ED) for fever and cough. Upon presentation to the ED, her vital signs show that she is febrile with a temperature of 39.6 °C (103.3 °F), and her oxygen saturation is 86% on room air. She is placed on oxygen at 2 L/min via nasal cannula, which normalizes her saturations to 98%. Her oxygen requirement prompts the ED physician to request that you evaluate Maryam for admission.

Patient History and Review of Systems

Q: What information should you collect from Maryam and her caregivers?

- History of present illness
  - Onset, duration, and frequency of cough and fever
  - Evolution of symptoms since illness onset
  - Quality of cough (eg, dry, productive, barking)
  - Signs of increased work of breathing (eg, nasal flaring, head bobbing, retractions, belly breathing, grunting)
  - Palliating and provoking factors of symptoms
  - Recent respiratory infections or history of choking
  - Sick contacts and exposure details: household members, school, child care, travel, *Mycobacterium tuberculosis*, tobacco or other smoke
- Associated symptoms, such as tachypnea, rhinorrhea, congestion, wheezing, stridor, sore throat, chest pain, cyanosis, anorexia, altered mental status, rash, or posttussive emesis
- Medical history
  - Underlying health status and birth history, specifically noting any history of asthma, sickle cell disease, immunodeficiency disorders, premature birth and bronchopulmonary dysplasia, neuromuscular disorders and other aspiration risks, congenital heart disease, or cystic fibrosis
  - Similar past illnesses
  - Recent hospitalizations, to assess risk of nosocomial pathogens
  - Vaccination status, including pneumococcal, *Haemophilus influenzae* type b, pertussis, influenza, measles, and varicella vaccines

- Recent medications, including over-the-counter medications, supplements, antibiotics, or other prescription medications
- Family history, especially of respiratory conditions or immunodeficiency disorders

CASE FOCUS

History and Review of Systems

Upon meeting Maryam and her parents in the ED, you learn that Maryam first developed a cough 7 days ago and fever 2 days ago. Prior to developing fever, she had 5 days of rhinorrhea, congestion, and cough, but her behavior and temperament were otherwise normal. Maryam has had several fevers between 38.8 °C (101.8 °F) and 39.4 °C (102.9 °F) over the past 2 days. Her cough sounds wet to her parents, but they have not seen her cough up any sputum. She coughs several times per hour, and the cough seems to be increasing in frequency. Maryam's mother tried giving her "natural cough medicine" containing honey, with no improvement. This morning, her parents noticed that Maryam was breathing faster than normal and taking large breaths with her belly, prompting them to bring her to the ED. Maryam has never had these types of symptoms previously, though her older brother had similar symptoms as an infant when he was hospitalized and diagnosed with bronchiolitis. Maryam appears too shy to answer questions about how she is feeling but nods her head "yes" when asked if she is feeling sick.

Maryam's parents state she has not had any associated wheezing, stridor, or cyanosis. They are unsure if she has a sore throat. They say she has occasionally complained of poorly localized pain in her chest and abdomen. She has had minimal appetite, had an episode of emesis yesterday, and has been drinking less than she normally does. She has had decreased urine output, down to 2 voids over the past 24 hours from her baseline of 4 to 5. She has appeared tired and less playful but is still acting like herself overall. They have not seen any rashes.

Maryam's parents say she was born full term with no perinatal complications. She has no other medical conditions and has never been hospitalized. She is up to date on her vaccines after a recent visit to her pediatrician following her fourth birthday. She takes a multivitamin daily, and during this illness she has taken acetaminophen, ibuprofen, and "natural cough medicine" 1 to 2 times per day as needed. Other than occasional viruses, she has not had any recent illnesses or taken any antibiotics. She does not have any known sick contacts, though she does attend preschool. She lives at home with her mother, father, 2 older siblings, 1 younger sibling, and 2 maternal grandparents. Everyone at home is generally healthy, though her maternal grandparents both have hypertension, and her maternal grandfather has diabetes. Everyone in the house has had the occasional cold this winter. No one at home smokes. The family has no known contacts with tuberculosis and has not traveled in the past 3 months.

Physical Examination

Q: What parts of the physical examination should you focus on for Maryam?

- Complete set of vital signs
- General appearance: level of consciousness and activity
- Head, eyes, ears, nose, and throat: associated conjunctivitis, otitis media, and pharyngitis
- Signs of hydration status: sunken eyes, ability to produce tears, and mucous membranes (moist, sticky, or dry)
- Cardiovascular: murmurs or gallops, peripheral perfusion (peripheral pulses and capillary refill time)
- Respiratory: inspection of the chest wall, chest expansion, respiratory rate, work of breathing (eg, nasal flaring; head bobbing; suprasternal, subcostal, or intercostal retractions; abdominal breathing; grunting), auscultation and percussion of the anterior and posterior lung fields
- Skin: rashes and other lesions

CASE FOCUS

Physical Examination

Maryam's fever is down to 38.4 °C (101.1 °F) after receiving a dose of ibuprofen 1 hour ago. She is tachycardic with a heart rate of 137 beats/min. She has tachypnea with a respiratory rate of 52 breaths/min, and her oxygen saturation is 97% on 2 L/min nasal cannula. She is normotensive.

Maryam appears fatigued but is responsive to your examination and interactive with her parents and siblings in the room. Her head, eyes, ears, nose, and throat examination is normal, with the exception of slightly sticky mucous membranes and the absence of tears. Her eyes are not sunken. She is tachycardic on cardiac examination but has no rhythm abnormalities or murmurs. She has weak radial and pedal pulses, and her capillary refill is mildly prolonged at 3 seconds. On her respiratory examination, Maryam is tachypneic, though her parents note that she looks more comfortable now, after being started on the nasal cannula. She displays subtle nasal flaring and mild suprasternal and subcostal retractions. She has symmetric chest wall expansion and no apparent chest wall abnormalities. Pulmonary auscultation is notable for the presence of decreased breath sounds and fine crackles at her right posterior lower lung field. There is dullness to percussion at the right lower lung field as well. Her abdomen is soft and nondistended with no tenderness to palpation. She has no significant skin findings, and the remainder of her examination is unremarkable.

Differential Diagnosis

Q: What is the differential diagnosis for a child with fever, cough, and difficulty breathing?

The differential diagnosis for a child with respiratory distress is shown in Table 12.1 and is divided into causes that seem more and less likely based on Maryam's presentation.

Table 12.1. Differential Diagnosis for a Child With Respiratory Distress

Diagnoses of highest suspicion	Pneumonia (bacterial,[a] atypical, viral, fungal)
Other diagnoses to consider	• Asthma exacerbation • CF • Foreign body aspiration • Intra-abdominal pathology causing diaphragmatic irritation • Myocarditis or congestive heart failure • Pertussis • Pneumonitis (chemical or otherwise) • Pulmonary TB infection • Rheumatologic processes (in older patients; eg, sarcoidosis, systemic lupus erythematosus, and granulomatosis with polyangiitis) • Viral URTI, including croup

Abbreviations: CF, cystic fibrosis; TB, tuberculosis; URTI, upper respiratory tract infection.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is indicated for patients who present with fever, cough, and difficulty breathing?

Maryam's respiratory distress, hypoxemia, and pulmonary examination findings make you most suspicious of a lower respiratory tract infection (LRTI) such as pneumonia. The diagnostic evaluation of patients with suspected pneumonia differs based on both the severity of their illness and the suspected etiology.

- Mild illness: For children with fever, cough, and difficulty breathing who are well appearing and do not require hospitalization, a laboratory and/or radiographic evaluation may be unnecessary. The diagnosis of the most common etiologies of these symptoms in the pediatric population, such as viral upper respiratory tract infections (URTIs), viral bronchiolitis, or community-acquired pneumonia (CAP), can usually be made clinically, based solely on the patient's history and examination. Viral testing can occasionally be useful to aid in diagnosis or treatment, especially if the identification of certain infections would alter management, such as with influenza. A 2-view chest radiograph is also recommended for patients with pneumonia who are not improving on empiric antibiotics. However, most of the time, symptomatic management or oral antimicrobials (if needed) can be initiated without further evaluation.
- Moderate to severe illness: Children with signs of respiratory distress and/or sustained hypoxemia with oxygen saturations below 90% generally require hospitalization and further diagnostic evaluation. Diagnostic evaluation is guided by the suspected etiology of LRTI.
  - Suspected viral etiology: Otherwise healthy patients with a suspected viral LRTI (eg, bronchiolitis, viral pneumonia) who are being hospitalized related to poor oral intake, mild hypoxemia, or respiratory distress may not require any diagnostic evaluation and can generally be managed empirically. However, those with more severe illness concerning for pending or acute respiratory failure or who have an unclear diagnosis may benefit from further testing, including chest radiographs and serum laboratory studies, depending on the clinical scenario. Rapid viral testing should also be considered, especially if the results would impact clinical management decisions.
  - Suspected bacterial etiology: In patients with moderate to severe LRTI symptoms and suspected bacterial etiology (bacterial CAP), the following evaluation should be considered:
    - Chest radiograph: A 2-view chest radiograph (posteroanterior and lateral) is recommended for CAP requiring admission because it provides an assessment for the complications of pneumonia and other diagnoses in the differential.
    - Blood culture: Blood cultures are positive in only 2.2% of pediatric pneumonia cases, though the identification of certain organisms may aid in treatment decisions.
    - Sputum sample: Sputum for Gram stain and culture should be obtained if the patient is an older child or adolescent who is able to produce sputum.
    - Rapid diagnostic tests, such as respiratory pathogen panels using antigen detection or polymerase chain reaction, can be useful to identify viral and atypical bacterial causes of pneumonia and may help guide treatment. Clinicians should note that the presence of a viral pathogen on nasopharyngeal swab does not rule out the diagnosis of bacterial CAP, as coinfection is frequent. When considering whether you should order these tests, it is important to note that if the diagnosis of bacterial CAP is suspected based on the overall evaluation, the patient should be treated for bacterial pneumonia regardless of the panel results. The results of the respiratory pathogen panel may help indicate whether additional treatment with an antiviral medication or an antimicrobial covering organisms that cause atypical bacterial CAP may be helpful.
    - Complete blood cell count (CBC), particularly the white blood cell count, may be useful to inform clinical diagnosis and management in the inpatient setting.

— Additional testing that may be indicated by certain clinical scenarios includes the following:

- Basic metabolic panel (BMP) can be useful when there is concern about a patient's hydration, renal, or electrolyte status.
- Although not routinely obtained, acute-phase reactants, such as C-reactive protein concentration and erythrocyte sedimentation rate, can be used to help assess therapeutic response in complicated pneumonia; however, they are not reliable for distinguishing between bacterial and viral pneumonia.
- There is some evidence that obtaining a procalcitonin level aids in the diagnosis of pediatric CAP, but this has been studied primarily in the adult population. In pediatric patients, low procalcitonin levels can be used to help rule out bacterial CAP when it is clinically unclear whether a patient has viral or bacterial pneumonia.
- Obtaining a venous or capillary blood gas may help determine the need for escalating respiratory support in a patient with severe or worsening respiratory distress. The decision to escalate respiratory support is clinical, however, and should not be made based solely on the result of a blood gas.
- Invasive forms of testing, such as bronchoalveolar lavage, are only used in cases of severe or refractory CAP after blood and sputum cultures are not diagnostic.
- Lung ultrasonography or chest computed tomography (CT) can be used for further evaluation of radiographic findings or assessment of CAP complications. For example, in a patient with recurrent pneumonia in the same location, pulmonary sequestration could be evaluated with the use of CT.
- For patients with a subacute or chronic cough, concerning exposures, immunocompromising conditions, or other associated symptoms, testing for *M tuberculosis* or causes of fungal pneumonia, such as *Coccidioides* spp, may be indicated. Further workup in these cases is often done in collaboration with an infectious disease specialist.

CASE FOCUS

Diagnostic Evaluation

Based on Maryam's symptoms, examination findings, and oxygen requirement, you decide to order a chest radiograph, CBC, BMP, blood culture, and respiratory pathogen panel. You forgo sputum Gram stain and culture because of her age. A blood gas is not currently indicated given her improving symptoms on 2 L/min nasal cannula.

The results of Maryam's laboratory tests are as follows:

Laboratory test	Result	Reference range
	CBC	
WBC count	20,200/μL (20.2 × 10^9/L)	4,000–13,000/μL (4–13 × 10^9/L)
Hemoglobin	12.6 g/dL (126 g/L)	11.5–14.5 g/dL (115–145 g/L)
Hematocrit	37.9% (0.379)	33%–43% (0.33–0.43)
Platelet count	320 × 10^3/μL (320 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	71% (0.71)	35%–55% (0.35–0.55)
Absolute neutrophils	14,300/μL (14.3 × 10^9/L)	1,500–8,500/μL (1.5–8.5 × 10^9/L)
Lymphocytes	25% (0.25)	25%–33% (0.25–0.33)
Monocytes	2.5% (0.025)	3%–7% (0.03–0.07)
Eosinophils	1.5% (0.015)	1%–3% (0.01–0.03)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
BMP		
Sodium	132 mEq/L (132 mmol/L)	134–145 mEq/L (134–145 mmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	98 mEq/L (98 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	22 mEq/L (22 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	12 mEq/L (12 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	10 mg/dL (3.57 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.4 mg/dL (35.4 µmol/L)	0.2–0.4 mg/dL (17.7–35.4 µmol/L)
Glucose	83 mg/dL (4.61 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Infectious disease testing		
Respiratory pathogen panel by PCR[a]	Negative	Negative
Blood culture	Pending	No growth for 5 days
Imaging		
Chest radiograph (2-view)	Opacification of the right lower lobe. There is no pneumothorax. Normal cardiac size and bones.	

Abbreviations: BMP, basic metabolic panel; BUN, blood urea nitrogen; CBC, complete blood cell count; PCR, polymerase chain reaction; WBC, white blood cell.

[a] Respiratory pathogen panel by polymerase chain reaction tests for the presence of certain organisms in the nasopharynx, including *Mycoplasma pneumoniae*, *Bordetella pertussis* and *Bordetella parapertussis*, and the following viruses: respiratory syncytial virus, adenoviruses, influenza viruses, human rhinovirus/enteroviruses, human metapneumovirus, parainfluenza viruses, and coronaviruses (including SARS-CoV-2).

Arriving at a Diagnosis

Q: How do you develop an assessment for Maryam?

Maryam's symptomatology and diagnostic findings are consistent with pneumonia, but you realize the importance of thinking through your diagnosis and recognizing the other findings that should be addressed during Maryam's hospitalization.

1. **Interpret key findings on history and physical examination.**
   - History: Maryam has a worsening cough and high fever with preceding URTI symptoms. She also has recent onset of tachypnea and increased work of breathing without wheezing or stridor, as well as decreased oral intake and decreased urine output.

- Physical examination: On examination, Maryam has hypoxemia, fever, tachycardia, and tachypnea. She has signs of increased work of breathing including nasal flaring, retractions, and belly breathing. On her lung examination, she has crackles and dullness to percussion in the right posterior lower lung field. Additionally, she has signs of moderate clinical dehydration including sticky mucous membranes and absence of tears.

2. **Interpret diagnostic studies.**
   - Laboratory test results
     - Maryam has leukocytosis with neutrophilic predominance. This finding is characteristic, though not specific, for bacterial infection.
     - Maryam also has mild hyponatremia. Dehydration prompts appropriate increased antidiuretic hormone release to retain free water, which subsequently lowers serum sodium concentrations. Persistent hyponatremia in patients with pneumonia who have been sufficiently rehydrated may be due to the syndrome of inappropriate antidiuretic hormone secretion, a frequent complication of pulmonary infections.
     - A negative respiratory pathogen panel decreases, but cannot eliminate, concern for atypical bacterial and viral disease.
   - Imaging: The opacification in Maryam's right lower lobe on chest radiograph is consistent with a lobar consolidation. Lobar consolidations are characteristic, though not diagnostic, of bacterial pneumonia.
3. **Assess for sepsis.**
   - Maryam's fever, leukocytosis, and tachypnea in the setting of an infection are concerning for sepsis. Other than her decreased urine output, however, which is likely due to her dehydration, she has no signs of organ dysfunction or hypotension, so you are not concerned about septic shock at this time.
   - Refer to Section IV in the Appendix for age-based systemic inflammatory response syndrome and sepsis criteria.
4. **Develop the list of findings.**

Q: What major findings have you identified for Maryam?

- Right lower lobe lung consolidation
- Respiratory distress with hypoxemia
- At risk for sepsis
- Dehydration
- Hyponatremia

5. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Maryam's presentation?

Based on Maryam's history, examination, oxygen requirements, and chest radiograph findings, you are most suspicious of an LRTI, specifically CAP.

Q: What is CAP, and how is it diagnosed?

- Pneumonia is an infection located in the lung parenchyma, where pus and fluid collect in the alveoli. Pneumonia is described as *community-acquired* when it occurs in a previously healthy patient who contracted the disease outside of the hospital. Although much is understood about the pathology of pneumonia, there are no universally recognized diagnostic criteria.
- Pneumonia is commonly defined as fever and respiratory symptoms (cough, tachypnea, or respiratory distress) associated with evidence of parenchymal involvement on physical examination or radiography.

Q: What are the most common infectious etiologies of pediatric CAP? How do a patient's clinical features help clinicians differentiate among them?

CAP is caused by several different viruses, bacteria, and atypical organisms that occur at differing rates depending on a patient's age.

- Viral: According to the 2015 *New England Journal of Medicine* study involving US children hospitalized with CAP in the United States, viruses were present in 66% of CAP cases and are most frequently present in children younger than 1 year. The most common viral causes of CAP are respiratory syncytial virus, rhinovirus, influenza, parainfluenza, adenovirus, human metapneumovirus, and coronavirus.
  - In viral infections, fever, when present, usually appears early in the illness course. Over the following several days, rhinorrhea, cough, and other viral symptoms will continue while the fever typically resolves. Although these viral symptoms may persist for 1 to 2 weeks or longer, significant clinical worsening is generally uncommon after the first 5 days of illness.
  - In young children, viral CAP is usually characterized by gradually worsening symptoms over several days, a nontoxic clinical appearance, diffuse bilateral lung examination findings, wheezing, and interstitial, atelectatic, or peribronchial findings on chest radiograph. Positive findings on respiratory pathogen panel support the diagnosis of a viral etiology. It is important to note, however, that a positive result on respiratory pathogen panel does not rule out bacterial CAP.
- Bacterial: Bacteria alone (including atypical bacteria) and bacterial-viral coinfection account for 8% and 7%, respectively, of hospitalized pediatric CAP cases.
  - *Streptococcus pneumoniae* is by far the most common typical bacterial cause of CAP. *Staphylococcus aureus*, *Streptococcus pyogenes*, and *H influenzae* type b (in underimmunized children) are other common causes.
    - Clinical features of typical bacterial pathogens may include an abrupt onset of symptoms and focal pulmonary findings. When chest radiographs are obtained, lobar, round, and segmental consolidations are most characteristic of typical bacterial pathogens.
    - Routine immunizations against *S pneumoniae* and *H influenzae* type b have greatly decreased rates of invasive disease, including CAP, but pneumococcal infection continues to be prevalent. Several serotypes of *S pneumoniae* cause disease, prompting each iteration of pneumococcal vaccine to expand its coverage. The 13-valent pneumococcal conjugate vaccine (PCV13) is currently used for routine immunization of healthy children. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is used for children older than 2 years with certain medical conditions, including chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid leaks, and cochlear implants.
    - CAP caused by *S aureus* is important to recognize because of its association with severe presentations and complicated pneumonia, including necrotizing pneumonia, lung abscess, or pneumatoceles.
  - Atypical bacterial organisms, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, are significant causes of CAP in older children and adolescents. *M pneumoniae* is estimated to be the cause of disease in up to 6.5% of children and adolescents hospitalized with CAP. Most commonly, atypical CAP is characterized by constitutional symptoms and cough evolving over several days. Cough may be present for 3 to 4 weeks. A maculopapular rash is noted in approximately 10% of children infected with *Mycoplasma pneumoniae*. This type of pneumonia may be focal or diffuse, with crackles and wheezing. Pleural effusions are common, and hilar adenopathy may be present.
  - *M tuberculosis* infection should be considered for patients with chronic symptoms who have concerning risk factors (eg, travel to an endemic area, household exposure), or certain chest radiograph features. Chest radiograph findings may be nonspecific but can include interstitial cavities, miliary pattern infiltrates, or hilar, mediastinal, paratracheal, or subcarinal lymphadenopathy. Pleural effusions may be present, and infiltrates and atelectasis can be segmental or lobar.

- Fungal: Fungal pneumonia (eg, coccidiomycosis, blastomycosis, histoplasmosis) is an important consideration in patients presenting with pneumonia; however, these etiologies tend to be associated with more indolent/chronic symptoms, certain geographic regions, and other recreational or occupational exposures.

Q: Which key findings from Maryam's evaluation help you decide between viral, bacterial, or atypical bacterial causes of her illness?

- Maryam's abrupt symptom onset, moderate respiratory distress, and focal lung examination findings increase your suspicion for bacterial pneumonia. Supporting evidence from your diagnostic workup includes the leukocytosis on laboratory evaluation and the lobar consolidation on her chest radiograph.
- Maryam experienced several days of milder symptoms of cough and rhinorrhea followed by fever and clinical worsening, which is suspicious for a community-acquired bacterial pneumonia following a URTI. Maryam's presentation appears less consistent with an atypical bacterial or primary viral pneumonia given her age and focal findings, respectively.

Q: How do you assess the severity of Maryam's CAP?

- Mild CAP is characterized by a presentation that is suitable for outpatient treatment. Moderate CAP is diagnosed when a patient meets criteria for hospital admission. Severe CAP is established through major and minor criteria stated in the clinical practice guidelines on the management of CAP by the Pediatric Infectious Disease Society/Infectious Diseases Society of America.
- Severe CAP is indicated by 1 or more major or 2 or more minor criteria, as follows:
  - Major criteria include the need for invasive mechanical ventilation, shock refractory to fluid resuscitation, acute need for noninvasive positive pressure ventilation, or hypoxemia requiring fraction of inspired oxygen (F_{IO_2}) support that cannot be achieved in a general care area.
  - Minor criteria include respiratory rate higher than World Health Organization classification for age, increased work of breathing, P_{O_2}/F_{IO_2} ratio less than 250, multilobar infiltrates, Pediatric Early Warning Score greater than 6, altered mental status, hypotension, presence of effusion, comorbid conditions, and unexplained metabolic acidosis.
- Maryam meets 2 minor criteria, elevated respiratory rate and increased work of breathing, which classifies her as having severe CAP. Other clinical factors that indicate severe disease are cyanosis, prolonged capillary refill time, dehydration, and tachycardia. Of these, Maryam exhibits all except cyanosis.

6. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with CAP?

- The patient has moderate to severe CAP evidenced by respiratory distress, hypoxemia, or other vital sign abnormalities.
- The patient has CAP caused by an organism associated with increased virulence, such as methicillin-resistant *S aureus*.
- The patient presents with an effusion or complicated pneumonia.
- The patient is an infant younger than 3 to 6 months with suspected bacterial CAP.
- The patient has a medical history that places them at higher risk for severe or refractory pneumonia.
- Two to three days of outpatient therapy has failed.
- The patient presents with dehydration that cannot be addressed through enteral fluid resuscitation alone.

Maryam has severe CAP as evidenced by her levels of respiratory distress and hypoxemia. She also has clinical signs of dehydration. She therefore meets the criteria for inpatient admission.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Maryam is a fully immunized 4-year-old girl with no significant medical history presenting with fever, cough, and respiratory distress concerning for severe community-acquired bacterial pneumonia complicated by moderate dehydration. Her respiratory distress, oxygen requirement, and dehydration necessitate hospitalization for ongoing treatment, including parenteral antibiotics and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The management of CAP includes acute respiratory and hemodynamic support, antimicrobial treatment, and careful monitoring for clinical complications. You decide to divide treatment considerations into the following components:

1. **Respiratory support**
   - Nasal cannula and face masks are common methods of oxygen delivery. Clinicians should be familiar with their institutional policies regarding appropriate level of care based on the patient's respiratory support requirements; however, any patient with an oxygen saturation below 92% on F_{IO_2} greater than or equal to 0.5 should be admitted to the intensive care unit (ICU) for close monitoring and the ability to quickly escalate support if needed. The need for noninvasive ventilation using positive airway pressure or invasive mandatory ventilation for respiratory support is also an indication for ICU admission. If a patient's respiratory status is worsening and they require more support than a nasal cannula or simple mask, obtaining a venous or capillary blood gas may be helpful in guiding management.
   - A patient's work of breathing and oxygen saturation should be monitored closely to assess their response to the respiratory support being provided.
2. **Antimicrobials:** Although mild cases of pneumonia can be treated with oral antimicrobials, patients with pneumonia requiring hospitalization are started on parenteral treatment. Response to treatment can be expected within 48 to 72 hours of therapy, with a total duration of 7 to 10 days for uncomplicated CAP. Although there is no definitive timing for transition to oral antibiotic therapy, transition usually occurs 2 to 3 days after starting treatment, when there is clear evidence of improvement and the patient is tolerating oral intake.
   - Bacterial pneumonia
     - High-dose oral amoxicillin is the first-line choice for outpatient treatment of immunized patients with suspected mild bacterial CAP.
     - Ampicillin or penicillin G is the first-line intravenous (IV) therapy indicated for immunized patients in areas where local epidemiology demonstrates a low prevalence of penicillin-resistant *S pneumoniae*.
     - Third-generation cephalosporins (ie, ceftriaxone) are indicated for incompletely immunized patients or patients from a region with high levels of penicillin-resistant *S pneumoniae*. Vancomycin is an alternative option.
     - Vancomycin or clindamycin should be added to the therapeutic regimen if *S aureus* infection is suspected. Cefazolin or oxacillin are preferred if the *S aureus* strain detected is confirmed to be methicillin susceptible.

- Atypical bacterial pneumonia: Macrolide antibiotics, usually azithromycin, should be considered if atypical pathogens are suspected. Although there are some conflicting studies, recent evidence demonstrates that length of hospital stay for school-aged children is slightly decreased when a macrolide is added to the treatment regimen.
- Viral pneumonia: Supportive care alone is indicated in the majority of cases. Viral pneumonia caused by influenza that requires hospitalization should be treated with antiviral therapy, such as oseltamivir.

3. **Rehydration and maintenance fluids**
   - Oral rehydration is recommended over IV rehydration when possible in patients with dehydration because it is equally effective and associated with fewer complications; however, in many clinical scenarios, an ill patient is unable to keep up with their fluid requirement through oral administration. For such patients, nasogastric rehydration is an option.
   - For maintenance fluids, isotonic fluids should be used for all patients between 1 month and 18 years of age unless an alternative fluid is indicated by a specific clinical issue or chronic medical condition. Patients with pneumonia are at risk for syndrome of inappropriate antidiuretic hormone secretion, which can be exacerbated by iatrogenic hyponatremia from the use of hypotonic IV fluids. The utilization of isotonic fluids helps avoid this complication. Most patients within the aforementioned age range should also receive 5% dextrose if they present with anorexia. In the absence of anuria or renal disease, maintenance levels of potassium should be added to patients' fluids.
4. **Monitoring**
   - Patients hospitalized with respiratory distress or oxygen requirement should be on continuous pulse oximetry. Continuous cardiopulmonary monitoring is indicated for patients with severe pneumonia. Measuring vital signs every 4 hours is appropriate in a patient without an oxygen requirement who is not at risk for deterioration. Strict intake and output measurements should be recorded for any patient ill enough to require hospitalization, especially those with dehydration.
   - Maryam's respiratory status warrants continuous cardiopulmonary monitoring. Additionally, Maryam's weak pulses and prolonged capillary refill time are concerning findings, and her fluid status should be monitored closely with repeat examinations. Indications of severe systemic illness would alter monitoring and treatment protocols, including broadened antibiotic therapy.
5. **Diet:** Unrestricted diet for age as tolerated is appropriate for patients admitted for CAP unless the patient is exceptionally tachypneic or feeding exacerbates their respiratory distress. In those cases, nasogastric feeding or IV fluids may be warranted. Clinicians may also choose to utilize parenteral nutrition if the patient's nil per os (nothing by mouth) time is sufficiently prolonged or if warranted based on their nutritional status.
6. **Antipyretics and analgesia:** Acetaminophen and/or nonsteroidal anti-inflammatory drugs are appropriate to decrease illness-associated discomfort. Around-the-clock administration of antipyretics should be avoided because it may interfere with effective monitoring of a patient's fever curve. This is important to assess therapeutic response to their current antibiotic regimen.
7. **Further laboratory/diagnostic testing**
   - Repeat chest radiography is unnecessary in the treatment of uncomplicated CAP unless indicated by clinical decompensation, a lack of response to therapy, or concern for complication.
   - Other laboratory studies including white blood cell count, C-reactive protein level, and/or erythrocyte sedimentation rate can be useful to assess treatment response and monitor for complications. Periodic BMPs can be obtained to monitor for hyponatremia in the setting of pulmonary infection, other electrolyte derangement during IV fluid use, and renal function in the context of dehydration and sepsis.

CASE FOCUS

Plan for Treatment and Monitoring

- **Respiratory support:** Maryam exhibits improving respiratory distress and normal oxygen saturation on 2 L/min oxygen via nasal cannula. You plan to wean the support as tolerated or escalate as needed, depending on Maryam's respiratory status.
- **Antimicrobials:** You start Maryam on IV ampicillin because her presentation is characteristic of uncomplicated CAP with no sign of disease contribution from *S aureus*, atypical bacteria, or influenza.
- **Rehydration:** Given that Maryam has had decreased oral intake and already has an IV placed for her antibiotics, you administer a 20 mL/kg bolus of normal saline. You plan to reassess her signs of dehydration after the bolus to guide your decision to provide additional boluses. You then start maintenance IV fluids comprising 5% dextrose in normal saline with added potassium chloride at 54 mL/h.
- **Monitoring:** You order continuous cardiopulmonary monitoring, vital signs every 4 hours, and strict monitoring of intake and output.
- **Diet:** You order an unrestricted diet for age as tolerated.
- **Antipyretics and analgesia:** You order acetaminophen and ibuprofen every 6 hours as needed for discomfort or pain associated with Maryam's fever or other symptoms.
- **Further laboratory/diagnostic testing:** You have no current plans for repeat imaging. You plan to obtain a BMP every 48 hours until Maryam's sodium level normalizes and she is no longer on IV fluids.

Case Resolution

Maryam's respiratory effort continues to improve after admission, and she is weaned to room air by hospital day 2. Her tachycardia and physical examination findings improve as well. Her last fever occurs approximately 36 hours after her first dose of ampicillin. Her sodium level normalizes on hospital day 3. She is maintaining her fluid requirements orally and tolerating more than 50% of her meals, prompting discontinuation of her IV fluids on hospital day 4. Her blood culture remains negative, and given her good clinical response to ampicillin, she is transitioned to high-dose oral amoxicillin. She is discharged home after tolerating 1 dose of amoxicillin with plans to treat for a total of 10 days. At the time of discharge, a follow-up appointment is scheduled with her pediatrician for 3 days after discharge.

Discharge Criteria

Q: How do you know when Maryam is ready to go home?

You can feel comfortable discharging your patient with CAP when the following criteria are met:

- The patient demonstrates improved oral intake and activity level with baseline mental status.
- The patient has decreasing work of breathing and tachypnea with fever improvement.
- The patient's oxygen saturation is above 92% on room air for longer than 12 to 24 hours.
- The patient is able to tolerate oral medications.

Anticipatory Guidance

Q: What instructions should you provide to Maryam's caregivers upon discharge?

- Administer antibiotics as prescribed for the total duration recommended.
- Although the cough can persist for several weeks, it should steadily improve. Worsening cough, return of fever, chest pain, or increased work of breathing would be concerning for development of a complicated pneumonia and should prompt a visit to a health care provider.
- Continue encouraging oral fluid intake to maintain hydration.

Clinical Pearls

- Pneumonia is defined as fever and respiratory symptoms (cough, tachypnea, or respiratory distress) associated with evidence of parenchymal involvement on physical examination or radiography.
- Mild CAP is a clinical diagnosis that can be managed without radiographs, laboratory tests, or hospital admission.
- Patients with moderate to severe CAP, characterized by respiratory distress, hypoxemia, dehydration, complicated pneumonia, outpatient treatment failure, or patient factors such as young age or significant medical history, need further evaluation and hospitalization.
- When there is concern for moderate to severe CAP, testing includes a 2-view chest radiograph, blood culture, sputum culture and Gram stain (if possible), testing for viral or atypical pathogens when indicated, and a CBC.
- If a typical bacterial pneumonia is suspected, ampicillin or penicillin G are the first-line IV therapies for hospitalized children with CAP.

Documentation Tips

- Document the suspected or confirmed etiology (eg, viral or bacterial, community acquired, aspiration).
- Be as specific as possible about the location of the infection (eg, right lower lobe pneumonia).
- Include a detailed description of the patient's work of breathing, including tachypnea and the severity of retractions.

Suggested Readings

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CASE 13

Freddy, a 9-Week-Old Boy With an Episode of Decreased Responsiveness

CASE PRESENTATION

Freddy, a 9-week-old previously healthy boy born at 37 weeks' gestational age, presented to the emergency department (ED) by emergency medical services after an event at home in which he had decreased responsiveness, blue discoloration around his mouth, irregular breathing, and poor muscle tone. He has now returned to baseline, and the physician in the ED notes that Freddy has normal vital signs and a normal physical examination. The ED physician places Freddy on a pulse oximeter and obtains an electrocardiogram (ECG) and chest radiograph. The results of these studies are reassuring, but the physician calls you because she is concerned Freddy will need further observation.

Patient History and Review of Systems

Q: What information should you collect from Freddy's caregivers?

- History of present illness
  - Details of the event, including the following:
    - General description
    - Witnesses to the event
    - Conditions immediately before the event: patient location and positioning at event onset, patient activity just prior to the event (eg, feeding, sleeping), any preceding vomiting or spitting up, risk of choking or smothering (eg, objects in patient's mouth; blankets/objects, animals, or other children nearby who could choke or smother the patient)
    - During the event: choking or gagging, whether the patient was active/moving or quiet/flaccid, level of consciousness, muscle tone (increased or decreased), repetitive movements, signs of distress or alarm, description of breathing (present or absent, any struggle to breathe, or noisy breathing), changes in skin tone, any bleeding from nose or mouth, color of lips (normal, pale, or blue)

  - End of the event: approximate duration, circumstances contributing to event's end (eg, no intervention, picking up, positioning, rubbing or clapping back, mouth-to-mouth breathing, cardiopulmonary resuscitation [CPR]), manner of event end (abrupt or gradual), and any treatment provided by the witness/caregiver
  - After event: whether patient returned to baseline immediately or experienced period of increased sleepiness or fussiness
- Recent history, including injuries, falls, or previous unexplained bruising

- Associated symptoms, such as fever, cough, congestion, vomiting, diarrhea, sweating, rash, decreased oral intake, or decrease in number of wet diapers
- Medical history, including birth history, birth weight, neonatal intensive care unit course (if applicable), maternal pregnancy history (including medications or infections), newborn screening results, growth pattern and development, immunization status, similar past episodes, surgeries, prior hospitalizations, prior ED visits, reflux, or breathing difficulty
- Feeding history: breastfeeding, formula, or both; frequency, duration, and volume of feedings
- Family history, including sudden unexplained death in first- or second-degree family members, siblings with a brief resolved unexplained event (BRUE), long QT syndrome, arrhythmia, inborn error of metabolism or genetic disease, or developmental delay
- Parental mental health, including parental mental health screening (such as the Edinburgh Postnatal Depression Scale) and assessment of social support
- Social history, including household members, tobacco exposure, toxic substances, substance use by anyone in household, pets, travel history, sleep environment, housing, recent changes/stressors at home, and any sick contacts (including child care attendance)
- Previous Child Protective Services or law enforcement involvement

CASE FOCUS

History and Review of Systems

When you meet Freddy, his mother explains to you that she was reading at home alone with Freddy asleep and lying on his back across her lap when she looked down at him and noticed that his facial coloration seemed abnormal. When she picked him up, he was limp and difficult to arouse. His breathing appeared shallow, and he was gasping for air. His face had purplish-blue coloration around the mouth. She patted him on the back a few times and then blew some air in his face. According to Freddy's mother, this seemed to help, and after about 45 seconds he awoke, was crying, and was less floppy. His mother immediately called 911. Prior to the episode, Freddy had last breastfed approximately 2 hours earlier. Freddy did not demonstrate any signs of distress prior to the episode. His mother states that Freddy was not lying with his head in the chin-to-chest position while in her lap and denies any choking/gagging sounds or associated spit-up. He did not have any repetitive movements during the episode.

Since the event, Freddy has been at his baseline and directly breastfed for 20 minutes without difficulty. Freddy's mother denies any nasal congestion, fever, cough, body shaking, repetitive movements, gagging, bleeding from the nose or mouth, or emesis prior to or directly after this event.

You learn that Freddy has no history of similar episodes, and his review of systems is negative. He has not had any recent infectious symptoms. Freddy has no history of injuries, falls, or unexplained bruising. Freddy has not had any sick contacts. Freddy exclusively breastfeeds 8 to 10 times per 24 hours for approximately 20 minutes' duration and has occasional spit-ups a few times per week. His mother denies any symptoms concerning for dysphagia, reflux, aspiration, or difficulty breathing. Freddy has been growing and developing normally. His weight-for-length has been tracking along the 40th percentile. He has had 4 follow-up visits with his pediatrician since discharge from his birth hospitalization. No concerns have been identified at these visits.

CASE FOCUS

History and Review of Systems *(continued)*

Freddy was born at 37 weeks' gestational age by cesarean section due to fetal distress. His birth weight was 2.7 kg. His mother had routine prenatal care. Neither Freddy nor his mother had any antenatal or intrapartum infections. Freddy was discharged from the hospital 36 hours after birth. He received his hepatitis B vaccine, vitamin K, and erythromycin eye ointment per routine protocol. He was also circumcised in the newborn nursery. His mother reports that Freddy's newborn screens were normal. Since his discharge from the nursery, he has not had any other hospitalizations or surgeries.

When taking a family history, you learn that Freddy's 3-year-old brother has asthma and an innocent heart murmur, and his 6-year-old sister has a history of febrile seizures. Neither of Freddy's siblings had a BRUE during infancy. His mother has no medical diagnoses and does not take any daily medications. There is no family history of sudden unexplained death, long QT syndrome, arrhythmia, inborn error of metabolism or genetic disease, or developmental delay.

Freddy lives at home with his mother, father, 3-year-old brother, and 6-year-old sister. There have been no major changes or new stressors at home, and Freddy's mother states that she and Freddy's father feel well supported. There are no pets in the home. Freddy's father smokes tobacco outside of the house. Freddy's mother denies any alcohol or substance use by anyone in the home. Freddy's mother reports that she is bed-sharing with Freddy because it is easier to breastfeed him at night when he is close. She reports that she had postpartum depression following her second pregnancy but so far has not experienced similar symptoms since Freddy's birth. Freddy's mother scores a 0 on the Edinburgh Postnatal Depression Scale. Freddy's mother denies that Child Protective Services or law enforcement has been involved with her family in any way.

Physical Examination

Q: What parts of the physical examination should you focus on for Freddy?

- Complete set of vital signs
- Weight in comparison to birth weight, length, occipitofrontal circumference
- General: hydration status, evidence of craniofacial abnormalities (mandible, maxilla, nasal), age-appropriate responsiveness to environment
- Head: shape, fontanelles, bruising or other injury
- Ears: tympanic membranes (effusion or hemotympanum), external bruising
- Eyes: extraocular movements, eye deviation, pupillary response, subconjunctival hemorrhages, conjunctival injection or discharge
- Mouth: evidence of obstruction, torn labial or lingual frenulum
- Nose: congestion, coryza, blood
- Throat: lesions on tongue or mucous membranes
- Neck: mobility, masses
- Neurologic: alertness, responsiveness to sound and visual stimuli, general muscle tone and primitive reflexes (Moro, suck, grasp, parachute), presence of symmetric reflexes, symmetry of movement/muscle tone/strength

- Cardiovascular: auscultation for heart rhythm, presence of murmur, and quality of heart sounds; femoral and brachial pulses; palpation of chest wall for rib tenderness, crepitus, or irregularities
- Respiratory: auscultation of lung fields for any focal findings and observation for increased work of breathing
- Gastrointestinal: abdominal masses, organomegaly, distension or tenderness; quantity and quality of bowel sounds
- Genitourinary: external genitalia for signs of injury
- Musculoskeletal: muscle tone, limb deformities, signs of injury
- Skin: turgor, rashes, bruising, petechiae, or other lesions

CASE FOCUS

Physical Examination

Freddy is afebrile without tachycardia or tachypnea. He has a normal blood pressure for age and a normal oxygen saturation. You note that since his last health supervision visit, he is gaining an average of 28 g/d. His current weight is 5.5 kg, and his weight-for-length percentile is 40%. His head circumference is 39 cm (46th percentile).

On examination, Freddy is fussy but consolable. He is alert and appropriately responsive to sound and visual stimuli. He does not have a dysmorphic appearance or micrognathia. He is normocephalic and has no signs of head or neck trauma. His fontanelle is open, soft, and flat. He has appropriate muscle tone and primitive reflexes for age. He is moving all extremities and his neck appropriately. He has moist mucous membranes and no oral or throat lesions or signs of oral trauma. He has no congestion, coryza, or blood in his nares. You find no abnormality on otoscopic examination. He fixates on your face with no abnormal eye movements, deviation, subconjunctival hemorrhages, conjunctival injection, or discharge. His pupillary response is normal. He is warm and well perfused, with normal heart sounds and normal peripheral pulses bilaterally. His lungs are clear to auscultation. His abdomen is soft, nontender, and without any organomegaly. He has normal bowel sounds. He has normal male genitalia, and his testicles are descended and palpable bilaterally. There is no grossly visible swelling, warmth, or tenderness of the extremities. His clavicles are intact. He has no rashes or other skin lesions.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with an episode of cyanosis, change in muscle tone, and altered level of responsiveness?

You are most concerned for an idiopathic BRUE. Because the diagnosis at the top of your differential is a diagnosis of exclusion, it can be helpful to systematically list other possible diagnoses, as shown in Table 13.1.

Table 13.1. Differential Diagnosis for a Child With an Episode of Cyanosis, Change in Muscle Tone, and Altered Level of Responsiveness

Category	Etiology
Diagnosis of highest suspicion	
Idiopathic	BRUE
Other diagnoses to consider	
Otolaryngologic (ie, airway obstruction)	• Adenotonsillar hypertrophy • Choanal atresia • Laryngo- or tracheomalacia/anomalies • Macroglossia • Maxillary hypoplasia/micrognathia • Obstructive sleep apnea • Pyriform aperture or subglottic stenosis • Unintentional suffocation or strangulation • Vasovagal response
Pulmonary	• Aspiration pneumonia • Congenital lower airway anomalies/malacia • Foreign body aspiration • Pulmonary hemorrhage
Gastrointestinal	• Bowel obstruction • Dysphagia/choking • Esophageal dysmotility • Esophageal foreign body • Gastroesophageal reflux • Intussusception • Laryngeal chemoreflex • Tracheoesophageal fistula
Cardiovascular	• Arrhythmia/syncope • Cardiomyopathy/myocarditis • Channelopathies (prolonged QT syndrome, short QT syndrome, Brugada syndrome) • CHD • Vascular ring/sling/compression • Ventricular preexcitation (WPW syndrome)
Genetic/metabolic	• Electrolyte disturbances • Hypoglycemia • Inborn errors of metabolism (fatty-acid oxidation disorders, urea cycle disorders) • Mitochondrial disorders

(continued)

Table 13.1. Differential Diagnosis for a Child With an Episode of Cyanosis, Change in Muscle Tone, and Altered Level of Responsiveness *(continued)*

Other diagnoses to consider *(continued)*	
Neurologic	• Brain/intracranial structural, vascular abnormality, or mass lesion • Congenital central hypoventilation syndrome • Demyelinating disorder (TM, MS, ADEM) • Hydrocephalus • Infant botulism • Intracranial hemorrhage or ischemic event • Neuromuscular disorder • Seizure
Infectious	• Croup • Gastroenteritis (if vomiting with aspiration) • LRTI (RSV, other seasonal viruses) • Meningitis • Pneumonia (bacterial or viral) • Sepsis • URTI (especially pertussis) • UTI
Toxin exposure	• Environmental exposure • Medication adverse effect • Substance exposure via direct intake or through human (breast) milk • Vaccine reaction
Child maltreatment	• AHT • Caregiver-fabricated illness (also known as MCA) • Intentional suffocation, strangulation, or poisoning • Medical neglect
Miscellaneous	• Acrocyanosis • Breath-holding spell • Hypothermia

Abbreviations: ADEM, acute disseminated encephalomyelitis; AHT, abusive head trauma; BRUE, brief resolved unexplained event; CHD, congenital heart disease; LRTI, lower respiratory tract infection; MCA, medical child abuse; MS, multiple sclerosis; RSV, respiratory syncytial virus; TM, transverse myelitis; URTI, upper respiratory tract infection; UTI, urinary tract infection; WPW, Wolff-Parkinson-White.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with an episode of cyanosis, change in muscle tone, and altered level of responsiveness?

- As illustrated by the differential diagnosis, an event of this nature can be the presenting symptom for a broad range of conditions. Often, however, these events are benign and idiopathic in origin.
- The term *BRUE* is used to describe an event in which an infant younger than 1 year has a sudden episode of 1 or more of the following symptoms:
  - Cyanosis or pallor
  - Absent, decreased, or irregular breathing

- Marked change in muscle tone
- Changing level of responsiveness

- To be classified as a BRUE, the event must be brief, fully resolved (ie, the patient returns to their baseline after the event), and unexplained, meaning that no etiology is found after a history and examination.
  - BRUE is only diagnosed when no other explanation for the event can be identified; therefore, the presence of fever, other signs/symptoms of infection, choking/gagging, or vomiting/spitting up would indicate a clear etiology, and the patient would not be diagnosed with a BRUE.
  - To qualify as a BRUE, the patient must have normal vital signs and a reassuring physical examination at the time of their medical evaluation. The presence of abnormal findings likely points toward another cause for their symptoms.
- Freddy's history and physical examination are consistent with a BRUE. When BRUE is suspected, the next task is to determine if the infant with a BRUE is considered to be at lower or higher risk of having another BRUE or having a serious underlying disorder causing their symptoms. Determining if the patient is at low or high risk will help guide evaluation and management.

Q: Which infants are considered to be at lower risk of a subsequent BRUE or underlying disorder?

- An infant with a BRUE is at lower risk for recurrence of BRUE or having a serious underlying disorder if all of the following patient and event characteristics are met:
  - Age older than 60 days
  - Gestational age of at least 32 weeks and postconceptional age of at least 45 weeks (postconceptional age = current age in weeks + gestational age at birth)
  - First such event occurrence
  - Event duration of less than 1 minute
  - No CPR required by trained medical provider
  - No concerning historical features, such as a family history of sudden cardiac death, concerns for possible child abuse (eg, an inconsistent history from caregiver), or cardiorespiratory symptoms suggestive of an underlying condition (For a complete list of historical features to consider, refer to Table 2 from the 2016 American Academy of Pediatrics clinical practice guideline on BRUE: https://pediatrics.aappublications.org/content/137/5/e20160590.)
  - No concerning physical examination findings, such as cardiorespiratory instability, dysmorphic features, unexplained bruising, or injuries
- Infants determined to be at lower risk for recurrence of BRUE or having a serious underlying disorder can generally be managed without the need for further diagnostic testing, although clinicians may consider obtaining an ECG, infectious disease testing (for pertussis, in particular), and a period of observation with serial assessments and continuous pulse oximetry.
- The American Academy of Pediatrics recommends that lower-risk infants need not undergo an extensive diagnostic evaluation, such as complete blood cell count, blood culture, cerebrospinal fluid studies, serum electrolytes/renal function, serum and urine metabolic studies, chest radiography, echocardiography, and electroencephalography.

Q: Which infants are considered to be at higher risk of a subsequent BRUE or serious underlying disorder?

- Any infant with a BRUE that does not fit all of the lower-risk characteristics is considered to be at higher risk for recurrence of BRUE or of having a serious underlying disorder. It is important to note that the term *higher risk* is only relative to the lower-risk group; most patients in the higher-risk group do not have a serious underlying cause of the BRUE.

- There is no consensus guideline for the evaluation and management of the higher-risk infant; however, a 2019 study suggested that clinicians may consider the following evaluation:
  - For the primary evaluation of higher-risk infants with BRUE, clinicians should consider the following:
    - Continuous pulse oximetry monitoring for at least 4 hours
    - Consultation with a social worker (or other health care worker with similar experience and skills)
    - Bedside feeding evaluation by a feeding therapist, if available
    - ECG to be read by a pediatric cardiologist
    - Rapid viral respiratory panel testing
    - Rapid pertussis polymerase chain reaction testing in endemic areas, during regional outbreaks, or in under-immunized patients
    - Hematocrit level
    - Serum glucose level, bicarbonate level or venous pH, and lactate level
  - If there is concern for child maltreatment, skeletal survey and head imaging with computed tomography or magnetic resonance imaging is recommended. Consultation with a child abuse expert is useful when available.
  - If no explanation has been identified at this point in the evaluation, or if concerning events continue to occur, then consider a secondary evaluation tailored to specific individual concerns, with possible specialty consultations either after discharge or during a hospitalization. These evaluations and consultations may include the following:
    - Videofluoroscopic swallowing study for "silent" oropharyngeal dysphagia not seen on bedside evaluation
    - Continuous prolonged oximetry to characterize recurring events
    - Comprehensive polysomnography to characterize and quantify central versus obstructive apnea
    - Prolonged (12–24 hours) electroencephalogram
    - Serum sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium, and ammonia levels to evaluate for metabolic disturbance

Q: How would the identification of sentinel injuries or historical red flags for child abuse change your diagnostic evaluation?

- Although less common, some of the most emergent diagnoses presenting similar to a higher-risk BRUE are abusive head trauma (AHT), inflicted suffocation or poisoning, and medical child abuse (MCA). Historical red flags and sentinel injuries concerning for child abuse can be subtle and easily missed during a BRUE presentation, so a high index of suspicion, thorough physical examination, and appropriate consultation with a child abuse team is important.
  - Social risk factors for abuse (eg, caregiver substance use, domestic violence, prior history of Child Protective Services or law enforcement involvement) should heighten concern for abuse; however, it is important to remember that child maltreatment can occur in families without these risk factors. Additionally, factors such as caregiver affect, eye contact, and the amount of detail in an offered history are erroneously considered important in estimating the likelihood of abuse. These features are difficult to measure objectively and susceptible to medical provider bias. Remembering to adhere to protocols regardless of race or socioeconomic status is crucial to decreasing the harmful consequences of provider bias and accurately identifying maltreatment.

HEALTH EQUITY FOCUS

Implicit Bias and Race

Implicit biases are unconscious attitudes and stereotypes held by individuals. Everyone, including physicians, has implicit biases. Biases can be negative or positive. Specifically regarding race, evidence shows that, similar to the general population, physicians have implicit biases that include positive attitudes towards white patients and negative attitudes towards patients of color. Growing evidence indicates that this bias impacts clinical decisions regarding diagnosis and treatment.

All healthcare providers are encouraged to become aware of their own personal biases using tools, such as the Harvard Implicit Association Test (https://implicit.harvard.edu/implicit), so that they can make a deliberate effort to mitigate negative implicit biases that may compromise patient care.

- Sentinel injuries are subtle but visible injuries that are unlikely to have occurred accidentally in a young child. Examples include the following:
  - Bruising: highly concerning in infants who are not mobile, especially when the bruises occur on the face, trunk, or ears
  - Subconjunctival hemorrhage
  - Oronasal injuries such as frenulum tears
- AHT
  - AHT may present as an initially suspected BRUE with high-risk criteria, with symptoms that can likely be attributed to central apneic episodes.
  - Although children may be symptomatic immediately after the initial trauma, if care is delayed, children with AHT can appear neurologically normal and may not have external signs of trauma.
- Intentional suffocation, which can manifest with sentinel injuries including facial petechiae, scleral or subconjunctival hemorrhages, oronasal trauma, or bleeding from the nose or mouth
- MCA is a form of injury in which a child receives unnecessary harmful or potentially harmful medical care at the instigation of the caregiver, most often a parent. Diagnosis of MCA requires a careful review of all available medical records. When evaluating a higher-risk infant after a BRUE, the following features should raise concern for MCA:
  - Recurrent episodes, only occurring in the presence of a particular person
  - Presenting symptoms that are described in a way that is out of proportion to the physical examination
  - Caregiver providing a complex history of multiple concerns or diagnoses involving multiple systems
  - Caregiver having a complex personal medical history or other children with undiagnosed illness or multiple illness diagnoses

- When child abuse is suspected, an evidence-based approach should be taken, which may include neuroimaging and skeletal survey. Consultation with a child abuse pediatrician and social worker is also beneficial to help guide the diagnostic workup.

CASE FOCUS

Diagnostic Evaluation

Freddy underwent an ECG and chest radiography in the ED, which you have reviewed, and both are normal. You consider pertussis testing due to Freddy's age but ultimately decide against this because there were no respiratory symptoms on history, no signs on examination, and no known sick contacts. There were no other findings on history or examination to suggest the need for further medical workup, and therefore you do not order any further diagnostic evaluation at this time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Freddy?

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Freddy is a 9-week-old infant who was born at 37 weeks' gestational age presenting after a 45-second episode of perioral cyanosis, decreased responsiveness, decreased muscle tone, and shallow breathing with gasping. The episode started when Freddy was sleeping in his mother's lap, and it resolved after his mother patted his back and blew in his face. Following the event, he quickly returned to his baseline and has since breastfed well. His review of systems is negative. His medical history, social history, and family history appear noncontributory.
   - Vital signs and physical examination: Freddy's vital signs and physical examination are normal, without any dysmorphic features or signs of illness or injury.
   - Diagnostic evaluation: Freddy has had normal cardiorespiratory monitoring in the ED in addition to a normal ECG and chest radiograph.
2. **Develop the list of findings.**

   ### Q: What major finding have you have identified for Freddy?

   - Episode of perioral cyanosis, decreased responsiveness, decreased tone, and shallow irregular breathing with gasping
3. **Revisit the differential diagnosis.**

   ### Q: Based on the differential diagnosis and list of findings, are you able to choose one diagnosis to explain Freddy's presentation?

   The diagnosis of BRUE is a diagnosis of exclusion; however, Freddy has no history of infectious symptoms, frequent spitting up, choking, coughing, or obstructive breathing, and his physical examination is normal. Additionally, the event does not seem consistent with seizure activity. Although a normal ECG cannot fully eliminate the possibility of a transient cardiac arrhythmia, it has decreased the likelihood of long QT syndrome, Brugada syndrome, and Wolff-Parkinson-White syndrome. Although it cannot be completely excluded, you are less concerned about child abuse based on a clear, consistent story from Freddy's mother and a lack of sentinel injuries noted on Freddy's examination. Because of this, Freddy's presentation is most consistent with lower-risk BRUE.

   ### Q: Is there an association between BRUE and sudden infant death syndrome (SIDS)?

   Parents of infants who have experienced a BRUE are often concerned that their infant is at an increased risk for SIDS. BRUE is not a predisposing factor for SIDS. In the vast majority of SIDS cases, infants do not experience apnea prior to death.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with a BRUE?

- Patients with a lower-risk BRUE may benefit from a short period of observation and serial assessment in the ED or an observation unit but likely do not require hospital admission.
- There is very little evidence to guide which infants with a higher-risk BRUE will benefit from hospitalization. Decisions regarding admission should consider caregiver and primary care pediatrician preferences.
- If the decision is made to admit the patient, it is important to establish and communicate the goals of hospitalization with the caregivers prior to admission.

After discussions with Freddy's mother, she feels reassured by his return to baseline and normal evaluation thus far. She prefers to take him home and does not want to stay overnight in the hospital.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Freddy is a 9-week-old baby boy who was born at 37 weeks' gestational age and who presented with a lower-risk BRUE. He is currently well appearing and back to his baseline. His mother prefers to take him home and declines a period of further observation in the hospital.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

After reviewing the literature on BRUE, you decide to divide your management considerations into the following categories.

1. **Observation:** A period of brief observation and monitoring consisting of noninvasive cardiorespiratory monitor with pulse oximetry and shared decision-making regarding inpatient or outpatient disposition may be considered in patients with lower-risk BRUE. The duration of this monitoring may vary. It is reasonable to discuss the option of observation with Freddy's caregivers and decide together what an appropriate duration of observation may be.
2. **Further workup:** In patients with BRUE, further diagnostic workup may be considered if the event is classified as a higher-risk BRUE or if specific concerns are identified (eg, cardiac, pulmonary, infectious). As no specific concerns have been identified in Freddy's history, physical examination, or diagnostic workup, and you have classified him as having a lower-risk BRUE, you do not think that Freddy would benefit from any additional workup.
3. **Consultation:** Consultation with various specialists and interdisciplinary providers should be considered in patients with BRUE when specific concerns are identified. These consultations vary widely depending on what specific concerns are identified and may include cardiology, pulmonology, neurology, gastroenterology, or speech therapy. Consultation with social work should be considered to help address any psychosocial concerns identified. Given Freddy's current sleeping environment, his mother's history of postpartum depression, and his father's tobacco use, it is reasonable to consider a social work consultation for discussion of safe sleep practices and resources for parental mental health services and smoking cessation.

4. **Education:** Physicians should educate caregivers about BRUEs and provide reassurance that BRUEs are not associated with SIDS. To help decrease parental anxiety, physicians should shift the focus away from what is unexplained to what is known: the condition is *not* life-threatening, and a serious underlying diagnosis or recurrence is extremely unlikely. CPR training (either in hospital or as an outpatient) should be offered to caregivers as a resource. It is also appropriate to provide information and education on other newborn and postpartum topics, such as safe sleep and postpartum depression.
5. **Outpatient monitoring:** At-home apnea monitors are not recommended for patients with a BRUE. In general, there is no evidence that their use reduces the risk of SIDS, and these devices can lead to false reassurance, unnecessary alarm fatigue, and increased caregiver anxiety. Furthermore, false alarms may also lead to an unnecessary medical workup. Some families may feel reassured by these devices, and therefore shared decision making should be employed to help caregivers understand the limitations and risks of these devices.

CASE FOCUS

Plan for Treatment and Monitoring

Before discharging Freddy, you take the following steps in his care:

- **Observation: After discussing with his caregivers, you decide to observe Freddy in the ED on pulse oximetry for a period of 4 hours.**
- **Further workup: You decide no further diagnostic workup is indicated at this time.**
- **Consultations: You obtain a social work consult while Freddy is in the ED.**
- **Education: You will provide safe sleep education to Freddy's mother. You will provide a referral to Freddy's parents for CPR training to be completed as an outpatient.**
- **Outpatient monitoring: You recommend against an at-home apnea monitor. You contact Freddy's primary care pediatrician with information about your evaluation and suggest that the Freddy's caregivers follow up by phone or visit within a few days.**

Case Resolution

After you meet with Freddy and his mother, you speak to the ED physician and request continued observation in the ED on continuous pulse oximetry for Freddy for a total of 4 hours. During that time, Freddy does not have any observed desaturations. A social work consultation does not identify any resource needs or social concerns, but the social worker does discuss safe sleep with Freddy's mother.

Because Freddy is appropriately evaluated and monitored in the ED, he is discharged home with strict anticipatory guidance, including safe sleep precautions, education on signs and symptoms to watch for, smoking cessation education for his father, and information about postpartum depression based on his mother's history. You recommend that Freddy follow up with his pediatrician within a few days. You recommend against an at-home apnea monitor, and Freddy's family agrees that they do not want to pursue this option.

Discharge Criteria

Q: How do you know when Freddy is ready to go home?

You can feel comfortable discharging your patient with a BRUE when the following criteria are met:

- The caregivers are comfortable that their concerns have been addressed.
- The patient's vital signs are appropriate for age for at least 4 hours.
- Appropriate and timely follow-up with patient's primary care pediatrician has been established.
- Caregiver CPR training has been identified and offered.
- Identified psychosocial concerns such as safe sleep, parental tobacco use, and risk of postpartum depression have been addressed.

Anticipatory Guidance

Q: What instructions should you provide to Freddy's caregivers upon discharge?

- BRUEs are not life-threatening, and the chance of a serious underlying diagnosis or recurrence of BRUE is highly unlikely.
- CPR training is offered as a useful resource, not because Freddy is believed to be at an increased risk of death.
- At-home apnea monitors are not recommended because their use can lead to false reassurance, unnecessary alarm fatigue, and increased caregiver anxiety.

Clinical Pearls

- Clinicians should diagnose a BRUE only when there is no explanation for a qualifying event after conducting a thorough history and physical examination.
- Patients with BRUE should be categorized as having higher risk or lower risk for recurrence of BRUE or having a serious underlying disorder. This categorization is used to help guide diagnostic workup and management.

Documentation Tips

- Specify lower-risk versus higher-risk BRUE, including history of prematurity, need for CPR, and BRUE reoccurrences.
- Document the need for continuous cardiac monitoring, respiratory monitoring, and intermittent neurologic checks.
- If symptoms ultimately can be attributed to an alternate diagnosis, then a final diagnosis of BRUE should not be documented.

Suggested Readings

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Brian, a 2-Year-Old Boy With Fussiness and Fever

CASE PRESENTATION

You are on night call in the hospital, and a nurse pages you to speak with parents who are concerned about their son's clinical status. The patient is a previously healthy 2-year-old boy named Brian. You review your patient list and see that Brian was admitted yesterday for intravenous (IV) rehydration after experiencing fever, vomiting, poor oral intake, and diarrhea. The team caring for him attributed his symptoms to a viral infection. His nurse reports that his parents are concerned because, although his oral intake has improved, his fevers have not resolved, and he remains fussy. As you speak with the nurse, you begin to wonder if Brian's symptoms reflect something other than a routine viral illness.

Patient History and Review of Systems

Q: What information should you collect from reviewing Brian's medical record and speaking to Brian's caregivers and nurses?

- History of present illness, including presenting symptoms and their duration
  - Description of parents' concerns and observations, including changes they have noticed since admission
  - Nursing observations about his clinical status
  - Fever history, including onset, duration, method of measurement, height, frequency, pattern, and any fever-free days since onset
  - Recent behavior compared to usual
  - Associated symptoms, such as current or recent headache, runny nose, nasal congestion, eye redness or drainage, sore throat, neck pain or stiffness, swollen lymph nodes, vomiting, diarrhea, abdominal pain, dysuria, urine output, joint pain or swelling, swelling or redness of the hands and feet, or rash
- Medical history, including underlying health status, chronic medical conditions, and vaccination status
- Medications (current and recent)
- Social history, particularly sick contacts (eg, household or child care contacts with fever, upper respiratory, or gastrointestinal symptoms) and environmental exposures (eg, travel, animal exposures, flea or tick bites)

CASE FOCUS

History and Review of Systems

In reviewing Brian's medical record and in discussion with his family, you learn that Brian's symptoms started 5 days ago with daily fever, fussiness, and poor oral intake. Today is Brian's fifth day of fever. Prior to presentation, his parents were checking axillary temperatures each day at home, and the nursing staff in the hospital have been checking his temperature orally. His parents confirm he has had temperatures of at least 38.3 °C (100.9 °F) each day, with a maximum temperature of 40.1 °C (104.2 °F) yesterday. He has been fussy, difficult to console, and unlike himself during the illness, and his fussiness has not improved significantly on IV fluids or with use of acetaminophen or ibuprofen during his hospitalization. His parents were treating his fever and fussiness at home with acetaminophen.

Brian's diarrhea and vomiting started on day 2 of his illness. His diarrhea was watery but infrequent, with approximately 3 episodes each day, and it has resolved. He did have a few episodes of nonbloody, nonbilious vomiting early in the illness but has not had any episodes in the past several days. His oral intake has remained poor, but his urination has improved while on IV fluids.

His parents first noticed a rash on his trunk on the third day of his illness (2 days ago) and describe its appearance as red and bumpy. His rash has now spread to his arms, legs, and diaper area. The rash does not appear to be bothering him (ie, it is not itchy or painful), and his parents have not noticed any peeling or blisters.

Brian's parents recall that his eyes appeared red for several days during this illness but note that this is improved. He has not had associated eye discharge, runny nose, cough, sore throat, headache, lethargy, abdominal pain, dysuria, or difficulty breathing. His parents have not noticed any swelling or redness to his hands or feet.

You confirm that Brian is previously healthy, fully immunized, and has no recent travel history, major illnesses, or significant exposures. He has no known sick contacts, though he does attend child care. He does not take any regular medications. His parents report he has had typical development and has never had any illness like this in the past.

At the time of his admission to the hospital, Brian was noted to have mild to moderate dehydration. A mild, scattered papular rash was observed on his trunk, but his examination was otherwise benign. His symptoms seemed to reflect a viral illness. Since admission, he has received acetaminophen, ibuprofen, and ondansetron in addition to his IV fluids. His parents have become more concerned throughout the day today because he continues to have fever and fussiness.

Brian's nurse reports that Brian appears to be either sleeping or fussy when she enters his room. She has not observed him to be playful, and he has not wanted to interact with her. She has also noticed persistent fever up to 39.1 °C (102.4 °F) and tachycardia around 150 beats/min during her shift. She says that he seems adequately hydrated on IV fluids.

Physical Examination

Q: What parts of the physical examination should you focus on for Brian?

- Complete set of vital signs
- General appearance, including assessment of mental status, observing child's interaction with family members, and noting whether he seems appropriately fussy from stranger anxiety or fussiness is symptomatic of his illness
- Eyes: signs of inflammation or infection (eg, exudates or scleral injection)
- Mouth: oropharynx, lips, and mucous membranes, specifically noting any ulcerations, erythema, cracking, swelling, or exudate and appearance of the tongue
- Cardiopulmonary: murmurs, adventitious breath sounds
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Gastrointestinal: abdominal tenderness, masses, organomegaly

- Musculoskeletal and extremities: joint swelling, erythema, edema (including diffuse edema to hands or feet), limited range of motion
- Lymphadenopathy: cervical, axillary, inguinal
- Skin: rash, with description of appearance (refer to Section VI of the Appendix for an example of rash characterization)
  - Color and appearance of individual lesions
  - Blanching under pressure
  - Distribution, including the palms and soles
  - Presence of bullae and Nikolsky sign

CASE FOCUS

Physical Examination

Upon reviewing Brian's vital signs, you note that he has had persistent fevers with a maximum temperature of 39.8 °C (103.7 °F) since admission. He has also remained tachycardic despite fluid resuscitation, with his heart rate ranging from 140 beats/min to more than 150 beats/min. He has had normal respiratory rates and normal oxygen saturations. Review of his intake and output shows that his urine output today is 1.5 mL/kg/h.

As you are speaking with his family, you notice that Brian is lying on the bed crying and is not particularly consolable, even when his mother picks him up to comfort him. He has a normal respiratory rate and no increased work of breathing when he is not crying. His eyes have mild bilateral bulbar conjunctival injection without exudate. He appears to be moving his neck without signs of difficulty or pain. His lips are noted to be erythematous and cracked.

On examination, you notice diffuse erythema of the lips, buccal mucosa, and tongue. There are no discrete intraoral lesions or exudate. You confirm that his neck is supple and do not note any cervical adenopathy. Likewise, you do not palpate any lymphadenopathy in his axilla or groin. Other than his tachycardia, there are no significant findings noted on the cardiopulmonary examination, and his peripheral perfusion is normal. His abdomen is soft. Assessing for abdominal tenderness and organomegaly is difficult because he struggles and cries throughout your examination, but his fussiness does not seem to be exacerbated by abdominal palpation. On his skin examination, you note blanching erythematous papules located in the perineal area, on the trunk, and on the extremities. There are no vesicles, bullae, desquamation, or petechiae. His palms and soles do not appear red or swollen, but Brian resists your efforts to examine them. There are no apparent focal neurologic deficits or joint abnormalities.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with a febrile illness associated with a rash and mucous membrane changes?

Fever and rash are common symptoms in children, with self-limited infectious etiologies being among the most likely causes. The presence of mucous membrane changes and the persistence of fever require the consideration of multiple noninfectious etiologies, as shown in Table 14.1. In reviewing this list and applying it to Brian's case, you are most concerned about an adenoviral or enteroviral infection, murine typhus, multisystem inflammatory syndrome in children (MIS-C), and Kawasaki disease (KD).

Table 14.1. Differential Diagnosis for a Child With Fever, Rash, and Mucous Membrane Changes

Category	Etiologies
Infectious	• Bacteria — Atypical bacteria: *Mycoplasma pneumoniae* (specifically *M pneumoniae*–induced rash and mucositis) — Rickettsiae (eg, Rocky Mountain spotted fever, murine typhus,[a] ehrlichiosis) — Spirochetes: leptospirosis — *Streptococcus pyogenes* or *Staphylococcus aureus* infections (particularly staphylococcal scalded skin syndrome, scarlet fever, or TSS) • Viruses: adenoviruses,[a] EBV, enteroviruses,[a] HSV, measles
Hypersensitivity reactions	• DRESS syndrome • Mercury hypersensitivity reaction (specifically acrodynia) • Serum sickness–like reaction • SJS • Urticaria multiforme
Autoimmune/ inflammatory disease	• Acute rheumatic fever • Autoinflammatory syndromes, such as TNF-associated periodic syndrome or periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis • KD[a] (complete or incomplete) • MIS-C[a] related to SARS-CoV-2 • Systemic JIA
Oncologic processes	• HLH • Leukemia • Lymphoma

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; SJS, Stevens-Johnson syndrome; TNF, tumor necrosis factor; TSS, toxic shock syndrome.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is indicated for patients who present with a prolonged febrile illness associated with rash and mucous membrane changes?

(For this discussion, a *prolonged* febrile illness is defined as fever lasting 5 days or longer.)

- The approach to evaluating these patients should be guided by findings from their history and examination.
- Considering that the most likely differential diagnoses for this presentation are infectious and inflammatory processes, initial testing may include the following:
  - Complete blood cell count (CBC) with differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level can be helpful to evaluate the degree of inflammation. Additionally, some findings on the CBC may support certain etiologies. For example, in the absence of shock/disseminated intravascular coagulation, the presence of cytopenias may suggest a viral, oncologic, rheumatologic, or rickettsial illness.

- Obtaining electrolytes, renal function testing, and liver enzymes is reasonable to assess for signs of liver or kidney dysfunction, although mild abnormalities in these laboratory test results are nonspecific.
- To evaluate for infectious etiologies, clinicians should consider infectious disease testing as dictated by the patient's symptoms, examination, and other risk factors, including geographic location, sick contacts, and travel history. Infectious testing may include a throat swab for streptococcal antigen/culture, a nasopharyngeal swab for viruses or *Mycoplasma pneumoniae*, and serum viral or rickettsial antibody titers, among others.
- If there is concern for a central nervous system infection (eg, meningitis, encephalitis) based on the presence of nuchal rigidity or altered level of consciousness, clinicians should obtain a cerebrospinal fluid (CSF) sample for testing and consider central nervous system imaging (computed tomography scan of the head or magnetic resonance imaging of the brain, depending on the clinical scenario). CSF tests generally include Gram stain, cell counts, protein, glucose, and culture. Polymerase chain reaction (PCR) testing on the CSF can also be useful in certain situations.
- Even though oncologic etiologies may be less likely to cause this constellation of findings, it is important for clinicians to consider this possibility. If there is diffuse adenopathy, hepatosplenomegaly, or blood cell line cytopenias, further testing and consultation with an oncologist may be indicated.
- For patients with tachycardia without a clear etiology that is unresponsive to fluids or antipyretics, an electrocardiogram (ECG), troponin, or echocardiogram may be warranted as part of an evaluation for viral myocarditis.
- MIS-C: This inflammatory process related to recent SARS-CoV-2 infection or exposure is generally diagnosed by a combination of clinical and laboratory findings. These findings include fever, laboratory evidence of inflammation, evidence of multisystem involvement, and evidence of recent exposure to or infection with SARS-CoV-2. MIS-C is considered a diagnosis of exclusion. Clinicians should refer to the Centers for Disease Control and Prevention website for the full list of testing recommendations, which includes multiple serum studies, nasopharyngeal testing for SARS-CoV-2, and cardiac studies (ECG and echocardiogram).
- KD: There is no one specific blood test to diagnose KD. Instead, the diagnosis relies on a combination of clinical features and supportive laboratory findings.
  - Complete (or *classic*) KD is defined solely by clinical findings. Patients must have experienced 5 days of fever and at least 4 of the following 5 clinical criteria: (1) erythema or cracking of the lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa; (2) bilateral bulbar conjunctival injection without exudate; (3) rash (maculopapular, diffuse erythroderma, or erythema multiforme–like); (4) erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; and (5) cervical lymphadenopathy (≥ 1.5 cm in diameter), usually unilateral. Some of these features may have resolved prior to the patient's presentation but still count toward the clinical criteria.
  - Incomplete KD is defined as at least 5 days of fever, no alternative plausible diagnosis, at least 2 of the previously listed clinical criteria, and 3 or more supplemental laboratory criteria. Refer to Figure 14.1 for the incomplete KD diagnostic algorithm.
  - Diagnostic tests: As part of the diagnostic evaluation of KD, patients generally undergo multiple laboratory studies, especially when the diagnosis is uncertain. These tests usually include a CBC, liver function tests, a urinalysis, ESR, and CRP level. Additionally, an echocardiogram is recommended as soon as possible once the diagnosis is suspected.

- Table 14.2 details various suspected diagnoses that may prompt further specific testing in patients with prolonged febrile illnesses associated with rash and mucous membrane changes.

Table 14.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Fever, Rash, and Mucous Membrane Changes

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
URTI or viral syndrome	Variable, but the presence of oral ulcers or erosions, tonsillar exudates, or exudative conjunctivitis suggests an infectious (rather than inflammatory) etiology.	None required, but depending on the scenario, consider PCR for enteroviruses, HSV, or *Mycoplasma pneumoniae*; rapid strep testing and/or throat culture; EBV and CMV antibody testing; heterophile antibody test; direct antigen testing for adenoviruses; or a respiratory viral panel by PCR.
Systemic JIA	Joint effusions or arthritis; salmon-pink, evanescent rash; high, spiking fevers, commonly in a quotidian pattern; lymphadenopathy and hepatosplenomegaly may be present. Can present with features of macrophage activation syndrome (a severe illness featuring cytopenias, transaminitis, and significantly elevated ferritin).	CBC, ESR, CRP, liver enzymes, ferritin Diagnosis of exclusion, therefore testing for infectious, oncologic, and other inflammatory etiologies is generally recommended.
Measles	Fever, cough, coryza, conjunctivitis, Koplik spots (precedes other findings), maculopapular rash (cephalocaudal and centrifugally spreading) Risk factors include unimmunized status and recent travel to an endemic area.	PCR for measles virus RNA (preferably from a respiratory sample)
Scarlet fever	Erythematous, sandpaper-like rash; pharyngitis	Rapid strep testing, throat culture; consider ASO or anti-DNase B titers if diagnosis is uncertain for a hospitalized patient
TSS	Erythroderma, fever, tachycardia, hypotension; erythema of mucosal surfaces may be present.	CBC, blood cultures, liver function panel, serum chemistries, coagulation profile.
Rickettsial illnesses (eg, RMSF, murine typhus)	Headache, fever, rash Abdominal pain, vomiting, and diarrhea are common. The rash of RMSF starts on the wrists before spreading and commonly involves the palms and soles. Risk factors include certain geographic locations and exposure to fleas (murine typhus) and ticks (RMSF).	CBC, serum electrolytes, renal function, liver enzymes, rickettsial antibody titers Hyponatremia, transaminitis, and cytopenias are common laboratory findings.
KD	Fever, rash, nonexudative conjunctivitis, erythema of oral mucosa or lips, cervical lymphadenopathy, edema or erythema of hands or feet Fussiness and tachycardia are common.	CBC, ESR, CRP, serum electrolytes, renal function, liver enzymes, urinalysis, echocardiogram

Table 14.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Fever, Rash, and Mucous Membrane Changes *(continued)*

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
MIS-C	Fever, recent infection or exposure to SARS-CoV-2, severe illness requiring hospitalization Hypotension and cardiac dysfunction are common. GI symptoms (eg, abdominal pain, diarrhea) are common.	CBC; SARS-CoV-2 testing (PCR, antibody tests); serum chemistries, renal function, and liver enzymes; inflammatory markers (eg, ESR, CRP, procalcitonin, D-dimer, ferritin); cardiac enzymes or markers (troponin, BNP); ECG; echocardiogram.

Abbreviations: ASO, antistreptolysin O; BNP, B-type natriuretic peptide; CBC, complete blood cell count; CMV, cytomegalovirus; CRP, C-reactive protein; DNase, deoxyribonuclease; EBV, Epstein-Barr virus; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; RMSF, Rocky Mountain spotted fever; TSS, toxic shock syndrome; URTI, upper respiratory tract infection.

CASE FOCUS

Diagnostic Evaluation

You review Brian's medical record and find that an electrolyte and renal function panel was obtained upon admission. The results of this panel are as follows:

Laboratory test	Result	Reference range
Sodium	140 mEq/L (140 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.3 mEq/L (4.3 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	100 mEq/L (100 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)	18–24 mEq/L (18–24 mmol/L)
Anion gap	24 mEq/L (24 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	23 mg/dL (8.21 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.5 mg/dL (44.2 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	75 mg/dL (4.16 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)

Abbreviation: BUN, blood urea nitrogen.

For Brian, you are most suspicious of KD or an infectious etiology. To evaluate for common infections that can present in a similar manner, you order a nasopharyngeal viral respiratory panel by PCR, Epstein-Barr virus (EBV) titers, SARS-CoV-2 antibodies, and a rapid strep test with reflex throat culture.

The results of your tests to evaluate for the possibility of KD or an infectious etiology are as follows:

Laboratory test	Result	Reference range
CBC		
WBC count	23,300/µL (23.3 × 10^9/L)	7,000–13,000/µL (7–13 × 10^9/L)
Neutrophils	80% (0.80)	23%–70% (0.23–0.70)
Hemoglobin	10.1 g/dL (101 g/L)	10.5–14 g/dL (105–140 g/L)
Hematocrit	31% (0.31)	32%–42% (0.32–0.42)
Platelet count	513 × 10^3/µL (513 × 10^9/L)	150–400 × 10^3/µL (150–400 × 10^9/L)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	135 mEq/L (135 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	105 mEq/L (105 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	19 mEq/L (19 mmol/L)	18–24 mEq/L (18–24 mmol/L)
BUN	12 mg/dL (4.28 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.4 mg/dL (35.4 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Albumin	2.7 g/dL (27 g/L)	3.6–5.2 g/dL (36–52 g/L)
AST	136 U/L (2.27 µkat/L)	9–80 U/L (0.15–1.34 µkat/L)
ALT	121 U/L (2.02 µkat/L)	5–45 U/L (0.08–0.75 µkat/L)
Total bilirubin	0.6 mg/dL (10.3 µmol/L)	<1.2 mg/dL (<20.5 µmol/L)
Inflammatory markers		
ESR	75 mm/h	0–10 mm/h
CRP	15.1 mg/dL (151 mg/L)	<1 mg/dL (<10 mg/L)
Urinalysis		
Specific gravity	1.010 mg/mL	1.005–1.030 mg/mL
Leukocyte esterase	Negative	Negative
Nitrites	Negative	Negative
WBC count	15/HPF	None
Bacteria	None	None
Infectious disease testing		
Respiratory pathogen panel by PCR	Negative[a]	None
Serum EBV panel	Negative	Negative
SARS-CoV-2 antibodies	Negative	Negative

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HPF, high-power field; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; WBC, white blood cell.

[a] Respiratory pathogen panel by PCR tests for certain infections of the nasopharynx, including *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Bordetella parapertussis*, and the following viruses: respiratory syncytial virus, adenoviruses, influenza viruses, human rhinovirus/enteroviruses, human metapneumovirus, parainfluenza viruses, and coronaviruses (including SARS-CoV-2).

Arriving at a Diagnosis

Q: How do you develop an assessment for Brian?

First, you decide to summarize the key findings from his history, examination, and diagnostic studies; develop a list of findings; and then narrow your differential diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History and physical examination: Brian is an otherwise healthy 2-year-old boy with a recent history significant for 5 days of fever, vomiting/diarrhea (resolved), poor intake, irritability, tachycardia, rash, nonexudative conjunctivitis (resolved), and erythema of his oral mucosa with cracking of his lips. Despite Brian's cracked lips and tachycardia, he does not currently have any other findings of dehydration and is noted to have been urinating well while receiving IV fluids.
   - Laboratory tests: Brian's laboratory test results show findings consistent with inflammation, including leukocytosis, elevated inflammatory markers, transaminitis, and thrombocytosis. Although these findings are fairly nonspecific, his limited infectious evaluation did not detect any of the infectious etiologies that are highest on your differential. The acute kidney injury and metabolic acidosis that were present on his admission have resolved. Hypoalbuminemia is now present.
   - Assessment for sepsis: When assessing Brian for the presence of sepsis criteria, you note that his fever, tachycardia, and leukocytosis meet his age-based criteria for systemic inflammatory response syndrome (SIRS); however, because you are not currently suspicious for an infectious etiology, he cannot be diagnosed with sepsis at this time. Refer to Section IV in the Appendix for definitions of SIRS and sepsis.
2. **Develop the list of findings.**

   ### Q: What major findings have you identified for Brian?

   - Fever for 5 days
   - Rash
   - Mucositis
   - Conjunctivitis without exudate
   - Fussiness
   - Vomiting and diarrhea (resolved)
   - Anemia
   - Thrombocytosis
   - Hypoalbuminemia
   - Transaminitis
   - Elevated inflammatory markers (ESR and CRP)
   - Pyuria
   - SIRS (fever, leukocytosis, and tachycardia)
3. **Revisit the differential diagnosis.**

   ### Q: Based on your initial differential diagnosis and list of findings, are you able to select one diagnosis to explain Brian's presentation?

   - You suspect KD to be the most likely diagnosis based on Brian's prolonged fever and the constellation of findings on his physical examination and laboratory evaluation.
   - Although infectious etiologies cannot be entirely ruled out, these acute infections seem less likely based on negative respiratory pathogen panel testing, lack of exudative conjunctivitis, discrete oral lesions, or tonsillar exudates.
   - Accompanying infections do not exclude the diagnosis of KD. Some studies demonstrate up to 40% of pediatric patients with KD may present with a positive respiratory viral PCR at the time of diagnosis.

Q: What are the diagnostic criteria of complete KD?

To diagnose complete KD, the patient must have fever for 5 days or longer *and* have 4 or more of the following symptoms: mucositis, conjunctivitis, rash, erythema and edema of hands and feet, and lymphadenopathy.

- Fever: Temperature is typically higher than 39 °C (102.2 °F) and may last 1 to 3 weeks without treatment. The day of fever onset is counted as day 1.
- Mucositis: The lips may be red, cracked, peeling, or bleeding. The patient may have a strawberry tongue, with inflammation and prominent fungiform papillae. The oropharyngeal mucosa may appear generally erythematous. Note that exudates or other discrete intraoral lesions may suggest an alternative diagnosis.
- Conjunctivitis: Patients commonly experience bilateral bulbar conjunctivitis without exudate, which is generally described as sparing the limbus.
- Rash
  - Acute phase (within the first week of illness): The rash, typically described as a polymorphous rash, may have a maculopapular appearance and be broadly distributed. Additionally, there may be erythema multiforme-like lesions. Less commonly, patients may present with an urticarial-like rash, fine micropustular eruptions, or a psoriasis-like outbreak.
  - Subacute phase (second week of illness and beyond): Desquamation of the perineum, digits, palms, and soles may occur, and new-onset atopic dermatitis may develop. Occasionally, desquamation of the perineal area may occur in the first week of illness. Note that desquamation in areas other than the perineal area in the first week of illness may suggest an alternative diagnosis.
  - It is important to note that skin findings such as rashes may be less apparent in some patients. Evidence suggests that in some diagnoses in which characteristic rashes are clinical criteria, diagnosis may be missed or delayed in individuals with dark skin tones. This is a potential source of health care disparity and should be diligently considered during clinical evaluation.
- Erythema and edema of hands and feet: These symptoms are observed in the acute phase of illness. Hands and feet may be tender to the touch. Desquamation of hands and feet may occur in the second week of illness.
- Lymphadenopathy: Lymphadenopathy is the least common of the 5 KD criteria; when present, it is usually (but not always) unilateral, located in the anterior cervical region, and greater than 1.5 cm in diameter.
- Other supportive findings (not part of diagnostic criteria): Children with KD are commonly irritable. Neck stiffness related to an aseptic meningitis may occasionally be present, in which case, CSF pleocytosis can be noted on lumbar puncture. Other potential findings include murmurs (valvulitis, systolic flow murmur, S_3 gallop due to diastolic dysfunction from myocarditis, pericardial friction rub from pericarditis), persistent resting tachycardia (even in the absence of fever), interstitial pneumonitis, hepatomegaly, gallbladder hydrops, abdominal pain, diarrhea, pancreatitis, urethritis, peripheral facial nerve palsy (usually unilateral), arthritis or arthralgia, Raynaud phenomenon, and sensorineural hearing loss. Additionally, some patients experience shock with the need for vasopressor support.
- Supplementary laboratory criteria may include an elevated white blood cell count with neutrophil predominance, elevated ESR and CRP levels, hyponatremia, hypoalbuminemia, transaminitis, and sterile pyuria. Thrombocytosis is common in the second week of symptoms.

Q: Given that Brian appears to be meeting only 3 of the clinical criteria for KD (mucositis, conjunctivitis, and rash), how does this change your assessment?

- Brian's clinical picture seems most consistent with incomplete KD, which refers to a subset of patients who do not display the number of clinical criteria required for complete KD.
  - Incomplete KD affects young infants or older children more often than toddlers.
  - Refer to Figure 14.1 for the recommended evaluation approach for such patients.

Based on the algorithm in Figure 14.1, Brian does have sufficient examination findings and supplemental laboratory test criteria to be diagnosed with incomplete KD, even without the addition of an echocardiogram.

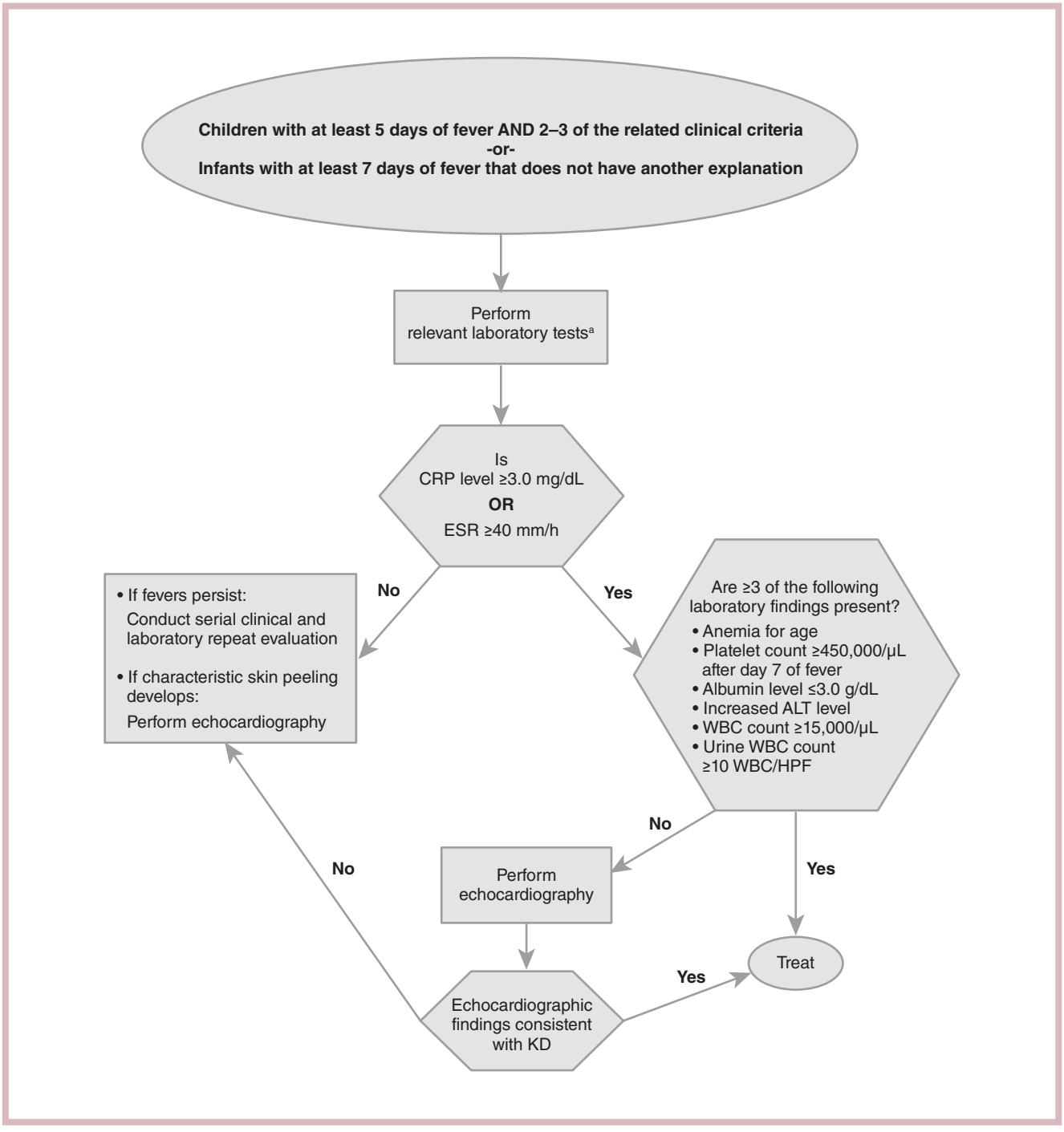

Figure 14.1. Recommended evaluation of patients suspected to have incomplete Kawasaki disease.

Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HPF, high-power field; KD, Kawasaki disease; WBC, white blood cell.

[a] Relevant laboratory tests include a complete blood cell count, renal function and liver function tests, ESR, CRP, and a urinalysis.

Derived from McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927–e999.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with incomplete KD?

Although Brian is already hospitalized, his presentation and diagnosis prompt you to consider admission criteria for patients with suspected KD. Hospitalization is warranted for all children with suspected KD to ensure both timely diagnosis and initiation of therapy, which are key to reducing morbidity and mortality in KD. Furthermore, inpatient monitoring and repeat evaluations may identify and treat complications earlier in the course of the disease.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Brian is a 2-year-old boy who was initially hospitalized with dehydration associated with a febrile illness attributed to a viral infection. His clinical picture has evolved, however, and now features 5 days of fever; an erythematous papular rash; conjunctival injection without exudates; erythematous, cracked lips and intraoral erythema; and abnormal laboratory findings, including leukocytosis, anemia, thrombocytosis, hypoalbuminemia, transaminitis, pyuria, and elevated ESR and CRP. The constellation of these findings is consistent with incomplete KD.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goal of treatment of KD is to prevent coronary artery aneurysm formation by reducing vasculitis and systemic inflammation. This in turn decreases the risk of coronary artery thrombosis and myocardial infarction. Fatality rates are less than 1% with treatment. In the United States, intravenous immunoglobulin (IVIG) is considered the first choice of disease-modifying therapy options.

1. **IVIG**
   - Research has supported the efficacy of IVIG at reducing rates of coronary artery dilation when administered within the first 10 days of illness. For patients with a delayed diagnosis, there is evidence that treatment after the tenth day may still be effective if the patient has evidence of ongoing inflammation (persistent fever or elevated inflammatory markers) or coronary artery aneurysm.
   - When treated with a high-dose IVIG regimen in the first 10 days of illness, 5% of patients will develop significant coronary artery injury, compared to approximately 25% without treatment. With treatment, 1% of patients will develop giant coronary artery aneurysms.
   - Dosing: The first dose of IVIG should be administered at 2 g/kg and should be infused over 8 to 12 hours. A second dose is often given if fever/symptoms persist more than 36 hours after completion of IVIG.
   - Adverse effects: Headache is the most common side effect reported, and IVIG may cause aseptic meningitis. Nausea and vomiting are also seen. Less common potential side effects include anaphylaxis, with immunoglobulin A–deficient patients at an increased risk; thrombosis; acute kidney injury; hemolytic anemia; or exposure to bloodborne pathogens. Most side effects can be prevented or ameliorated by ensuring adequate hydration, slowing the infusion rate, and using acetaminophen or diphenhydramine.

2. **Acetylsalicylic acid (ASA, also referred to as *aspirin*):** ASA is given for its antiplatelet effects (at low dosing) and its anti-inflammatory effects (at high dosing); however, its use does not affect the incidence of coronary abnormalities.
   - Dosing: ASA should be given at higher dosage (80 mg/kg/day divided into doses every 6 hours) during the acute phase of illness. There is some debate regarding timing of transition to low-dose aspirin (3–5 mg/kg/day). Some experts recommend transitioning dosing after 48 hours without a fever, whereas others advocate continuing until at least 14 days into illness.
   - Low-dose aspirin is continued until follow-up echocardiograms show no evidence of coronary abnormalities 4 to 6 weeks after illness onset. Patients with baseline aneurysms or new aneurysms on follow-up echocardiogram will need to continue low-dose aspirin until it is discontinued by their cardiologist.
   - Adverse effects: There is potential concern for Reye syndrome; however, the lower dosage of ASA has not been shown to be associated with developing Reye syndrome.
   - Other nonsteroidal anti-inflammatory drugs should be avoided while on ASAs because they interfere with ASA's antiplatelet effects.
3. **Additional therapies:** For patients considered to be at high risk of coronary aneurysm development, adjunctive therapies can be considered. Infants younger than 6 months are considered to be especially high risk; older children and adolescents are at increased risk. Also at increased risk are patients with thrombocytopenia, those who do not respond to IVIG therapy, those with a CRP level greater than 13 mg/dL (130 mg/L), those with a baseline coronary *z* score greater than or equal to 2.0, and those presenting with shock. Consultation with a local KD expert should be considered in these situations. Adjunctive therapeutic options include corticosteroids (most common), etanercept, or infliximab.
4. **Additional diagnostic evaluation**
   - Echocardiography should be ordered at the time of diagnosis to establish a baseline coronary artery diameter and to identify other signs of cardiac inflammation, but treatment should not be delayed to obtain an echocardiogram. Typically, an echocardiogram is repeated at 2 weeks and 4 to 6 weeks after the start of the illness. More frequent monitoring may be needed if coronary dilation, myocarditis, or other myocardial dysfunction is present.
   - In certain cases, an ECG may be helpful to evaluate for arrhythmia or to quickly screen for cardiac ischemia.
5. **Assessing response to therapy**
   - Laboratory tests: CRP should be followed periodically during hospitalization to ensure that levels are decreasing. Other abnormal laboratory test results should be repeated as needed (eg, ensuring resolution of hyponatremia/transaminitis, obtaining a serum albumin level in cases of continued peripheral edema). The ESR is affected by IVIG therapy and should not be used to assess therapeutic response.
   - Vital sign monitoring: Repeating vital signs at regular intervals is important to follow trends and assess a patient's clinical course. More frequent monitoring of vital signs may be beneficial during IVIG infusion to monitor for adverse reactions. Brian's fever is expected to resolve within 36 hours post IVIG infusion. Approximately 15% of children will not defervesce within this time frame; in this case, a second IVIG infusion may be considered.
     - IVIG resistance is defined as persistence or recurrence of fever for more than 36 hours and less than 7 days after completion of first IVIG infusion.
     - For patients who are refractory to IVIG therapy, the most common treatment options include providing a second dose of IVIG, a second dose of IVIG plus corticosteroids, or changing to infliximab.
   - Monitoring for other complications of KD: Clinicians should be aware of several other clinical manifestations and complications that could develop. In addition to the more common findings included in the diagnostic criteria, it is well recognized that children with KD may develop aseptic meningitis, shock (Kawasaki shock syndrome), myocarditis, gallbladder hydrops, diarrhea, pancreatitis, urethritis, peripheral facial nerve palsy (usually unilateral), arthritis or arthralgia, Raynaud phenomenon, macrophage activation syndrome, or sensorineural hearing loss. Cardiac monitoring via telemetry may be indicated when there are signs of significant cardiac pathology on echocardiography or an arrhythmia on ECG, in which case, transferring the patient to an intensive care unit may be warranted.

6. **Consultations:** Inpatient consultation with pediatric cardiologists, infectious disease specialists, or rheumatologists may be beneficial, especially for atypical or refractory cases. Patients with large or giant coronary aneurysms are at high risk of coronary artery thrombosis related to stasis and may also benefit from consultation with hematology specialists in addition to a cardiologist.

CASE FOCUS

Plan for Treatment and Monitoring

- **IVIG:** After discussing Brian's suspected diagnosis with his family, you offer immediate initiation of IVIG. His parents agree to start treatment.
- **ASA:** You order high-dose ASA therapy to start now, with plans to change to low-dose once Brian is afebrile.
- **Echocardiogram:** Given that Brian meets criteria for incomplete KD based on his clinical findings and laboratory data, the results of the echocardiogram are unlikely to change your acute management decisions. You order an echocardiogram to be done in the morning.
- **Monitoring:** You review Brian's current orders for vital signs (temperature, heart and respiratory rate, blood pressure, and oxygen saturation) and keep them as they are: repeating every 4 hours. You add special orders that vital signs should be checked 15 minutes prior to IVIG infusion, 15 minutes after the start of IVIG infusion, and 30 minutes after completion of IVIG infusion, in addition to the regularly scheduled checks. You determine that more intensive monitoring is not needed at this time based on the absence of signs of cardiac dysfunction. You order repeat serum chemistries in 12 hours to ensure that Brian's liver function tests remain stable.
- **Consultation:** You plan to notify cardiology about Brian's case early the next morning so they can review his echocardiogram, provide an inpatient consultation if any changes are noted, and arrange follow-up care.

Case Resolution

After your discussions with Brian's family, he is started on high-dose aspirin and given an infusion of IVIG. He appears increasingly uncomfortable while receiving IVIG, but this resolves with slowing the infusion rate and administering acetaminophen. The following morning, Brian undergoes echocardiography and is found to have mild dilation of the main right coronary artery. He remains febrile for the next 20 hours, at which point he defervesces. During this time, there is noted improvement in his rash. A CRP level is obtained 36 hours after resolution of his fever and is trending downward at 5.7 mg/dL (57 mg/L). Subsequently, Brian is transitioned to low-dose aspirin and discharged with plans to follow up with cardiology in several days (approximately 2 weeks after the start of his illness).

Brian's follow-up cardiology appointment 2 weeks later reveals that his right coronary artery remains dilated, but the internal diameter has not significantly increased, and there are no other signs of aneurysm. At his 6-week cardiology follow-up, Brian's echocardiogram reveals the return of the right coronary artery to normal size, and he is able to discontinue taking daily aspirin.

Discharge Criteria

Q: How do you know when Brian is ready to go home?

You can feel comfortable discharging your patient with KD when the following criteria are met:

- The patient has been monitored at least 36 hours after completion of IVIG infusion.
- The patient is afebrile, and vital signs are otherwise stable.
- The patient is tolerating oral intake, including medications, and is maintaining hydration.
- The patient's KD symptoms are resolving, and inflammatory markers (eg, CRP) are trending downward.

Anticipatory Guidance

Q: What instructions should you provide to Brian's caregivers upon discharge?

- Follow-up echocardiograms will be critical to ensuring that Brian does not develop coronary lesions. Brian should undergo another echocardiogram in 2 weeks and then again in 4 to 6 weeks.
- Continuing to take low-dose aspirin after discharge may help reduce cardiovascular complications.
- For the next 2 weeks, Brian should be monitored closely for recurrence of his fever. If he develops fever, contact his pediatrician or cardiologist right away.
- Because of lack of adequate immunologic response caused by IVIG infusion, live vaccines (eg, the measles, mumps, rubella, and varicella vaccines) should be deferred for 11 months following receipt of IVIG.
- Acute KD can recur in 1% to 3% of cases in the years following diagnosis, so patients should return to care for any recurrent symptoms (eg, prolonged fever, rash, or redness of eyes, mouth, or lips) or for the onset of fatigue, chest pain, or dyspnea on exertion, which should be considered signs of cardiac insufficiency and treated as a medical emergency.
- There is a risk of developing Reye syndrome when a child receives ASA during active influenza or varicella infections. Because of this, the child's caregivers should contact their child's pediatrician to discuss withholding aspirin if the child develops a febrile illness; however, the risk of Reye syndrome is low for children taking low-dose ASA.
- The patient should avoid other nonsteroidal anti-inflammatory drugs while taking ASAs.

Clinical Pearls

- There is no diagnostic test for KD; the diagnosis is made based on clinical criteria.
- Not all features of the diagnostic criteria for KD need to be present at the same time to make the diagnosis in the acute phase of the illness.
- Correctly diagnosing and treating patients is critical: up to 25% of untreated patients will develop coronary artery aneurysms with significant associated morbidity and mortality.
- Serial echocardiograms are critical to ensure stability of the coronary arteries.
- If the coronary artery diameters are within normal limits within the ensuing 4 to 6 weeks, the chance that dilation will occur is exceedingly low.
- Mortality is highest in the year following the acute illness.

Suggested Reading

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CASE 15

Liam, a 6-Week-Old Boy With Poor Weight Gain

CASE PRESENTATION

Before morning rounds, you are preparing to see a 6-week-old boy named Liam who was admitted yesterday from the emergency department (ED) to the pediatric inpatient ward with dehydration and pyelonephritis. Overnight, he received intravenous (IV) fluids and IV ceftriaxone, and his vital signs demonstrate an improving fever curve and improving tachycardia. You note that Liam's blood culture has no growth at 18 hours but find that his urine culture is growing more than 100,000 CFU/mL gram-negative rods. Renal and bladder ultrasonography was completed earlier this morning and was normal.

When you open Liam's growth charts, you notice 2 points, one at birth and one for the current hospitalization. His birth weight was 3.6 kg (69th percentile weight for age), and his weight on the inpatient unit after rehydration is 4.1 kg (6th percentile weight for age). You are concerned about poor weight gain given this drop in his weight-for-age percentiles and realize you need to investigate further.

Patient History and Review of Systems

Q: What information should you collect from Liam's caregivers?

- Symptoms of dehydration, such as a decrease in the number of wet diapers in a 24-hour period, the absence of tears with crying, and the appearance of skin (turgor) and mucous membranes (sticky or dry)
- Presence of emesis and/or reflux, and if present, frequency, amount, and associated symptoms
- Voiding and stooling patterns, color and consistency of stool (eg, watery, solid, seedy, hard), and presence of visible blood or mucus in stool
- A complete feeding history, including the following:
  - The method of feeding (breastfeeding or bottle feeding)
    - If directly breastfeeding, feeding frequency in a typical day (including scheduled or on-demand feeding), total number of breastfeeding sessions in a 24-hour period, feeding positions used, average duration of each breastfeeding session, whether both breasts are offered with each feeding, sensation of breast fullness or engorgement, whether breasts feel less full following a feeding, any pain with latch, leakage of excess milk, and whether the infant is satisfied following breastfeeding.
    - If bottle feeding, the type of milk/formula provided (ie, expressed human [breast] milk or infant formula), the frequency and duration of feedings in a typical day, amount given with each feeding, and the total ounces taken in a 24-hour period.
      - If expressed breast milk is supplied for bottle feeding, volume expressed with each pumping session.

    - If formula is provided, the type of formula, any changes in formula since birth, the method of formula preparation, and who in the household provides the feedings.
  - Comparison of current intake (while ill) to intake when previously well
  - Difficulty with feeding (eg, sweating, choking, gagging, fatigue, cyanosis)
  - Any history of other dietary offerings (eg, water, tea, juice, rice cereal)
- Developmental history
- Medical history
  - Complete birth history, including gestational age, birth weight, maternal history of prenatal care, maternal age, location and mode of delivery, any complications or infections during pregnancy, abnormalities on fetal ultrasound or genetic screening, postnatal complications, and any noted changes to the mother's breasts during pregnancy, especially an increase in size
  - Newborn screening results
  - Number of visits to the pediatrician's office with growth parameters at each visit
  - Any history of evaluation for poor weight gain
- Medication history, including over-the-counter medications or supplements
- Complete family history, including any history of renal disease as well as heights and weights of parents and siblings
- Social history, including information about the infant's caregivers and the presence of additional stressors, postpartum depression, and food insecurity

CASE FOCUS

History and Review of Systems

You learn that Liam was born at 37 6/7 weeks' gestation via spontaneous vaginal delivery to a 25-year-old gravida 1, para 1 mother. Prenatal care occurred at the university clinic and was negative for complications. There were also no complications with Liam's delivery. His newborn course was unremarkable, with passage of his meconium in the first 24 hours after birth and adequate urine output. Liam breastfed every 2 to 3 hours during his birth hospitalization, and the nursing staff felt his latch was adequate. Liam and his mother were both discharged 30 hours after delivery. Because Liam was born and discharged on a weekend, his mother did not see a lactation consultant during their hospitalization. Liam was seen by his pediatrician for a weight check the day after discharge, and his weight at that time per his parents was "fine." Because Liam's father returned to work a few days after his birth, his mother did not have transportation to Liam's 2-week appointment, and he has not been seen in the clinic since the initial postdischarge pediatrician visit. He has his 2-month visit scheduled in 2 weeks' time.

Liam is exclusively breastfeeding every 3 to 4 hours for 45 to 60 minutes at a time and once overnight (6–7 times in a 24-hour period). His mother offers both breasts with each breastfeeding session. He is usually fed in the cradle or side-lying positions. His mother has never noticed Liam to have any choking, sweating, or difficulty breathing during his feedings. Liam tends to fall asleep while breastfeeding. He always seems fussy at the end of breastfeeding sessions, but his parents give him a pacifier and soothe him until he falls asleep. His mother reports that feeding is going fairly well but does sometimes hurt. Liam does not frequently spit up. His mother has never attempted to express her breast milk but says her breasts do feel full before feeding and empty at the end. She has a history of breast reduction surgery 3 years ago but states her breasts did grow in size during pregnancy and denies any other risk factors for breastfeeding challenges. She does not take any medications or supplements.

Liam has 4 to 5 wet diapers in a day. He stools 2 or 3 times per day, and it is small in volume and yellow in color with a seedy texture. Developmentally, Liam fixes on faces and has started to smile. He does not enjoy tummy time but is able to lift his head when prone.

CASE FOCUS

History and Review of Systems *(continued)*

Liam's family history, social history, and review of systems are otherwise unremarkable. In the electronic medical record, you are able to see that Liam's newborn screen from his birth hospitalization was normal.

Liam's mother reports that since birth, she thinks that Liam has been doing well. She did not notice any problems with his weight and thought that breastfed infants were supposed to be smaller than formula-fed infants. She and her partner brought Liam into the ED yesterday morning because of 1 day of increased fussiness and fever. Liam continued to feed fairly well despite being ill, and she reports that his intake overnight and this morning is at his baseline. His fussiness has improved overnight with treatment of his pyelonephritis.

Physical Examination

Q: What parts of the physical examination should you focus on for Liam?

- Complete set of vital signs
- Current weight, length, and head circumference compared with his birth weight, length, and head circumference
- General appearance: alertness, level of distress, hydration status, presence of cachexia or dysmorphic features, any obvious loose skin, temporal wasting, or loss of typical infant fat pads (eg, the cheeks)
- Evaluation of the infant's oral anatomy, latch, and suck, including evidence of ankyloglossia or cleft lip or palate
- Presence of scleral icterus or jaundice
- Abdominal: masses, hepatosplenomegaly, ease of palpitation of kidneys
- Cardiopulmonary: cardiac murmurs or gallops, work of breathing
- Presence of edema (eg, periorbital, peripheral, ascites) or abnormalities of the hair or nails
- Examination of a stool sample, if available
- Parent-infant interaction

CASE FOCUS

Physical Examination

Liam is afebrile with normal vital signs for his age. His weight is 4.1 kg (6th percentile weight for age), head circumference is 38 cm (43rd percentile for age), and length is 56 cm (39th percentile for age) on the World Health Organization (WHO) birth–to–2 year growth charts. You note that at birth, his weight was 69th percentile, head circumference was 50th percentile, and length was 50th percentile.

Liam is asleep but arouses when undressed and appears thin for a 6-week-old infant. His anterior fontanelle is open, soft, and flat, and there is no scleral icterus. His facies appear normal with symmetric expression, but his cheeks do not have fat pads. There is no periorbital edema. His oral examination demonstrates normal suck without evidence of cleft palate

(continued)

CASE FOCUS

Physical Examination *(continued)*

or ankyloglossia. His cardiac and lung examinations are benign. His abdomen is flat without masses or organomegaly. His kidneys are not easily palpated, and his genitourinary examination shows a normal, uncircumcised boy with descended testes. His buttocks are thin with no subcutaneous fat, and some loose skin folds are noted on his buttocks and thighs. There is no jaundice or rash. On neurologic examination, Liam has mild head lag when pulled to sit and slightly decreased head control when upright. He is able to lift his head slightly when prone. At rest, Liam's arms are open with fingers slightly relaxed, and his legs are flexed. His muscle tone is normal. His deep tendon reflexes and primitive reflexes are normal, including Moro, rooting, palmar and plantar grasp, suck, cough, and gag reflexes. He has sparse hair on his head, and his fingernails and toenails are normal. He has stool in his diaper that is yellow and seedy, without evidence of gross blood or mucus.

During your time in the room, you observe that Liam's parents respond to his cues and seem concerned about his comfort. They attempt to console him when he cries during and after your examination. Both parents appear well bonded with Liam.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an infant with poor weight gain?

The causes of poor weight gain in an infant or child are commonly divided into 4 categories, although some etiologies involve elements of more than one category. See Table 15.1 for a list of many possible causes.

In reviewing this table and taking into consideration Liam's age, the most likely etiology for his poor weight gain is suboptimal intake related to low maternal breast milk production, uncoordinated suck/suboptimal latch, or insufficient number of daily feedings. Decreased intake or increased metabolic requirements related to recurrent or chronic urinary tract infections also needs to be considered. Cow milk protein intolerance, dysphagia, and insufficient caloric intake related to significant gastroesophageal reflux or vomiting from pyloric stenosis are among the other causes to consider in young infants.

Table 15.1. Differential Diagnosis of Poor Weight Gain in Infants and Children

Category	Potential causes
Decreased caloric intake	• Ankyloglossia (tongue-tie)[a] • Behavioral causes, such as picky eating or oral aversion • Brain tumor • Child abuse/neglect • Decreased intake related to illness or medication side effect • Food insecurity or inappropriate dietary offerings (eg, excessive juice consumption) • Gastroesophageal reflux or vomiting • Hypothyroidism • Incorrect formula preparation • Low breast milk production[b] • Neuromuscular disease • Oral motor dysfunction • Other causes of inadequate total daily caloric intake, such as prolonged time between feedings[b] • Uncoordinated suck/dysphagia with poor transfer of breast milk[b]

Table 15.1. Differential Diagnosis of Poor Weight Gain in Infants and Children *(continued)*

Category	Potential causes
Failure to absorb nutrients (malabsorption)	• Biliary atresia • Celiac disease • Chronic intestinal inflammation such as IBD • Cow milk protein allergy, such as FPIAP or FPIES • CF • GI infection • GI malformation • Genetic disorders • Short-bowel syndrome/intestinal failure
Increased or altered metabolic requirements	• Burn injuries • Chronic lung disease • CHD or heart failure • Genetic disorders • Hyperthyroidism • Illness or inflammatory process, such as with sepsis or UTI • Immunodeficiency • Inborn error of metabolism • Malignancy • Prematurity (high metabolic demand) • RTA
Fluid or nutrient losses	• Adrenal insufficiency or CAH • Chronic diarrhea • DI or DM • GI infection • Genetic disorders • Nephrotic syndrome • Prematurity (high risk for fluid loss) • Protein-losing enteropathy • Renal disorders

Abbreviations: CAH, congenital adrenal hyperplasia; CF, cystic fibrosis; CHD, congenital heart disease; DI, diabetes insipidus; DM, diabetes mellitus; FPIAP, food protein–induced allergic proctocolitis; FPIES, food protein–induced enterocolitis syndrome; GI, gastrointestinal; IBD, inflammatory bowel disease; RTA, renal tubular acidosis; UTI, urinary tract infection.

[a] Care should be taken when attributing poor weight gain in a breastfed infant to ankyloglossia, and other possible etiologies should be considered.

[b] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for infants who present with poor weight gain?

- The diagnostic evaluation for poor weight gain in infants is highly variable, depending upon the severity and the findings from the infant's history and examination.
- Given that inadequate caloric intake is the most common cause of poor weight gain in infants, for breastfed infants, it is important to first evaluate the latch, the quality of breastfeeding, and the breastfeeding parent's breast milk

supply. Pediatricians should be able to evaluate the breastfeeding dyad effectively; however, when physicians are not skilled at performing this assessment, it should be done by a lactation consultant.

- If consent is granted by the breastfeeding parent, the session can begin with inspection of the breast fullness and shape and appearance of the nipples (evaluating for flat or inverted nipples or signs of nipple irritation). The breastfeeding parent can also manually express the breasts to demonstrate the presence of milk. Following the feeding session, physicians should again inspect the breastfeeding parent's breasts to note the appearance of the nipple. Breast nipple shape should be domed without any slanting, chapping, or injury that would indicate suboptimal latch.
- Observing a breastfeeding session can allow assessment of the latch and signs of milk transfer, such as audible swallowing and observation of jaw movement. Infants should demonstrate a good latch with an adequately wide-open jaw that latches over the breastfeeding parent's nipple and onto the areola. Feeding should be associated with audible and visualized swallows of milk. Nipple pain during breastfeeding may be another sign of an inadequate latch. Refer to Figure 15.1 for an illustration of infant latching.
- Obtaining weight differences, or test weights, before and after breastfeeding can give the physician an approximate measurement of the amount of milk transferred per breastfeeding session. To ensure accuracy, a hospital-grade infant scale should be used and the infant should have test weights done over several days at different times of the day.
- Another option to evaluate the milk supply is for the breastfeeding parent to express breast milk using a hospital-grade double electric breast pump 2 to 3 hours after the last breastfeeding session started. It should be noted, though, that the volume of milk the infant transfers during feedings at the breast may differ from the pumped volume.

- For formula-fed infants with poor weight gain without a clear etiology, the diagnostic evaluation may include an observation of formula preparation and a bottle-feeding session.
- For both formula and breastfed infants with poor weight gain of unknown etiology, an evaluation by a speech-language pathologist and a period of close outpatient or in-hospital observation with documentation of serial weight measurements and the frequency, duration, and volume of feedings (calorie counts) can be helpful. Clinicians can then compare this with expected caloric and weight goals for the infant's age. During the first 3 months after birth, term infants should consume between 95 and 110 kcal/kg/d and gain approximately 25 to 30 g/d.
- For infants with poor weight gain, the yield of routine laboratory testing is low unless there is clinical suspicion for an underlying disorder. If clinicians have concerns that would require further screening, it is reasonable to obtain laboratory tests, which may include
  - Complete blood cell count (CBC) with red cell indices to screen for anemia caused by certain micronutrient deficiencies.

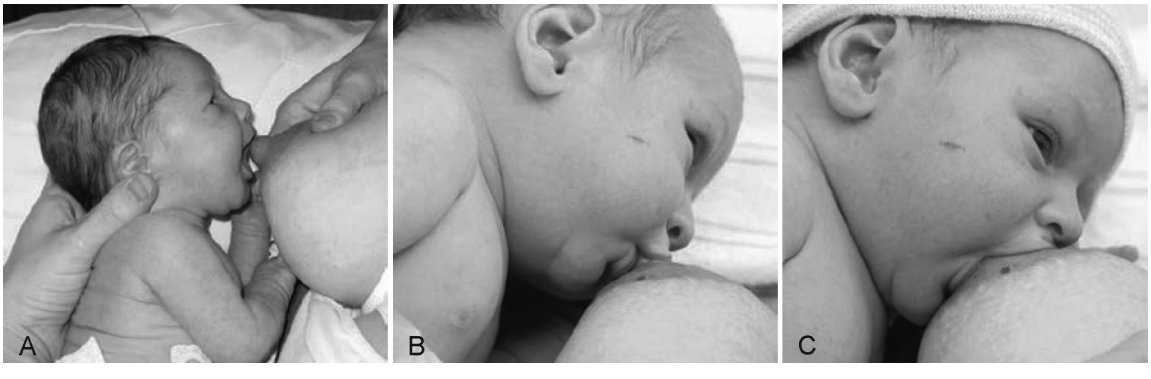

Figure 15.1. Infant latching. A, Initiation of the latch with proper positioning and insertion of the breastfeeding parent's nipple into a widely opened mouth. B, Illustration of a shallow, inadequate latch. C, Illustration of an appropriate latch.

Reprinted with permission from UC San Diego Health. *Breastfeeding Guide and Log Book*. San Diego, CA: UC San Diego Health.

- Serum chemistries to screen for overt renal and hepatic disease or electrolyte abnormalities. Abnormalities in these laboratory test results could be a clue to the underlying etiology of poor weight gain but also may be caused by poor nutrition or dehydration.
- Stool studies, such as fecal fat and reducing substances to test for malabsorption, if suspected.
- Celiac disease screening if the infant's diet contains gluten.
- Sweat chloride testing if the infant has no known newborn screen or if there is additional history concerning for cystic fibrosis (eg, persistently poor growth, family history, history of meconium ileus).
- Screening for endocrinopathies (eg, hyperthyroidism, adrenal insufficiency).
- Serum amino acids, urine organic acids, urine reducing substances, and serum acylcarnitine profile, if there is concern for an inborn error of metabolism.

- In all infants with weight loss or poor weight gain, clinicians should strongly consider a multidisciplinary evaluation involving a pediatrician, a pediatric speech-language pathologist, a pediatric-certified registered dietician, and a lactation consultant (for infants who breastfeed).

CASE FOCUS

Diagnostic Evaluation

With the mother's permission, you examine her breasts and observe a breastfeeding session, including pre- and postfeeding weights of the infant. You note that Liam's mother's breasts are full, symmetric, and have well-healed periareolar scars on both breasts. Her nipples are everted and appear mildly inflamed. You ask her to manually express, and this does elicit milk from both breasts.

Liam's prefeeding weight is 4,030 g. His mother holds him in a cradle hold and uses a pillow to help support his body. You note that Liam latches to the left breast and sucks actively for about 4 minutes; he then falls asleep at the breast, during which time his sucking slows. After short bursts of sucking, audible swallows are noted. His upper and lower lip appear flanged but are not covering the areola. He will briefly suck faster when stimulated. After 20 minutes of being calm at the breast and sucking, Liam is taken off the breast and cries. The same pattern is repeated on the right breast.

After the feeding session, maternal breast examination reveals everted inflamed nipples that are slanted at the tips. Liam's postfeeding weight is 4,060 g for a net gain of 30 g. When asked, his mother states that this breastfeeding session was typical, except that she usually allows Liam to sleep and feed at the breast for a total of 45 to 60 minutes.

You review Liam's previously obtained laboratory test results, screening, and imaging:

- **The results of Liam's CBC and comprehensive metabolic profile are normal except for a mild leukocytosis, with a white blood cell (WBC) count of 14,700/μL (14.7 × 10^9/L). His creatinine level is normal at less than 0.3 mg/dL (26.5 μmol/L). His liver enzymes, bilirubin, and serum albumin are within normal limits.**
- **His urinalysis shows a large number of WBCs, large leukocyte esterase, and nitrites but is otherwise normal without hematuria or proteinuria.**
- **His renal and bladder ultrasonography, obtained earlier in the day, is normal.**

Arriving at a Diagnosis

Q: How do you develop an assessment for Liam?

The assessment of a young infant with poor weight gain can be complicated. To arrive at the underlying etiology for Liam's poor weight gain, you will need to interpret his growth charts to formally assess his nutritional status, assess his developmental status, and then interpret the other findings from his history, examination, and diagnostic evaluation. You can then develop a list of findings to arrive at an underlying etiology for Liam's presentation.

1. **Interpret key findings from the history, growth curve, examination, and diagnostic evaluation.**
   - Assessment of growth and nutritional status: Because Liam was noted to have a significant drop-off in his weight-for-age percentiles (69th to 6th), it is important to define his nutritional status more accurately, because this may affect your interventions.
     - In the past, poor growth in an infant was commonly referred to as *failure to thrive*; however, this term has largely been replaced with a more precisely defined term: *malnutrition*. Although malnutrition can be categorized into either overnutrition or undernutrition, it is commonly used to mean undernutrition.
     - *Undernutrition* is defined as an imbalance between nutrient requirements and intake. It results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other outcomes.
     - When an infant or child's height/length, weight, or body mass index parameters cross percentiles over time, clinicians should evaluate for the possibility of malnutrition and, when present, seek to find the etiology. Furthermore, during any hospitalization for an acute illness, assessment of an infant's nutritional status is an important component of their care. Not only is malnutrition/undernutrition associated with an increased susceptibility to infection, poor wound healing, and an increased mortality during illnesses, but malnutrition/undernutrition also places infants and children at risk of not realizing their full cognitive potential and not achieving their full height. Additionally, malnutrition in infancy/childhood can lead to muscle weakness and is thought to affect health outcomes even in adulthood.
     - For infants, malnutrition/undernutrition is commonly defined through use of anthropometric *z* scores based on WHO growth curves. A *z* score is defined as the number of SDs away from the mean. A *z* score of 0 is equivalent to the 50th percentile, a *z* score of +1 is 1 SD above the mean, a *z* score of −1 is 1 SD below the mean, and so forth. Refer to Table 15.2 for how to classify the severity of malnutrition in infants.

Table 15.2. Classification of the Severity of Malnutrition/Undernutrition in Infants

	Mild malnutrition/ undernutrition	Moderate malnutrition/ undernutrition	Severe malnutrition/ undernutrition
Weight-for-length (*z* score)	−1 to −1.9	−2 to −2.9	≤ −3
Deceleration in weight-for-length (*z* score)	Decline of 1 *z* score	Decline of 2 *z* scores	Decline of 3 *z* scores
Weight gain velocity	<75% of the norm for expected weight gain	<50% of the norm for expected weight gain	<25% of the norm for expected weight gain
Inadequate nutrient intake	51%–75% of estimated energy/protein need	26%–50% of estimated energy/protein need	≤25% of estimated energy/ protein need

Adapted with permission from Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. American Academy of Pediatrics; 2019:785–786.

     - Defining chronicity: Malnutrition/undernutrition can be classified as acute (<3 months) or chronic (≥3 months).
       - Acute malnutrition/undernutrition results in a change in weight over time that is characterized by a decrease in the infant's weight-for-length percentile. In other words, the infant usually continues to grow appropriately in length in the short term.
       - Chronic malnutrition/undernutrition is commonly characterized by a faltering length-for-age and can affect the infant's long-term growth.
     - To apply these definitions to Liam's case, you first begin by plotting Liam's values for weight, height, and head circumference on WHO growth curves. Finding an infant's exact growth curve percentiles and *z* scores can be facilitated by the use of online calculators such as those found at https://PediTools.org.

- Liam's birth measurements are as follows:
  - Weight of 3.6 kg (69th percentile weight-for-age, *z* score 0.5)
  - Head circumference of 34.5 cm (approximately 50th percentile head circumference-for-age, *z* score 0)
  - Length of 50 cm (approximately 50th percentile length-for-age, *z* score 0)
- Liam's current measurements are as follows:
  - Weight of 4.1 kg (6th percentile weight-for-age, *z* score −1.5)
  - Head circumference of 38 cm (43rd percentile head circumference–for–age, *z* score −0.2)
  - Length of 56 cm (39th percentile length-for-age, *z* score −0.3)
- His current weight-for-age has a *z* score of −1.5, and his birth weight *z* score was 0.5. Comparing these 2 values shows a change of −2 *z* scores since birth. Applying this change in his *z* scores to Table 15.2, Liam demonstrates evidence of moderate malnutrition/undernutrition. See Figure 15.2 for an illustration of Liam's weight percentiles and *z* scores over time.

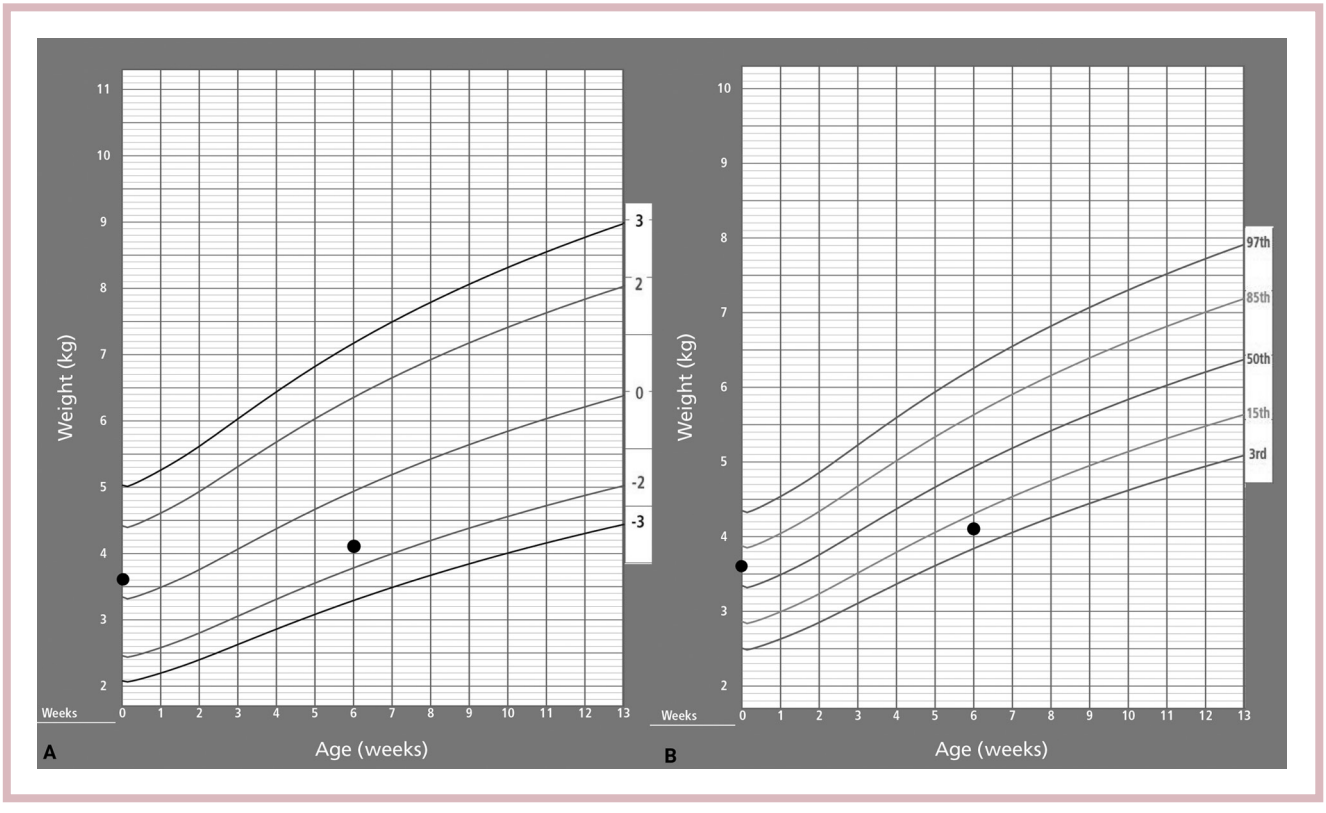

Figure 15.2. Liam's weight-for-age plotted for both his birth weight and his current weight, using the WHO growth curves. A, Liam's weight-for-age *z* scores. B, Liam's weight-for-age percentiles.

Growth charts courtesy of WHO. Adapted from Weight-for-Age Boys Growth Chart (*z* scores). World Health Organization. Accessed February 1, 2022. https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-age/boys-charts---weight-for-age-birth-to-6-months-(z-scores).pdf?sfvrsn=dd5d32be_6; Weight-for-Age Boys Growth Chart (percentiles). World Health Organization. Accessed February 1, 2022. https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-age/boys-charts---weight-for-age-birth-to-6-months-(percentiles).pdf?sfvrsn=2a49ab55_6. WHO is not responsible for the content or accuracy of this adaptation.

  - For an infant born at or near the 50th percentile in weight-for-age, expected weight gain for the first 3 months after birth should average 25 to 30 g/d. For Liam, his weight gain averages at just under 12 g/d, slightly less than half of what is expected. Comparing this to Table 15.2 also places Liam in the moderate malnutrition/undernutrition category.
- Assessment of Liam's developmental status: Because malnutrition/undernutrition can adversely impact an infant's cognitive and motor development, an infant's development should be assessed as part of a malnutrition assessment.

- Liam is described as being able to look at faces, starting to smile, and able to slightly lift his head up when prone. On examination, you also noted that he spontaneously opens his fingers.
- According to Table 15.3, Liam is demonstrating appropriate developmental skills for his age.

Table 15.3. Developmental Milestones for Young Infants

Age	Social language and self-help	Verbal language (expressive and receptive)	Gross motor	Fine motor
Newborn–1 week	Makes brief eye contact with adult when held	Cries with discomfort Calms to an adult voice	Reflexively moves arms and legs Turns head to side when on stomach	Holds fingers closed Grasps reflexively
1 month	Calms when picked up or spoken to Looks briefly at objects	Alerts to unexpected sound Makes brief short vowel sounds	Holds chin up in prone position	Holds fingers more open at rest
2 months	Smiles responsively (ie, social smile)	Vocalizes with simple cooing	Lifts head and chest in prone position	Open and shuts hands

Adapted with permission from Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents* [pocket guide]. 4th ed. American Academy of Pediatrics; 2017:113–117.

- Other important findings from the history, examination, and diagnostic evaluation
  - History: Liam is an exclusively breastfed term infant who nurses for 45 to 60 minutes per session approximately 6 to 7 times in a 24-hour period. He is offered both breasts during each feeding session, and his mother feels that her breasts are empty postfeeding. Liam is fussy after being taken off the breast and is soothed through use of a pacifier. He does not have significant spit-ups. His parents report normal stooling but fewer daily voids than would be expected, suggesting inadequate intake. He currently has an acute illness (pyelonephritis) for which he is hospitalized, but his mother reports his intake has not been significantly affected by this illness. His mother has a history of reduction mammoplasty, which is a known cause of low breast milk production; however, she notes that her breasts did grow in size during her pregnancy, suggesting that she does have some glandular tissue.
  - Physical examination: On examination, Liam has a thin appearance, with mildly decreased strength, which may be related to his nutritional status. He is noted to have very little subcutaneous fat in his cheeks and buttocks and loose skin on his buttocks and thighs. Liam's examination is otherwise normal with no signs of ankyloglossia, a genetic disorder, or congenital heart disease. His stool has a normal appearance for a breastfed infant. He does not have other abnormal examination findings associated with kwashiorkor or severe micronutrient deficiencies, such as edema, hepatomegaly, or abnormalities of skin, hair, and nails.
  - Diagnostic evaluation: Liam's CBC and serum chemistries are normal except for mild leukocytosis, which is likely related to his acute infection. His urinalysis does show WBCs, leukocyte esterase, and nitrites consistent with infection but is otherwise normal. Renal and bladder ultrasonography is normal as well.
  - During the observed breastfeeding session, Liam's mother's breasts are noted to be full and symmetric, with everted nipples. Liam's latch appears shallow, with inadequate coverage of the areola. He does have audible swallowing, which indicates some milk transfer, but he falls asleep quickly and does not actively suck for much of the time at the breast. Following the feeding, Liam demonstrated a weight gain of 30 g during a test weight, which corresponds to a feed of 30 mL of breast milk. Ideally, infants at 6 weeks of age will drink between 60 and 120 mL during a feeding session, so this breastfeeding session had suboptimal transfer of breast milk. Additionally, assessment of Liam's mother's nipples following the feeding session shows signs of inadequate latch, with nipple inflammation and a slanted nipple tip.

2. **Develop the list of findings.**

Q: What major findings have you identified for Liam?

- Acute moderate malnutrition
- Insufficient transfer of breast milk during an observed feeding session
- Suboptimal latch
- Pyelonephritis

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Liam's presentation?

Determining the etiology of inadequate breast milk intake is complex, and Liam's malnutrition/undernutrition is likely multifactorial.

- Understanding the norm: During breastfeeding sessions, each breast should be offered, and sessions should last between 20 to 30 minutes total and occur 8 to 12 times per day in the first 1 to 2 months after birth. At Liam's age, it is expected that he will transfer at least 2 oz of breast milk per session, but his intake during his observed session was 1 oz. It seems that Liam's breastfeeding sessions are characterized by low breast milk transference, inefficient breastfeeding (sleeping at the breast with infrequent sucking), prolonged duration at the breast (45–60 minutes instead of 20–30 minutes), and decreased frequency compared with the norm (every 3–4 hours instead of every 2–3 hours). Additionally, he was found to have a suboptimal latch during an observed feeding. The American Academy of Pediatrics recommends delaying introduction of a pacifier until after breastfeeding is well established, and it is possible that pacifier use is contributing to breastfeeding difficulties for Liam.
- Based on the history, examination, and diagnostic evaluation, you are concerned about 3 major contributing factors:
  - The possibility of low milk production in the mother related to reduction mammoplasty
  - Suboptimal latch and inefficient sucking contributing to poor milk transference (which can contribute to the mother's inadequate milk production)
  - Fewer daily breastfeeding sessions than expected, with prolonged duration of each session
- Although malnutrition/undernutrition can be a symptom of renal disease in infants, following Liam's laboratory evaluation, imaging, and considering his history and examination findings, you suspect that he does not have any underlying urinary or renal abnormalities. Additionally, although an acute illness, such as pyelonephritis, can lead to poor intake and acute malnutrition, Liam's illness has been present only for 1 to 2 days, and his intake appears to have remained close to his baseline throughout his illness. At this point, it seems less likely that his malnutrition is related exclusively to his acute infection of pyelonephritis, given that his diagnostic testing does not seem to indicate any chronicity to his illness or renal problems.
- Other findings from Liam's history, examination, and diagnostic evaluation appear to decrease the likelihood of the other diagnoses in Table 15.1; however, this list of diagnoses should be revisited if Liam does not appear to gain weight and improve his strength as you would expect after the reintroduction of adequate nutrition.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for an infant or child with malnutrition/undernutrition?

Ideally, an infant or child with malnutrition/undernutrition would be evaluated and managed by their pediatrician in their medical home, but some infants and children with malnutrition require hospitalization for evaluation, treatment, and monitoring. Indications for hospitalization in infants or children with malnutrition/undernutrition include, but are not limited to, the following:

- The infant or child has severe protein-energy malnutrition, and thus is at risk of refeeding syndrome.
- The infant or child's condition continues to worsen despite outpatient management.

- The infant or child's family is unable to follow up closely with their pediatrician.
- There is concern for the safety of the infant or child.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Liam is a 6-week-old former term infant boy admitted for pyelonephritis and found to have acute moderate malnutrition likely from inadequate intake of breast milk. A suboptimal latch resulting in poor milk transference, infrequent feeding sessions, and low milk production in a primiparous mother with a history of reduction mammoplasty are likely contributing factors.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The primary goals when caring for a breastfeeding infant with malnutrition/undernutrition are to improve their nutritional status with supplementation while working to increase breast milk supply and improve milk transference during breastfeeding sessions. If this proves successful, supplementation can be discontinued at a later time. Although breast milk is the ideal nutritional source for infants, and clinicians should promote breastfeeding whenever feasible, it is also important to incorporate the breastfeeding parent's goals into the treatment plan and ensure they desire to continue breastfeeding. Liam's mother has told you that her goal is to continue to breastfeed and hopes to be able to exclusively breastfeed Liam in the future.

Breaking down Liam's treatment plan into actionable steps will help formulate an appropriate inpatient plan of care and facilitate transition to outpatient care.

1. **Feeding and supplementation for the exclusively breastfed baby:** To determine how much supplementation to provide Liam, it is important to first consider how much energy infants require for adequate growth and development. Table 15.4 demonstrates energy requirements by age and sex. It should be noted that energy requirements may be higher in infants with some underlying chronic medical conditions (such as chronic heart failure) and in states of malnutrition/undernutrition when additional energy for catch-up growth is required. Consultation with a pediatric registered dietician is recommended when available.
   - Using Table 15.4, male infants between 1 and 2 months of age should consume approximately 104 kcal/kg/d, which is equivalent to 156 mL/kg/d of 20 kcal/oz breast milk or formula ([104 kcal/kg/d] × [1 oz/20 kcal] × [30 mL/1 oz] = 156 mL/kg/d).
     - At 4.1 kg of weight, using 156 mL/kg/d as the goal to maintain adequate growth, Liam should be consuming approximately 640 mL/d (or 80 mL every 3 hours). If he is taking 30 mL per breastfeeding session every 3 hours, he requires an additional 50 mL at each feeding to meet his energy requirements. A dietician may recommend a larger amount to provide extra energy for catch-up growth. This additional intake can be provided as expressed breast milk, donor human milk, or formula. If desired, supplemental feedings can be given via an at-breast lactation aid device, for which supplies and teaching can be offered during hospitalization to ensure success with transition to home.
     - When feasible while hospitalized, Liam's nurses can continue to obtain pre- and postfeeding test weights to assess approximate breast milk intake with breastfeeding sessions.

Table 15.4. Average Energy Requirements for Infants, Based on Age and Sex

Age (mo)	Energy requirements (kg/kg/d) boys	Energy requirements (kcal/kg/d) girls
0–1	113	107
1–2	104	101
2–3	95	94
3–4	82	84
4–5	81	83
5–6	81	82
6–7	79	78
7–8	79	78
8–9	79	78
9–10	80	79
10–11	80	79
11–12	81	79

Adapted from the Food and Agricultural Organization of the United Nations (FAO). *Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation*. October 17–24, 2001; Rome. Accessed April 12, 2022. http://www.fao.org/3/y5686e/y5686e00.pdf

- If an infant is unable to meet their nutritional goals with oral feeding, a nasogastric tube (NGT) can be considered for short-term supplementation. Most commonly, the NGT is used as a method to provide extra calories immediately after the infant nurses or drinks from a bottle. This technique involves the infant first drinking by mouth (usually limited to 15–20 minutes so as not to cause excess calorie expenditure) and then receiving the remainder of their nutritional goals by NGT gavage. Longer-term feeding difficulties can be managed by a pediatrician with expertise in managing feeding difficulties, often in collaboration with a registered dietician, speech-language pathologist, and lactation specialist (if breastfeeding). For infants with longer-term feeding challenges, surgical gastrostomy tubes are sometimes indicated.

2. **Optimization of breastfeeding and milk supply**
   - For a 6-week-old infant, direct breastfeeding should occur at least 8 times in a 24-hour period. For an infant who nurses efficiently and for a mother with an adequate milk supply, ideal breastfeeding sessions will last 20 to 30 minutes total, and the infant will feed from both breasts during each session. For infants that quickly fall asleep and suck infrequently, frequently stimulating the infant during the feed can help them to nurse more effectively.
   - For Liam, maternal breast examination following the observed breastfeeding session found signs of suboptimal latch, including lack of coverage of the areola during the feed and inflamed nipples with slanted tips after the feed. Because Liam's mother desires increased success with breastfeeding, working closely with a lactation consultant can help improve Liam's latch and help her increase milk production. Additionally, an evaluation by a speech-language pathologist can be helpful when there are concerns for uncoordinated suck and swallow.

- To increase milk production, breastfeeding parents should be encouraged to breastfeed on demand and then pump or manually express milk following a feed.
  - More frequent feedings and completely emptying the breasts with each feed will help stimulate milk production.
  - Manual compression of the breast tissue during expression can also help to drain the breast as much as possible. Small volumes collected from manually expressing or pumping can then be fed to the baby via an at-breast lactation aid device, cup, syringe, or a baby bottle. Use of an at-breast lactation aid device has the advantage of being able to further help to stimulate milk production.
  - Galactagogues are not routinely recommended until there has been formal evaluation by a breastfeeding medicine physician or lactation consultant, other etiologies of low milk production have been considered, and the milk supply has not improved after a trial of more frequent and more complete breast drainage.
  - To determine if routine use of these interventions is helping to increase the breastfeeding parent's milk supply, the parent and infant will need to be evaluated in approximately 1 week. This evaluation can be done by the infant's pediatrician or a lactation specialist.
- The American Academy of Pediatrics recommends against pacifier use until breastfeeding is well established. For Liam, it is reasonable to minimize pacifier use until his intake of breast milk improves.

3. **Monitoring:** To monitor for weight gain, daily weights should be obtained while the infant is an inpatient, followed by twice weekly and then weekly weights as indicated following discharge. In addition, documentation of the infant's intake and output is useful to approximate their caloric intake. In severely malnourished infants or children, frequent vital sign monitoring and daily laboratory monitoring for signs of refeeding syndrome may be needed.

BACK TO BASICS

Refeeding Syndrome

- Refeeding syndrome can occur in infants and children who suffer from chronic severe malnutrition or rapid weight loss.
- Refeeding syndrome is a metabolic consequence of reintroduction of carbohydrates in patients experiencing severe malnutrition. During starvation, the body consumes all glycogen storage, conserves protein for amino acid synthesis, and uses fat as the primary energy source. In addition, ions that are normally in the intracellular and extracellular environment are depleted. When carbohydrates are reintroduced to the diet, the body switches to catabolic pathways by using glucose. In this switch, phosphorus is consumed in the creation of high-energy bonds in the production of adenosine triphosphate. This leads to life-threatening hypophosphatemia.
- Refeeding syndrome typically presents on day 5 of treatment. In addition to hypophosphatemia, refeeding syndrome can cause other abnormal laboratory test results, including hypomagnesemia, hypokalemia, hyperglycemia, and thiamine deficiency.

4. **Treatment of pyelonephritis:** Refer to Case 8 for a detailed discussion of the treatment of pyelonephritis in infants. For Liam, you will continue ceftriaxone while his urine culture results and sensitivities are pending and then switch to an appropriate oral antibiotic as indicated by the laboratory test results.
5. **Other considerations for infants with malnutrition/undernutrition:** An infant who meets the definition of malnutrition/undernutrition should undergo a multidisciplinary assessment, especially when the infant's history and examination do not clearly point to a unifying diagnosis.
   - Ancillary medical staff, such as social workers, can be of vital assistance in providing resources for families to best care for their infant, such as access to programs or benefits for families needing financial assistance, food bank information, parenting classes, resources related to homelessness, information for parents experiencing mental health issues, and much more.
   - If there is suspicion of neglect or child abuse, child protective services and the hospital's child abuse specialist should be contacted. For Liam, you have a low suspicion for abuse or neglect but will continue to monitor for any concerning behaviors by the parents while he remains hospitalized.
   - Concerns for developmental delay may require consultation with or referral to developmental pediatrics, physical therapy, occupational therapy, or speech therapy. For Liam, you will also request consultation with speech therapy to ensure there are no signs of dysphagia. You plan to monitor his mild weakness for resolution as his nutritional status improves.
   - Malnutrition/undernutrition, in particular in a young infant, can be a herald sign of postpartum depression in a new parent. The Edinburgh Postnatal Depression Scale and a careful history can help elucidate this diagnosis. With her permission, you will provide a scale to Liam's mother.

CASE FOCUS

Plan for Treatment and Monitoring

- **Feeding and supplementation:** Liam's mother should breastfeed for 20 to 30 minutes at least 8 to 12 times in a 24-hour period and supplement each feeding with approximately 50 mL of expressed breast milk, donor human milk, or formula, based on parental preference. You also order a dietician consultation and pre- and postfeeding test weights for 2 feedings while Liam is an inpatient. You will adjust the supplemented volumes if he appears to have improved milk transference during his hospital stay.
- **Improving latch and milk supply:** You will encourage his mother to express breast milk via a hospital-grade breast pump following each breastfeeding session to increase her supply. You will request a lactation consultation to help with his latch and to assist with the plan to increase his mother's breast milk production. You order a speech therapy consultation for a close evaluation of Liam's suck. You suggest application of breast milk to her irritated nipples and discuss recommendations about pacifier use.
- **Monitoring:** You ensure that Liam has all of his intake and output recorded as well as routine vital sign monitoring. You will also order daily weights to monitor for weight gain.
- **Treatment of pyelonephritis:** You order that ceftriaxone be continued while urine culture and sensitivities are pending. You plan to transition to oral antibiotics once the sensitivities return if Liam is otherwise doing well.
- **Other considerations:** You will perform postpartum depression screening for Liam's mother and request an evaluation by social work.

Case Resolution

Over the next 2 days, Liam's urine culture and sensitivities show pan-sensitive *Escherichia coli*, and his antibiotic therapy is changed to oral amoxicillin. His mother's Edinburgh Postnatal Depression Scale is concerning for depression, and the hospital social worker helps her make an appointment with her obstetrician and start telehealth visits with a licensed psychologist. The social worker also identifies that Liam's family qualifies for transportation assistance to and from appointments and provides them with resources about accessing this program.

A lactation consultant, speech therapist, and registered dietician see Liam and his mother and formulate a plan for breastfeeding session duration and frequency, strategies for improved latching and milk transference, expressed breast milk or formula supplementation via a bottle, and routine use of a breast pump after breastfeeding in an attempt to increase her milk supply. Multiple pre- and postfeeding weights show approximately 30 mL of breast milk intake when Liam is breastfeeding for 10 minutes on each breast (20 minutes total), and Liam does well with supplemental expressed breast milk and formula using a bottle with a slow flow nipple in an elevated side-lying position. His mother is able to pump approximately 15 to 30 mL following most breastfeeding sessions, and Liam averages 40 to 60 mL of supplemental expressed breast milk and formula with each feeding. With continued breastfeeding and supplementation with expressed breast milk and formula, Liam demonstrates a weight gain of approximately 40 g/d, and you can see that his strength and appearance are improving.

Upon discharge home on hospital day 4, Liam's parents express comfort with his feeding plan, and they have arranged a follow-up appointment with Liam's pediatrician in 2 days. They have also arranged an appointment with the lactation consultant later in the week to reassess his mother's milk supply.

Discharge Criteria

Q: How do you know when Liam is ready to go home?

You can feel comfortable discharging your infant with malnutrition when the following criteria are met:

- Infant and caregivers demonstrate success with the feeding plan. For Liam, this includes his mother feeling comfortable with latch, the ability to express milk, and plans for supplemental nutrition in addition to direct breastfeeding.
- Stabilization or improvement is noted in the infant's weight.
- Vital signs and examination remain normal without concern for refeeding syndrome.
- Follow-up has been established with the pediatrician, local breastfeeding medicine physician (if available), and/or lactation consultant.

Anticipatory Guidance

Q: What instructions should you provide to Liam's caregivers upon discharge?

- Continue to breastfeed Liam at least 8 to 12 times in a 24-hour period, including overnight. After breastfeeding sessions, continue to pump breast milk and provide Liam with expressed breast milk (or formula supplementation) via cup, syringe, or preferred parental method.
- Follow-up with the lactation consultant to reassess Liam's latch and his mother's breast milk production.
- Return to the pediatrician for any recurrence of fever or emesis, or if Liam otherwise appears unwell.

Clinical Pearls

- There is not a universal definition for *failure to thrive*, and the term refers to a finding or symptom rather than a discrete diagnosis.
- *Malnutrition* is a more specific term with standard definitions. Malnutrition is a common symptom of many conditions. Its cause can be multifactorial and can often be elucidated by careful history and examination rather than laboratory studies.
- The breastfeeding infant-parent dyad should have a careful breastfeeding evaluation by a pediatrician or lactation consultant, which may include an observed breastfeeding session and breast examination of the breastfeeding parent.
- The cause of malnutrition can be straightforward with a clear path to wellness; however, an infant experiencing malnutrition can take months to reach catch-up growth. Often, the pathway to successful growth includes a multidisciplinary team (ie, pediatrician, dietician, nurses, occupational and speech therapists, social workers, and psychologists). In addition, the breastfeeding parent may require additional support from an obstetrician-gynecologist or mental health practitioner.

Documentation Tips

- Use of the term *malnutrition* instead of *failure to thrive* is more descriptive and is preferred for documentation.
- Use of the terms *poor weight gain* or *poor feeding* does not equate to a diagnosis of malnutrition.
- Document the degree of malnutrition (mild, moderate, or severe).
- Include any confirmed or suspected reasons for the malnutrition. Specify whether there is concern for abuse or neglect.
- Document the need for consulting services, (eg, nutrition, gastroenterology, psychology, lactation, women's health, social work).
- Include the need for daily weights, strict monitoring of intake and output, and any need for monitoring for refeeding syndrome.
- Document the need for supplemental tube feeding or parenteral nutrition.
- It is important to include malnutrition as part of the active diagnoses of any hospitalized infant, even if it is not the primary reason for hospitalization, as this can often impact both the severity of illness and the expected duration of hospitalization.

Suggested Readings

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Simon, a 15-Month-Old Boy With Abnormal Movements and Fever

CASE PRESENTATION

A 15-month-old boy, Simon, is brought to the emergency department (ED) by ambulance after his mother witnessed him become unresponsive and have rhythmic movements of his extremities. The movements resolved by the time emergency medical services (EMS) arrived at the family's home. EMS measured Simon's temperature as 40 °C (104 °F) and administered a dose of rectal acetaminophen. His blood glucose level en route to the hospital was 82 mg/dL (4.55 mmol/L). Shortly after arrival at the ED, Simon has another shaking episode witnessed by his nurse. This episode lasts 90 seconds and involves unresponsiveness, rhythmic bilateral flexion and extension of his arms, and eye deviation. The episode resolves without intervention. The ED physician orders a normal saline bolus, acetaminophen, a complete blood cell count, a complete metabolic panel, and a rapid influenza test. She then calls you with an admission request because of Simon's most recent episode.

Patient History and Review of Systems

Q: What information should you collect from Simon's caregivers?

- History of present illness
  - Detailed description of the event at home, including activities and location leading up to the event, description of movements, duration of episode, presence of eye deviation, bladder or bowel incontinence, level of consciousness during and after the episode, and behavior after the episode resolved
  - Fever history, including duration and severity
  - Recent head trauma or the possibility of an unwitnessed ingestion, including availability of medications or other toxic substances in the home
  - Recent illnesses or symptoms such as rhinorrhea, cough, congestion, diarrhea, or vomiting
  - Sick contacts or exposures, including child care attendance
- Associated symptoms, including changes in mental status, abnormal gait, weakness, or neck pain or stiffness
- Medical history, including history of similar or unexplained episodes, vaccination status, allergies, and developmental history
- Medications, including current prescription medications, over-the-counter medications, supplements, or recent antibiotic usage
- Family history, specifically noting seizures, cardiac disease, or sudden death

CASE FOCUS

History and Review of Systems

From your conversation with Simon's mother, you learn that Simon was his normal self until this morning, when he developed a fever up to 38 °C (100.4 °F), a mild cough, congestion, malaise, and a poor appetite. Simon attends child care, and several children there have been sick with similar symptoms. His mother therefore assumed Simon had a viral upper respiratory tract infection and decided to keep him home from child care today because he was not feeling well. Simon has had minimal intake of liquids today and was not interested in eating. He was playing quietly on the floor in the living room just before the abnormal movements began. When his mother looked over at him, she noticed he was lying on his back and was having jerking movements consisting of bilateral rhythmic arm flexion and extension and movements of his lower extremities. His eyes then rolled backward, and he did not respond to his name being called during the episode. His mother immediately called EMS. She thinks the movements lasted "2 or 3 minutes" before ending spontaneously. She noted that Simon had a wet diaper after the event, but she is unsure if his diaper had been wet prior to the episode. He was acting sleepy and less responsive than normal during the ambulance ride.

This is Simon's first such episode. He does not have any significant medical history, does not take any medications, and has received all of his routine vaccinations. He has been developing normally throughout infancy. He currently says "mama" and "dada," is very active and social, and has taken a few steps. Simon's mother denies that he has had abnormal gait, weakness, neck pain or stiffness, or known head trauma recently. She reports that Simon's paternal uncle had seizures with fever when he was a child. She does not think there is any family history of cardiac issues or sudden death. Neither she nor Simon's father has any chronic medical conditions, and they keep only routine antipyretics and multivitamins in the home. They have no reason to believe that Simon could have accidentally ingested any substances.

Physical Examination

Q: What parts of the physical examination should you focus on for Simon?

- Complete set of vital signs
- Level of consciousness, ability to arouse normally, fussiness, ability to console
- Hydration status: mucous membranes (moist, sticky, or dry), presence or absence of tears
- Peripheral perfusion: capillary refill time, temperature of extremities, quality of peripheral pulses
- Head, eyes, ears, nose, and throat: tympanic membranes (bulging, erythema, mobility, purulence), signs of head or neck trauma (bruising, tenderness to palpation), papilledema, oral lesions
- Respiratory: accessory muscle use, auscultation for abnormal breath sounds
- Skin: rashes, bruising, lacerations or other lesions
- Neurologic: fontanelle (bulging, flat, sunken) if not yet closed, presence or absence of meningeal signs, cranial nerve examination, pupillary examination, presence or absence of focal neurologic findings (eg, hemiparesis), signs of increased intracranial pressure (eg, lethargy, altered mental status)

CASE FOCUS

Physical Examination

Simon's vital signs reveal a temperature of 38.7 °C (101.7 °F) and tachycardia with a heart rate of 168 beats/min. His respiratory rate and blood pressure are within normal limits for age.

On physical examination, he is fussy but consolable by his mother. His oral mucosa is dry, but there are no oral lesions. He has decreased tear production, and his capillary refill time is about 4 seconds. His extremities are warm with normal pulses throughout. On head and neck examination, there are no signs of trauma or meningeal signs. His tympanic membranes are normal. Cardiovascular examination reveals a regular heart rate and rhythm without murmur. On his respiratory examination, he is breathing comfortably and his lungs are clear to auscultation bilaterally. No rash, bruising, or other skin lesions are noted. Simon's anterior and posterior fontanelles are closed. On ophthalmologic examination, Simon's pupils are equally round and reactive to light, and his extraocular eye movements are intact. You are unable to assess for papilledema, as Simon is unable to remain still for this portion of the examination. There are no focal findings on neurologic examination. His deep tendon reflexes are brisk, normal, and equal throughout. He has no ankle clonus, and his muscle tone is normal. As you observe him, you note that he is moving all extremities equally and there is no dysmetria or ataxia.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a young child with first-time convulsive movements in the setting of a fever?

The events witnessed by Simon's mother and then in the ED are concerning for seizures. The differential diagnosis for a child with a first-time convulsive seizure in the setting of a fever is shown in Table 16.1 and is divided into causes that seem more and less likely based on Simon's presentation.

Table 16.1. Differential Diagnosis for a Child With Suspected First-Time Convulsive Seizure in the Setting of a Fever

Diagnoses of highest suspicion	• Electrolyte imbalance • Encephalitis (infectious or immune mediated) • Febrile myoclonus • Febrile seizure[a] • Meningitis (viral, bacterial) • New-onset epilepsy • Rigors
Other diagnoses to consider	• Accidental ingestion • ADEM • Cardiac arrhythmia • Convulsive syncope • Hypoglycemia • Intracranial hemorrhage • Metabolic disease • *Shigella* enterocolitis • TBI (accidental or nonaccidental) • Venous sinus thrombosis

Abbreviations: ADEM, acute disseminated encephalomyelitis; TBI, traumatic brain injury.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with first-time convulsive seizure in the setting of a fever?

The diagnostic workup for children presenting with a first-time seizure in the setting of fever may consist of evaluation for both fever and/or seizure activity.

- Workup may be indicated to identify the source of fever if it is not apparent based on history and physical examination.
  - General infectious diagnostic evaluation may include complete blood cell count, C-reactive protein level/erythrocyte sedimentation rate, procalcitonin level, urinalysis (when signs, symptoms, or risk of urinary tract infection exist), and/or blood culture (if bacteremia is suspected).
  - Stool studies or swabs for rapid influenza or streptococcal antigens, SARS-CoV-2, or other viral/bacterial polymerase chain reaction panel should also be considered.
- The need for seizure workup is determined by several factors, including the number and duration of seizures, the pattern of seizure (generalized vs focal), and the patient's clinical status postseizure. In patients with a single, full-body convulsive seizure in the setting of fever who have returned to their neurologic baseline after the expected amount of time (about 1–2 hours postseizure), further diagnostic workup is not generally indicated. If the child has more than one seizure within 24 hours in the setting of fever and/or a seizure lasting longer than approximately 15 minutes and/or focal features, the clinician may have a lower threshold to pursue further seizure workup.
  - When there is concern for meningeal infection or inflammation causing seizure, cerebrospinal fluid studies should be obtained, including red blood cell count, total neutrophil count, glucose, protein, and bacterial culture. Additionally, a meningitis/encephalitis panel by polymerase chain reaction should also be considered when available. History and examination findings concerning for meningeal infection or inflammation as seizure etiologies in infants and toddlers include the following:
    - Inconsolability, poor feeding, or lethargy
    - Persistently abnormal mental status (eg, altered consciousness or confusion) beyond the expected postictal period
    - Bulging fontanelle or focal neurologic findings on examination
    - Pretreatment with antibiotics, which may mask the previously listed signs and symptoms
    - Unimmunized or underimmunized status for *Streptococcus pneumoniae* and/or *Haemophilus influenzae* type b
    - Status epilepticus, which is defined as 5 minutes of continuous seizure activity or 2 or more discrete seizures over a 30-minute period, during which the patient does not return to baseline neurologic function between ictal events
  - Although electrolyte abnormalities are uncommon in healthy toddler-aged children without a preceding history of vomiting or diarrhea, hyponatremia, hypocalcemia, hypomagnesemia, and hypoglycemia can all cause seizure activity. A chemistry panel should be obtained if electrolyte disturbances are suspected.
  - For patients like Simon, with a seizure in the setting of fever who have returned to their neurologic baseline after the expected amount of time, urgent neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) is usually not indicated.
    - Neuroimaging should be considered if the clinician suspects a focal intracranial lesion, hemorrhage, abscess, increased intracranial pressure, trauma, or new-onset epilepsy. Clinical suspicion is dependent on the patient's physical examination and history. CT is useful to exclude emergent lesions, and MRI can be obtained at a later time, typically after neurology consultation.

- An urgent noncontrast CT scan of the head, which can be obtained quickly, should be considered if the patient remains with altered mental status past the expected time frame, focal neurologic findings are present, or there is a history of trauma or concern for nonaccidental trauma.

— Electroencephalography (EEG) should be considered in patients with focal findings on neurologic examination and also can be considered in patients determined to have complex febrile seizure (see discussion of simple vs complex febrile seizures in the Arriving at a Diagnosis section). Consultation with a pediatric neurologist can be helpful in deciding whether to obtain an EEG and appropriate timing. There are some instances in which an urgent EEG might be useful, such as when there are signs of ongoing altered mental status and concern for nonconvulsive status epilepticus.

CASE FOCUS

Diagnostic Evaluation

The results from Simon's laboratory tests obtained in the ED are as follows:

Laboratory test	Result	Reference range
Basic metabolic panel		
Sodium	139 mEq/L (139 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	105 mEq/L (105 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	17 mEq/L (17 mmol/L)	18–24 mEq/L (18–24 mmol/L)
Anion gap	17 mEq/L (17 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	22 mg/dL (7.85 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.5 mg/dL (44.2 μmol/L)	0.1–0.4 mg/dL (8.8–35.4 μmol/L)
Glucose	87 mg/dL (4.83 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Calcium	9.6 mg/dL (2.4 mmol/L)	9.2–10.5 mg/dL (2.3–2.6 mmol/L)
CBC		
WBC count	8,000/μL (8×10^9/L)	7,000–13,000/μL ($7–13 \times 10^9$/L)
Hemoglobin	13 g/dL (130 g/L)	10.5–14 g/dL (105–140 g/L)
Platelet count	191×10^3/μL (191×10^9/L)	$150–400 \times 10^3$/μL ($150–400 \times 10^9$/L)

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; WBC, white blood cell.

Simon's rapid influenza antigen swab returns positive for influenza A.

Given Simon's alertness and well appearance between seizures and following his second seizure, you decide not to perform a lumbar puncture (LP); however, if Simon develops signs of meningismus, such as neuroirritability, poor feeding, or lethargy, an LP will be warranted.

You also decide that urgent neuroimaging is not indicated in the absence of any focal neurologic findings and considering that Simon is returning to his neurologic baseline.

Additionally, an EEG is not warranted emergently but should be considered if Simon has further seizure activity, especially if he has focality with his seizure or if he has a seizure in the absence of fever.

Arriving at a Diagnosis

Q: How do you develop an assessment for Simon?

In thinking through Simon's case, you decide to first interpret his history, vital signs, examination findings, and diagnostic evaluation to develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology and determining whether hospitalization is necessary.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Simon's history includes fever and upper respiratory symptoms that preceded a seizure. His mother reports that he was at his neurologic baseline immediately prior to the seizure, and he is returning to his neurologic baseline quickly following the seizure. Both of these findings would be unusual in the setting of a central nervous system (CNS) infection. Simon is fully vaccinated and has no history of seizures. He does have relatives with a history of febrile seizures. His history does not suggest electrolyte abnormality, head trauma, or ingestion.
   - Physical examination: On physical examination, Simon currently has no signs of meningitis or encephalitis and is not in status epilepticus. His neurologic examination is symmetric and without focal abnormalities. He does have a fever, is tachycardic, and has a prolonged capillary refill, suggesting some degree of dehydration.
   - Laboratory tests: Based on Simon's laboratory test results, he does not have any electrolyte abnormalities. He has mild anion gap metabolic acidosis (elevated anion gap and low bicarbonate), and his blood urea nitrogen and creatinine levels are above the upper limit of normal. This likely results from poor oral intake, causing dehydration. Simon tests positive for influenza A, which is likely the cause of his fever and upper respiratory symptoms.
2. **Develop the list of findings.**

Q: What major findings have you identified for Simon?

- Recurrent seizure
- Fever
- Tachycardia
- Dehydration
- Rash
- Influenza A infection

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Simon's presentation?

- Given that Simon's neurologic examination is normal and he is an otherwise healthy, fully vaccinated, and neurotypical child without a prior seizure history, his most likely diagnosis is a febrile seizure provoked by influenza infection.
- It is important to consider 2 diagnoses commonly mistaken for febrile seizure: febrile myoclonus (myoclonic movements associated with fever) and rigors. Loss of consciousness is not associated with either of these diagnoses. Based on his history, Simon's episodes are not consistent with either of these diagnoses.
- It is also possible that Simon's seizures are indicative of new-onset epilepsy. This diagnosis is less likely for Simon, however, because this is his first seizure and it was directly associated with a fever, but new-onset epilepsy should remain on the differential should he have recurrence of seizures not associated with fever.

Q: What are febrile seizures?

- Febrile seizures are seizures associated with a temperature of 38 °C (100.4 °F) or above, typically occurring in patients between the ages of 6 months and 5 years. Such seizures occur in the absence of a metabolic disturbance, CNS infection, intracranial abnormality, or history of prior seizures without fever. Between 2% and 5% of healthy children will have at least one febrile seizure. Febrile seizures are categorized as simple or complex.
  - To be classified as a simple febrile seizure, a seizure must be generalized, tonic-clonic, last no longer than 15 minutes, and not recur within a 24-hour period.
  - Febrile seizures that do not meet the preceding criteria are categorized as complex.

The distinctions between simple and complex febrile seizures are outlined in Table 16.2.

Table 16.2. Categorization of Febrile Seizures

Criterion	Simple febrile seizure	Complex febrile seizure
Percentage of cases	70%	30%
Duration	<15 min	May be >15 min
Occurrence	One episode in 24 h	May be more than one episode in 24 h
Description	Generalized	Can be focal with or without secondary generalization
Presence of postictal state	Full return to baseline neurologic status	Might not have full return to baseline neurologic status within expected time frame

- In patients with prolonged seizures (>5 minutes), the diagnosis would be febrile status epilepticus. Fever is a well-known factor that can lower the seizure threshold in patients with epilepsy.

Q: What are the recurrence rates of febrile seizures, and do children diagnosed with febrile seizures have an increased risk of developing epilepsy?

- Febrile seizures recur in about one-third of children who have experienced one seizure, in approximately half of children who have experienced 2 or more seizures, and in half of infants who were younger than 1 year at the time of their first febrile seizure.
- Risk factors for higher rate of recurrence of febrile seizure include the following:
  - Age younger than 12 months at first febrile seizure
  - Fever onset occurring less than 1 hour before onset of seizure
  - First-degree relative with febrile seizure
  - Temperature less than 40 °C (104 °F) at first febrile seizure
- Future epilepsy likelihood is 2% after a single simple febrile seizure, with epilepsy being defined as at least 2 unprovoked (in the absence of fever) seizures occurring more than 24 hours apart
- Risk of development of epilepsy increases with the following risk factors:
  - History of complex febrile seizure
  - Family history of epilepsy
  - Fever duration of less than 1 hour before onset of seizure
  - Previous neurologic abnormality (ie, cerebral palsy or hydrocephalus)

Because Simon had a second seizure within 24 hours, he qualifies for a diagnosis of complex febrile seizure, likely triggered by an influenza A infection.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with febrile seizure?

- The child has more than one seizure in 24 hours.
- The child has meningeal signs.
- The child has significant somnolence or inconsolability.
- The child has a residual neurologic deficit or abnormal level of consciousness.
- The child has intractable seizures.
- The child has other findings that need to be addressed, such as significant dehydration or sepsis.

Because of Simon's recurrent seizure and poor oral intake resulting in mild dehydration, he warrants hospitalization for monitoring.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Simon is a 15-month-old otherwise healthy, fully vaccinated boy who presents with a first-time complex febrile seizure, likely secondary to influenza A infection. He requires inpatient observation to monitor for further seizure activity or development of signs or symptoms of meningitis or encephalitis, which would warrant further diagnostic workup.

Developing a Plan for Treatment and Monitoring

The initial focus of Simon's medical management will be on treating his underlying infection and supporting him throughout his hospitalization. Other elements of his treatment plan relate to determining whether he is at increased risk of seizure recurrence or development of epilepsy and whether any further intervention or diagnostic testing is necessary.

1. **Treatment of infection:** Treatment with antimicrobials is based on patient presentation and the underlying febrile illness. Because Simon has influenza, antiviral treatment with oseltamivir should be considered. Treatment with oseltamivir is generally indicated for children who are hospitalized, have severe or complicated infection, and who are at higher risk of complications, such as infants younger than 2 years, or patients with asthma or who are immunocompromised. Based on his age and the timing of his presentation, Simon qualifies for antiviral treatment with oseltamivir. Use of oseltamivir has been associated with adverse effects, such as gastrointestinal distress (eg, nausea, vomiting, abdominal pain). There are controversial claims that oseltamivir use is associated with increased risk of seizures, but there is no significant evidence to support this.
2. **Seizure management:** Although antiseizure medications (ASMs) are effective in reducing recurrence of febrile seizures, these agents are not routinely recommended for febrile seizures because of their adverse effects, the burden of long-term compliance, and a lack of data showing a reduced risk of future epilepsy. The use of rescue rectal or buccal diazepam for home is also not routinely indicated but is occasionally recommended by pediatric neurologists for patients to have on hand as a resource that can be used in cases of seizure recurrence. The use of scheduled ASMs is not indicated for Simon at this time.

3. **Supportive management:** Supportive measures include treatment of fever and adequate hydration for the patient.
   - Antipyretics: Fevers can be treated with nonsteroidal anti-inflammatory drugs or acetaminophen as needed, though antipyretics have not been proven to reduce seizure recurrence rates.
   - Hydration: Patients with fever require ongoing rehydration to make up for insensible losses, and thus it is important to ensure that the patient is tolerating oral liquids at or above maintenance rate and has appropriate urine output. If that is not the case, then the patient might need rehydration via enteral (nasogastric tube) or intravenous (IV) fluids.
4. **Monitoring:** All patients admitted with febrile seizures should be monitored for signs or symptoms that may indicate a diagnosis other than febrile seizure. Additionally, Simon should also be monitored closely and treated appropriately for complications from his underlying influenza diagnosis, which may include respiratory distress, secondary bacterial pneumonia, myocarditis, or myositis.
5. **Consultations:** For most patients with simple febrile seizures, consultation with the neurology team is not routinely warranted. For patients with complex febrile seizures or status epilepticus, consultation with a pediatric neurologist is recommended because of the heightened risk of seizure recurrence and epilepsy in addition to the likelihood of needing further diagnostic testing.
6. **Additional diagnostic testing:** Further diagnostic testing (EEG and/or MRI) is not routinely performed but should be considered on a case-by-case basis in children with complex febrile seizures, especially if the patient has several episodes within 24 hours, has a prolonged postictal state, or has a history or physical examination findings suggestive of neurologic abnormality. For Simon, it is reasonable to discuss further diagnostic testing with the pediatric neurology team before moving forward.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment of infection:** You order oseltamivir to help treat Simon's influenza.
- **Seizure management:** You do not start Simon on any ASMs at this time.
- **Supportive management**
  - Antipyretics: You order acetaminophen as needed to control fevers and make Simon more comfortable.
  - Hydration: You ensure appropriate hydration status for Simon by monitoring his oral intake and urine output. You start Simon on IV fluids because he was not able to tolerate adequate oral intake on admission.
- **Monitoring:** You plan to monitor Simon for signs or symptoms that may indicate a diagnosis other than febrile seizure. Additionally, you monitor his respiratory status closely and his vital signs every 4 hours.
- **Consultations:** Because you have diagnosed Simon with complex febrile seizure, you decide to consult the pediatric neurology team to discuss his case and help navigate decisions regarding further diagnostic testing.
- **Additional diagnostic testing:** You decide that Simon does not need any further diagnostic testing at this time.

Case Resolution

Over the course of the day, Simon returns to his baseline neurologic status, and serial neurologic examinations are normal. He continues to have fever for the duration of the observation, presumably from his influenza infection, but he does not have any further seizures and is well appearing when afebrile. The morning after admission, he is awake, alert, and interactive. He is feeding himself finger foods and is having appropriate oral intake and urine output. As a result, his IV fluids are discontinued. His clinical course supports the diagnosis of a complex febrile seizure without any further complications, and thus no further workup is pursued in the hospital. He is discharged home and you instruct his caregivers to follow up with his primary care physician.

Discharge Criteria

Q: How do you know when Simon is ready to go home?

You can feel comfortable discharging your patient with febrile seizure when the following criteria are met:

- The patient has returned to baseline neurologic status or has improved significantly since initial presentation.
- The patient has no further seizure activity.
- The patient shows no signs or symptoms of meningitis or encephalitis.
- The patient is tolerating oral intake and has appropriate hydration status, and a treatment plan is formulated for the underlying febrile illness.

Anticipatory Guidance

Q: What instructions should you provide to Simon's caregivers upon discharge?

- Febrile seizures are unlikely to lead to long-term neurologic complications.
- For future febrile illnesses, treat fever with acetaminophen or nonsteroidal anti-inflammatory drugs as needed for Simon's comfort; however, antipyretics have not been proven to reduce the recurrence rate of febrile seizures.
- Febrile seizures may recur in future febrile illnesses. In the event of another seizure, take the following steps:
  - Remain calm and note the duration of the episode. If the seizure lasts more than 5 minutes, administer a rescue medication (if available) and/or call 911 for assistance. If the seizure lasts less than 5 minutes, call Simon's primary pediatrician for guidance.
  - Place Simon on his side, attempt to remove any harmful objects nearby, and create a safe surrounding environment.
  - Do not place anything inside Simon's mouth or attempt to insert fingers into his mouth.
  - Monitor Simon's breathing and call 911 if he is turning blue or having trouble breathing.
- Supervise Simon when he is swimming or in a bathtub.

Clinical Pearls

- In young children, febrile seizures are a common and benign type of seizure that occur with fever.
- Some causes of seizure in the setting of fever (eg, meningitis, encephalitis) may have significant morbidity and mortality, and clinicians must be careful to exclude such etiologies.
- Residual altered mental status can sometimes occur following a febrile seizure but should resolve completely within 1 to 2 hours of the event.
- Transient paralysis (or *Todd paralysis*) can be seen following a seizure and usually resolves gradually within 24 hours.
- Febrile seizures are considered simple if they are less than 15 minutes long, occur only once in 24 hours, and are nonfocal, and patients have full return to neurologic baseline. If any of these criteria are not met, the febrile seizure is considered complex.
- Many children will experience repeat febrile seizures with future febrile illnesses. There is no significant data to support early or stringent antipyretic use as a prevention strategy.
- Most children do not require treatment with ASMs or any further diagnostic testing, although such treatment and testing can be done on a case-by-case basis.

Documentation Tips

- Document whether the febrile seizure is simple or complex, and note status epilepticus if present.
- Include documentation when there is a need for additional evaluation (eg, CNS imaging, EEG, LP) or if starting the patient on ASMs.

Suggested Readings

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CASE 17

Polly, a 16-Year-Old Girl With Fever, Abdominal Pain, and Vomiting

CASE PRESENTATION

Polly is a 16-year-old girl with no significant medical history who presents to the emergency department (ED) with fever, lower abdominal pain, and vomiting. In the ED, ultrasonography of the right lower quadrant (RLQ) shows a normal-appearing appendix, and a pelvic ultrasound with Doppler is normal. Polly is given a 1-L intravenous (IV) bolus of normal (0.9%) saline and oral ondansetron, but she vomits during an oral challenge. A urinalysis and urine culture have been ordered, but these results are still pending. The physician caring for her in the ED calls you with a request for admission, and you begin your patient evaluation.

Patient History and Review of Systems

Q: What information should you collect from Polly and her caregivers?

- History of present illness
  - Onset, duration, and progression of symptoms
  - Frequency and color of emesis, provoking factors, presence of nausea
  - Height of fever and method of temperature measurement
  - Characteristics of abdominal pain (timing, location/radiation, severity, quality, alleviating/exacerbating factors)
  - Recent oral intake and signs of dehydration, including an estimation of urine output in the last 24 hours
  - Associated symptoms, such as headache, myalgias, sore throat, rash, cough, difficulty breathing, back/flank pain, hematuria, dysuria, urinary frequency and urgency, diarrhea, or abnormal vaginal discharge
- Medical and surgical history, including underlying health status, any chronic medical conditions, and immunization status
  - Urologic history, including urinary tract infections (UTIs), vesicoureteral reflux, urolithiasis, or prior urologic procedures
  - Gynecologic history, including menarchal status, date of last menstrual period (LMP), general characteristics of menses, and any history of vaginal douching or sexually transmitted infections (STIs)

- Current or recent medications and medication allergies
- Social history, including sick contacts, recent travels, and relevant exposures
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, specifically sexual activity, number of sexual partners, and use of contraception (refer to Section VII in the Appendix for an example of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

From your conversation with Polly and her family, you learn that Polly has been feeling sick for 2 days, during which time she has experienced lower abdominal pain and fevers to a maximum temperature of 38.2 °C (100.8 °F), obtained orally. She has also developed nausea; a few episodes of nonbloody, nonbilious emesis; decreased oral intake; and decreased urine output. Today, her pain is localizing to the suprapubic region and left lower quadrant (LLQ). She describes her abdominal pain as constant, moderate in intensity (characterized as 4 on a scale of 10), and dull. She has not had any diarrhea and reports that her last bowel movement yesterday was "normal." She denies dysuria, urinary frequency, back pain, or hematuria. She also denies abnormal or malodorous vaginal discharge. She has never experienced similar symptoms, and she denies other symptoms on review of systems.

Polly has no chronic medical conditions, has never experienced a UTI, and has never had surgery. She does not take any medications, is fully vaccinated, and denies any medication allergies. Her menarche was 3 years ago. Her LMP was 5 days ago and ended yesterday. She describes her periods as regular without dysmenorrhea or menorrhagia.

After asking her parents to step out of the room, you learn that Polly identifies as female and is attracted to boys. She has had penile-vaginal intercourse with 2 lifetime male partners. She does not use vaginal douching products. She has never been tested for an STI; however, she inconsistently uses condoms and does not use any other method of birth control. Her last sexual encounter was 2 weeks ago, and she did not use any protection. Her parents do not know about her sexual activity, and she requests that this information remains confidential. She is not currently in a relationship.

Physical Examination

Q: What parts of the physical examination should you focus on for Polly?

- Complete set of vital signs
- Assessment of hydration, including mucous membranes (dry, sticky, moist) and skin turgor
- Peripheral perfusion: capillary refill time, peripheral pulses, temperature and color of extremities
- Abdomen: inspection for distension, auscultation for quality and quantity of bowel sounds, percussion for dullness or tympany, palpation for location of tenderness, presence of guarding or rebound, masses, or organomegaly
- Back: costovertebral angle tenderness
- Genitourinary: external appearance; characteristics of vaginal discharge; bimanual examination, evaluating for cervical motion tenderness, adnexal or uterine tenderness, and/or ovarian masses

CASE FOCUS

Physical Examination

Polly's vital signs reveal that she is febrile with a temperature of 38.3 °C (101 °F) (obtained orally), tachycardic with a heart rate of 100 beats/min, normotensive with a blood pressure 118/75 mm Hg, and has a normal respiratory rate of 12 breaths/min. Her oxygen saturation is normal on room air. Her weight is 62.3 kg (78th percentile).

Polly is sitting upright in bed and appears uncomfortable but not toxic. After receiving an IV fluid bolus in the ED, her mucous membranes are moist and she has good skin turgor. Her capillary refill time is less than 3 seconds, and her extremities are warm and well perfused. Her peripheral pulses are normal. Her cardiac examination reveals mild tachycardia but no murmurs, rubs, or gallops. Her lungs are clear to auscultation. Her abdomen has normoactive bowel sounds and does not appear distended. Her abdomen is soft, but Polly does indicate that she has LLQ and suprapubic tenderness on palpation. She also has some guarding with palpation of her left LLQ but exhibits no rebound tenderness. No masses or organomegaly are palpated. She denies costovertebral angle tenderness. After receiving permission from Polly and her parents, you perform a genital examination in the presence of a chaperone. No lesions are noted on visual inspection of her perineum. Her bimanual examination is significant for cervical motion tenderness and left adnexal tenderness. No adnexal masses are palpated. With Polly's permission, you perform a speculum examination, which shows thick, white vaginal discharge and an otherwise normal appearing cervix. You collect a vaginal swab to send for wet prep, potassium hydroxide (KOH) prep, and STI testing.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a female adolescent with fever, lower abdominal pain, and vomiting?

Although these symptoms can be nonspecific and seen with a variety of conditions (as shown in Table 17.1), for adolescent girls, complications related to the genital tract need to be considered.

Table 17.1. Differential Diagnosis for a Female Adolescent With Fever, Lower Abdominal Pain, and Vomiting

Diagnoses of highest suspicion	• Colitis or enteritis, bacterial or inflammatory • Ectopic pregnancy • Nephrolithiasis • Ovarian/adnexal torsion • Ovarian cyst, ruptured or hemorrhagic • PID,[a] including tubo-ovarian abscess • UTI, including pyelonephritis[a]

(continued)

Table 17.1. Differential Diagnosis for a Female Adolescent With Fever, Lower Abdominal Pain, and Vomiting *(continued)*

Other diagnoses to consider	• Acute viral gastroenteritis • Appendicitis • Bowel obstruction • Endometriosis • Epiploic appendagitis • Hematometrocolpos • Intraabdominal abscess • Mesenteric adenitis • Mesenteric or omental ischemia • Ovarian mass, such as teratoma • Peritonitis • Urinary tract obstruction, such as acute urinary retention

Abbreviations: PID, pelvic inflammatory disease; UTI, urinary tract infection.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for adolescent girls who present with acute onset of fever, lower abdominal pain, and vomiting?

- Given that the differential diagnosis for these symptoms is broad, the diagnostic evaluation should be guided by the suspected etiology based on specific details from the patient's history and examination.
- Clinicians evaluating patients with these symptoms should first consider etiologies that may require urgent surgical intervention, such as acute appendicitis, ileocolic intussusception (for young children), bowel obstruction, peritonitis, tubo-ovarian abscess, ovarian torsion, ruptured ovarian mass, or ruptured ectopic pregnancy.
- A serum or urine pregnancy test is an important first step in the diagnostic evaluation. If positive, pelvic ultrasonography be performed to confirm an intrauterine pregnancy.
- Because pelvic inflammatory disease (PID) can present with mild symptoms, a high index of suspicion should be maintained and testing should be initiated for at-risk patients complaining of lower abdominal pain. When PID is suspected, diagnostic testing should include the following:
  - Bimanual examination to assess for cervical motion, uterine, or adnexal tenderness; ideally, a speculum examination should also be performed to allow for visualization of the cervix and assessment of the quality and quantity of cervical and vaginal secretions.
  - Saline microscopy of vaginal secretions ("wet prep"), which can evaluate for the presence of white blood cells (WBCs), bacterial vaginosis (clue cells), and trichomoniasis. These secretions can also be tested for the presence of fungal elements (ie, *Candida albicans*) by use of KOH prep.
  - Vaginal or cervical swab for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing via nucleic acid amplification test (NAAT). When available, NAAT for *Mycoplasma genitalium* and polymerase chain reaction testing for trichomoniasis should also be obtained.
  - Imaging is not necessary for the diagnosis of PID; however, if the diagnosis is in question or when a tubo-ovarian abscess is suspected, transvaginal or pelvic ultrasonography with Doppler or magnetic resonance imaging of the pelvis should be considered.
  - Serum laboratory tests are not necessary for the diagnosis of PID, but an elevated erythrocyte sedimentation rate or C-reactive protein level may help further support the diagnosis.
  - Rarely, laparoscopy or endometrial biopsy may be needed for testing and direct or microscopic visualization of the involved areas, respectively.

- For patients with a suspected UTI, a urinalysis and urine culture should be obtained. If the urinalysis is suspicious for UTI, additional testing may be indicated depending on whether the infection is a lower UTI or an upper UTI.
  - Lower UTI: Cystitis and urethritis are considered lower UTIs. Although a urinalysis with microscopy and urine culture are needed as part of the diagnostic evaluation, these infections generally do not require further testing except in certain scenarios, such as recurrent infections or when there is concern for treatment failure. Symptoms of lower UTIs commonly include dysuria, urinary urgency and frequency, suprapubic pain/tenderness, and occasionally gross hematuria.
  - Upper UTI: Pyelonephritis (infection of the renal parenchyma), pyelitis (renal infection without parenchymal involvement), renal or perinephric abscesses, and ureteritis are considered upper UTIs. These infections are more commonly characterized by fever, nausea, vomiting, abdominal pain, and/or flank pain. Lower UTI symptoms may or may not be present as well.
    - A complicated upper UTI is defined as an upper UTI associated with any of the following features: treatment failure (no signs of clinical or laboratory improvement despite 48 to 72 hours of appropriate antimicrobials), bacteremia, sepsis, pregnancy, urologic anatomic anomalies, uncontrolled diabetes mellitus, the presence of a urinary catheter or stent, an immunocompromised status, renal failure, or renal transplantation. For patients with a complicated upper UTI, a blood culture, complete blood cell count (CBC), serum chemistries, renal function, and inflammatory markers should be obtained.
    - Imaging of the urinary tract is commonly indicated for patients with complicated upper UTIs and can be considered for patients with uncomplicated upper UTIs. Common imaging modalities include renal bladder ultrasonography and computed tomography with or without IV contrast, depending on the suspected complication.
- Table 17.2 lists other possible etiologies of fever, vomiting, and lower abdominal pain with the associated diagnostic evaluation.

Table 17.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Female Patients With Fever, Vomiting, and Lower Abdominal Pain

Diagnosis	Clinical features and/or risk factors	Diagnostic evaluation to consider
Acute viral gastroenteritis or bacterial colitis or enteritis	Acute onset of vomiting and diarrhea, with or without fever; abdominal pain generally more prominent with bacterial infections	Electrolytes, BUN, and creatinine if severe dehydration is present; stool culture if bacterial etiology suspected
Appendicitis	Periumbilical pain that migrates to the RLQ; tenderness at McBurney point	US of the appendix or CT scan of the abdomen/pelvis, CBC with differential
Ectopic pregnancy	Commonly asymptomatic, lower abdominal pain possible; rupture usually characterized by acute onset of severe pain and hypovolemic shock can develop	Urine pregnancy test, transvaginal or pelvic US
Nephrolithiasis	Flank or lower abdominal pain; vomiting is common.	UA for blood, renal US (can be useful if concerned for obstruction), noncontrast helical CT scan of the abdomen (best modality), abdominal radiograph (can detect radiopaque stones)
Ovarian cyst, ruptured	Acute onset of moderate to severe unilateral pelvic pain, usually midcycle; history may reveal onset of pain following sexual intercourse.	Pelvic US for ovarian cysts or free fluid

(continued)

Table 17.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Female Patients With Fever, Vomiting, and Lower Abdominal Pain *(continued)*

Diagnosis	Clinical features and/or risk factors	Diagnostic evaluation to consider
Ovarian torsion	Abrupt onset of moderate to severe lower abdominal pain, frequently with nausea and emesis; increased risk in the setting of a large ovarian cyst	Pelvic US with Doppler, although early findings may be limited to ovarian enlargement or impaired venous flow; early surgical consultation is needed if torsion is suspected.
PID	Commonly asymptomatic; pelvic pain with or without changes in quality or quantity of vaginal discharge; occasionally fever, nausea, or vomiting can be present.	Bimanual examination; urine NAAT for gonorrhea and chlamydia; cervical or vaginal swab for wet prep; ESR; CRP; cervical swab for culture if sensitivities are needed (or in cases of sexual abuse); pelvic US with or without Doppler; MRI of the pelvis
UTI	Lower UTI: dysuria, urinary frequency, urinary urgency, with or without hematuria Upper UTI: flank or lower abdominal pain, fever, vomiting, with or without lower UTI symptoms	UA and urine culture; consider blood culture, CBC, and inflammatory markers for complicated upper UTIs. Renal bladder US or CT scan of the abdomen/pelvis for patients with a suspected complicated UTI or concern for complications

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NAAT, nucleic acid amplification test; PID, pelvic inflammatory disease; RLQ, right lower quadrant; UA, urinalysis; US, ultrasonography; UTI, urinary tract infection.

CASE FOCUS

Diagnostic Evaluation

While reviewing Polly's laboratory test results, you note that the result of Polly's CBC ordered in the ED shows a WBC count of 14,400/µL (14.4 × 10^9/L) with 82% (0.82) segmented neutrophils. Her RLQ ultrasound shows a well-visualized, normal-appearing appendix. Her pelvic ultrasound with Doppler shows a normal uterus, normal appearance of bilateral ovaries, and good arterial and venous Doppler flow.

The results of Polly's urinalysis, urine pregnancy test, wet prep, and KOH prep are available for you to review and are as follows:

- **Urinalysis: Small leukocyte esterase with 10 to 20 WBC per high-power field (HPF) and abundant epithelial cells; otherwise normal**
- **Urine pregnancy test: Negative**
- **Saline microscopy of vaginal secretions: Positive for abundant WBCs, negative for *Trichomonas vaginalis* or clue cells**
- **KOH prep of vaginal secretions: Negative**
- **Urine culture and NAAT for *C trachomatis* and *N gonorrhoeae* pending**

Arriving at a Diagnosis

Q: How do you develop an assessment for Polly?

To arrive at Polly's diagnosis, you will think through the important elements of her history, examination, and diagnostic evaluation; assess her hydration status; evaluate her for sepsis criteria; and develop a list of major findings. This list of findings can be used to narrow her differential diagnosis to arrive at her final diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Polly's history is significant for 2 days of progressive symptoms, including fever, lower abdominal pain, vomiting, decreased oral intake, and decreased urine output. She reports unprotected vaginal intercourse, and her LMP was 5 days ago.
   - Physical examination: Her examination is notable for suprapubic and LLQ tenderness without signs of peritonitis. Her genital examination reveals white vaginal discharge, cervical motion tenderness, and left adnexal tenderness.
   - Diagnostic evaluation: Her RLQ and pelvic ultrasounds are normal. Her CBC shows leukocytosis, and her urine human chorionic gonadotropin is negative. Her urinalysis shows small leukocyte esterase and 10 to 20 WBC/HPF but without nitrites. Microscopy of her vaginal secretions demonstrates abundant WBCs.
   - Assessment of hydration status: Her history of poor oral intake and decreased urinary output is consistent with mild to moderate dehydration upon presentation, but your examination finds moist mucous membranes and normal peripheral perfusion after receiving an IV normal saline bolus in the ED.
   - Assessment for sepsis: Polly has leukocytosis, but her fever and other vital signs do not meet her age-based definition of sepsis. Refer to Section IV of the Appendix for pediatric systemic inflammatory response syndrome and sepsis criteria.
2. **Develop the list of findings.**

   ### Q: What major findings you have identified for Polly?

   - Nausea and vomiting
   - Fever
   - LLQ and suprapubic abdominal pain and tenderness
   - Cervical motion tenderness, left adnexal tenderness, and white vaginal discharge
   - Leukocytosis
   - Mild to moderate dehydration (resolving)
   - Elevated WBCs in vaginal secretions
   - Urinalysis with pyuria
3. **Revisit the differential diagnosis.**

   ### Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Polly's presentation?

   - Although Polly's diagnosis may seem obvious based on your evaluation, you still would like to think through the differential diagnosis in detail. You know that Polly's negative urine pregnancy test eliminates the possibility of a pregnancy-related complication, and her lack of diarrhea lowers the likelihood of enteritis or colitis. She does not have any costovertebral angle tenderness, decreasing the likelihood of pyelonephritis. You had a low suspicion for appendicitis based on your examination, and this is confirmed by visualization of a normal appendix on her RLQ ultrasound. Her normal pelvic ultrasound makes ovarian torsion and tubo-ovarian abscess less likely. Nephrolithiasis is unlikely without hematuria and, in the absence of a concomitant UTI, would not explain her fever and leukocytosis.
   - Based on Polly's history and examination, PID is at the top of the differential diagnosis. Your suspicion for PID seems to be confirmed by her wet prep findings that suggest inflammation of her genital tract.

Q: Given that Polly's urinalysis is positive for leukocyte esterase and WBCs, how do you know she does not have a UTI?

- A urinalysis can provide important information regarding presence of infection, and although leukocyte esterase and WBCs on microscopy can indicate inflammation, neither finding is specific for UTI. Contamination of the urine specimen with vaginal secretions can also result in the presence of leukocyte esterase and WBCs in a urine sample.
- Additionally, squamous epithelial cells suggest the urine sample has been contaminated with cells and other matter from the genital skin. The presence of significant numbers of squamous epithelial cells should suggest a poor urine sample, therefore rendering a urinalysis less reliable.

Q: What is PID, and how is it diagnosed?

- PID is a spectrum of inflammatory diseases of the upper genital tract that includes endometritis, parametritis, salpingitis, oophoritis, tubo-ovarian abscess, and pelvic peritonitis.
- Symptoms may include pelvic pain, unilateral or bilateral lower abdominal pain, fever, dysuria, nausea, vomiting, abnormal vaginal discharge, irregular vaginal bleeding, and dyspareunia. Patients may also present with right upper quadrant pain caused by perihepatitis (Fitz-Hugh-Curtis syndrome) or a pseudoappendicitis syndrome from nearby salpingitis.
- Risk factors for PID include inconsistent use of barrier contraception, recent placement of an intrauterine device, vaginal douching, increased number of sexual partners, use of alcohol and/or drugs during sexual activity, and ectopic cervical tissue (a common finding in adolescents).
- Historically, *N gonorrhoeae* and *C trachomatis* were the pathogens most commonly associated with PID, but this proportion is now declining. Polymicrobial infections are common and other organisms that contribute to PID include anaerobes, *Gardnerella vaginalis, Haemophilus influenzae, Streptococcus agalactiae,* enteric gram-negative rods, cytomegalovirus, *M genitalium, Mycoplasma hominis,* and *Ureaplasma urealyticum*. In 50% of cases, no organism is isolated from cervical or vaginal specimens.
- The diagnosis of PID is usually made through a combination of history, physical examination, and laboratory findings.
- Acute PID can be difficult to diagnose, and many subclinical cases are misdiagnosed due to lack of recognition. This can ultimately result in tubal scarring, which can cause infertility, ectopic pregnancy, and chronic pelvic pain. Clinicians should use their judgment to aid in the diagnosis of mildly symptomatic patients. See Table 17.3 for the Centers for Disease Control and Prevention diagnostic criteria for PID.

Table 17.3. Criteria for the Diagnosis of Pelvic Inflammatory Disease

Criteria category	Diagnostic criteria
Minimum criteria	Empiric treatment of PID should be initiated in sexually active young women if they are experiencing pelvic or lower abdominal pain, if one or more of the following minimum criteria are present, and no other cause(s) for the illness can be identified: ● Uterine tenderness ● Adnexal tenderness ● Cervical motion tenderness
Additional criteria	One or more of the following criteria can enhance the specificity of the minimum criteria: ● Oral temperature >38.3 °C (101 °F) ● Abnormal mucopurulent cervical discharge[a] or cervical friability ● Abundant WBCs on saline microscopy of vaginal secretions (ie, wet prep)[a] ● Elevated ESR or CRP level ● Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

Table 17.3. Criteria for the Diagnosis of Pelvic Inflammatory Disease *(continued)*

Criteria category	Diagnostic criteria
Most specific criteria	• Endometrial biopsy with histopathologic evidence of endometritis • Transvaginal US or MRI showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler US with increased fallopian tube blood flow suggestive of infection (eg, tubal hyperemia) • Laparoscopic findings consistent with PID (the standard of reference for diagnosis)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; PID, pelvic inflammatory disease; US, ultrasonography; WBC, white blood cell.

[a] These findings are present in the majority of women with PID, and the diagnosis of PID is unlikely if neither is present.

Adapted from Pelvic inflammatory disease. Centers for Disease Control and Prevention. Accessed February 2, 2022. https://www.cdc.gov/std/treatment-guidelines/pid.htm

- In reviewing the criteria in Table 17.3, Polly does have left adnexal tenderness without an alternative etiology, meeting the minimum criteria for PID. Additionally, she has fever and abundant WBCs on saline microscopy of her vaginal secretions. Because of this, you are confident that she meets criteria for the diagnosis of PID.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with PID?

Although most patients with PID can be treated in the outpatient setting, clinicians should consider hospitalization to treat patients with suspected PID in the following situations:

- The patient cannot tolerate oral hydration and/or oral antibiotic therapy.
- The patient has not responded to an appropriate trial of outpatient treatment.
- The patient has an oral temperature greater than 38.3 °C (101 °F).
- Concern exists for severe disease or complications such as peritonitis or tubo-ovarian abscess.
- The patient has significant pain that cannot be controlled with oral pain medications.
- The patient is pregnant.
- Other severe illness, such as ovarian torsion, cannot be ruled out.

Because Polly has nausea and vomiting, you decide she warrants hospitalization for her initial treatment and other supportive care.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Polly is a 16-year-old healthy adolescent girl with acute onset of fever, nausea and vomiting, LLQ abdominal pain, left adnexal tenderness on bimanual examination, and resolving mild to moderate dehydration. Her symptoms are suspected to be due to acute PID. Given that she is unable to tolerate oral hydration despite antiemetics, she warrants hospitalization for further treatment and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Prompt and appropriate treatment of PID, even for mild cases, is important to prevent the risk of long-term complications such as tubal infertility, chronic pelvic pain, and ectopic pregnancy.

1. **Antibiotic therapy:** In preparing to treat Polly's infection, you review the Centers for Disease Control and Prevention 2021 PID treatment guidelines, which are summarized in Boxes 17.1 and 17.2.
   - Because there are many organisms that can cause PID, broad-spectrum antibiotic therapy that targets *N gonorrhoeae*, *C trachomatis*, and other vaginal flora is recommended.
   - When PID is suspected, antibiotic therapy should be continued for the entire duration, regardless of STI test results.
   - Because Polly has nausea and vomiting, you plan to initiate her PID treatment intravenously.

Box 17.1. Recommended Parenteral Treatment of Pelvic Inflammatory Disease

Recommended parenteral options for the treatment of PID include one of the following regimens[a]:

- Ceftriaxone 1 g IV every 24 hours *plus* doxycycline[b] 100 mg orally or IV every 12 hours *plus* metronidazole 500 mg orally or IV every 12 hours.
- Cefotetan 2 g IV every 12 hours *plus* doxycycline[b] 100 mg orally or IV every 12 hours.
- Cefoxitin 2 g IV every 6 hours *plus* doxycycline[b] 100 mg orally or IV every 12 hours.

- Parenteral therapy can be discontinued 24 hours after the patient shows clinical improvement.
- Continuing oral therapy should consist of doxycycline (100 mg orally twice a day) *plus* metronidazole (500 mg orally twice a day) to complete a total of 14 days of therapy.

Abbreviations: IV, intravenous; PID, pelvic inflammatory disease.

[a] Additional parenteral regimens are available on the CDC website: https://www.cdc.gov/std/treatment-guidelines/pid.htm

[b] Because of the pain associated with IV doxycycline infusion, oral doxycycline is preferred.

Adapted from Pelvic inflammatory disease. Centers for Disease Control and Prevention. Accessed February 1, 2022. https://www.cdc.gov/std/treatment-guidelines/pid.htm

Box 17.2. Recommended Intramuscular/Oral Regimens for Treatment of Pelvic Inflammatory Disease

Recommended intramuscular or oral regimens for the treatment of PID include any of the following:

- Ceftriaxone 500 mg IM in a single dose[a] *plus* doxycycline 100 mg orally twice a day for 14 days *plus* metronidazole 500 mg orally twice a day for 14 days
- Cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently in a single dose *plus* doxycycline 100 mg orally twice a day for 14 days *plus* metronidazole 500 mg orally twice a day for 14 days
- Other parenteral third-generation cephalosporin (eg, ceftizoxime or cefotaxime) *plus* doxycycline 100 mg orally twice a day for 14 days *plus* metronidazole 500 mg orally twice a day for 14 days

Abbreviations: IM, intramuscular; PID, pelvic inflammatory disease.

[a] For persons weighing greater than 150 kg with documented gonococcal infection, 1 g of ceftriaxone should be administered.

Adapted from Pelvic inflammatory disease. Centers for Disease Control and Prevention. Accessed February 1, 2022. https://www.cdc.gov/std/treatment-guidelines/pid.htm

2. **Supportive care**
   - Hydration: For patients with dehydration who are unable to tolerate oral rehydration and maintain their hydration orally, fluids intravenously or via nasogastric tube may be needed. Refer to Case 1 for a detailed discussion of rehydration and maintenance of hydration.
   - Antiemetics: To treat nausea and vomiting, ondansetron can be helpful. Promethazine is an additional option for adolescents in whom ondansetron is not effective or for whom it is contraindicated (eg, patients with long QT syndrome).
   - Treatment of pain: Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids can be used to treat pain. NSAIDs should be used cautiously in patients with dehydration or with concomitant use of nephrotoxic medications.
   - Fever reducers: Acetaminophen can also be used to reduce fever. NSAIDs can be used with the previously mentioned cautions.
   - Because Polly has nausea, vomiting, pain, and fever, you plan to add supportive measures for symptomatic relief and provide her with IV hydration.
3. **Monitoring**
   - Patients admitted to the hospital with dehydration and an acute infection should undergo vital sign monitoring every 4 hours. An increased frequency may be needed for those with sepsis or severe dehydration. Additionally, patients with dehydration should undergo monitoring of their intake and output and changes in weight.
   - For Polly, you will order 4-hour monitoring of her vital signs as well as intake and output.
4. **Screening for other STIs**
   - In sexually active adolescents, especially those who endorse a lack of consistent barrier protection, it is important to obtain testing for STIs, including HIV, gonorrhea, chlamydia, syphilis, and hepatitis C (when risk factors, such as multiple sexual partners or IV drug use, are present). Hepatitis B testing should also be considered for sexually active adolescents who have not been vaccinated against it. Because *T vaginalis* is commonly asymptomatic and is transmitted sexually, screening with a wet prep or NAAT of vaginal secretions should be considered as well.
   - Because Polly has a history of unprotected sexual intercourse, it is important that screening for STIs is performed.

BACK TO BASICS

Adolescent Sexual Health Counseling and Confidentiality

Adolescents who are considering or currently engaging in sexual activity should be counseled about pregnancy and STI prevention options. Although hormonal contraception can provide protection against unintended pregnancy, adolescents should understand that use of barrier protection is essential for prevention of STIs.

Most states have laws regarding the adolescent's right to confidentiality for counseling, diagnosis, and treatment of some conditions, including STIs; however, in the hospital setting, maintaining confidentiality when treating PID can be very challenging. Clinicians may consider requesting consent from the adolescent to disclose the diagnosis to their parent or guardian.

CASE FOCUS

Plan for Treatment and Monitoring

- **Antibiotics:** You decide to empirically treat Polly's PID with IV ceftriaxone, doxycycline, and metronidazole. You will switch to oral antibiotics when she is tolerating fluids by mouth. You will also follow up on her urine culture and pending STI testing.
- **Supportive care**
  - Antipyretics and analgesics: You order acetaminophen and ibuprofen as needed for fever and pain. You will consider IV ketorolac (an NSAID) if Polly's pain is uncontrolled with this regimen unless concern for decreased renal function develops.
  - Hydration: You do not think that Polly requires any further rehydration but order IV fluids at her maintenance rate until her oral intake improves.
  - Diet: You order a regular diet as tolerated.
- **Monitoring:** You order vital signs every 4 hours, tracking of intake and output, and monitoring of Polly's urine culture for growth.
- **STI screening and counseling:** You order testing for HIV and syphilis. You plan to counsel Polly on pregnancy and STI prevention and provide her with resources as indicated. You plan to discuss with Polly her options for maintaining confidentiality or disclosing her diagnosis to her parents.

Case Resolution

Polly provides you with permission to disclose her diagnosis to her parents. They are upset but continue to allow you to provide Polly with confidential pregnancy and STI counseling. The following day, Polly's urine culture shows low colony counts of multiple organisms, consistent with contamination. Over the next 48 hours, Polly reports symptomatic improvement of her lower abdominal pain and nausea and her fevers resolve. Her vaginal NAAT is positive for *C trachomatis* and her other STI testing is negative. On hospital day 3, she is discharged home with 12 additional days of oral doxycycline and metronidazole.

Discharge Criteria

Q: How do you know when Polly is ready to go home?

You can feel comfortable discharging your patient with PID when the following criteria are met:

- The patient's pain and fever curve have improved on appropriate antibiotic therapy.
- The patient is able to maintain oral hydration without vomiting.
- Appropriate follow-up with the patient's pediatrician is ensured.
- The patient has been appropriately counseled about STI and pregnancy prevention.

Anticipatory Guidance

Q: What instructions should you provide to Polly upon discharge?

- Complete the full course of antibiotics as prescribed.
- To reduce the risk of pregnancy and STI, it is very important to consistently use barrier protection, such as latex condoms, during sexual intercourse in the future.
- It is important to notify recent sexual partners of your diagnosis of chlamydia so that they can be treated. Do not engage in sexual intercourse until symptoms have resolved and until your partner has been treated.
- Because of your positive test for *C trachomatis*, repeat testing is indicated in 3 months.
- Return to care for recurrence of fevers, lower abdominal pain, or vomiting.

Clinical Pearls

- PID is commonly asymptomatic or mildly symptomatic and should be considered in every female adolescent presenting with lower abdominal pain.
- Undiagnosed and untreated PID can lead to severe consequences, such as future infertility.
- PID is diagnosed clinically, based on the presence of either uterine tenderness, adnexal tenderness, or cervical motion tenderness on examination in the absence of another etiology. The presence of fever, mucopurulent or increased vaginal discharge, abundant WBCs on wet prep, elevated inflammatory markers, or detection of *C trachomatis* or *N gonorrhoeae* are not necessary for the diagnosis but help support the diagnosis.
- Although *C trachomatis* and *N gonorrhoeae* were the most common causes of PID in the past, polymicrobial infections or infections attributable to other infectious agents are increasing.
- Treatment of PID can be oral or parenteral, depending on the severity of presentation and the patient's tolerance of oral medications. Treatment is continued for 14 days.

Documentation Tips

- Document whether there has been a failure of outpatient treatment.
- Include the presence of dehydration or acute kidney injury and the need for IV fluid rehydration.
- Include whether there is refractory pain requiring IV pain medications.
- Include the need for further evaluation, including pelvic imaging.

Suggested Readings

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CASE 18

Payton, a 14-Year-Old Boy With Throat Pain and Fever

CASE PRESENTATION

Payton, a healthy 14-year-old boy, presents to the emergency department (ED) with a sore throat and difficulty swallowing for the last 4 days. This morning, he woke up with worsening throat pain and fever, so his father brought him to the ED. In the ED, Payton is unable to swallow oral pain medications secondary to odynophagia. For this pain, he is given a dose of intravenous (IV) ketorolac that results in mild improvement. The ED physician caring for him notes that he is tachycardic and is concerned that Payton is dehydrated. To address his dehydration, the ED physician administers a 1-L IV bolus of normal saline (0.9%). The physician in the ED calls you to express concern that Payton will not be able to tolerate oral fluids at home and requests that you evaluate him for admission to the inpatient unit.

Patient History and Review of Systems

Q: What information should you collect from Payton and his caregivers?

- History of present illness
  - Duration and characteristics of symptoms, including location and description of throat pain and its progression over time
  - Presence of neck stiffness, pain with neck movement, or inability to open the mouth secondary to pain or trismus (commonly known as *lockjaw*)
  - Height and duration of fever
  - Change in the quality of voice
  - Recent dental infection or dental pain
  - History of trauma to head or neck
  - Exposure history, including sick contacts, recent travel, or animals
- Associated symptoms, such as cough, nasal congestion, runny nose or postnasal drip, ear pain, facial or neck swelling, difficulty breathing, stridor, vomiting, diarrhea, abdominal pain, headache, or chest pain
- Medical and surgical history, including history of food allergies, atopy, recurrent streptococcal infections, and immunization status, including seasonal influenza vaccine
- Medications including recent antibiotic use and over-the-counter medication use
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment (Refer to Section VII in the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

From your conversation with Payton and his father, you confirm that Payton has been sick for 4 days, during which time he has experienced worsening throat pain, particularly with swallowing, and subjective fevers. He has also noted some pain in the left side of his neck but denies any cough, nasal symptoms, ear pain, difficulty breathing, stridor, chest pain, vomiting, diarrhea, headache, or abdominal pain. He has pain when opening his mouth. He has not noticed any changes to the quality of his voice. Since last night, he has been avoiding turning his head to the side because of pain and neck stiffness. He denies any tooth pain or recent dental infection. He has not had any trauma to the head or neck, and he denies any recent sick contacts. On awakening this morning, Payton realized his throat pain was much more severe, and he was unable to swallow because of the pain. He took his temperature orally and had a fever of 38.6 °C (101.5 °F). He told his father about his symptoms, who then brought him into the ED for an evaluation.

Payton is a healthy and typically developing adolescent boy who does not have any history of allergies, atopy, or recurrent throat infections. He does not take any medications regularly, has not taken any recent antibiotics, and did not try any over-the-counter medications at home for his symptoms. He has never had surgery. He is up to date on all vaccinations, including his seasonal influenza vaccine. Payton's father is with him at the bedside during your interview and confirms this history. Payton also denies any known sick contacts. A HEADSS assessment with Payton alone is unremarkable.

Physical Examination

Q: What parts of the physical examination should you focus on for Payton?

- Complete set of vital signs
- Hoarseness, muffled voice
- Level of distress, including assuming tripod position, stridor, cyanosis, or drooling
- Ears: signs of middle ear infection (bulging of tympanic membrane with effusion), evaluation of the mastoid process
- Mouth and oral cavity: ability to fully open mouth; mucous membranes (moist, sticky, or dry); signs of dental caries, dental abscess, trauma, or burns
- Throat: tonsils (enlargement, asymmetry, erythema, exudates); uvular deviation, fullness of soft palate/anterior tonsillar pillar, or palatal petechiae; any fullness of the posterior or lateral pharyngeal walls
- Neck: range of motion (particularly full neck extension when looking up), symmetry, tenderness, lymphadenopathy
- Cardiovascular: heart rate, rhythm, peripheral perfusion
- Respiratory: auscultation of lung sounds, signs of respiratory distress (tachypnea, stridor, subcostal/intercostal/suprasternal retractions, tracheal tugging, nasal flaring)

CASE FOCUS

Physical Examination

Payton's vital signs reveal that he is febrile, with a temperature of 39.1 °C (102.4 °F) without significant tachypnea (respiratory rate: 16 breaths/min). He does continue to have tachycardia (heart rate: 110–120 beats/min), although this has improved after receiving the IV fluid bolus in the ED. His blood pressure is normal for age, and his oxygen saturation is above 97%. His weight is 54.2 kg (55th percentile).

On examination, Payton is lying in bed and appears uncomfortable related to pain; however, he is able to answer questions appropriately and fully complies with your examination. His voice is noted to be hoarse and muffled. You do not note any drooling. His eyes are slightly sunken. Because of pain, he has slightly decreased range of motion of his neck with lateral rotation. You note three 1.5-cm left-sided anterior cervical lymph nodes that are tender and mobile, but you do not note any significant neck swelling. Bilateral otoscopic examination is unremarkable. On oral examination, Payton is able to fully open his mouth, which reveals dry oral mucous membranes with several dental caries; however, there is no evidence of a dental abscess. His throat examination reveals both tonsils to be erythematous without purulent exudates, and his left tonsil is noted to be bulging with mild uvular deviation to the right. You do not note any palatal fullness or petechiae. His capillary refill is 3 seconds. Payton has a normal respiratory examination, and his cardiac examination is only remarkable for mild tachycardia. The rest of his examination is unremarkable.

Differential Diagnosis

Q: What is the differential diagnosis for a child or adolescent with acute-onset odynophagia, neck pain, and fever?

The differential diagnosis for child or adolescent with acute-onset odynophagia, neck pain, and fever is shown in Table 18.1 and is divided into causes that seem more and less likely based on Payton's presentation.

Table 18.1. Differential Diagnosis for a Child or Adolescent With Acute-Onset Odynophagia, Neck Pain, and Fever

Diagnoses of highest suspicion	• Bacterial pharyngitis or tonsillitis • Parapharyngeal abscess • Peritonsillar abscess[a] • Retropharyngeal abscess • Viral pharyngitis or tonsillitis
Other diagnoses to consider	• Airway foreign body • Chemical esophagitis (eg, pill esophagitis, caustic ingestion) • Diphtheria (consideration in unimmunized or underimmunized children) • Eosinophilic esophagitis • Epiglottitis • Esophageal food impaction or foreign body • Esophageal stricture • Infectious esophagitis (HSV, Candida albicans, CMV, HIV, *Mycobacterium tuberculosis*) • Trauma

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with odynophagia, neck pain, and fever?

The differential diagnosis for odynophagia, neck pain, and fever is fairly limited, and many of the etiologies on the differential diagnosis list can be diagnosed or ruled out on the basis of the patient's history and physical examination without the need for diagnostic studies. If the diagnosis is not clear based on history and examination, further diagnostic evaluation may be considered.

- For all patients with odynophagia and fever, it is important to first consider and exclude life-threatening conditions such as epiglottitis, bacterial tracheitis, diphtheria, airway or esophageal foreign body (in particular, magnets and button batteries), and caustic ingestion.
  - Epiglottitis is a rare diagnosis and is generally diagnosed clinically. Epiglottitis can be confirmed with lateral neck films; however, imaging is not required for diagnosis. Diphtheria, also rare, is diagnosed when polymerase chain reaction or throat culture is positive for *Corynebacterium diphtheriae*. Given the high risk of airway compromise in both of these diseases, a rapid but controlled airway evaluation by an otolaryngologist or anesthesiologist is preferentially indicated before further workup.
  - When an airway or esophageal foreign body is suspected based on history, the presence of a radiopaque/metallic foreign body can be confirmed with soft tissue radiographs of the airway and/or radiographs of the chest. For a radiolucent esophageal foreign body (including food impaction), an upper gastrointestinal series or upper endoscopy performed by a gastroenterologist may be needed.
  - When there is concern for a caustic ingestion, often identified in the history, in a patient with respiratory symptoms, a chest radiograph to rule out esophageal perforation or pneumonitis is a useful initial test. Early consultation with a gastroenterologist can be useful to help guide the next steps in the patient's evaluation.
  - For Payton, you are less suspicious of the aforementioned diagnoses.
- Other diagnoses that seem more likely in Payton's case include a peritonsillar and/or a deep neck space infection.
  - Findings consistent with a peritonsillar abscess include fever, unilateral throat pain, muffled voice, trismus, asymmetric tonsillar size, uvular deviation, and bulging/fluctuance of the unilateral soft palate. Generally, imaging and blood work are unnecessary when the corresponding physical examination findings are present. The diagnosis of an abscess can be confirmed by needle aspiration or incision and drainage. When purulent fluid is obtained, bacterial cultures should be ordered.
  - Patients with parapharyngeal, retropharyngeal, and prevertebral infections commonly describe pain and stiffness with neck rotation. Parapharyngeal infections commonly cause asymmetry and fullness of the lateral neck. Confirmation of these diagnoses generally requires a computed tomography (CT) scan of the neck with contrast, which will also allow evaluation of the possible complications associated with these infections. If the diagnosis of a retropharyngeal abscess is being considered, a screening lateral neck film may demonstrate widening of the prevertebral soft-tissue space but is not a necessary part of the patient's evaluation.
- Other testing to consider
  - Serum laboratory tests are not indicated for the diagnosis of deep neck infections; however, if done, a complete blood cell count (CBC) may show a leukocytosis and/or left shift. C-reactive protein is generally elevated and may also be useful for assessing response to therapy in complicated cases.
  - A blood culture may be useful in particularly ill-appearing patients to evaluate for bacteremia because it is a potential complication of deep neck space infections.
  - Rapid streptococcal antigen should be considered. If negative, a throat culture should be sent because of a high false negative rate of rapid antigen testing. If suspected, the diagnosis of group A streptococcus (GAS) pharyngitis should be confirmed prior to prescribing antibiotics.
  - Mononucleosis test may be considered when exudative tonsilitis is present.

CASE FOCUS

Diagnostic Evaluation

You note that the ED physician obtained a rapid streptococcal antigen test, which was negative, and thus a throat culture was obtained. As part of the initial workup, the ED physician also obtained a blood culture and CBC with differential after an IV line was placed. The laboratory test results are as follows:

CBC		
Laboratory test	**Result**	**Reference range**
WBC count	16,000/μL (16 × 10^9/L)	4,000–10,500 × 10^3/μL (4.0–10.5 × 10^9/L)
Hemoglobin	11.5 g/dL (115 g/L)	12.5–16.1 g/dL (125–161 g/L)
Hematocrit	35% (0.35)	36%–47% (0.36–0.47)
MCV	85 μm^3 (85 fL)	78–95 μm^3 (78–95 fL)
MCHC	34 g/dL (340 g/L)	32–36 g/dL (320–360 g/L)
RDW	12.5% (0.125)	11.4%–13.5% (0.114–0.135)
Platelet count	385 × 10^3/μL (385 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	85% (0.85)	54%–62% (0.54–0.62)

Abbreviations: CBC, complete blood cell count; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red blood cell distribution width; WBC, white blood cell.

Given Payton's presentation, you are most concerned with a peritonsillar abscess or deep neck infection. Although Payton's examination shows many findings consistent with a peritonsillar abscess, he also has left-sided neck fullness and pain with range of motion. Based on this, you order a soft tissue neck CT scan with contrast.

His CT scan shows tonsillitis and a 25-mm left peritonsillar hypodense mass with ring enhancement. Edema and inflammation extend into the left parapharyngeal space, with lateral displacement of his carotid sheath, but his internal jugular vein and internal carotid artery are patent. Reactive left-sided cervical adenopathy is noted.

Arriving at a Diagnosis

Q: How do you develop an assessment for Payton?

In thinking through his case, you decide to first interpret Payton's history, vital signs, examination findings, and the results from your diagnostic evaluation to develop a list of findings that aids in narrowing your differential diagnosis. After next considering Payton's hydration status and level of pain control, admission criteria can be generated for your specific diagnosis.

1. **Assess airway, breathing, and circulation.**
   - With deep neck space infections, especially retropharyngeal abscess, there may be concern for airway compromise secondary to airway edema.
   - If there is a concern for impending airway compromise, which may be indicated by poor respiratory effort, stridor, grunting, or a change in level of consciousness, then urgent intubation should be considered. Based on your current assessment, this is not needed for Payton.
   - Payton does not have any stridor or stertor and is not demonstrating any signs of respiratory distress. He has a normal respiratory rate, a normal oxygen saturation on room air, and good air movement in his lung fields.
   - Although Payton shows signs of dehydration on examination, his circulation is not impaired.

2. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History, vital signs, and examination: Payton has a history of acute-onset throat pain with odynophagia, fever, neck pain, neck stiffness, and muffled voice. On physical examination, he has left tonsillar protrusion with uvular deviation, fullness of his left neck, slightly decreased range of motion, and left cervical adenopathy. He also has findings consistent with mild to moderate dehydration but no respiratory compromise. Payton's history, symptoms, and examination findings suggest a left-sided peritonsillar abscess with extension into the left-sided neck spaces.
   - Diagnostic evaluation: Payton's CBC with differential shows an elevated white blood cell count with neutrophil predominance, which is consistent with an inflammatory process. A contrast-enhanced CT scan of the neck reveals a 25-mm left peritonsillar abscess with inflammation extending into the parapharyngeal space.
   - Assessment for sepsis: Payton's vital signs in conjunction with his suspected infection indicate that he is at risk for sepsis; however, there is no significant concern for severe sepsis or septic shock at this time. Refer to Section IV in the appendix for definitions of system inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock as well as age-based SIRS criteria.
3. **Develop the list of findings.**

   Q: What major findings you have identified for Payton?
   - Hypodense peritonsillar abscess on CT scan
   - At risk for sepsis
   - Mild to moderate dehydration
   - Odynophagia
4. **Revisit the differential diagnosis.**

   Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Payton's presentation?

   You are confident diagnosing Payton with a left peritonsillar abscess and parapharyngeal cellulitis as the etiology of his symptoms. Importantly, although the peritonsillar infection and inflammation are extending into the parapharyngeal space, there are no signs of severe complications, such as internal jugular vein thrombosis or abscess within the parapharyngeal space.
5. **Consider admission criteria.**

   Q: What are reasonable admission criteria for a patient with a deep neck infection?

   Except in cases of peritonsillar abscesses that are drained in the ED, most children with deep neck infections require a period of monitoring on IV antibiotics to assess the need for surgical intervention, evaluate for complications, and ensure clinical improvement prior to discharge.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Payton is a previously healthy 14-year-old boy with acute onset odynophagia, fever, neck pain, and subsequent poor oral intake resulting in mild to moderate dehydration. Additionally, he was found to be at risk for sepsis secondary to a left-sided peritonsillar abscess with extension into the parapharyngeal space. He is not currently tolerating oral intake due to severe throat pain. He requires hospital admission for continued antibiotic treatment, hydration, pain control, monitoring for complications, and evaluation for potential surgical intervention.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to develop your plan for management, you review the literature to remind yourself about the treatment of a peritonsillar abscess in children and adolescents. You decide to divide treatment considerations into the following components:

1. **Stabilization of airway, breathing, and circulation:** At the time of your evaluation, Payton is not demonstrating any signs of respiratory distress or stridor, so you have no concern for airway compromise. Progression to intubation may be necessary to protect the airway if worsening edema causes airway compromise. If concern about airway compromise develops, IV steroids (such as dexamethasone) can be used to decrease airway edema. At this time, Payton is at risk for sepsis, but his hemodynamic status is stable with good perfusion and an appropriate blood pressure for age; however, he has evidence of continued dehydration requiring the use of IV fluids.
2. **Surgical management:** In general, surgery is indicated if there is airway compromise, presence of complications, or no improvement after 48 hours of IV antibiotics. For peritonsillar abscesses greater than 2 cm on CT scan, it is recommended to consult an otolaryngologist to evaluate the patient for needle aspiration or incision and drainage. Likewise, large retropharyngeal abscesses (>2.2 cm) will generally require surgical drainage. Treatment of smaller abscesses with medical therapy alone has good success rates.
3. **Antibiotic therapy:** Most cases of deep neck infections are polymicrobial, and thus empiric antibiotic therapy should include coverage for GAS, *Staphylococcus aureus,* and respiratory anaerobes.
   - IV empiric antibiotic regimen options include IV ampicillin-sulbactam or IV clindamycin with or without vancomycin (if there is concern for clindamycin-resistant methicillin-resistant *S aureus*).
   - Once the patient is afebrile and clinically improving on parenteral antibiotic therapy, transition to oral antibiotics to complete a 14-day course of either amoxicillin-clavulanate or clindamycin is appropriate.
4. **Pain control**
   - Oral or IV nonsteroidal anti-inflammatory drugs and acetaminophen are appropriate to use for pain. If pain remains uncontrolled, oral or IV opioids may be needed in addition to nonsteroidal anti-inflammatory drugs and acetaminophen.
   - If pain is not controlled by an escalation of medications to IV ketorolac or opioids, physicians should reassess for progression of disease, such as extension of infection resulting in Lemierre syndrome or mediastinitis.
   - Nonpharmacologic measures can be beneficial to help reduce stress and anxiety, especially in patients undergoing invasive procedures. These measures may include the following:
     - Physical measures: massage, heat application, cold stimulation
     - Behavioral measures: physical therapy, relaxation, biofeedback, desensitization, art therapy
     - Cognitive measures: distraction, imagery, hypnosis, psychotherapy
5. **Rehydration:** Patients with peritonsillar abscesses often experience pain when drinking and therefore may have difficulty staying hydrated. Payton will need to be continued on IV fluid hydration until he is able to maintain his hydration by drinking fluids.
6. **Diet:** When surgery is being considered, patients should be given nothing by mouth until evaluated by the surgical team so as not to delay surgical intervention if needed. Payton will need to be made nil per os (nothing by mouth) while awaiting otolaryngology evaluation to determine if surgical intervention is required.
7. **Steroids:** A recent study noted IV dexamethasone combined with IV antibiotic therapy was associated with a decreased need for surgical drainage in peritonsillar abscess. For those patients with retropharyngeal abscess and parapharyngeal abscess, no statistically significant outcomes have been found for IV dexamethasone therapy. However, if there is impending airway obstruction, IV steroids are indicated to decrease edema and reduce the need for aggressive airway intervention.

8. **Monitoring for complications:** Clinicians should be vigilant to monitor for complications of deep neck infections, which may include the following:
   - Airway obstruction related to edema and worsening infection
   - Severe sepsis and septic shock
   - Thrombosis of the internal jugular vein, including Lemierre syndrome
     - Lemierre syndrome is a complication of oropharyngeal infections that leads to septic thrombophlebitis of the internal jugular vein, with bacteremia and possible septic metastasis. Lemierre syndrome is classically caused by the bacteria *Fusobacterium necrophorum*. This diagnosis should be considered in a patient with pharyngitis who develops worsening neck pain and persistent fever.
     - Patients may also have neck swelling and tenderness on the side of the thrombosis. Pleuritic chest pain, dyspnea, and hypoxemia may develop as manifestations of pulmonary septic emboli. Microabscesses in the brain may also be seen. Treatment includes providing antibiotic coverage for *F necrophorum*, adding anticoagulants, and considering surgical intervention.
   - Internal carotid artery aneurysm/rupture, cranial nerve palsy
   - Meningitis
   - Spontaneous rupture of the abscess into the pharynx (including the risk of subsequent aspiration pneumonia)
   - Mediastinitis
     - Mediastinitis can be a life-threatening complication of deep neck infections. Spread of infection occurs through the deep neck space fascial planes causing extension of the infection into the mediastinum.
     - Clinicians should consider this diagnosis in a patient with a previous oropharyngeal infection (eg, retropharyngeal abscess, peritonsillar abscess) who continues to have pain despite appropriate pain management (eg, narcotics) or develops respiratory symptoms. Mediastinitis may also be suspected by a widening mediastinum on chest radiographs. A chest CT scan with contrast should be used to confirm the diagnosis of mediastinitis.
     - Treatment of mediastinitis includes IV broad-spectrum antibiotics, airway management, and complete drainage of the neck and the mediastinum.

CASE FOCUS

Plan for Treatment and Monitoring

- **Airway, breathing, and circulation:** You plan to monitor Payton's respiratory status, vital signs, and perfusion closely. You will consider dexamethasone for airway edema if his respiratory status worsens. Given his dehydration, you provide another 1-L bolus of normal saline.
- **Surgical intervention:** You place Payton on nil per os status and consult an otolaryngologist to evaluate Payton for surgical intervention.
- **Antibiotics:** You start IV ampicillin-sulbactam, which will be continued until clinical improvement is appreciated and Payton is able to transition to oral medications. At that time, you plan to transition him to oral amoxicillin-clavulanate to continue following discharge.
- **Pain control:** You decide to start with acetaminophen and ibuprofen for pain. If Payton's pain is not well controlled with acetaminophen and ibuprofen, you will use IV ketorolac instead of ibuprofen and add oral oxycodone or IV morphine as needed for breakthrough pain.

CASE FOCUS

Plan for Treatment and Monitoring *(continued)*

- **Rehydration:** Using the Holliday-Segar calculations, you estimate that Payton requires 100 mL/h of 5% dextrose in normal saline. You will continue administration of IV fluid until Payton is able to maintain appropriate oral fluid intake.
- **Steroids:** No glucocorticoids will be used for Payton's treatment given the inconsistent clinical evidence for supporting the use of glucocorticoids in the management of peritonsillar abscess.
- **Monitoring:** You will continue to monitor Payton for signs of complications that would indicate progression of infection and the need to escalate care.

Case Resolution

On the evening of Payton's admission, the otolaryngologist on call performs a surgical incision and drainage of the abscess. Payton tolerates the procedure well. Purulent discharge is obtained during the procedure and sent for culture. The throat culture sent in the ED is positive for GAS, and Payton's surgical culture ultimately grows GAS and mixed oral flora. The following day, Payton shows significant improvement. His fever has resolved, and he is tolerating a soft diet. He is discharged home on oral amoxicillin-clavulanate to complete a 14-day course.

Discharge Criteria

Q: How do you know when Payton is ready to go home?

You can feel comfortable discharging your patient with a deep neck infection when the following criteria are met:

- The patient has symptomatic improvement after more than 24 hours of antimicrobial therapy, including improvement in throat pain, fever, neck range of motion, and/or tonsillar swelling.
- The patient is able to transition to oral antibiotic therapy to complete the course of treatment.
- The patient is tolerating oral intake to maintain an appropriate level of hydration.
- Pain is well controlled with oral analgesic medications.
- Appropriate follow-up is ensured.

Anticipatory Guidance

Q: What instructions should you provide to Payton and his caregivers upon discharge?

- Return to care for dyspnea; worsening throat pain, neck pain, or trismus; an enlarging neck mass; return of fever; neck stiffness; or bleeding from surgical site.
- Follow-up with Payton's primary care physician within 1 to 2 days after discharge for a posthospitalization appointment.

Clinical Pearls

- Peritonsillar abscess is the most common pediatric deep neck space infection, occurring most commonly in adolescents. Retropharyngeal abscess and parapharyngeal abscess are both seen more often in children younger than 5 years.
- The classical clinical presentation of a peritonsillar abscess is fever, severe sore throat, muffled voice, drooling, or trismus.
- Physical examination findings consistent with peritonsillar abscess include an enlarged and fluctuant tonsil with deviation of the uvula to the opposite side.
- The diagnosis of a peritonsillar abscess can be a clinical diagnosis based on history and physical examination findings without the need for laboratory or imaging studies. However, clinical features cannot always distinguish peritonsillar abscess from peritonsillar cellulitis or other serious infections, such as parapharyngeal abscess, retropharyngeal abscess, or epiglottitis.
- Immediate surgical intervention is indicated in patients with impending airway compromise, complications, enlarging masses, or significant comorbidities.
- Empiric therapy for peritonsillar abscess should include coverage for GAS, *S aureus*, and respiratory anaerobes. The choice of antibiotic and route of treatment depends upon the patient's degree of illness and local patterns of antibiotic resistance.

Documentation Tips

- Include outpatient treatment course prior to hospitalization, especially if outpatient therapy failed.
- Document exact or suspected location of infection and whether an abscess is present.
- Include whether surgical intervention is anticipated or scheduled.
- Document the presence of sepsis or suspected airway compromise.

Suggested Reading

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CASE 19

Ida, a 15-Month-Old Girl With Pallor and Fatigue

CASE PRESENTATION

Ida is a 15-month-old girl who presents to her pediatrician for a health supervision visit. Her parents express that Ida seems more pale and tired than normal but otherwise has been doing well. Her pediatrician checks a complete blood cell count (CBC), and Ida is found to have anemia with a hemoglobin level of 5.4 g/dL (54 g/L). Her pediatrician is concerned that Ida might need a red blood cell (RBC) transfusion, and she calls you to consider a direct admission to your hospital for further evaluation and treatment. You agree that Ida should be admitted. You discuss the family's preferences and Ida's current hemodynamic stability with Ida's pediatrician, and you agree that private transport from home would be appropriate. An hour later you are notified of Ida's arrival to the unit by her nurse.

Patient History and Review of Systems

Q: What information should you collect from Ida's caregivers?

- History of present illness
  - Duration of fatigue and pallor
  - Detailed dietary intake, including amount of cow milk, screening for food insecurity (see "Health Equity Focus: The Hunger Vital Sign" for a sample food security screener)
  - Frequency of bowel movements, color and consistency of stool, presence of visible blood or mucus in stool
  - History of any nonfood ingestions
  - Immigration history or recent travel
- Associated symptoms, such as fever, headache, abdominal pain, altered mental status, syncope, increased heart rate, nausea, vomiting, diarrhea, rashes, abnormal bruising or petechiae, lumps or masses, or weight loss
- Medical history, including birth history, immunization status, growth history, and review of growth charts, if possible
- Medications, including supplements
- Family history, especially of hematologic disorders
- Social history, including lead exposure risk assessment (eg, living in a home built before 1978, persons working in construction living in the home, living in a high-risk zip code)

HEALTH EQUITY FOCUS

The Hunger Vital Sign

The Hunger Vital Sign is a validated screening tool that identifies households as being at risk for food insecurity. The screen is considered positive if the family answers "often true" or "sometimes true" (vs "never true") to one or both of the following 2 statements:

- "Within the past 12 months, we worried whether our food would run out before we got money to buy more."
- "Within the past 12 months, the food we bought just didn't last, and we didn't have money to get more."

It is important to note that there is evidence that there are higher rates of food insecurity among immigrant families. This and all screening tools should be adapted in terms of language and literacy for the local population.

Hunger Vital Sign reprinted with permission from Hager ER, Quigg AM, Black MM, et al. Development and validity of a 2-item screen to identify families at risk for food insecurity. *Pediatrics*. 2010;126(1):e26–e32.

CASE FOCUS

History and Review of Systems

When you arrive at her room, you meet Ida and her parents, and obtain her history from her 2 mothers. Ida was conceived with the help of an anonymous sperm donor, and her birth mother had no prenatal complications apart from mild anemia. Ida was born via spontaneous vaginal delivery at 34 weeks' gestation and underwent cord clamping less than 30 seconds after delivery. She spent 1 week in the neonatal intensive care unit for hypoglycemia but otherwise did well. Her mothers report Ida's fatigue and pallor started about 1 to 2 months after her first birthday, but they did not think there was reason for concern until Ida's aunt came to visit a few days ago and expressed worry.

In obtaining a detailed diet and intake history, you learn that Ida drinks about 30 oz of whole cow milk every day and is a picky eater. Her diet mainly consists of fruits and yogurt, but she occasionally eats chicken and bread. Her parents screen negative for food insecurity. They have not noticed her ingesting dirt or any other nonnutritive substances. Prior to transitioning to table foods, Ida's diet consisted entirely of human (breast) milk, without any iron-fortified formula. She also took a vitamin D supplement.

No one in the home works in an environment with lead exposures. Their house was built recently and is in a low-risk zip code for lead exposure. Ida has 2 soft, brown bowel movements every day, and her parents have not noted any blood in her stool. Ida has not had any fevers, headache, abdominal pain, rashes, or easy bruising. She has not had any syncope, increased heart rate, vomiting, or skin lesions. Other than fatigue, Ida has not had any changes in her mental status. Her height and weight have been tracking appropriately according to her mothers and she has not had any recent weight loss. She does not take any medications or vitamins and has been healthy aside from a few colds after discharge from the neonatal intensive care unit. Ida is up to date on her vaccinations, including her seasonal influenza immunization. There is no family history of hematologic disorders in Ida's birth mother or her sperm donor.

Physical Examination

Q: What parts of the physical examination should you focus on for Ida?

- Complete set of vital signs
- General: level of consciousness and ability to arouse and interact appropriately, hydration status
- Head, eyes, ears, nose, and throat
  - Mucous membranes, conjunctiva
  - Head size and shape
  - Eyes for microphthalmia or blue sclera
  - Oral examination for glossitis, angular stomatitis, cleft lip or palate, pigmentation in mouth, or telangiectasias
- Cardiorespiratory
  - Heart rate, presence of a systolic flow murmur, capillary refill time, color and temperature of extremities, quality of peripheral pulses
  - Auscultation and depth of respirations
- Gastrointestinal
  - Abdominal tenderness, guarding, palpation of liver and spleen to evaluate for hepatosplenomegaly
  - Visual examination of the stool, rectal examination for hemorrhoids or active rectal bleeding
- Skin
  - Turgor, presence of rashes, pallor of the palmar creases, nail beds, or conjunctivae
  - Hyperpigmentation, café au lait spots, vitiligo, jaundice, petechiae, ecchymoses, or purpura
- Neurologic: peripheral neuropathy, dementia or confusion, ataxia, irritability
- Extremities: thumb abnormalities, spoon nails, lines in nails, edema
- Lymphadenopathy: cervical, supraclavicular, axillary, inguinal

In patients with anemia, certain specific physical examination findings can provide diagnostic clues as illustrated in Table 19.1.

CASE FOCUS

Physical Examination

Ida's vital signs show that she is afebrile (temperature: 37 °C [98.6 °F]), slightly tachycardic (heart rate: 150 beats/min), and normotensive (blood pressure: 90/40 mm Hg) with an oxygen saturation of 98% on room air.

Ida is alert and interactive but fussy on your examination. You note no craniofacial abnormalities. Her pupils are equal and reactive, and her conjunctiva are pale. She has moist mucous membranes, with no abnormalities noted in her oropharynx. She has a normal respiratory examination, but on cardiac examination, you note a II/VI systolic ejection murmur with tachycardia. You do not note any rubs or gallops. Her capillary refill time is less than 2 seconds. Her abdomen is soft, nontender, and without any masses or hepatosplenomegaly. She has a normal genitourinary examination, with no rectal bleeding or hemorrhoids. She does not have any neurologic signs of symptoms on examination. There is no lymphadenopathy. On skin examination, you note pallor in the palmar creases and nail beds. There are no rashes, petechiae, or other skin lesions. She does not have any musculoskeletal abnormalities.

Table 19.1. Physical Examination Findings and Associated Diagnoses in Patients With Anemia

Physical examination finding	Potential diagnoses
Frontal bossing	Thalassemia, severe iron deficiency, chronic subdural hematoma
Microcephaly	Fanconi syndrome, Diamond-Blackfan anemia
Microphthalmia	Fanconi syndrome
Blue sclera	Iron deficiency, osteogenesis imperfecta leading to iron deficiency
Glossitis	Vitamin B_{12} or iron deficiency
Angular stomatitis	Iron deficiency
Cleft lip or palate	Diamond-Blackfan anemia
Pigmentation in mouth	Peutz-Jeghers syndrome (leading to intestinal blood loss)
Mucocutaneous telangiectasia	Hereditary hemorrhagic telangiectasia (causing blood loss)
Hepatosplenomegaly	Thalassemia, sickle cell anemia, malignancy
Hemorrhoids	Portal hypertension
Café au lait spots	Fanconi syndrome
Vitiligo	Vitamin B_{12} deficiency
Jaundice	Hemolysis, hepatitis
Petechiae or purpura	Bone marrow dysfunction, autoimmune hemolysis and thrombocytopenia, hemolytic uremic syndrome
Peripheral neuropathy	Vitamins B_1 and B_{12} deficiencies, lead poisoning
Dementia or confusion	Vitamins B_{12} and E deficiencies
Ataxia	Vitamins B_{12} and E deficiencies
Thumb abnormalities	Fanconi syndrome
Thenar eminence hypoplasia or triphalangeal thumb	Diamond-Blackfan syndrome
Spoon nails	Iron deficiency anemia
Lines in nails	Heavy metal intoxication
Edema	Milk-induced protein-losing enteropathy with iron deficiency anemia

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a young child with anemia?

The differential diagnosis for a young child with anemia is shown in Table 19.2 and is divided into causes that seem more and less likely based on Ida's presentation.

Table 19.2. Differential Diagnosis for a Young Child With Anemia

Diagnoses of highest suspicion	• Hemolytic anemia (G6PD, hereditary spherocytosis, immune mediated) • Iron deficiency anemia[a] • Thalassemias • Vitamin B_{12} deficiency, folate deficiency
Other diagnoses to consider	• Aplastic anemia • Anemia of inflammation (commonly referred to as *anemia of chronic disease*) • Blood loss (acute or chronic), including – Blood loss into a body cavity (eg, intra-abdominal, intracranial, intrathoracic) – GI losses associated with peptic ulcer, Meckel diverticulum, polyp, hemangioma, IBD, infections, milk-protein allergy – Hematuria – Postoperative loss – Trauma • CKD • Diamond-Blackfan anemia • Heavy metal poisoning (lead toxicity) • Hemoglobinopathy • Hypothyroidism • Infection (eg, CMV, parvovirus, malaria, hepatitis, TB) • Lead toxicity • Malignancy • Medication side effect • Transient erythroblastopenia of childhood

Abbreviations: CKD, chronic kidney disease; CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; IBD, inflammatory bowel disease; TB, tuberculosis.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with anemia?

- As illustrated by the differential diagnosis, anemia can be the presenting sign for a broad range of conditions. The diagnostic evaluation should focus on the suspected diagnosis as determined by history and physical examination while ruling out some of the more serious diagnoses. Certain physical examination findings can provide diagnostic clues, as illustrated in Table 19.1.
- Any time there is concern that a packed red blood cell (pRBC) transfusion might be needed, it is imperative to urgently obtain a blood type and screen. Indications that the patient may need a pRBC transfusion include hemodynamic instability (tachycardia, hypotension, poor peripheral perfusion), suspected ongoing blood loss, or mental status changes.
- If not already obtained, a CBC with differential and reticulocyte count should be collected to determine the severity of anemia, to provide important indicators about the RBCs (eg, mean corpuscular volume, mean corpuscular hemoglobin concentration), and to verify which cell lines are affected.
- A peripheral smear review will help evaluate for any cell dysmorphology, which could indicate malignancy, hemolysis, abnormal RBC structure, or oxidative cell damage.
- When there is concern for iron deficiency anemia (based on dietary history or CBC indices), iron studies will help confirm this diagnosis. For patients with mild anemia or anemia found incidentally on admission, it is reasonable to start treatment with iron supplementation prior to obtaining iron studies. These studies include ferritin, serum iron, total iron-binding capacity (TIBC), and transferrin.
  - In iron deficiency anemia, ferritin, a marker of iron storage, decreases first, followed by the serum iron level.
  - Serum iron can be low or high depending on recent meals and is not the most sensitive indicator.
  - As iron levels decrease in the body, TIBC increases and transferrin decreases.
- If there is concern for hemolysis (eg, family history of jaundice, hemoglobinopathy or autoimmune disorders, recent medication change, patient history of jaundice), obtaining total bilirubin, direct bilirubin, and haptoglobin levels is recommended.
- Hemoglobin electrophoresis may be obtained if there is concern for hemoglobinopathies (based on family history or ancestry, such as Mediterranean, Middle Eastern, Southeast Asian, or African descent). This study must be obtained prior to pRBC transfusion so as not to alter the results of electrophoresis.
- In cases of acute blood loss, the evaluation may be broad and guided by the location of suspected blood loss.

CASE FOCUS

Diagnostic Evaluation

You decide to start Ida's evaluation with a repeat CBC with differential to evaluate her current hemoglobin level and red cell indices. You also order iron studies to evaluate her iron stores. You order a blood type and screen given her slight tachycardia, which may be an early sign of hemodynamic instability. Additionally, you order a reticulocyte count and peripheral smear. The results of Ida's laboratory studies are as follows:

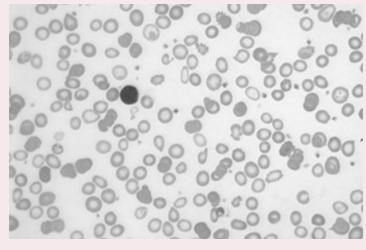
CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
CBC with differential		
WBC count	5,000/μL (5 × 10^9/L)	4,000–10,500/μL (4.0–10.5 × 10^9/L)
RBC count	3.5 × 10^6/μL (3.5 × 10^{12}/L)	4.2–5.6 × 10^6/μL (4.2–5.6 × 10^{12}/L)
Hemoglobin	5.4 g/dL (54 g/L)	11.7–15.7 g/dL (117–157 g/L)
Hematocrit	20.2% (0.202)	34.8%–45.8% (0.348–0.458)
MCV	60 μm^3 (60 fL)	78–95 μm^3 (78–95 fL)
MCH	24.0 pg/cell	26.0–32.0 pg/cell
MCHC	32 g/dL (320 g/L)	31–37 g/dL (310–370 g/L)
RDW	18.3% (0.183)	11.0%–15.0% (0.11–0.15)
Platelet count	250 × 10^3/μL (250 × 10^9/L)	150–450 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	70% (0.70)	23%–70% (0.23–0.70)
Lymphocytes	21% (0.21)	10%–60% (0.10–0.60)
Monocytes	7% (0.07)	5%–20% (0.05–0.20)
Eosinophils	1% (0.01)	2%–5% (0.02–0.05)
Basophils	1% (0.01)	0%–1% (0–0.01)
Reticulocyte count	1.3% (0.013)	0.5%–2.0% (0.005–0.02)
Iron studies		
Ferritin	4 ng/mL (4 μg/L)	10–60 ng/mL (10–60 μg/L)
Transferrin	100 mg/dL (12.3 μmol/L)	220–337 mg/dL (27.1–41.5 μmol/L)
TIBC	500 μg/dL (89.5 μmol/L)	100–400 μg/dL (17.9–71.6 μmol/L)

Abbreviations: CBC, complete blood cell count; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; TIBC, total iron-binding capacity; WBC, white blood cell.

You review Ida's peripheral smear, which looks like this:



Reprinted with permission from Fleming M. Disorders of iron and copper metabolism, the sideroblastic anemias, and lead toxicity. In: Orkin SH, Nathan DG, Ginsburg D, et al, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Elsevier Saunders; 2015:344-381.

Pathologist report: Abundant small, pale (microcytic and hypochromic) RBCs of variable size and shape (anisopoikilocytosis). There are occasional target cells. Smear is consistent with possible iron deficiency anemia or thalassemia. Clinical correlation recommended.

Arriving at a Diagnosis

Q: How do you develop an assessment for Ida?

Because patients with anemia may require urgent intervention, you decide to first assess Ida's hemodynamic status. Next, you will interpret her history, vital signs, examination findings, and diagnostic evaluation to develop a list of findings that aids in determining the most likely etiology of her anemia. You can then generate admission criteria for your specific diagnosis.

1. **Assess hemodynamic stability.**
   - When a patient's hemoglobin level is between 6 and 10 g/dL (60–100 g/L), compensatory mechanisms may mask many symptoms of anemia, but when the hemoglobin level is less than 6 g/dL (60 g/L), patients will often begin to demonstrate lethargy, irritability, anorexia, and/or a systolic flow murmur.
   - Ida is showing evidence of being symptomatic from her anemia given the fatigue reported by her mothers. Her tachycardia with a normal blood pressure and normal perfusion indicates that her body has compensated for her anemia and is maintaining end-organ function. This suggests that her anemia is likely chronic and is inconsistent with rapid blood loss.
2. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Ida was born prematurely at 34 weeks to a mother who had mild anemia during pregnancy. Ida underwent early umbilical cord clamping. For the first year after birth, she mostly took breast milk without the addition of iron supplementation. Her current diet consists mainly of cow milk, fruit, and yogurt, with occasional chicken and bread. These details place Ida at increased risk for iron deficiency. However, the family reports no food insecurity, which, when present, is also an independent risk factor for iron deficiency.
   - Physical examination: Ida is showing signs of cardiovascular stress with tachycardia, and what you suspect is a flow murmur as a result of the body's response to the low oxygen binding capacity of the blood, which causes tachycardia and hyperdynamic blood flow. Ida is otherwise well hydrated with good peripheral pulses and perfusion. Ida's skin examination reveals that she has pallor throughout with pale conjunctiva. She does not have any petechiae, bruising, lymphadenopathy, or hepatosplenomegaly.
   - Diagnostic evaluation: Ida's hemoglobin level is stable from the results obtained at her pediatrician's office but is still low at 5.4 g/dL (54 g/L). She has a mean corpuscular volume of 60 μm^3 (60 fL), indicating microcytosis. Her white blood cell and platelet counts are normal. Her RBC count is low at $3.5 \times 10^6/\mu L$ ($3.5 \times 10^{12}/L$). Additionally, her red blood cell distribution width (RDW) is elevated, indicating RBCs of varying sizes. Her ferritin is decreased at 4 ng/mL (4 µg/L), and her TIBC is elevated at 500 µg/dL (89.5 µmol/L).
3. **Further interpret the hematologic evaluation.**
   Knowing that Ida has microcytic hypochromic anemia with a high RDW, you consider what this might mean. See Figure 19.1 for the decision process related to anemia.

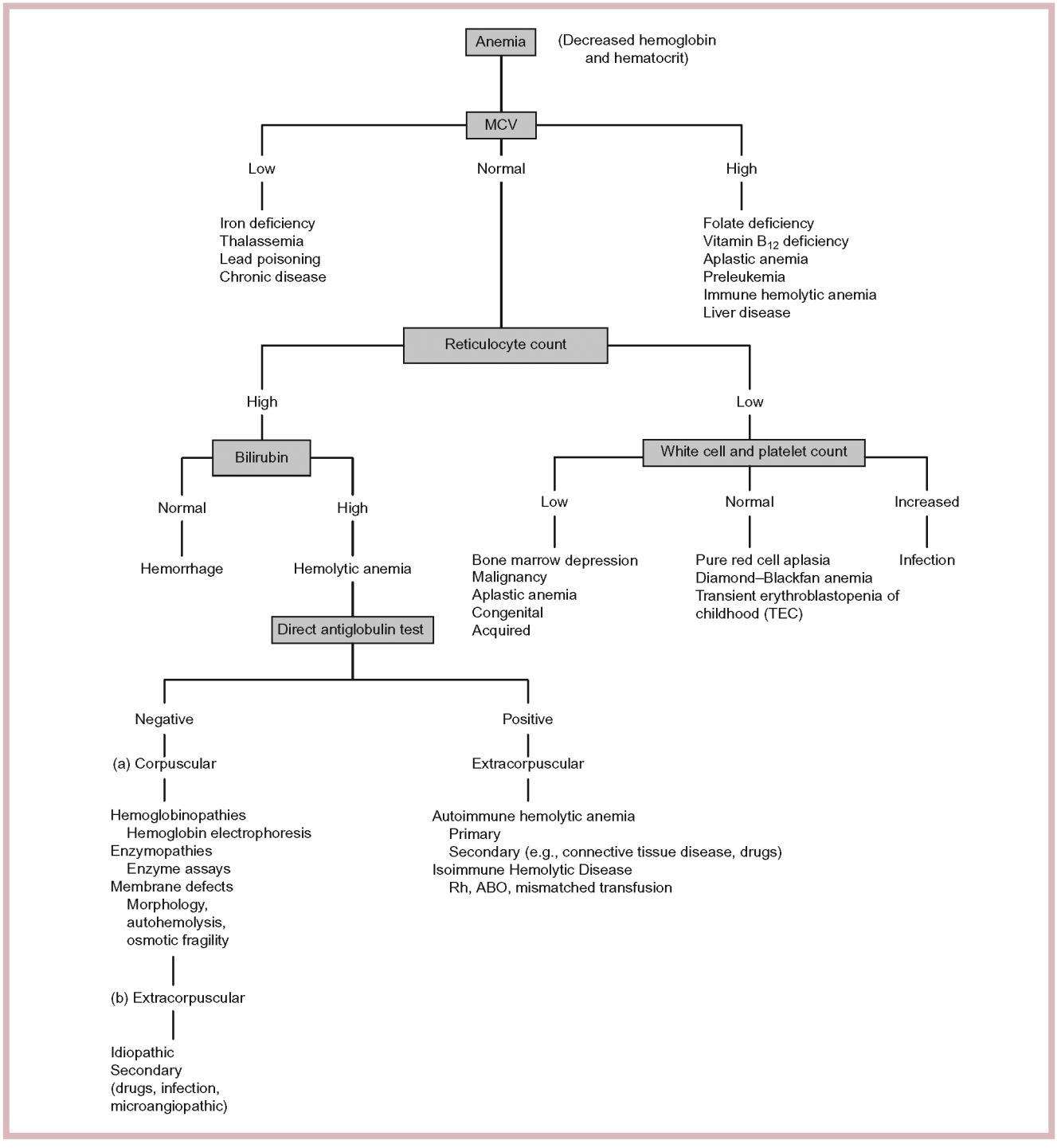


Figure 19.1. Classification and diagnosis of anemia based on laboratory findings.

Abbreviation: MCV, mean corpuscular volume.

Reprinted with permission from Lanzkowsky P. Classification and diagnosis of anemia in children. In: Fish J, Lipton J, Lanzkowsky P, eds. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*. 6th ed. Elsevier; 2016:32–41.

As shown in Table 19.3, there are many similarities among microcytic anemias; however, one key difference is the RBC count. Unless pretreated with iron, the RBC count will always be low in cases of iron deficiency anemia. If the patient's RBC count is normal, clinicians can rule out iron deficiency anemia as the sole etiology of the patient's anemia and expand the evaluation. Ida's RBC count is low at $3.5 \times 10^6/\mu L$ ($3.5 \times 10^{12}/L$), which is consistent with iron deficiency anemia.

Table 19.3. Laboratory Differences Among Microcytic Anemias

Laboratory study	Iron deficiency anemia	α- or β-thalassemia	Anemia of chronic disease
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal to decreased
RDW	Increased	Normal to minimally increased	Normal to increased
RBC count	Decreased	Normal to increased	Normal to decreased
Serum ferritin	Decreased	Normal	Increased
TIBC	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal to decreased

Abbreviations: MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; TIBC, total iron-binding capacity.

Adapted with permission from Sills R. Iron-deficiency anemia. In: Kliegman R, Stanton BF, St Geme JW, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Elsevier; 2016:2323–2326.

4. **Develop the list of findings.**

Q: What are the major findings you have identified for Ida?

- Microcytic hypochromic anemia with a high RDW
- Tachycardia
- Iron deficiency
- Holosystolic murmur
- Limited diet
- History of prematurity

5. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Ida's presentation?

- Ida's history, physical examination, and diagnostic evaluation are consistent with iron deficiency anemia.
- Ida's history of prematurity is significant because iron is accumulated in the third trimester of pregnancy. Infants of mothers with anemia, maternal hypertension, or diabetes and infants with intrauterine growth restriction are predisposed to have low fetal iron stores. It is probable that Ida started out with lower iron stores than a child born full term (37–40 weeks). Given her "picky eating," Ida likely has very limited sources of iron and other essential vitamins in her diet. Some children may have difficulties with feeding stemming from aspiration, reflux, rumination, sensory, or motor disabilities, but this does not appear to be the case for Ida.
- On physical examination, Ida has pallor that is consistent with anemia but no petechiae or bruising that would lead you to suspect coagulopathy. She has no lymphadenopathy or hepatosplenomegaly, lowering your suspicion of malignancy as the cause of her anemia.
- Ida has no physical examination findings or history to suggest acute or chronic blood loss.

- In addition to clearly demonstrating microcytic anemia, Ida's WBC and platelet counts are normal, decreasing any suspicion of infectious etiologies or malignancy. Her low RBC count is consistent with iron deficiency anemia or anemia of chronic disease and makes hemoglobinopathies less likely. Additionally, her elevated RDW indicates RBCs of varying sizes, which is typically the first marker of iron deficiency identifiable on blood work. Her ferritin level is consistent with low iron stores. Her elevated TIBC indicates she has an increased amount of binding sites available on transferrin in her serum for iron to bind, which differentiates iron deficiency anemia from anemia of chronic disease. Serum ferritin is normally decreased in iron deficiency anemia but can be increased in inflammatory states.
- Ida's reticulocyte count is within normal range. Given her anemia, you would expect her reticulocyte count to be elevated. This indicates that her bone marrow is not producing increased numbers of RBCs from normal. This is an abnormal response, which is indicative of decreased hemoglobin synthesis as a result of poor iron stores.

6. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with iron deficiency anemia?

Most patients with iron deficiency anemia can be managed out of the hospital; however, it is reasonable to consider hospital admission in the following circumstances:

- The child has symptomatic anemia causing hemodynamic instability (eg, hypotension, dizziness, tachycardia, syncope, poor peripheral perfusion because of hypoxemia).
- The child has severe anemia requiring pRBC transfusion.

You determine that Ida requires inpatient admission given her severe, symptomatic anemia.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Ida is a 15-month-old previously healthy girl presenting with a newly discovered severe iron deficiency anemia likely related to a history of poor dietary iron intake, with her premature birth to a mother with gestational anemia contributing to poor iron stores as well. She is symptomatic from her anemia and requires hospitalization for possible RBC transfusion and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In thinking through Ida's presentation, suspected diagnosis, and clinical status, you decide to divide treatment considerations into the following components:

1. **Hemodynamic stability:** The threshold used for transfusion is variable among institutions and physicians; however, RBC transfusion is a reasonable consideration when a patient's hemoglobin level is less than 8 g/dL (80 g/L) or there are signs of hemodynamic instability (eg, tachycardia, orthostatic hypotension, delayed capillary refill, dizziness) or signs of ongoing blood loss. In the setting of chronic anemia, hemodynamic compensation allows the patient with a low hemoglobin level to be relatively asymptomatic. This compensation is likely the reason that despite having a hemoglobin of 5.4 g/dL (54 g/L), Ida is hemodynamically stable.

2. **Monitoring:** Patients receiving transfusions may experience reactions to pRBC cell transfusions, including allergic reaction, fever, possibility of transmission of infection, mismatched blood product, or the need for additional transfusions; therefore, they should be monitored closely.
3. **Treatment of underlying iron deficiency:** Although pRBC transfusion will acutely treat Ida's anemia, it is important to develop a plan to treat the underlying cause. Data on the long-term impact of iron deficiency anemia in toddlers are inconclusive; however, some data indicate the potential for cognitive impacts if left untreated.
   - Supplementation: Treatment of iron deficiency includes oral or intravenous supplementation. Generally, oral supplementation is preferred unless the child has a contraindication to oral supplementation or is unable to tolerate oral intake. Administering iron between meals with juice containing vitamin C can increase absorption of iron. Milk products should be avoided for at least an hour before and after oral iron supplementation, which can decrease iron absorption.
   - Dosing: Iron supplementation may be given in treatment dosing or prophylactic dosing. It is dosed in mg/kg of *elemental* iron per day. Most formulations are delivered as ferrous sulfate or ferrous gluconate. Oral treatment of iron deficiency anemia can be challenging; although iron is dosed as elemental iron, many formulations are prescribed in mg/mL. It is essential to ensure proper dosing to prevent undertreatment or iron overload.
   - Diet: Iron deficiency treatment also includes a dietary component. Young children should eat 3 or more servings each day of iron-containing foods (eg, iron-fortified cereals, meats, seafood, leafy vegetables). It is also important to limit intake of cow milk to less than 20 oz/day. Consumption of greater than 24 oz/day of cow milk is associated with increased rates of iron deficiency anemia. In toddlers, this association is attributed to inhibition of iron absorption by calcium and casein present in cow milk and decreased intake of other foods that may have higher iron content when there are high levels of milk in the diet. Parents may also consider cooking with cast iron skillets or using cooking utensils containing iron to help increase iron intake in children who continue to be picky eaters or who will not take supplements.
4. **Social determinants of health:** Food insecurity commonly affects children in lower socioeconomic communities and children of immigrant families. It is essential that physicians ensure proper nutrition is available and accessible to families. All patients should be screened for food insecurity. If food insecurity is identified, inpatient social workers should be consulted to assist families in finding resources to obtain adequate nutrition for their children. Ida's mothers report no food insecurity when screened, and you are confident that food insecurity did not contribute to Ida's anemia.
5. **Consultations to consider**
   - Dietician: A consultation with a dietician may be useful to assess dietary intake and provide education on iron-rich foods to families. It is important to ensure that dietary recommendations are patient centered, accounting for cultural preferences and economic limitations.
   - Occupational therapy: In patients with oral aversions, consultation with an occupational therapist may be helpful in developing a long-term treatment plan. As you currently do not have concerns for oral aversions in Ida, you decide not to consult this team at this time.
   - Child life: Oral iron supplementation can be challenging, as the taste may be unappealing to young children. Child life experts can help develop strategies for taking iron supplementation and can assist children in coping with unpleasant procedures and treatments, such as IV placement, that are part of the hospital stay.
   - Social work: Social workers can help address any food insecurity or socioeconomic concerns limiting a family's ability to obtain the quality and quantity of foods necessary to thrive.
   - Hematology: Consultation with a hematologist can be considered, especially when there is suspicion of blood disorder.

6. **Follow-up:** Monitoring by a primary care pediatrician for resolution of iron deficiency anemia following initiation of treatment is important to prevent ongoing anemia; treatment should be adjusted as appropriate. After 1 month of iron supplementation, hemoglobin should increase by 1 to 2 g/dL (10–20 g/L) in most patients. In those with very severe anemia, the increase may take more time, but reticulocytosis should be evident within 48 to 96 hours. Clinicians should continue iron supplementation at treatment dosing for 2 to 3 months after normalization of hemoglobin to replenish the iron stores in the body. Clinicians can then change to prophylaxis if continued supplementation is required from a nutrition standpoint. A CBC should be checked 6 months after discontinuation of iron supplementation.

CASE FOCUS

Plan for Treatment and Monitoring

- **Airway, breathing, and circulation/hemodynamics:** Given Ida's tachycardia and severe anemia, you discuss pRBC transfusion with her family. You review the risks of blood transfusion with them. They are concerned that her symptoms have recently worsened and would like to proceed with the transfusion. Ida is given a 10 mL/kg transfusion of pRBCs.
- **Monitoring:** Ida's vital signs are checked more frequently during transfusion to help monitor for a transfusion reaction. Following the transfusion, you plan to monitor Ida overnight to observe for any complications that may arise related to her transfusion. You also plan to obtain a repeat CBC in the morning as a baseline for her pediatrician.
- **Iron deficiency:** Ida has severe iron deficiency anemia, so you decide to give her treatment dosing of elemental iron. You confirm that you are dosing in elemental iron and not ferrous sulfate or ferrous gluconate.
- **Nutrition consultation:** You consult a dietician to assess Ida's nutritional intake in more detail and provide education to the family regarding iron-containing foods and appropriate cow milk consumption.
- **Child life consultation:** A child life specialist is engaged to help Ida cope with intravenous line placement and assist with oral iron supplementation.
- **Social work consultation:** You did not elicit any indications of food insecurity that could be limiting Ida's intake, and therefore you decide not to consult social work at this time.
- **Follow-up:** When you call to update Ida's primary care pediatrician regarding Ida's status, you ensure her pediatrician is able to see Ida in clinic and obtain a CBC to ensure resolution of iron deficiency anemia following initiation of supplementation.

Case Resolution

Following admission, Ida tolerates the 10 mL/kg transfusion of pRBCs well, without complications. The dietician discusses Ida's diet with her mothers and helps them develop a plan to increase the amount of iron in Ida's diet. The next morning, you recheck Ida's CBC, and her hemoglobin has risen appropriately to 6.7 g/dL (67 g/L). Her tachycardia has resolved as well. Her mothers are excited to report that Ida seems more energetic than she has been in weeks. The child life specialist works with them to ensure Ida is able to take her oral iron supplement. You discharge Ida home with plans for Ida and her mothers to follow up closely with their pediatrician.

Discharge Criteria

Q: How do you know when Ida is ready to go home?

You can feel comfortable discharging your patient with iron deficiency anemia when the following criteria are met:

- The patient's evaluation excludes life-threatening causes of anemia.
- The patient demonstrates hemodynamic stability.
- The patient's ability to complete outpatient treatment has been verified prior to discharge. This includes ensuring that the patient is able to tolerate oral iron, a prescription for oral iron is written if the patient is not able to obtain oral iron supplementation over the counter, and iron dosing is confirmed.
- You have adequately provided dietary education to the family and addressed any identified food insecurity.

Anticipatory Guidance

Q: What instructions should you provide to Ida's caregivers upon discharge?

- Increase Ida's dietary intake of iron-rich foods, including leafy greens, lean meats, and beans, and provide her with no more than 20 to 24 oz of cow milk in 24 hours.
- Ida should see her primary care physician for a posthospitalization follow-up to ensure she continues to be hemodynamically stable and asymptomatic.
- It is important to consider safe storage of all supplements and medications in the household. Iron overload can cause toxicity in young children, and care should be taken to ensure that supplements and medications are not accessible to children.

Clinical Pearls

- In the United States, 8% to 14% of children ages 12 to 36 months are iron deficient, and approximately 30% of this group progresses to iron deficiency anemia. Most pediatricians screen for anemia by obtaining a hemoglobin level at the 12-month health supervision visit; however, a hemoglobin level less than 11 g/dL (<110 g/L) is only 30% sensitive for iron deficiency at this age.
- Dosing of iron replacement should be done as elemental iron.
- Toddlers should have no more than 20 to 24 oz of cow milk in 24 hours.

Documentation Tips

- When possible, specify whether the anemia is acute, chronic, or acute in addition to chronic.
- Be as specific as possible in documenting of the type of anemia (ie, microcytic, normocytic, macrocytic).
- Document the cause of anemia when possible (eg, blood loss, iron deficiency, aplastic, chronic disease).
- For nutritional anemias, specify the deficient vitamin or mineral.

Suggested Reading

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CASE 20

Jenny, a 14-Year-Old Girl With a Severe Headache

CASE PRESENTATION

Jenny is a 14-year-old girl who is being seen in the emergency department (ED) for a severe headache that started 3 days ago. The ED physician reports Jenny has a history of recurrent headaches and currently has a normal neurologic examination. At home, Jenny tried ibuprofen and sumatriptan for her pain without any relief. In the ED, she receives intravenous (IV) ketorolac, a normal saline bolus, diphenhydramine, and prochlorperazine without significant improvement in her pain. The ED physician requests that you evaluate Jenny for admission to provide her with ongoing treatment and further evaluation of her symptoms, if needed.

Patient History and Review of Systems

Q: What information should you collect from Jenny and her caregivers?

- Description of headache episode
  - Timing: headache onset and whether pain is constant or intermittent; if intermittent, duration when present
  - Location: frontal, temporal, facial, retrobulbar, posterior, or occipital, and whether the pain is unilateral or bilateral
  - Quality of pain: pulsating/throbbing, pressure-like, or squeezing
  - Intensity: current pain severity and severity at onset (on a scale of 0–10); changes in pain over time
  - Modifying factors: aggravating factors (eg, activity, light, sounds, position changes [upright vs supine], Valsalva maneuvers) and any alleviating factors
  - Associated symptoms, including fullness in the ears, dizziness, vision changes, excessive tearing, nasal congestion, runny nose, swelling around the eyes, nausea, or vomiting
  - Prodromal symptoms in the 1 to 2 days prior to headache onset, such as fatigue, vision changes, nausea, difficulty concentrating, neck stiffness, photophobia or phonophobia, yawning, depression, or pallor
  - Possible aura symptoms, duration, and progression, including changes in vision (eg, a blind spot or jagged or curved scintillating line in the visual field), numbness or tingling of the body/face/tongue, word-finding difficulties/aphasia, motor weakness, ataxia, or changes in sense of smell
  - Prescribed or over-the-counter (OTC) medications taken for pain and frequency of use
- "Red flag" symptoms
  - Associated fever, back pain, neck pain, or neck stiffness
  - Headache that is sudden and severe at onset
  - Recent onset (< 6 months) of headaches that are progressively worsening

  - Pain that is worse in the morning or wakes the patient from sleep
  - Vomiting (a more prominent symptom than nausea)
  - Pain focused in the occiput
  - Worsening pain with straining or changing positions
  - Retrobulbar pain or pain with eye movement
  - Recent trauma to the head in the 7 days prior to the onset of pain
  - Neurologic symptoms: focal neurologic deficits, difficulty in maintaining balance or with ambulation, dizziness, diplopia, seizures, pulsatile tinnitus, or cognitive or psychiatric changes
- Headache history
  - Timing: initial onset, frequency, duration, and any associations with triggers (eg, menstruation, sinus/nasal symptoms)
  - Usual headache severity, including whether headaches result in missed school days or other missed activities
  - Medications that have worked well in the past and any preventive medications used
  - Comparison of current headache to prior headaches
  - Headache descriptors, including common prodromal symptoms, presence of an aura, and other associated symptoms
  - Postdromal symptoms, including associated fatigue or elation, excessive sleepiness, or difficulty falling asleep
- Medical history, including chronic medical conditions, mental health diagnoses, immunization status, recent weight gain, or sleep apnea
- Medication history, especially oral contraceptives, growth hormone, tetracycline, vitamin A/retinoid, immunosuppressive therapies (eg, tacrolimus, cyclosporine), or recent corticosteroid use
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) examination, especially noting illicit substance use and social stressors (refer to Section VII in the Appendix for an example of a complete HEADSS assessment)
- Family history, especially of migraines, malignancy, intracranial aneurysms/bleeds, or bleeding disorders

CASE FOCUS

History and Review of Systems

From these questions, you learn that Jenny has been having these headache episodes for over a year, and they generally occur 2 or 3 times monthly. Each episode follows a typical progression of symptoms, starting with fatigue and followed by the appearance of "scintillations" or "flashing lights" in her visual field bilaterally. This is then followed by a "blind spot" in her right visual field. Within 10 to 15 minutes, she starts experiencing a tingling sensation on the left side of her face that then spreads to her left arm, which then becomes slightly numb. During this time, she becomes hypersensitive to bright lights and loud noises. About an hour later, her visual and sensory symptoms resolve and the pain starts over her left temporal area, quickly spreading to the right. Use of ibuprofen and sumatriptan can frequently abort her headaches within a few hours of onset. Other times, bitemporal, throbbing pain can last 1 to 2 days. During that time, she often feels nauseous, is unable to tolerate anything orally, and continues to have sensitivity to light and sound. Her headaches are usually between a 4 and a 6 in severity on a scale of 0 to 10 and result in approximately 1 day of missed school each month. They do not correspond with her menses. After her headache pain resolves, she commonly experiences fatigue until the following day.

Jenny's current headache episode has been present for 3 days. This headache seems similar to previous episodes except for the duration and severity. Her pain is currently 8 on a scale of 0 to 10. Prior to arrival to the ED, Jenny was using ibuprofen 3 times per day for the past 3 days and has used 2 doses of sumatriptan as prescribed by her pediatrician. Unfortunately, these medications have not helped her pain. Because of nausea, Jenny has not had any solid foods for the past 2 days but has been sipping water. Her urine output is decreased from normal. Jenny denies any features on your list of red flag symptoms.

There are no sick contacts at home, and Jenny denies having a fever, neck stiffness, dizziness, or vomiting. Other than her use of ibuprofen and sumatriptan, she does not take any medications, supplements, or oral contraceptives. She is fully immunized and developmentally appropriate for age.

History and Review of Systems *(continued)*

To evaluate her recurrent headaches, Jenny's primary care physician obtained magnetic resonance imaging (MRI) of the brain 6 months ago that was reportedly unremarkable. Her pediatrician also referred her to a pediatric neurologist, but Jenny's parents have not been able to schedule an appointment yet. Of note, Jenny has a history of seasonal allergic rhinitis and eczema, and both of her older siblings experience migraines. Otherwise, there is no family history of hereditary diseases.

Physical Examination

Q: What parts of the physical examination should you focus on for Jenny?

- Complete set of vital signs, specifically evaluating for Cushing triad (bradycardia, bradypnea, and hypertension)
- Level of cognition and alertness
- Neck: stiffness/meningismus (eg, Kernig and Brudzinski signs)
- Respiratory: respiratory pattern
- Cardiovascular: heart rhythm and rate, cervical bruits
- Neurologic
  - Cranial nerve examination
  - Fundoscopic examination to assess for papilledema
  - Muscle tone, strength, and reflexes
  - Evaluation of sensation bilaterally
  - Gait, balance, and coordination
- Skin: lesions, birthmarks, rashes

Physical Examination

Jenny's vital signs are reassuring, with a normal blood pressure for her age and height. She is afebrile, with a temperature of 36.7 °C (98.1 °F) but has mild tachycardia (resting heart rate: 110 beats/min). Her weight today is 56.7 kg, giving her a body mass index of 25.

On examination, Jenny is awake and interactive but uncomfortable and reserved. She is able to answer questions appropriately. She appears mildly dehydrated with cracked lips and dry mucous membranes. She has negative Kernig and Brudzinski signs and can move her neck in all directions comfortably. Cranial nerves II through XII are intact. Fundoscopic examination shows normal retinas and optic discs without papilledema bilaterally. She has normal peripheral sensation on her upper and lower limbs. Her muscle strength and tone are equal bilaterally and are normal. On standing, she demonstrates appropriate balance and a normal gait. The rest of her examination is unremarkable, with normal heart and breath sounds and a soft and nontender abdomen without organomegaly. She has no rashes or skin lesions.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child or adolescent with an intractable headache?

As demonstrated in Table 20.1, headaches can be classified as either being caused by a primary headache disorder or as secondary to another etiology (ie, a symptom of an underlying disorder). In Jenny's case, you are most concerned about the possibility of migraine with aura, tension-type headache, new daily persistent headache, idiopathic intracranial hypertension (IIH), and cerebral ischemia. Medication overuse headache also must be considered.

Table 20.1. Classification of Headache Disorders

Primary headache syndromes	• Migraine — Migraine with aura[a] ▪ Hemiplegic migraine ▪ Migraine with brainstem aura (previously referred to as *basilar-artery* or *vestibular migraine*) ▪ Migraine with typical aura (previously referred to as *classic migraine*) ▪ Retinal migraine — Migraine without aura • Tension-type headache[a] • Trigeminal autonomic cephalalgias, including cluster headache and paroxysmal hemicrania • Other primary headache disorders, including new daily persistent headache[a]
Secondary headache syndromes	• Cranial nerve disorders and facial pain syndromes (eg, trigeminal neuralgia) • Disorders of homeostasis (eg, hypoxia, hypercapnia, sleep apnea, hypertension, dialysis, high altitude, anemia) • Disorders of the head and neck, including sinusitis, refractive errors, and temporomandibular disorder • Infection (intracranial or systemic) • Nonvascular intracranial disorders — Chiari malformation, type I — Increased CSF pressure: IIH[a] (previously referred to as *pseudotumor cerebri*) or intracranial hypertension secondary to other causes — Intracranial neoplasia — Low CSF pressure, including spontaneous intracranial hypotension or postdural puncture — Noninfectious inflammatory diseases (eg, neurosarcoidosis) — Seizure related (ictal or postictal) • Psychiatric disorders, including somatization • Substance use or withdrawal, including medication overuse headache • Traumatic injury of the head or neck • Vascular disorders, including cerebral ischemia,[a] nontraumatic ICH, unruptured aneurysm or vascular malformation, arteritis, cranial venous disorder (eg, cerebral venous thrombosis), intracranial vasculopathy (including moyamoya disease), or reversible cerebral vasoconstriction syndrome

Abbreviations: CSF, cerebrospinal fluid; ICH, intracranial hemorrhage; IIH, idiopathic intracranial hypertension.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with an intractable headache?

- When evaluating a pediatric patient with an intractable headache, a detailed history and physical examination, including a thorough neurologic examination, may be sufficient to diagnose a primary headache disorder. If there are no red flags on the patient's history and the neurologic examination is normal, diagnostic testing may not be required; however, if concerning findings are present, then a secondary headache syndrome may exist, and further evaluation is warranted.
- Neuroimaging
  - When neuroimaging is desired based on the presence of concerning features on history or examination, a noncontrast MRI of the brain is the imaging study of choice. Despite the superiority of MRI, a computed tomography (CT) scan of the head without contrast is the first study obtained in emergent situations (eg, concern for intracranial hemorrhage [ICH] or herniation) because it is rapid, widely available, and can quickly identify issues that require urgent surgical attention. Magnetic resonance (MR) venography or MR angiography of the head (with or without the neck) is rarely needed and typically obtained after subspecialist consultation when certain vascular etiologies are suspected.
  - Indications for neuroimaging may include the following:
    - Concern for increased intracranial pressure (ICP): Signs concerning for increased ICP may include an altered level of consciousness, hypertension with bradycardia and bradypnea, intractable vomiting, pupillary changes, an abnormal fundoscopic examination, palsy of cranial nerve VI, or an abnormal respiratory pattern. In the presence of these findings, immediate evaluation with a noncontrast CT scan of the head and escalation of care is needed.
    - Concern for ICH: Symptoms of ICH may include the severe and sudden onset of a headache with or without altered consciousness and vomiting. Immediate noncontrast CT scan of the head is indicated when these symptoms are present.
    - Presence of red flag features on the patient history and review of systems
    - Patient younger than 3 years
    - Recent onset of headaches (< 6 months) with a steadily worsening pattern in either frequency or intensity
    - A negative family history of migraines
    - Abnormal neurological findings on examination, including gait abnormalities
    - Recent development of seizures
    - The presence of neurocutaneous stigmata (café au lait or hypopigmented macules) on examination
- Lumbar puncture (LP): When there is clinical concern, an LP can be useful to evaluate for the presence of central nervous system (CNS) infection and/or to measure ICP with an opening pressure.
  - LP for CSF culture, Gram stain, cell counts, and molecular testing (eg, polymerase chain reaction) should be performed when there is concern for CNS infection such as meningitis or encephalitis. Signs of a CNS infection may include the presence of symptoms such as fever, mental status changes, seizure, or meningismus. Additional factors to consider that may increase the risk of a CNS infection include underimmunization, congenital immunodeficiency syndromes, certain infectious exposures, the presence of indwelling devices in the CNS (eg, shunts, cochlear implants), and the presence of craniofacial anatomical defects.
  - LP with opening pressure should be considered for patients with symptoms or physical examination findings indicative of increased ICP (ie, intracranial hypertension), such as papilledema or cranial nerve VI palsy. Additional features that may suggest intracranial hypertension include transient visual obscurations, pulsatile tinnitus, diplopia, and retrobulbar pain. When these findings are present, neuroimaging is commonly performed prior to LP to first evaluate for the possibility of cerebral edema, central venous thrombosis, hydrocephalus, midline shift, or space-occupying lesions.

CASE FOCUS

Diagnostic Evaluation

Based on Jenny's history and physical examination, you do not think that any urgent diagnostic evaluation is needed at this time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Jenny?

In thinking through her case, you decide to interpret the findings from Jenny's history, vital signs, and examination to develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology or etiologies. You can then generate admission criteria for your specific diagnosis.

1. **Interpret key findings from the history and examination.**
   - History: Jenny's history is notable for 3 days of nausea and severe headache pain that was preceded by visual and sensory symptoms. Her pain has been refractory to outpatient nonsteroidal anti-inflammatory drugs (NSAIDs) and use of a triptan. Jenny's current headache episode is similar to prior episodes that occur 2 to 3 times monthly. Jenny has a family history of migraines, which increases her risk for this condition. She does not have any concomitant fever, decreasing your suspicion of an acute infectious etiology. Although Jenny has complained of visual and sensory disturbances, they are transient, fully reversible, and are immediately followed by the headache, which is suggestive of a headache aura.
   - Physical examination: Assessing Jenny's neurological status includes evaluating her sensory and motor processing functions as well as cognition. On examination, she is found to have normal mentation and has no observable neurologic abnormalities. Her vital signs are reassuring against a rapidly evolving intracranial process, such as increased ICP.
   - On review of the information gathered on history and physical examination, Jenny has no red flag symptoms, which is reassuring against an infectious etiology or a neurologic emergency.
   - Assessment of hydration status: Jenny's recent nausea and vomiting have resulted in decreased urination and dry mucous membranes consistent with mild to moderate dehydration. Her dehydration is still present after an IV normal saline fluid bolus in the ED.
2. **Develop the list of findings.**

Q: What major findings have you identified for Jenny?

- Intractable headache that is unresolved despite treatment at home and in the ED
- Preceding symptoms of scotoma, scintillations, and sensory changes
- Photophobia and phonophobia
- Nausea and decreased oral intake
- History of multiple similar headache episodes
- Inadequate home prophylactic therapy
- Mild to moderate dehydration secondary to poor oral intake

3. Revisit the differential diagnosis.

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Jenny's presentation?

- You suspect that Jenny has an underlying primary headache disorder given the frequency, chronicity, and character of her pain, prior similar episodes, family history of migraines, and a lack of red flags for secondary causes on her history and examination.
- Based on Jenny's reported history, you can deduce that she has been having intermittent debilitating headaches that are accompanied by well-described prodromal and postdromal phases. She reports positive and negative symptoms consistent with an aura (a neurologic disturbance with subsequent complete recovery), and her pain is bilateral, which is typical of migraines in adolescents.
- You are reassured against other organic causes of headaches given her lack of neurologic or infectious findings. Her pain has been refractory to acute pharmacologic interventions at home and in the ED. Given these descriptors of her headache episode, you think that Jenny most likely has an intractable migraine (status migrainosus) with aura.

Q: What are the diagnostic criteria for migraine in children and adolescents?

- Features consistent with a migraine headache are as follows:
  - Duration of 2 to 72 hours
  - At least 2 of the following characteristics
    - Unilateral location (usually frontotemporal; can be bilateral in children and adolescents)
    - Pulsating quality
    - Moderate or severe intensity
    - Aggravated by or causing avoidance of routine physical activity (eg, walking, climbing stairs)
  - During the headache, at least 1 of the following are present:
    - Nausea and/or vomiting
    - Photophobia and/or phonophobia
- Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.
- For some patients, migraines may be accompanied by an aura. An *aura* is defined as fully reversible symptoms that immediately precede (within 60 minutes) or coincide with the onset of the headache. Occasionally, an aura can occur without headache. Aura symptoms tend to be unilateral and spread gradually over 5 or more minutes. Auras can be divided into the following categories: typical, brainstem, hemiplegic/motor, or retinal.
  - A *typical aura* is defined as fully reversible visual, sensory, and/or speech/language symptoms with no motor, brainstem, or retinal symptoms. Visual auras are the most common type of aura. Visual auras are present bilaterally (ie, binocular) and may manifest as flashes of light or a zig-zag or C-shaped scotoma, which may have a scintillating edge. It should be noted that blurry vision is not considered to be an aura.
  - A *brainstem aura* is defined as at least 2 of the following fully reversible brainstem symptoms: dysarthria, vertigo, tinnitus, hypoacusis, diplopia, ataxia not attributable to sensory deficit, or decreased level of consciousness (Glasgow Coma Scale score < 13). The patient must not be experiencing any motor or retinal symptoms to be diagnosed with a brainstem aura; however, patients with brainstem auras may experience typical aura symptoms.
  - The presence of a *motor aura* (ie, weakness) defines a subtype of migraine called a *hemiplegic migraine*. More specifically, a hemiplegic migraine is defined as a migraine accompanied by fully reversible motor symptoms. Most other aura symptoms resolve within 60 minutes, whereas motor symptoms may last up to 72 hours or longer. Hemiplegic migraines may be accompanied by typical or brainstem aura symptoms.
  - The presence of monocular scotoma or blindness defines a migraine subtype referred to as a *retinal migraine*. Other causes of a monocular visual disturbance need to be excluded prior to assigning the diagnosis of retinal migraine.

- *Status migrainosus* is defined as a debilitating migraine that has lasted more than 72 hours. In general, the migraine of status migrainosus should be similar to the patient's previous migraine episodes except for the severity and duration. Patients with symptoms of status migrainosus should be evaluated for the possibility of a medication overuse headache.

Q: What are the other common primary headache syndromes?

- Tension-type headache: Tension headaches are very common and are characterized by bilateral pain with a pressing or tightening quality that is of mild to moderate intensity. These headaches can last minutes to days, and the pain does not worsen with routine physical activity (eg, climbing stairs). There is no nausea or vomiting, but photophobia or phonophobia (but not both) may be present.
- Cluster headache: Cluster headaches involve severe, unilateral pain that is located in the orbital, supraorbital, or temporal areas, or in a combination of these sites. Cluster headaches last 15 minutes to 3 hours and can occur from once every other day up to 8 times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial sweating, miosis, ptosis, or eyelid edema. There may also be migrainous features. As a result of the severe pain characteristic of cluster headaches, patients may appear very uncomfortable and characteristically pace the floor. Age of onset is usually in the adult years, and men are affected more frequently than women.
- New daily persistent headache: New persistent daily headache is a persistent headache that occurs daily from its onset and quickly becomes unremitting. The onset of headache is easily recalled by the patient. The pain lacks characteristic features and may have elements of both migraine- and tension-type headaches. This type of headache usually occurs in patients without a previous headache history and lasts more than 3 months.

Q: What secondary headache syndromes should be considered for Jenny's presentation?

- Medication overuse headache is a secondary headache syndrome that is caused by consistent overuse (10–15 days per month for >3 months, depending on the medication) of a medication that is being taken for acute treatment of headache. Jenny does not take medications with this frequency, making this diagnosis unlikely.
- IIH: Although traditionally thought of as affecting overweight women of childbearing age, patients of any age, weight, and gender can develop this condition. The most common symptoms reported include headache, retrobulbar/orbital pain, visual changes, vision loss, diplopia, pulsatile tinnitus, photopsia, and back pain. Papilledema or cranial nerve palsies (most commonly affecting cranial nerve VI) may be detected on examination. The use of certain medications (eg, growth hormone, retinoids, and tetracyclines) increases the patient's risk of this disorder. An elevated CSF opening pressure is diagnostic in the setting of a normal MRI of the brain with MR venography. Jenny does not appear to have many features or risk factors concerning for IIH.
- Transient ischemic attack/cerebrovascular accident: Despite Jenny's neurologic symptoms, there is low concern for an acute neurologic event because her neurologic symptoms appear consistent with a migraine aura and are fully resolved within 60 minutes of the onset.
- Chiari malformation, type I: Headaches caused by Chiari I malformations commonly present as occipital or nuchal pain that is worsened by Valsalva maneuvers such as cough. Other features suggestive of Chiari I malformation are cranial nerve palsies, signs of cerebellar dysfunction (eg, ataxia, dysmetria, or nystagmus), sleep-disordered breathing, or symptoms of syrinx or syringomyelia (including pain in the upper back, neck, shoulders, or upper extremities and arm or hand weakness). Jenny's symptoms do not appear to feature findings of Chiari I malformation.

Based on the preceding criteria, you determine that Jenny has a migraine with aura. She is currently in status migrainosus.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with suspected status migrainosus?

- The patient has a severe and debilitating headache with exacerbation or limited improvement of pain after appropriate pharmacologic interventions in the acute setting or ED.
- The patient has intractable vomiting with an inability to tolerate oral intake.
- The patient has concerning features, such as neurological deficits.
- There is a need for urgent imaging and/or urgent neurology consultation.

Jenny meets criteria for admission based on her current headache, which has not responded to interventions in the ED, requiring escalation of therapeutic intervention.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Jenny is a 14-year-old girl with a history and examination suggestive of migraines with aura, presenting today in status migrainosus with debilitating pain despite use of abortive treatments both in the outpatient setting as well as in the ED. Additionally, she has mild to moderate dehydration secondary to inadequate oral intake. She requires admission for improved pain control, IV rehydration, and supportive care.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The primary goal for the treatment of status migrainosus is to provide relief of pain, dehydration, nausea, and vomiting. Prior to discharge from the hospital, it is also important to develop a home management plan.

1. **Acute medical management:** There are multiple medication options to help decrease the pain associated with status migrainosus in the hospital setting.
   - NSAIDs (such as IV ketorolac): NSAIDs are typically given as part of a migraine "cocktail" that also includes an antiemetic and an antihistamine. Ketorolac, with or without the cocktail, can be repeated every 6 to 8 hours as needed until the headache resolves.
   - Triptans: Triptans (eg, rizatriptan, sumatriptan) are most effective when given at the onset of the migraine headache or aura. Triptans should be used with caution in patients taking a selective serotonin reuptake inhibitor or monoamine oxidase inhibitor because of the risk of serotonin syndrome. The use of triptans should be avoided in patients with ischemic heart disease, history of cerebrovascular accident, peripheral vascular disease, uncontrolled hypertension, brainstem or hemiplegic migraines, aberrant cardiac conduction pathways, or recent use of an ergot derivative.
   - IV dopamine-receptor antagonists such as prochlorperazine or metoclopramide: These medications can alleviate both headache pain and nausea/vomiting. Because they have a risk of dystonic reactions and akathisia, they are frequently given with diphenhydramine to reduce this risk.

- Valproate: Studies in pediatric patients have shown that IV valproate is tolerable and effective for the treatment of refractory migraines. Side effects can include somnolence and dizziness. A pregnancy test is recommended in adolescent girls prior to valproate administration because of the risk of congenital malformations, especially neural tube defects.
- Magnesium: IV magnesium sulfate can be considered for the acute treatment of refractory migraines. Although evidence is limited, studies have demonstrated its efficacy and safety in the pediatric population.
- IV dihydroergotamine (DHE) for status migrainosus (migraine >72 hours).
  - Because of DHE's high emetogenic potential, it is important to pretreat patients with an antiemetic 30 minutes prior to each administration. In addition to nausea/vomiting, DHE can cause other side effects (eg, anxiety, dyskinesia). To determine the patient's tolerance of its side effects, it is important to first utilize a test dose (one-half of the usual dose of DHE).
  - DHE can be repeated every 8 hours during the admission, with a maximum of 20 doses.
  - Adolescent girls should have a negative pregnancy test prior to the use of DHE.
  - DHE should not be used within 24 hours of a triptan and has a similar list of cautions and contraindications as triptans.
- IV steroids, such as dexamethasone or methylprednisolone: When given in combination with the previously listed medications, IV steroids may reduce the incidence of headache recurrence.
- Opioids and barbiturates: These medications have not been shown to be helpful for acute headaches and may lead to induction of future headache and chronic migraine.
- To treat Jenny's pain, you plan to start with scheduled use of ketorolac, prochlorperazine, and diphenhydramine for up to 24 hours. Because her migraine has been present for 3 days, you think that a triptan is unlikely to be helpful and do not want a triptan to interfere with your ability to escalate to DHE if needed. You will also consider use of IV valproate and IV magnesium sulfate if she is not responding well to her migraine cocktail.

2. **Supportive therapy**
   - Patients should be encouraged to rest in a quiet, dark room.
   - IV hydration should be used for patients with signs of dehydration or nausea/vomiting.
   - For nausea and vomiting, promethazine or ondansetron can be considered in addition to the previously listed dopamine-receptor antagonists. Both promethazine and ondansetron may have side effects or interactions with other migraine medications that should be considered prior to administration.
   - You will provide IV hydration until Jenny is tolerating oral intake, have IV ondansetron available as needed, and encourage her to rest.
3. **Consultations:** Clinicians should consider consultation with a neurologist or other headache specialist for patients with atypical symptoms or a poor response to empiric migraine therapy. Jenny may benefit from inpatient neurology consultation if she does not respond well to her inpatient treatment plan.
4. **Development of a migraine plan for home:** Prior to discharge home, it is important for clinicians to educate patients and families about migraine triggers and develop a home management plan, including abortive therapies and prophylactic medications when indicated.
   - Avoidance of known triggers should be emphasized as the first step in the patient's pain plan. Caffeine, weather changes, certain odors, menstruation, sleep deprivation, stress, and certain foods may trigger migraines.
   - Lifestyle changes can also be effective at preventing migraines. These modifications include sleep hygiene, stress reduction, regular healthy meals and exercise, and maintaining adequate hydration.
   - Concurrent depression and anxiety should be addressed. Referrals to psychology or psychiatry may be needed.
   - The use of a headache diary can help with identification of triggers and track the frequency, severity, and duration of symptoms.

- Abortive therapy should be taken at the onset of headache or migraine aura. Abortive therapy options include OTC analgesics, triptans, and combination medications. Patients and families should be counseled about the possibility of medication overuse headache when abortive agents are used frequently.
  - Analgesics: For many patients, OTC analgesics (eg, ibuprofen, naproxen, acetaminophen) may provide adequate relief when given at the onset of a migraine headache or aura. Studies indicate that NSAIDs are more effective than acetaminophen. OTC analgesics can cause medication overuse headache when used more than 10 to 15 days per month.
  - Triptans: Triptans are indicated for patients 5 years and older with moderate to severe migraine attacks or acute migraine refractory to analgesics. See previously listed risks and contraindications.
    - Triptans can be redosed if the headache recurs within 24 hours.
    - Triptans are most effective if given early, at the first sign of headache.
    - If patients have previously failed to respond to a certain triptan, it is reasonable to prescribe an alternative triptan.
    - The use of triptans more frequently than 9 days per month has been associated with chronic migraine and medication overuse headache.
  - Combination therapy can be tried for children 5 years and older with migraines that are refractory to other medications. Combination therapies commonly include the following:
    - Triptan + analgesic, such as sumatriptan-naproxen oral tablets
    - Triptan + promethazine
    - Triptan + naproxen + promethazine
    - NSAID + (ondansetron or prochlorperazine) + diphenhydramine
- Initiation of migraine prophylaxis: Patients who experience a significant burden from recurrent migraines may benefit from initiation of daily prophylactic medications.
  - There are multiple classes of prophylactic medication options for migraine; however, there is minimal data that indicate any of these medications are better than placebo in the prevention of migraine headaches in pediatric patients. Individual patient characteristics and preferences should be considered when selecting a daily prophylactic medication.
  - Medication options that can be considered to decrease the frequency and severity of migraines in patients with inadequate headache control with abortive medications include the following:
    - Beta blockers (eg, propranolol): Beta blockers should be avoided in patients with asthma.
    - Antiseizure medications (eg, topiramate, gabapentin, valproic acid): Topiramate is approved by the Food and Drug Administration for migraine prophylaxis in adolescents and can concurrently treat seizure disorders. Topiramate, like most antiseizure medications, carries a risk of congenital malformations and may negatively impact the effectiveness of hormonal contraception. Antiseizure medications should not be used for migraine prophylaxis in patients who are pregnant or trying to become pregnant.
    - Tricyclic antidepressants (TCAs): TCAs can be helpful for patients with sleep problems that contribute to migraine but can be fatal when overdosed. Parents of children taking a TCAs should be counseled about safe medication storage to minimize the risk of overdose.
    - Cyproheptadine, an antihistamine and appetite stimulant, can be useful for migraine prophylaxis and sleep initiation when taken prior to bedtime. If tolerated, the dose can be titrated upward, with somnolence being a limiting side effect.
    - Melatonin, which also can be helpful with sleep.
    - Nutritional supplements, including magnesium oxide or riboflavin.

CASE FOCUS

Plan for Treatment and Monitoring

- **Acute medical management:** You will continue IV ketorolac, prochlorperazine, and diphenhydramine for Jenny, scheduled every 8 hours. If there is no improvement in Jenny's pain after 24 hours, you will consider other therapies (eg, IV valproate, DHE).
- **Supportive therapy**
  - General measures: You order rest/sleep in quiet dark room with minimal interruptions.
  - IV hydration: You give Jenny a second normal saline bolus and will continue maintenance IV fluids with normal saline until there is improvement in her oral intake.
  - For nausea, Jenny will be receiving IV prochlorperazine as part of her migraine cocktail, but you will also order IV ondansetron, which can be given as needed.
- **Consultations:** You decide not to obtain any consultations at this time but will consider a neurology consultation if Jenny's headache does not respond to the previously listed measures.
- **Discharge planning and prophylaxis**
  - You will develop an abortive plan for home, including NSAIDs and triptans, with Jenny and her family.
  - You plan to discuss options for migraine prophylactic therapy for home prior to Jenny's discharge.
  - You provide education regarding lifestyle modification factors for headache prevention, including avoidance of triggers and use of a headache diary for Jenny and her family.
  - After discussion and coordination with Jenny's primary outpatient pediatrician, you anticipate providing a referral to a headache specialist.

Case Resolution

On admission, Jenny is continued on IV ketorolac, prochlorperazine, and diphenhydramine with minimal improvement. Given the lack of significant improvement in her symptoms after 24 hours, IV DHE is started the following day after Jenny has a negative pregnancy test. Prior to the start of treatment, Jenny is pretreated with IV metoclopramide and tolerates the DHE treatment well. On her third day of admission, her pain has resolved, and she is able to tolerate a satisfactory amount of oral intake. Prior to discharge, follow-up with neurology is arranged, and Jenny is prescribed an abortive triptan to be taken at the first sign of aura and topiramate to be taken once daily as prophylaxis.

Discharge Criteria

Q: How do you know when Jenny is ready to go home?

You can feel comfortable discharging your patient with status migrainosus when the following criteria are met:

- Adequate oral hydration has been achieved.
- The patient's headache is controlled with oral analgesics.
- A prophylactic and abortive headache plan is in place.
- Appropriate follow-up with the patient's pediatrician and/or a headache specialist has been ensured.

Anticipatory Guidance

Q: What instructions should you provide to Jenny and her caregivers upon discharge?

- Keep a headache diary to try to identify migraine triggers.
- Incorporate lifestyle modifications to decrease the frequency of migraine episodes. These modifications include sleep hygiene, reduction of stress, regular exercise and meals, and adequate oral hydration.
- Do not use ibuprofen or acetaminophen more than 14 days per month as overuse of these medications can lead to medication overuse headache.
- Take triptans at the first sign of headache but do not use them more than 9 days per month as they can cause medication overuse headache or chronic migraine.
- Contact Jenny's primary care physician or headache specialist if she is requiring analgesics or triptans more times than recommended each month.
- Seek immediate medical attention if fever, neck pain or stiffness, seizure, a change in the quality of headaches or headache aura, vision changes, or gait abnormalities develop.

Clinical Pearls

- It is important to take a detailed history and perform a thorough examination of the patient with intractable headache. Features of the history and physical examination can often help to diagnose a primary headache disorder or raise suspicion for a secondary headache syndrome.
- Red flag features that should prompt further evaluation include young patient age (<3 years), neurocutaneous stigmata, fever, neck pain/stiffness, severe and sudden onset of pain, progressive worsening of pain, pain waking from sleep or pain that is worse in the morning, occipital pain, worsening pain with straining or changing positions, retrobulbar pain or pain with eye movement, recent trauma, or certain neurologic symptoms (eg, focal deficits, difficulty with balance or ambulation, dizziness, diplopia, seizures, pulsatile tinnitus, cognitive or psychiatric changes).
- There are several medications that can be used in the treatment of acute pain associated with migraine. For management in the ED or acute care setting, common first-line options include IV ketorolac, triptans, IV dopamine-receptor antagonists, and diphenhydramine.
- Data supporting the use of migraine prophylactic medications are limited, and patient factors and patient/family preferences should be used in decision-making when considering use of these medications.
- Medication overuse may be common in adolescents with migraines. Education should be provided to patients and families regarding the appropriate use of abortive medications.

Documentation Tips

- Document failed outpatient therapies trialed prior to admission.
- Note whether there is refractory/intractable pain not improved with ED therapies.
- Document red flag findings on history or physical examination, such as focal neurologic findings, which may indicate a secondary headache syndrome.
- Document the need for scheduled analgesics (including whether IV or oral) and response to therapies.

Suggested Readings

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Katelyn, a 4-Year-Old Girl With Fever and Neck Swelling

CASE PRESENTATION

Katelyn is a 4-year-old girl with no significant medical history who was accepted for direct admission to the acute care unit from her pediatrician's office, where she was seen for worsening fever and swelling on the right side of her neck. Her pediatrician has been treating her with amoxicillin-clavulanate for the past 3 days without improvement. The pediatrician requested admission for administration of intravenous (IV) antibiotics, imaging, and possible surgical consultation. You meet Katelyn and her family once they arrive to the acute care floor.

Patient History and Review of Systems

Q: What information should you collect from Katelyn's caregivers?

- History of present illness
  - Fever history: onset/duration, maximum temperature, and fever trend, including any noted improvement since starting antibiotics
  - Neck swelling history: onset and location, associated tenderness or pain, drainage, and characteristics of overlying skin, especially any color change or violaceous hue
  - Recent illness or injuries, especially related to the head or neck, such as scalp injuries, acute otitis media, pharyngitis, oral cavity injuries, or upper respiratory infections
  - Associated symptoms, such as weight loss, fatigue, recurrent cough, night sweats, easy bruising, pallor, drooling, difficulty breathing, nausea, vomiting, sore throat, abdominal pain, conjunctivitis, joint swelling, difficulty walking, or rash
- Social and exposure history
  - Sick contacts
  - Recent insect bites or animal exposures (cats, kittens, puppies, rabbits, hamsters, prairie dogs, fleas, ticks, goats, cattle, or swine)
  - Recent travel, especially travel to areas where tuberculosis or bubonic plague are endemic
  - Other tuberculous risk factors, such as close contact with a person who has chronic cough, has traveled internationally recently, is currently or has recently been incarcerated, uses illegal drugs, or who has experienced homelessness
  - Family members with similar symptoms of or risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Dietary intake, especially consumption of any unpasteurized dairy products or undercooked/raw meat

- Medical history, including underlying health status and any chronic diseases
  - History of similar episodes or skin and soft tissue infections
  - Dental history, including dental caries, odontogenic infections, or recent dental procedures
  - Immunization status, especially measles-mumps-rubella vaccine status and recent vaccinations
- Medications, especially antiseizure medicine (phenytoin, carbamazepine), recent use of antibiotics, or over-the-counter medications or supplements

CASE FOCUS

History and Review of Systems

From your conversation with Katelyn's parents, you learn that Katelyn's illness started 4 days ago with a fever of 38.8 °C (101.8 °F) and right-sided neck pain and swelling. The following morning, she saw her pediatrician, who prescribed amoxicillin-clavulanate. Katelyn has been taking her antibiotic as prescribed for the past 3 days, but her neck swelling and tenderness have not improved and seem to be getting worse. Her parents have also started to notice redness and warmth over the area, but there has not been any drainage. Her highest fever during the course of her illness was this morning, when she had a temperature of 39.7 °C (103.5 °F), which prompted their repeat visit to the pediatrician's office.

For the duration of this illness, Katelyn has been taking ibuprofen for pain and fever. Her fever and pain do improve with ibuprofen, but she has been needing the medication every 6 hours to help her symptoms. Her parents report that she has not had any injuries to her head or neck, weight loss, fatigue, night sweats, easy bruising, pallor, nausea, vomiting, abdominal pain, rash, or conjunctivitis. Katelyn does not have any dental caries. Two weeks ago, she had an upper respiratory tract infection (URTI) with cough, rhinorrhea, and nasal congestion that has since resolved.

Katelyn does not have any chronic health conditions, has had typical growth and development, and is up to date on her immunizations. She does attend child care, but no one there has had similar symptoms. Her parents deny recent dental work, travel, animal or relevant food exposures, insect bites, or tuberculosis risk factors. Katelyn has never been hospitalized, required surgery, or had previous similar episodes.

Physical Examination

Q: What parts of the physical examination should you focus on for Katelyn?

- Complete set of vital signs
- Scalp and face: evidence of injury or localized infection, such as tinea capitis, head lice infections, or wound infections
- Eyes: drainage or conjunctival injection
- Oropharyngeal: erythema of the gingiva, buccal mucosa, tonsils, or pharynx; tonsillar exudates; evidence of dental caries; ulcerations or other lesions
- Ears: abnormalities of the external ear canal, tympanic membrane, or mastoid process
- Neck: range of motion, location of neck swelling (anterior vs posterior cervical; midline or lateral neck), fluctuance/suppuration, drainage, skin color overlying neck swelling, warmth over area of swelling

- Location and characteristics of any swollen lymph nodes (eg, soft vs hard, tender vs nontender, large vs small, asymmetric vs round, matted vs discrete, mobile vs fixed) (Refer to Figure 21.1 for the anatomic location of lymph node groups)
- Inguinal and axillary lymph nodes
- Respiratory: signs of respiratory compromise, such as drooling, shortness of breath, tachypnea, increased accessory muscle usage, hypoxemia, or audible respiratory sounds (eg, stridor, stertor)
- Abdomen: masses or hepatosplenomegaly
- Skin: openings, rashes, animal scratches, tick or flea bites, papules or pustules, pallor, bruising

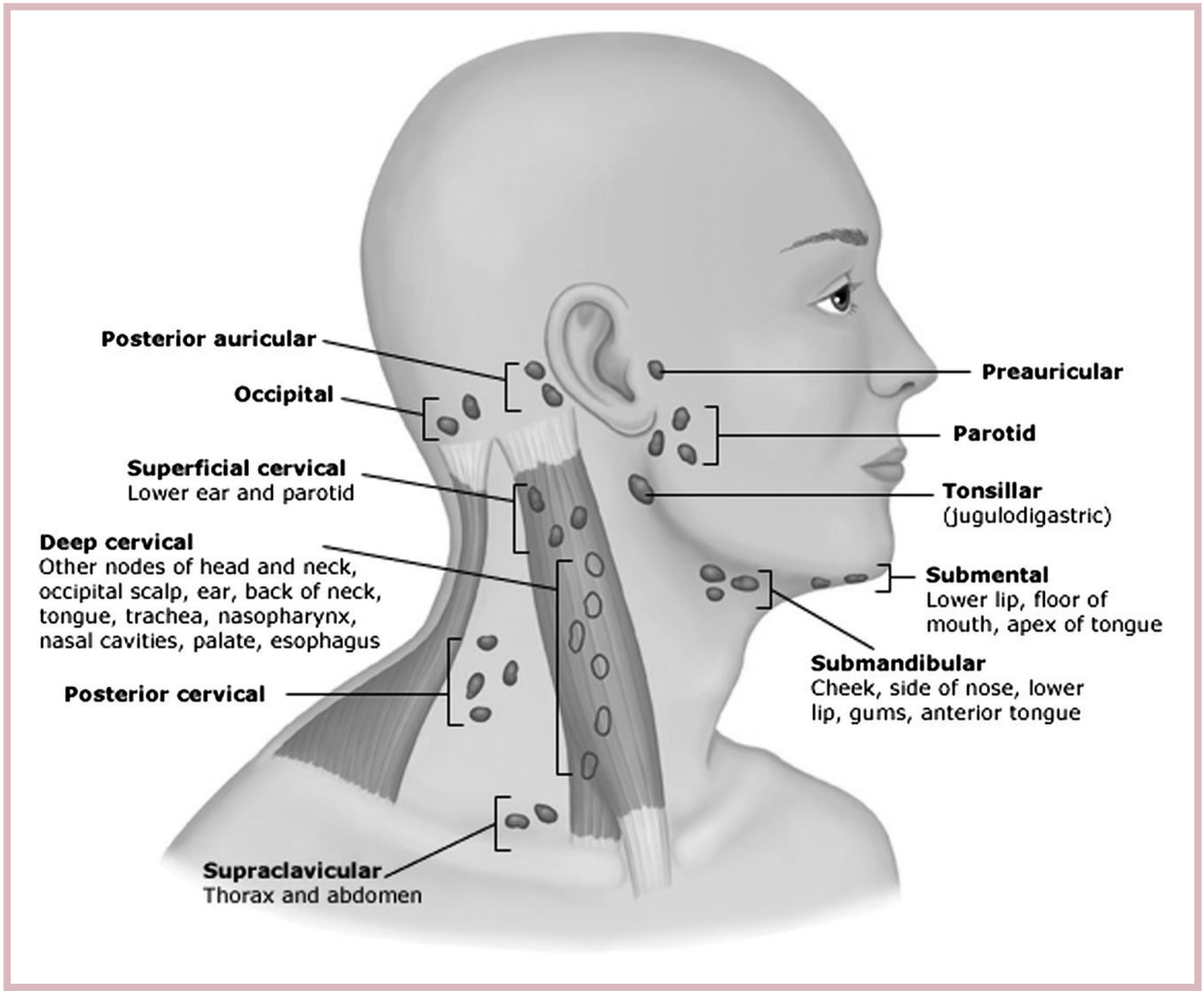

Figure 21.1. Cervical lymph nodes.

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CASE FOCUS

Physical Examination

Katelyn's vital signs show that she is febrile, with a temperature of 38.4 °C (101.1 °F) and mildly tachycardic with a heart rate of 110 beats/min. Her blood pressure is normal at 100/60 mm Hg. Her respiratory rate is 22 breaths/min, and her oxygen saturation is 100% on room air.

On examination, Katelyn is awake, resting comfortably in bed, and not in any apparent respiratory distress. She pushes your hand away when you try to examine her neck. You note prominent right-sided neck swelling with mild erythema overlying the area. You palpate a boggy, tender, mobile node in the area of the anterior cervical chain measuring approximately 2.5 × 2 cm. You also note a few other smaller, swollen right-sided cervical lymph nodes. The area is warm to the touch. You do not see any drainage from the area or any skin openings. You mark the area with a nontoxic pen, which will allow you to monitor the progress of Katelyn's neck swelling and erythema. She is able to rotate her head left but is slightly restricted in rotating her head right. She has full extension and flexion of her neck and is able to fully open her mouth. She has mild erythema of her posterior pharynx without exudates, lesions, or tonsillar asymmetry. She has good dentition and moist mucous membranes. Her ear examination reveals normal, bilateral tympanic membranes. You do not palpate any other areas of lymphadenopathy, including her axillary, supraclavicular, or inguinal nodes.

Her lungs are clear to auscultation, and she is breathing comfortably without any respiratory distress. She is mildly tachycardic, and her capillary refill is approximately 2 seconds. Her abdomen is soft, nontender, and nondistended, and bowel sounds are present. You do not appreciate any hepatosplenomegaly or masses. Other than her previously noted neck erythema, Katelyn does not have any rashes, and you do not find any skin abnormalities on her scalp or face. The remainder of her physical examination is normal.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with acute-onset unilateral neck swelling?

The differential diagnosis for patients with acute-onset unilateral neck swelling can be subdivided generally into infectious or noninfectious etiologies, as demonstrated in Box 21.1. For Katelyn, you are most concerned for bacterial cervical lymphadenitis, but you think that you also should consider an infected branchial cleft cyst, a deep neck infection, and Kawasaki disease.

Box 21.1. Differential Diagnosis for a Child With Acute-Onset Neck Swelling

Infectious etiologies	Noninfectious etiologies
• Cervical lymphadenitis (an infected/inflamed node that is warm and tender and may have overlying skin color changes; secondary abscess formation can occur) — Bacterial,[a] including mycobacterial — Fungal — Parasitic — Viral (most commonly bilateral) • Deep neck infection[a] (eg, peritonsillar, parapharyngeal, Lemierre syndrome) • Infected congenital neck mass (eg, infected branchial cleft cyst[a] or thyroglossal duct cyst) • Reactive cervical lymphadenopathy (cervical lymph node >1 cm) related to HEENT or systemic infection • Salivary gland infection, including parotitis	• Castleman disease • Congenital neck mass — Branchial cleft cyst — Dermoid cyst — Ectopic thymus — Hemangioma — Lymphovascular malformation — Thyroglossal duct cyst • Goiter or thyroid nodule • KD[a] • Kikuchi-Fujimoto disease • Langerhans cell histiocytosis • Malignancy (eg, lymphoma, leukemia, thyroid carcinoma, rhabdomyosarcoma, neuroblastoma, metastasis) • Medication reaction or side effect (commonly implicated medications include phenytoin and carbamazepine) • MIS-C • Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy • Rosai-Dorfman disease • SLE

Abbreviations: HEENT, head, eyes, ears, nose, and throat; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; SLE, systemic lupus erythematosus.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic testing is indicated for patients who present with fever and acute-onset unilateral neck swelling?

- Reactive cervical lymphadenopathy and cervical lymphadenitis can usually be diagnosed clinically, based on history and physical examination, and laboratory testing and imaging may not be required.
- When there is concern for malignancy, it is reasonable to obtain a complete blood cell count with peripheral smear, a comprehensive metabolic panel, lactate dehydrogenase and uric acid tests, and a chest radiograph to evaluate for hilar adenopathy or a mediastinal mass. Pathology from an excisional biopsy may be indicated if there is concern for malignancy. Findings suspicious for malignancy may include fever; weight loss; night sweats; a fixed, firm node; supraclavicular lymphadenopathy; abdominal masses; generalized lymphadenopathy; pallor; petechiae; hepatosplenomegaly; and an inability to walk.
- Table 21.1 lists the clinical features and diagnostic evaluation for various etiologies of cervical lymph node enlargement in a febrile patient.

Table 21.1. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Febrile Patients With Cervical Lymph Node Enlargement

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Acute bacterial lymphadenitis (*Staphylococcus aureus*, GAS, anaerobes)	Acute onset, unilateral, and tender lymph node, commonly with warmth and overlying erythema Abscess may develop and may be suspected based on the presence of fluctuance or a failure to respond to appropriate antibiotic therapy.	Blood culture if the patient appears toxic; if abscess is suspected, US or CT with contrast of the neck can assist with detection; Gram stain and culture of any purulent material
Atypical mycobacterium[a]	Cervical lymphadenitis, which can develop into chronic lymphadenitis or draining fistulas if untreated; disseminated infection is uncommon in immunocompetent children.	Tissue sample for AFB staining; special cultures with or without PCR testing; tuberculin skin test/PPD, which may be weakly positive
Mycobacterium tuberculosis	Initially firm, discrete, nontender nodes that progress to matted, adherent nodes, which can lead to spontaneous drainage if not treated	Chest radiograph, PPD, interferon-gamma release assays (eg, QuantiFERON-TB Gold Plus, T-SPOT.TB)
Bartonella henselae	Exposure to cats, especially kittens; a scratch that later develops an overlying papule or pustule at the site prior to the onset of more proximal lymphadenitis; overlying skin with erythema and induration; cervical lymphadenitis can occur; some nodes will develop suppuration; systemic or ocular symptoms can accompany lymphadenitis.	Serum or tissue PCR assays; serological testing
KD	Fever for ≥5 days and some combination of KD clinical features (rash, nonexudative conjunctivitis, mucous membrane changes, unilateral cervical lymphadenopathy, changes to the hands/feet); see Case 14 for more information	CBC, ESR, CRP, CMP, UA, echocardiogram
Toxoplasma gondii	Exposure to cats, especially their feces; commonly presents with tender lymph nodes and muscle aches	Serological testing; PCR or special stains on tissue sample
Deep neck infection	Decreased range of motion of neck, trismus	CT with contrast of the neck
GAS pharyngitis (strep throat)	Pharyngitis with or without tonsillar exudates; bilateral, tender cervical adenopathy	Rapid antigen test or throat culture
EBV	Fatigue, fever, bilateral, tender cervical lymphadenopathy, pharyngitis, sore throat, splenomegaly, headache	Monospot test, EBV antibody titers
CMV[b]	Presents similar to EBV, with fever, fatigue, and lymphadenopathy but usually lacks pharyngitis	CMV serologic assay
HIV	Acute retroviral syndrome is characterized by lymphadenopathy (usually subacute and chronic) along with fever, fatigue, and rash.	Serum HIV-1 and HIV-2 combined antigen/antibody testing or immunoassays

Abbreviations: AFB, acid-fast bacillus; CBC, complete blood cell count; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; GAS, group A *Streptococcus*; KD, Kawasaki disease; PCR, polymerase chain reaction; PPD; purified protein derivative; UA, urinalysis; US, ultrasonography.

[a] Organisms are ubiquitous in the environment.

[b] CMV infections are commonly asymptomatic in children.

CASE FOCUS

Diagnostic Evaluation

Based on Katelyn's history and physical examination, you are most concerned about the possibility of bacterial lymphadenitis with an abscess, so you decide to obtain neck imaging. To avoid radiation exposure, you choose to order neck ultrasonography of the swollen area instead of a computed tomography scan.

Neck ultrasonography shows several prominent and mildly enlarged right cervical chain lymph nodes, with the largest measuring 2.4 × 1.7 × 1.8 cm. There is no evidence of suppurative change.

Because Katelyn is nontoxic and you are not concerned for malignancy, you decide not to obtain further laboratory tests.

Arriving at a Diagnosis

Q: How do you develop an assessment for Katelyn?

As you think through Katelyn's case, you first decide to interpret the findings from her history, physical examination, and diagnostic studies to develop a list of findings and narrow the differential diagnosis to the most likely cause of her symptoms.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Katelyn's neck swelling is unilateral in nature and associated with fever, tenderness, and overlying erythema. The location of Katelyn's neck swelling and the ultrasonography results indicate that Katelyn's findings are originating from enlarged lymph nodes in her anterior cervical chain. Notably, she does not have enlarged lymph nodes in any other regions of her body. The associated tenderness of her lymph nodes is most consistent with the diagnosis of lymphadenitis. Additionally, the acute nature of Katelyn's symptoms and the presence of tenderness and overlying erythema appear most consistent with an infectious etiology. Noninfectious etiologies, such as malignancy or Kawasaki disease appear less likely based on her current history and examination findings.
   - Katelyn's cervical lymphadenitis developed less than 7 days ago, and therefore you classify her presentation as acute rather than subacute (2–6 weeks) or chronic (>6 weeks) cervical lymphadenitis.
   - Another relevant historical feature is Katelyn's preceding upper respiratory symptoms, which may have predisposed her to this current infection.
   - It is important to note that Katelyn's symptoms have progressed despite more than 48 hours of treatment with amoxicillin-clavulanate, an appropriate antibiotic. Although Katelyn has been taking the antibiotic as prescribed, when an infectious etiology is suspected, failure of appropriate antibiotic treatment could indicate 1 of 3 things about Katelyn's infection: the infection is not bacterial; the infection is bacterial, but the bacteria are not treated by or are resistant to this antibiotic; or there is an abscess requiring surgical drainage. Based on her ultrasound results, you know that an abscess is not present.
   - Assessment for sepsis: Although Katelyn does have fever and tachycardia in the setting of a suspected infection, her vital signs do not currently meet the criteria for sepsis. Additionally, there is no concern for severe sepsis or septic shock. Refer to Section IV in the Appendix for a discussion of systemic inflammatory response syndrome (SIRS), sepsis, and the age-based SIRS criteria.
2. **Develop the list of findings.**

Q: What major findings have you have identified for Katelyn?

- Acute unilateral infectious cervical lymphadenitis without abscess
- Failure of outpatient antibiotics

3. **Revisit the differential diagnosis.**

Q: Based on your differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Katelyn's presentation?

You have identified that Katelyn's symptoms are consistent with acute infectious cervical lymphadenitis. The next step is to identify the suspected infectious etiology and reason for treatment failure.

Q: What are common infectious etiologies for acute cervical lymphadenitis?

- The most common cause of acute infectious cervical lymphadenitis is a viral infection, which usually presents with bilateral cervical or diffuse lymphadenopathy and concurrent upper respiratory tract symptoms.
- The second most common cause is a bacterial infection. Group A *Streptococcus* (GAS) and *S aureus* cause up to 80% of cases of acute unilateral cervical lymphadenitis.
- Refer to Box 21.2 for a thorough list of the etiologies of acute infectious cervical lymphadenitis in children.

Box 21.2. Etiologies of Acute Infectious Cervical Lymphadenitis in Children

Viral	Bacterial	Other
Adenovirus[a]	Anaerobes[a] (including *Actinomyces*)	*Coccidioides*
CMV[a,b]	Atypical or nontuberculous mycobacteria[a,b]	*Histoplasma*
EBV[a,b]	*Bartonella henselae*[a,b]	Toxoplasmosis[a,b]
Enterovirus[a]	*Francisella tularensis*	
HIV[b]	Group A *Streptococcus*[a]	
HSV[a]	Group B *Streptococcus* (infants)	
Human herpesvirus 6 and 7	*Mycobacterium tuberculosis*[b]	
Human herpesvirus 8	*Mycoplasma pneumoniae*[a]	
Influenza[a]	*Pasteurella multocida*	
Measles	*Staphylococcus aureus*[a]	
Mumps	*Yersinia pestis*	
Parainfluenza		
Parvovirus B19		
Rhinovirus[a]		
RSV		
Rubella		

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus.

[a] Common etiologies.

[b] Etiologies that are more likely to evolve into chronic adenopathy/adenitis.

Q: What factors in Katelyn's history help you decide between viral, bacterial, or other infectious causes of her illness?

- The unilateral location of Katelyn's cervical lymphadenitis and the overlying erythema and lack of concurrent upper respiratory symptoms point to a bacterial etiology rather than a viral or fungal etiology. As previously noted, viral lymphadenopathy and lymphadenitis are most commonly associated with bilateral findings and typically do not feature overlying skin erythema.
- Although Katelyn does not currently have symptoms of a URTI, she did have symptoms in the preceding weeks. Viral URTIs can predispose children to the development of bacterial cervical lymphadenitis by causing disruption in the mucous membranes, allowing for bacteria to enter the lymphatic system.
- In the absence of an abscess, amoxicillin-clavulanate would have treated an infection caused by GAS, methicillin-sensitive *S aureus* (MSSA), or common oral anaerobes. Given that Katelyn's symptoms have not responded to this antibiotic, these etiologies appear less likely. Additionally, Katelyn does not have evidence of periodontal disease, which further decreases your suspicion of an oral anaerobe infection.
- The lack of improvement in Katelyn's symptoms while on amoxicillin-clavulanate indicates a less common or resistant organism; however, the acute nature of her symptoms and the lack of international travel, tuberculosis risk factors, or certain animal or food exposures decreases your suspicion for *Bartonella henselae*, *Toxoplasma gondii*, *Francisella tularensis*, *Mycobacterium tuberculosis*, and *Pasteurella multocida.*
- Although it should remain under consideration, an infection caused by atypical mycobacteria is less likely for Katelyn based on its lower incidence (when compared to GAS and *S aureus*) and the predilection of atypical mycobacteria for causing a subacute or chronic course.
- Based on the combination of the aforementioned factors, you determine that an organism resistant to amoxicillin-clavulanate, such as MRSA, is the most likely etiology of Katelyn's symptoms.

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with suspected acute cervical bacterial lymphadenitis?

The majority of patients with lymphadenitis can be managed as outpatients; however, clinicians should consider hospitalization in the following circumstances:

- The patient's clinical status has not improved despite outpatient treatment.
- The patient is unable to tolerate oral antibiotics.
- There is rapid progression of neck swelling.
- There is a need for further workup or surgical drainage of a lymph node abscess.
- The patient appears toxic, or there is concern about bacteremia.
- There is airway involvement, indicating the potential for respiratory distress or respiratory failure.

Katelyn meets criteria for hospital admission based on the failure of outpatient therapy.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Katelyn is a previously healthy 4-year-old girl who is admitted with fever and acute unilateral cervical lymphadenitis; a bacterial cause is suspected. She is not improving despite 3 days of amoxicillin-clavulanate therapy, and her neck ultrasonography does not show suppuration. She requires hospitalization for IV antibiotics and ongoing monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing your plan for treatment and monitoring, you review treatments of acute unilateral cervical lymphadenitis.

1. **Empiric treatment of acute unilateral cervical lymphadenitis**
   - The most common etiologies of acute unilateral cervical lymphadenitis are *S aureus* and GAS. Thus, empiric antibiotic therapy is targeted toward these organisms. Unless there is significant concern for community-acquired MRSA (CA-MRSA), empiric treatment generally includes penicillinase-resistant penicillins or cephalexin.
   - Oral versus IV antibiotics: The choice of oral or IV antibiotics depends on the patient's clinical presentation.
     - If the patient has marked lymph node enlargement, moderate to severe systemic symptoms, or associated cellulitis, IV antibiotics are preferred to allow for a higher concentration of antibiotic in the infected area. Otherwise, most patients respond to empiric oral antibiotics for a staphylococcal or streptococcal lymphadenitis.
     - If the patient requires IV antibiotics and CA-MRSA is uncommon in the region, oxacillin, nafcillin, cefazolin, or ampicillin-sulbactam can be used.
     - If the patient is being treated with oral antibiotics, dicloxacillin or cephalexin can be used. Amoxicillin-clavulanate is a reasonable choice because it is active against MSSA, GAS, and oral anaerobes.
     - If the patient has a mild penicillin allergy (eg, hives, itching), a first-generation cephalosporin (eg, cephalexin, cefadroxil) or clindamycin may be used.
     - There are several options for empiric treatment when there is concern for MRSA.
       - If CA-MRSA is prevalent and clindamycin resistance is low, IV or oral clindamycin may be used for empiric therapy. Note that there is an increasing prevalence of clindamycin resistance among CA-MRSA isolates. Thus, close clinical follow-up is needed when choosing clindamycin.
       - If the patient is toxic or their infection progresses rapidly, vancomycin in combination with nafcillin or oxacillin should be used until culture results are obtained. This regimen maximally covers MRSA and MSSA while also providing coverage for GAS.
       - Trimethoprim-sulfamethoxazole or doxycycline are alternative choices for oral therapy against CA-MRSA. Caution should be exercised when prescribing doxycycline to patients younger than 8 years, given the risk of permanent dental discoloration when children receive repeated courses.
       - Linezolid is active against MRSA and GAS but should be only used in cases in which microbiological need is confirmed or if there is failure of first-line therapies.
     - Duration of antibiotics: Total duration of antibiotics is usually between 10 and 14 days.
     - Indication for drainage: If an abscess forms, incision and drainage should be performed and antibiotics continued for another 5 to 7 days or until resolution of the acute process.
   - In specific scenarios, different treatment regimens should be considered.
     - If the patient has periodontal or dental disease, coverage for anaerobes should be considered. Antibiotic options include penicillin V, amoxicillin-clavulanate, and clindamycin.
     - If the patient has confirmed GAS cervical lymphadenitis, the patient should be treated with penicillin G or penicillin V for 10 days. If the patient has a penicillin allergy, clinicians may treat using (1) azithromycin for 5 days or (2) cephalexin for at least 10 days.
     - If *B henselae* is suspected, antimicrobial options include azithromycin, clarithromycin, doxycycline, trimethoprim-sulfamethoxazole, rifampin, and gentamicin. Needle aspiration may be needed for painful adenitis, but incision and drainage should be avoided as it can lead to fistula formation.

- For Katelyn, her infection worsened despite an adequate trial of oral antibiotics, so you decide to start her on IV antibiotics. Because you are not concerned about a zoonotic infection, she does not appear toxic, and she does not have a rapidly progressing infection, you decide to start her on IV clindamycin to provide coverage for MRSA. You feel comfortable choosing this antibiotic because more than 90% of your community's MRSA isolates are susceptible to clindamycin.

2. **Supportive care:** Other supportive measures may include treatment of dehydration, fever, and discomfort.
   - Antipyretics and analgesics (eg, acetaminophen, ibuprofen) are safe for treatment of fever and discomfort.
   - IV fluids may be required for patients who are unable to tolerate sufficient volumes by mouth or for patients who are placed on nil per os (nothing by mouth) status related to surgical intervention.
   - Because Katelyn does not appear significantly dehydrated on examination, you will encourage her to continue fluid intake by mouth and order analgesics and antipyretics to be used as needed.
3. **Monitoring for improvement**
   - Signs of clinical improvement include a decrease in pain, inflammation, and tenderness of the lymph node and an improving fever curve. These improvements should be evident within 48 to 72 hours.
   - If the patient does not improve within 72 hours, further investigation into uncommon causes of acute unilateral cervical lymphadenitis may be indicated. Additionally, clinicians should consider ordering repeat imaging to evaluate for abscess formation and changing the patient's antibiotic regimen.
   - Even with appropriate antibiotic treatment, lymph node enlargement could take up to 4 to 6 weeks to resolve. If the enlargement persists after 6 to 8 weeks, an underlying disorder needs to be excluded.
   - If lymphadenitis reoccurs, further evaluation for an untreated primary bacterial source, such as a dental abscess or foreign body, is indicated.
4. **Indications for consultation**
   - Otolaryngology: An otolaryngologist should be consulted if there is need for surgical incision and drainage or excisional biopsy or if there is concern for an infected congenital neck mass.
   - Infectious disease: An infectious disease specialist should be consulted if there is concern for highly resistant or atypical organisms (especially mycobacteria).

CASE FOCUS

Plan for Treatment and Monitoring

- **Antibiotics:** You order clindamycin to be given intravenously every 6 hours.
- **Supportive care:** You provide acetaminophen and ibuprofen as needed for pain and fever. You allow a regular diet as tolerated. No IV fluids are needed at this time.
- **Monitoring:** You measure and mark the area of cervical lymphadenitis and examine the area frequently for development of a drainable abscess or any improvement. You monitor Katelyn's intake and output and vital signs every 4 hours.
- **Consultations:** No consultations are needed at this time.

Case Resolution

Over the next 48 hours, Katelyn's neck swelling, erythema, and pain improves, and her fever resolves. She is switched to oral clindamycin and tolerates it well. She has good oral intake and remains afebrile for more than 24 hours; therefore, she is discharged home to finish her course of oral clindamycin. Her clinical course supports the diagnosis of acute infectious cervical lymphadenitis; thus, no further workup is required.

Discharge Criteria

Q: How do you know when Katelyn is ready to go home?

You can feel comfortable discharging your patient with acute cervical lymphadenitis when the following criteria are met:

- There is significant clinical improvement in neck swelling and erythema.
- The patient is able to tolerate oral antibiotics.
- Fever has resolved.
- The patient has outpatient follow-up with their pediatrician scheduled within 2 to 3 days of discharge.
- No concerns exist for malignancy.

Anticipatory Guidance

Q: What instructions should you provide to Katelyn's caregivers upon discharge?

- Complete the prescribed course of antibiotics.
- Continue to monitor the area of neck swelling for improvement.
- Return to care for worsening neck swelling, fever, inability to tolerate oral antibiotics, or any new concerns.
- Give over-the-counter antipyretics and analgesics (acetaminophen or ibuprofen) for pain or discomfort.
- Lymph node swelling may take up to 4 to 6 weeks to resolve completely.

Clinical Pearls

- The most common etiology of acute cervical lymphadenitis is infectious, and the most common organisms are viruses followed by *S aureus* (including MRSA) and *Streptococcus* species (especially GAS).
- If cervical lymphadenitis is prolonged, clinicians should assess for exposures to tuberculosis and/or unusual organisms.
- If the patient is not improving on empiric antibiotics, further evaluation with imaging may be warranted.

Documentation Tips

- Include the outpatient treatment prior to hospitalization, especially if outpatient therapy has failed.
- Document the exact or suspected location of the infection and whether an abscess is present.
- Include whether surgical intervention is anticipated or scheduled.
- Document the presence of sepsis or suspected airway compromise.

Suggested Reading

Weinstock MS, Patel NA, Smith LP. Pediatric cervical lymphadenopathy. *Pediatr Rev*. 2018;39(9):433–443 PMID: 30171054 https://doi.org/10.1542/pir.2017-0249

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CASE 22

Taj, a 12-Year-Old Boy With Hyperglycemia

CASE PRESENTATION

Taj is a 12-year-old previously healthy boy who presents to the emergency department (ED) with nausea, vomiting, and abdominal pain. He also has recently experienced frequent urination and weight loss. On evaluation in the ED, Taj is tired and appears mildly uncomfortable but is alert and interactive. The ED physician obtains a fingerstick glucose level, which is elevated at 450 mg/dL (24.98 mmol/L). The physician administers a 20 mL/kg normal saline (0.9%) intravenous (IV) bolus and obtains laboratory tests, including venous blood gas (VBG), complete blood cell count, comprehensive metabolic panel, magnesium, phosphorous, hemoglobin A_{1c} (HbA_{1c}), and urinalysis. Taj's VBG shows a pH of 7.25, P_{CO_2} of 38 mm Hg, and base deficit of 14 mEq/L (14 mmol/L). The remainder of his laboratory test results are pending. The physician is concerned about diabetic ketoacidosis (DKA) and calls you to request that you evaluate Taj for admission.

Patient History and Review of Systems

Q: What information should you collect from Taj and his caregivers?

- History of present illness
  - Duration, timeline, description, and extent of presenting symptoms
  - Abdominal pain: location, characteristics, and factors that worsen or alleviate pain
  - Previous history of abdominal pain
  - Timeline of recent weight changes
  - Presence of any neurologic symptoms (eg, headache, confusion, abnormal speech, weakness, blurry vision)
  - Any symptoms or notable signs of dehydration
- Associated symptoms, such as fever, dysuria, changes in urinary urgency, polyphagia, polydipsia, nocturia, or enuresis
- Medical history, including surgical history and immunization status
- Medications taken or available at home
- Family history, especially of diabetes mellitus (DM) or other autoimmune diseases

CASE FOCUS

History and Review of Systems

Upon arriving to the ED, you speak with Taj and his 23-year-old brother. You learn that Taj's nausea, vomiting, and abdominal pain started this morning. He describes his abdominal pain as hurting "all over," and he cannot tell what exacerbates or improves his pain. He has not had similar episodes of abdominal pain in the past. For the past 2 weeks, he has noticed that he has been very hungry, thirsty, and urinating frequently. He has not had any dysuria or fever. He notes that he has been waking up at night to urinate and drink water. He has been fatigued and has lost 10 lb (4.5 kg) over the last month, which he attributes to a dance program he started 2 months ago. He complained of a mild headache last night, but according to his brother, he has not acted confused or had any abnormal speech or weakness. His review of systems is otherwise negative. He occasionally takes acetaminophen or ibuprofen for headaches but otherwise does not take any medications or supplements regularly. He denies having any chronic medical concerns and has never had surgery. He is up to date on his immunizations. There are no family members with known DM, autoimmune diseases, or other chronic conditions.

Physical Examination

Q: What parts of the physical examination should you focus on for Taj?

- Complete set of vital signs
- General: signs of altered mental status, disorientation, or decreased level of consciousness; body habitus
- Mucous membranes: moist, sticky, or dry
- Peripheral perfusion: capillary refill time, warmth of extremities, pulses in upper and lower extremities
- Cardiac: auscultation for heart rate and murmurs
- Respiratory: auscultation and observation for presence of Kussmaul (deep and rapid) respiration
- Abdomen: bowel sounds, tenderness, guarding, masses
- Skin: acanthosis nigricans, rashes, other lesions
- Neurologic: signs of cerebral edema, such as decreased Glasgow Coma Scale score, cranial nerve palsies, papilledema, or abnormal respiratory pattern

CASE FOCUS

Physical Examination

Taj's vital signs show that he is afebrile, with a temperature of 37 °C (98.6 °F). He is mildly tachycardic (heart rate: 115 beats/min) and tachypneic (respiratory rate: 25 breaths/min) with a normal blood pressure for his age (105/65 mm Hg) and a normal oxygen saturation (99%). His weight upon arrival to the ED was 40 kg, his height is 1.5 m, and his body mass index is 17.8 kg/m^2.

CASE FOCUS

Physical Examination *(continued)*

On examination, Taj is awake and alert. He appears thin and not in distress. He is articulate and able to answer all of your questions. He does not seem confused, but he does indicate that he has a mild headache. His oral mucosa appears dry. His peripheral pulses are normal bilaterally, and his capillary refill time is 3 to 4 seconds, with warm extremities. On cardiac examination, he has a regular heart rhythm with no murmurs. He is taking deep and rapid breaths, but his lungs are clear to auscultation. His abdomen is soft with mild, diffuse tenderness to moderate palpation but no masses, organomegaly, rebound tenderness, or guarding. His bowel sounds are normal. He has no costovertebral angle tenderness. He has no hyperpigmentation, rash, or other abnormal skin findings. His neurologic examination is nonfocal.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with hyperglycemia?

The differential diagnosis for child with hyperglycemia is shown in Table 22.1 and is divided into causes that seem more and less likely based on Taj's presentation.

Table 22.1. Differential Diagnosis for a Child With Hyperglycemia

Diagnosis of highest suspicion	T1DM with DKA
Other diagnoses to consider	• DM with or without DKA – DM related to pancreatic insufficiency – Drug-related DM – Monogenic DM (previously referred to as *maturity-onset diabetes of the young*) – T2DM • Hypercortisolism (eg, stress-induced hyperglycemia, Cushing syndrome) • Laboratory error or sample contamination (eg, unwashed hand used for point-of-care glucose test) • Steroid-induced hyperglycemia without DM

Abbreviations: DKA, diabetic ketoacidosis; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus, T2DM, type 2 diabetes mellitus.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients with hyperglycemia?

- The differential diagnosis for hyperglycemia is relatively narrow. Taj's associated symptoms further narrow your list of potential diagnoses. Given Taj's polydipsia, polyuria, weight loss, severe hyperglycemia, and blood gas results in the ED, you are most suspicious of new-onset DM with DKA.
- The diagnostic evaluation for all patients presenting with suspected new-onset DM should focus on confirming the presence of DM, evaluating for DKA (or hyperosmolar hyperglycemic state) and its complications, and further characterizing the type of DM.

- Physicians should first obtain a serum blood glucose level, HbA_{1c}, VBG, basic metabolic panel, and urine and/or serum ketones (such as β-hydroxybutyrate), if available. Because of the high likelihood of electrolyte abnormalities, obtaining serum magnesium and phosphorus levels is also recommended. Unless there is significant clinical concern for pancreatitis, serum amylase and lipase levels are not usually obtained because they can commonly be elevated in patients with DKA.

Q: What diagnostic evaluation is needed to determine if a patient has type 1 or type 2 DM?

- Although the diagnosis of type 2 DM (T2DM) is commonly suggested by the presence of certain clinical features, such as obesity, acanthosis nigricans, metabolic syndrome, and a positive family history, patients with new-onset DM should be tested for serum autoantibodies specific for type 1 DM (T1DM). The presence of any one of these autoantibodies is suggestive of T1DM: islet-cell antibodies, insulin autoantibodies, glutamic acid decarboxylase antibodies, tyrosine phosphatase–like protein IA-2 antibodies, and zinc transporter 8 antibodies.

CASE FOCUS

Diagnostic Evaluation

You begin by reviewing the laboratory evaluation obtained for Taj in the ED, the results of which are as follows:

Laboratory test	Result	Reference range
CBC		
WBC count	8,000/μL (8.0 × 10^9/L)	4,000–10,500/μL (4.0–10.5 × 10^9/L)
Hemoglobin	13.2 g/dL (132 g/L)	12.5–16.1 g/dL (125–161 g/L)
Hematocrit	40% (0.40)	36%–47% (0.36–0.47)
Platelet count	250 × 10^3/μL (250 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
VBG		
pH	7.25	7.35–7.45
Pco_2	33 mm Hg	32–48 mm Hg
Bicarbonate	16 mEq/L (16 mmol/L)	20–28 mEq/L (20–28 mmol/L)
Base excess	−14 mEq/L (−14 mmol/L)	−4 to +2 mEq/L (−4 to +2 mmol/L)
CMP and other chemistries		
Sodium	134 mEq/L (134 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.3 mEq/L (3.3 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	99 mEq/L (99 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	19 mEq/L (19 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	34 mg/dL (12.14 mmol/L)	6–20 mg/dL (2.14–7.14 mmol/L)
Creatinine	1.4 mg/dL (123.8 μmol/L)	0.5–0.9 mg/dL (44.2–79.6 μmol/L)
Glucose	445 mg/dL (24.70 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Magnesium	1.3 mg/dL (0.53 mmol/L)	1.6–2.4 mg/dL (0.66–0.99 mmol/L)
Phosphorus	3.3 mg/dL (1.07 mmol/L)	3.3–5.4 mg/dL (1.07–1.74 mmol/L)
HbA_{1c}	>14% (>0.14)	4.6%–6.2% (0.046–0.062)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Urinalysis		
Appearance	Clear	Clear
pH	6.0	4.5–8.0
Protein	10 g/dL (100 g/L)	0–29 g/dL (0–290 g/L)
Glucose	>500 mg/dL (27.75 mmol/L)	Negative
Ketones	Moderate	Negative
Blood	Negative	Negative
Bilirubin	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; CMP, comprehensive metabolic panel; HbA_{1c}, hemoglobin A_{1c}; VBG, venous blood gas; WBC, white blood cell.

In addition to these laboratory tests, you order a T1DM autoantibody test, the results of which are pending.

Arriving at a Diagnosis

Q: How do you develop an assessment for Taj?

Although you believe Taj most likely has new-onset DM, you realize the importance of systematically thinking through his case. To arrive at Taj's final diagnosis, you will first interpret the key findings from his history, examination, and diagnostic studies; develop a list of findings; and then finalize your diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Taj has experienced 2 weeks of fatigue, 10 lb (4.5 kg) of weight loss, polyphagia, polydipsia, and polyuria. More acutely, he has had 1 day of vomiting and abdominal pain. His history of fatigue, weight loss, and polyphagia is consistent with insulin deficiency, and his abdominal pain and vomiting are consistent with ketosis resulting from lack of insulin.
   - Physical examination: On examination, Taj has findings of dehydration, as demonstrated by his dry oral mucosa and delayed capillary refill. He does not have acanthosis nigricans, hypertension, or obesity. His deep breathing is consistent with Kussmaul respirations resulting from his acidosis. You do not note any neurologic deficits, altered mentation, or fluctuating level of consciousness concerning for cerebral edema.
   - Diagnostic studies: Taj's laboratory test results demonstrate severe hyperglycemia, with a positive anion gap metabolic acidosis and the presence of ketones in his urine. His HbA_{1c} is highly elevated at greater than 14%. His elevated creatinine and blood urea nitrogen (BUN) to creatinine ratio are reflective of a prerenal acute kidney injury (AKI), which is not uncommon in patients presenting in DKA because of their dehydration. His potassium and magnesium levels are both low. His sodium level is slightly low at 133 mEq/L (133 mmol/L), but correction of his serum sodium value in relation to his hyperglycemia results in a sodium value of 140 mEq/L (140 mmol/L). Serum sodium values can be corrected for hyperglycemia according to the following formula:

$$\text{Corrected serum sodium} = \text{measured serum sodium} + [1.6\ (\text{serum glucose} - 100)/100]$$

BACK TO BASICS

Blood Gas Analysis

1. First, determine whether the patient's pH level is indicative of acidosis (pH ≤ 7.35) or alkalosis (pH ≥ 7.45).
2. Evaluate bicarbonate (HCO_3^-) and P_{CO_2} levels to determine the primary disorder.
   a. Acidemia with low HCO_3^- indicates metabolic acidosis, whereas acidemia with high P_{CO_2} indicates respiratory acidosis.
   b. Alkalemia with high HCO_3^- indicates metabolic alkalosis, whereas alkalemia with low P_{CO_2} indicates respiratory alkalosis.
3. Calculate the anion gap using the formula $Na - (Cl^- + HCO_3^-)$. An anion gap greater than 12 mEq/L (12 mmol/L) is abnormally elevated. It is helpful to determine anion versus nonanion gap metabolic acidosis to help with constructing the differential diagnosis.
4. When there is metabolic acidosis, use Winter's formula to determine completeness of respiratory compensation: $P_{CO_2} = (1.5 \times [HCO_3^-]) + 8 \pm 2$ mm Hg. The calculated P_{CO_2} should match the patient's measured P_{CO_2} if there is adequate respiratory compensation. If the 2 values differ, the acidosis is not compensated, and physicians should consider a mixed (metabolic and respiratory) disorder.
5. Define the disorder and construct a differential diagnosis.

2. Develop the list of findings.

Q: What major findings have you identified for Taj?

- Weight loss, polyphagia, polyuria, polydipsia
- Abdominal pain and vomiting
- Anion gap metabolic acidosis due to ketosis
- Hyperglycemia
- Dehydration
- AKI
- Hypokalemia
- Hypomagnesemia

3. Revisit the differential diagnosis.

You are fairly certain that Taj has new-onset DM with DKA, but you believe it is worthwhile to think about his diagnosis systematically.

Q: How is DM diagnosed?

- The diagnosis of DM is made based on any one of the following criteria:
  - HbA_{1c} greater than or equal to 6.5%
  - Symptoms (eg, polyuria, polydipsia, fatigue, weight loss) *plus* random plasma glucose greater than or equal to 200 mg/dL (≥ 11.10 mmol/L)
  - Two instances of either of the following:
    - Fasting plasma glucose greater than or equal to 126 mg/dL (≥ 6.99 mmol/L)
    - Two-hour oral glucose tolerance test reading greater than or equal to 200 mg/dL (≥ 11.10 mmol/L)
- For patients who present with symptoms of hyperglycemia, a random plasma glucose level typically yields the diagnosis of DM, although obtaining an HbA_{1c} level can also be helpful to indicate the severity of hyperglycemia in the 3 months prior to presentation.

Q: What historical clues and diagnostic evaluation are helpful in determining whether a patient has T1DM or T2DM?

- T2DM is more commonly associated with obesity, acanthosis nigricans, and features of metabolic syndrome, such as hypertension and dyslipidemia, whereas these features are less common in T1DM.
- Patients with new-onset T2DM are approximately 5 times more likely than those with new-onset T1DM to have an affected first-degree family member with the same type of diabetes.
- The presence of any autoantibodies (insulin, glutamic acid decarboxylase, tyrosine phosphatase, zinc transporter 8) classify a patient as having T1DM. Patients with T1DM may also have insulin resistance. Ideally, testing for autoantibodies should occur prior to starting exogenous insulin.
- Note that although some patients with new-onset DM have no obvious symptoms and are diagnosed after the incidental discovery of hyperglycemia, the majority of patients present with symptoms of polyuria and polydipsia, whereas some also experience polyphagia and/or weight loss. Most patients report the duration of their symptoms to be 1 to 2 weeks at the time of presentation, but for some, the duration can be several months. Often patients have enuresis or nocturia, which the patient's family recognizes as abnormal and precipitates an evaluation by their primary care provider.

Q: How is DKA diagnosed?

- Approximately 30% of patients with new-onset T1DM present in DKA.
- The common symptom progression of DKA is as follows:
  - Patients will initially experience symptoms of hyperglycemia including polyuria, polydipsia, polyphagia, and weight loss.
  - As acidosis develops, patients often lose their appetite and develop nausea, vomiting, and abdominal pain.
  - To compensate for the worsening ketoacidosis, patients develop hyperpnea (increasing respiratory rate) and will have Kussmaul respirations (deep and labored breathing).
  - Persistent, uncorrected acidosis and hyperosmolarity from the high serum glucose level will cause worsening of neurologic status, and the patient may become drowsy, then lethargic, and then obtunded.
- Risk factors for presenting in DKA at time of new onset T1DM include preceding viral illness (eg, upper respiratory infection), bacterial illness (eg, urinary tract infection), and younger age (especially <2 years of age). It is also worth noting that patients of color, those of lower socioeconomic status, and those with parents with less education are more likely to present in DKA.

HEALTH EQUITY FOCUS

Health Disparity and Demographic Data

It is important to note that disparities, such as those seen in DM, signal systemic problems in healthcare, including bias, racism, and a lack of access to care, which contribute to the delays in presentation for many patients, rather than genetic or lifestyle choices placing a patient at increased risk. When these disparities are identified, it is imperative to look at systemic solutions.

At the health systems level, it is important to ensure that patient demographic data is accurately collected. This data should be monitored to identify and address differences in health outcomes between patients of different abilities, races, socioeconomic statuses, ethnicities, and languages.

- DKA is diagnosed based on the presence of all 3 of the following criteria:
  - Hyperglycemia: blood glucose greater than 200 mg/dL (11.10 mmol/L)
  - Metabolic acidosis: venous pH less than 7.3 *or* serum bicarbonate less than 15 mEq/dL (15 mmol/L)
  - Ketosis: presence of ketones in the blood (≥3 mmol/L β-hydroxybutyrate) or urine (moderate or large number of urine ketones)

Taj's laboratory test results are consistent with DKA. Although his serum bicarbonate level does not meet DKA criteria, either a pH level less than 7.3 or a bicarbonate level less than 15 mEq/dL (15 mmol/L) can satisfy the criteria, and it is not uncommon to have a mismatch in these 2 values.

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Taj's presentation?

Taj is presenting with new-onset DM with DKA; however, you do not have enough information to determine whether he has T1DM or T2DM. It can be challenging to distinguish between these diagnoses at presentation. Differentiating between T1DM and T2DM does not change acute management but is helpful in guiding treatment following stabilization. T1DM is suspected in Taj's case, however, based on his history of acute weight loss, polyuria, polydipsia, and polyphagia, in addition to the lack of acanthosis nigricans, hypertension, or obesity on physical examination. Additionally, patients with T1DM are more likely to present with DKA than patients with T2DM. Given all of this information, it is reasonable to make a presumptive diagnosis of T1DM and initiate treatment accordingly.

Q: What additional life-threatening complication do you need to evaluate for in patients with DKA?

- If a patient is in DKA, it is important to evaluate their neurologic state to assess for cerebral edema using the diagnostic criteria outlined in Box 22.1. Note that one diagnostic criterion, 2 major criteria, or one major criterion plus 2 minor criteria suggests cerebral edema with a 92% sensitivity and 96% specificity.

Box 22.1. Bedside Evaluation of Neurologic Status of Children With DKA

Diagnostic criteria for cerebral edema

Any one of the following:

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially of cranial nerves III, IV, or VI)
- Abnormal neurogenic respiratory pattern (ie, grunting, tachypnea, Cheyne-Stokes respirations, apneusis)

Additional criteria to consider

Major criteria	Minor criteria
• Altered mentation or fluctuating level of consciousness	• Vomiting
• Sustained heart rate deceleration	• Headache
• Age-inappropriate incontinence	• Lethargy or not being aroused from sleep
	• Diastolic blood pressure > 90 mm Hg
	• Age < 5 years

Adapted with permission from Muir AB, Quisling RG, Yang MCK, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings and early identification. *Diabetes Care*. 2004;27(7):1541–1546.

- Risk factors associated with cerebral edema for patients in DKA include age younger than 5 years, new onset of diabetes, severe acidosis, administration of bicarbonate during medical treatment, and higher BUN level.

Q: Is cerebral edema a concern for Taj?

Although Taj has 2 minor criteria (vomiting and headache), he does not have any diagnostic or major criteria, and therefore clinically significant cerebral edema is unlikely at the time of your evaluation. He should still be monitored closely for development of cerebral edema.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with new-onset DM?

- The patient has newly diagnosed DM requiring initiation of insulin therapy and intensive patient/family education, and no option exists for outpatient care of this level within 12 to 24 hours.
- The patient has significant acidemia (pH < 7.3) consistent with DKA.
- The patient has severe electrolyte disturbances (potassium < 2.5 mEq/L [2.5 mmol/L]).
- The patient is unable to communicate symptom changes because of young age or disability.
- The patient has moderate to severe dehydration and is unable to rehydrate orally because of age, mental status, or intractable vomiting.
- The patient has altered mental status, shock, respiratory failure, dysrhythmias, or other presentation warranting intensive care unit management.

Based on Taj's history of weight loss and his physical examination findings on presentation, you classify him as having moderate dehydration. His laboratory test results show an anion gap metabolic acidosis with a base deficit, mild hypokalemia, hypomagnesemia, ketonuria, and AKI. You determine that Taj will need to be admitted to the hospital for stabilization and further management of his DKA and education about his new diagnosis of presumed T1DM.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Taj is a 12-year-old previously healthy boy who presented with nausea, vomiting, abdominal pain, and weight loss and was found to have new-onset DM complicated by DKA with associated moderate dehydration, AKI, hypokalemia, and hypomagnesemia. He requires admission for stabilization, treatment initiation, and close monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goals for managing patients with DM complicated by DKA are resolving DKA, initiating and titrating insulin therapy to achieve safe glucose levels, and providing education regarding home management of DM. You decide to divide your treatment considerations for Taj into the following categories:

1. **Treatment of DKA:** DKA is the most common cause of morbidity and mortality in children with T1DM. Intervention should occur quickly when DKA is suspected. The treatment of DKA involves hydration and correction of acidosis and other electrolyte disturbances. This is accomplished with an insulin drip, IV fluids, frequent laboratory testing, and electrolyte replacement.

- Hydration: Patients with DKA experience volume depletion as a result of urinary losses associated with osmotic diuresis. Many patients also experience nausea and vomiting that leads to further dehydration, as is the case for Taj. Rehydration is critical for these patients. A 20 mL/kg normal saline bolus over 20 to 60 minutes should be given as soon as possible and then repeated if there is evidence of inadequate perfusion.
  - After the initial IV fluid bolus, it is appropriate to correct the remaining fluid deficit using the "two-bag" system. In this system, 2 bags of fluids with electrolytes are at the bedside. (Fluids may comprise 0.9% sodium chloride or 0.45% sodium chloride with 20 mEq potassium acetate + 20 mEq potassium phosphate. One bag contains 0% dextrose and the other contains 10% dextrose.) The total rate of fluid infused from both bags should be 1.5 to 2 times the maintenance rate. The rate from each bag is titrated based on the patient's blood glucose level. See Table 22.2 for a sample titration using the two-bag system.

Table 22.2. Two-Bag System of Fluid Management for DKA Based on Patient Blood Glucose Levels

Patient blood glucose level (mg/dL [mmol/L])	Bag #1 (no dextrose) Rate (% of total)	Bag #2 (dextrose) Rate (% of total)
≥300 (16.65)	100	0
200–299 (11.10–16.59)	50	50
<200 (<11.10)	0	100

  - It is important to note that a significant amount of potassium is appropriately given with this method. This is because patients with new-onset diabetes are depleted of potassium (regardless of their serum potassium level, which may be artificially high due to intra- to extracellular shift). IV fluids with potassium, however, should not be initiated in patients who are anuric at time of presentation. Once the patient is rehydrated sufficiently to allow for urination, potassium can be added to the IV fluids.
- Insulin infusion: After initial rehydration has occurred, it is important to begin to correct the acidosis. This is done through insulin administration. Patients with DKA should receive an insulin infusion at a rate of 0.1 U/kg/h until resolution of acidosis. Insulin should be started approximately 1 hour after IV fluids and should not be administered as an IV bolus for the acute management of DKA. Glucose concentration will initially drop rapidly with rehydration and volume expansion, but after this initial drop, the goals of insulin infusion are to lower blood glucose by 50 to 100 mg/dL (2.78–5.55 mmol/L) every hour. To prevent hypoglycemia, dextrose should be added when plasma glucose is in the range of 250 to 300 mg/dL (13.88–16.65 mmol/L).
  - If the glucose level is less than 100 mg/dL (5.55 mmol/L) but ketoacidosis remains, physicians should increase the dextrose administered through IV fluids to allow continued insulin administration. Ketones will only clear with continued delivery of both dextrose and insulin. Physicians should consider decreasing the insulin drip rate only if normal glucose levels cannot be maintained with maximum dextrose delivery and/or when ketones are no longer present in urine or blood.
  - The insulin infusion should be stopped when DKA has resolved as evidenced by a closed anion gap and an improving bicarbonate level. Mild acidosis may persist due to hyperchloremia, which is common with administration of the large volume of fluids needed for DKA management.
- Monitoring during DKA treatment: During DKA treatment, is it imperative to monitor the patient's glucose and electrolyte levels frequently. While on the insulin infusion, patients should have point-of-care blood glucose checked every hour. Blood gases (venous or arterial blood gas) and electrolytes (basic metabolic panel, magnesium, phosphorus) should be collected every 3 to 6 hours to monitor for electrolyte abnormalities and closure of anion gap. Neurologic checks should be conducted every hour until DKA is resolved to evaluate for cerebral edema. Urine ketones should be checked with each void until cleared.

- Electrolyte repletion: Electrolytes should be repleted as needed based on laboratory results with the exception of bicarbonate, as this is associated with increased risk of cerebral injury.

2. **DM management:** Patients with a presumed diagnosis of T1DM should be initiated on a home insulin regimen and monitoring plan. As the insulin infusion is stopped, patients should be simultaneously transitioned to a subcutaneous insulin regimen, which is designed to replace endogenous pancreatic insulin secretion. The initial subcutaneous insulin regimen is prescribed to replicate pancreatic function. The most commonly used regimen (and a reasonable approach for Taj) consists of administering a basal insulin dose in addition to a bolus dose of insulin. Basal insulin, also known as *background insulin*, is a long-acting dose of insulin that stabilizes fasting blood glucose and prevents ketosis. Bolus insulin acts rapidly and is taken with meals to allow the body to utilize carbohydrates and treat high blood glucose.
   - Initial insulin regimens are calculated as follows:
     - As a first step, it is helpful to calculate the approximate total daily dose (TDD) of insulin that the patient requires. The TDD is usually between 0.5 and 1.0 U/kg/day of insulin; prepubertal children tend to require a lower TDD, whereas pubertal children usually need a higher TDD. Generally, 40% to 50% of the TDD is given as long-acting insulin, and the other half is given as rapid-acting insulin.
     - Long-acting insulin is generally given once per day.
     - Rapid-acting insulin is given with meals or episodes of hyperglycemia to emulate the physiologic spike of insulin that normally occurs with these events.
       - The mealtime insulin dose is based on the amount of carbohydrates consumed. This dose is given with carbohydrate-containing meals and snacks. An insulin to carbohydrate ratio is used to determine mealtime insulin dose. The "Rule of 500" can be used to calculate the initial insulin to carbohydrate ratio. To calculate this, 500 is divided by the TDD of insulin. The result of this calculation is the number of carbohydrate grams covered by 1 unit of insulin.
       - Correctional insulin is given for episodes of hyperglycemia. This dose of insulin is given if blood glucose is high to bring it back into target range. The amount of this dose is calculated using a "correctional factor," which estimates how much 1 unit of insulin should decrease blood glucose. The "Rule of 1800" may be used to calculate the initial correction factor dose. 1800 is divided by the estimated TDD. This formula gives the expected decrease in blood glucose for each unit of rapid-acting insulin administered.
       - These calculations help provide the initial maintenance dosing regimen. The regimen will be adjusted multiple times during the initial titration phase and will be changed repeatedly throughout the child's growing years.
   - Monitoring on maintenance insulin: When initiating insulin, it is critical to closely monitor the patient's blood glucose levels.
     - The patient's blood glucose level should be checked before each meal. The blood glucose level at this check, referred to as the *preprandial blood glucose check*, reflects the effects of the last mealtime dose and any intervening snacks and activity. This number is used to calculate the correction insulin dose given at mealtime.
     - Bedtime blood glucose checks should also be performed each evening. The blood glucose level at this check reflects the effect of the dinnertime insulin dose. The bedtime blood glucose level provides a baseline to trend overnight fasting blood glucose.
     - Checks at 2:00 am reflect basal insulin (and bedtime snack and/or the correction dose if given). These checks are used for information and to monitor for hypoglycemia. Typically, elevated blood glucose levels should *not be* "corrected" with more insulin if above target. If the blood glucose level is low, the patient will need fast-acting carbohydrates and a repeat blood glucose check in 15 minutes.
   - Hypoglycemia: Patients with T1DM are expected to have intermittent episodes of hypoglycemia if taking adequate insulin doses. These episodes should be treated promptly. If promptly addressed, episodes of hypoglycemia are not expected to cause long-term neurodevelopmental issues.

  - Blood glucose levels below 70 mg/dL (3.89 mmol/L) should be treated with 15 g of simple sugar (eg, 4 fl oz of juice), and blood glucose should be rechecked in 15 minutes to ensure the level has normalized. Treatment can be repeated if necessary. Do not give protein or fat (eg, chocolate, cookie, milk), because this will delay the carbohydrate absorption.
  - If a patient is unconscious, seizing, or not able to increase their blood glucose level by ingesting carbohydrates, emergency glucagon should be given either as an intramuscular shot or intranasal spray.

3. **Preparation for discharge:** After DKA has resolved, the patient and, ideally, at least 2 of their caregivers will need to learn how to manage T1DM.
   - Education should be provided to patients and families on the following aspects of T1DM management:
     - Checking blood fingerstick glucose levels, counting carbohydrates, and calculating and administering subcutaneous insulin doses
     - Recognizing the signs and symptoms of hyperglycemia, ketosis, and hypoglycemia
     - Understanding how to treat hypoglycemia and ketosis
     - Managing diabetes during illness
     - Obtaining the supplies needed for home management, including glucose meter, test strips, lancing device, lancets, insulin vials or pens, syringes or pen needles, ketone strips, and glucagon
   - As Taj arrived at the hospital with only his older brother, it is important to reach out to at least one additional caregiver to ensure that another individual receives education regarding the management of Taj's T1DM.
4. **Consultations:** The diagnosis of DM can be overwhelming to patients and families. There can be significant adjustments required to the daily lives of all members of the family. A multidisciplinary team can help support patients and families in multiple aspects of this transition. DM is best managed by a team consisting of a pediatric endocrinologist, mental/behavioral health providers, dietician, nurse educators, social workers, and child life specialist. Prior to discharge from the hospital, patients with DM and their caregivers should know how to contact their endocrinologist urgently for questions regarding home management.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment of DKA**
  - **Hydration: Taj completed the IV fluid bolus in the ED; thus, you will start IV fluids following the two-bag system.**
  - **Insulin infusion: You will begin an insulin infusion at a rate of 0.1 U/kg/h.**
  - **Electrolyte repletion: You will give IV potassium and magnesium to correct Taj's electrolyte abnormalities.**
  - **Monitoring during DKA treatment: You will monitor Taj's point-of-care blood glucose level, and you order neurologic checks every hour and monitoring of his VBG and serum electrolytes every 3 hours. You will also check for urine ketones with each void until ketones are cleared.**
- **DM management: After his DKA has resolved, Taj will be started on subcutaneous insulin based on the described calculations.**
- **Education: You plan intensive education from the medical team for Taj and his family that will address how to check blood glucose levels, calculate carbohydrates and insulin doses, give insulin, and manage hypoglycemia and ketones.**
- **Consultations: You consult a pediatric endocrinologist to help guide insulin titration and to establish care with Taj. You also consult the interdisciplinary team that works with patients who are diagnosed with DM. This team consists of mental/behavioral health providers, dieticians, nurse educators, social workers, and child life specialists.**

Case Resolution

Over the course of the next 24 hours, Taj's anion gap closes and his metabolic acidosis and AKI resolve. He does not develop symptoms that suggest cerebral edema. His headache, nausea, and abdominal pain resolve. He is transitioned to subcutaneous insulin, for which the calculations are as follows:

- Based on Taj's weight of 40 kg, you calculate his TDD to be 40 units (1 U/kg/day × 40 kg); 40% to 50% of his TDD should be given as long-acting insulin, and the remainder should be given as rapid-acting insulin.
- Using the Rule of 500, you calculate Taj's insulin to carbohydrate ratio to be 1:12 (500/40 = 12.5; you round to 12 to simplify calculations for Taj's family). You explain to Taj and his family that for every 12 g of carbohydrate consumed with meals or snacks, Taj will need to receive 1 unit of rapid-acting insulin.
- Using the Rule of 1800, you calculate Taj's correction factor to be 50 based on his TDD of 40 units (1800/40 = 45; you round to 50 to simplify calculations for Taj's family). You explain to Taj and his family that 1 unit of rapid-acting insulin will decrease the blood glucose level by 50 mg/dL (2.77 mmol/L). An appropriate correction scale would be as follows:

Blood glucose (mg/dL [mmol/L])	Rapid-acting insulin adjustment with meals	Rapid-acting insulin adjustment at bedtime
150–200 (8.33–11.10)	Add 1 unit	
201–250 (11.16–13.88)	Add 2 units	Add 2 units
251–300 (13.93–16.65)	Add 3 units	Add 3 units
301–350 (16.71–19.43)	Add 4 units	Add 4 units
>351 (19.48)	Add 5 units	Add 5 units

- You recommend that Taj and his family start correcting bedtime blood glucose when it is above 200 mg/dL (11.10 mmol/L) to minimize risk of hypoglycemia overnight. This bedtime target will likely be reduced by Taj's endocrinologist once effective insulin doses and glucose monitoring are confirmed.

By hospital day 3, Taj and 2 of his caregivers (his brother and mother) complete his diabetic education and his ketones are cleared. A social worker who specializes in DM care assists Taj's mother in obtaining all of the supplies Taj will need at home. He is discharged home with plans to follow up with the pediatric endocrinologist and the diabetic educator in the next few days.

Discharge Criteria

Q: How do you know when Taj is ready to go home?

You can feel comfortable discharging your patient with new-onset DM when the following criteria are met:

- The patient has trace or no ketones in the urine.
- Ideally, at least 2 family members or caregivers for the patient have received education on the following aspects of care:
  - Blood glucose checks, carb counting, and administering insulin.
  - Signs and symptoms of hypoglycemia and ketones and how to treat both.
- The patient's caregivers have obtained all supplies for home (glucose meter, test strips, lancing device, lancets, insulin vials or pens, syringes or pen needles, ketone strips, and glucagon).
- The patient has been referred to a pediatric endocrinologist for follow-up care, and the patient's caregivers know who to contact for any issues that arise between hospital discharge and the first endocrinology clinic visit.

Anticipatory Guidance

Q: What instructions should you provide to Taj's caregivers upon discharge?

- Seek immediate evaluation for persistent vomiting, moderate to high urine ketones, altered mental status, or abnormal breathing.
- When Taj is sick, check his blood glucose level every 3 to 4 hours, give a correction dose of rapid-acting insulin every 3 to 4 hours as needed based on the result of the blood glucose check, even if he is not eating, and check urine ketones every 3 to 4 hours.

Clinical Pearls

- Management of diabetes is complex and requires a multidisciplinary team of endocrinologists, nurses, diabetes educators, mental health professionals, dieticians, and social workers.
- Cerebral edema/injury is the leading cause of morbidity and mortality in DKA. Clinicians should be familiar with the diagnostic criteria for cerebral edema/injury and should carefully monitor the neurologic status of patients with new-onset diabetes.
- Despite adherence to their insulin regimens, patients with T1DM will have episodes of hyperglycemia and hypoglycemia; therefore, it is important that they are familiar with symptoms and aware of how to manage the episodes.

Documentation Tips

- Specify the type of diabetes, if known, and whether this is a new diagnosis for the patient.
- Describe whether there were key gaps in knowledge or management that led to the admission.
- Document the frequency of blood glucose checks needed during the admission.
- Include associated symptoms (eg, nausea, vomiting, dehydration) that require administration of IV fluids.
- For DKA, include blood gas pH, serum bicarbonate level, degree of hyperglycemia, and presence of ketonuria or ketonemia.
- Include associated electrolyte disturbances and the need for replacement or correction.

Suggested Readings

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CASE 23

Finn, a 2-Year-Old Boy With Fever and Leg Pain

CASE PRESENTATION

You have just finished morning rounds when you are asked to evaluate Finn, a 2-year-old boy who is being seen in the emergency department (ED) for fever and left lower extremity pain. The physician caring for him in the ED tells you that Finn has been sick for 2 days with fever and woke up this morning crying in pain. Since that time, he has been refusing to move his left lower extremity or ambulate. The ED team has started a preliminary evaluation, and consultation with the orthopedic surgeon is pending. After speaking to the physician caring for Finn in the ED, you begin your evaluation.

Patient History and Review of Systems

Q: What information should you collect from Finn's caregivers?

- History of present illness
  - Fever: duration, height, and method of measurement
  - Information about pain and degree of disability, including how the child is indicating pain to caregivers (eg, pointing to an area that hurts, crying when the area is touched, unwillingness to move the affected extremity); refusal to crawl, walk, or bear weight; and expressions of pain when picked up or carried
  - Swelling or redness of the joint or extremity
  - Any other affected regions
  - Recent trauma or injury to the extremity, including scratches or other skin wounds
  - Recent illnesses, including sore throat, upper respiratory infection, or diarrhea
  - Previous episodes of similar symptoms or skin and soft tissue infection
  - Associated symptoms, including weight loss, night sweats, conjunctivitis, rashes, fussiness, lethargy, upper respiratory infection, poor oral intake, vomiting, diarrhea, decreased urine output, and unexplained or excessive bleeding or bruising
- Medical history, including chronic medical conditions, surgeries, and immunization status
- Medications or recent courses of antibiotics
- Social history for exposures: outdoor activities that increase risk of tick exposure; encounters with animals (eg, dogs, cats, reptiles, birds); household contact with recent infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA)
- Family history of inflammatory bowel disease or rheumatologic conditions

CASE FOCUS

History and Review of Systems

From the admission history, you learn that Finn is otherwise healthy but has had a limp and fever for 2 days, with a maximum oral temperature of 39.4 °C (102.9 °F) this morning. Yesterday, Finn started to indicate that he was having pain in his left lower extremity, and his parents first noted some mild swelling of the upper left thigh last night. He woke up this morning in significant pain and has been refusing to move his left lower extremity or bear weight. His parents called his pediatrician, who recommended they bring him to the ED. For the past 2 days, his parents have been giving him acetaminophen and ibuprofen to treat his fever and pain.

When asking about recent injuries, his parents report that a few days ago, Finn was at the playground and bumped his left thigh on the edge of the slide while running. He cried briefly but quickly resumed playing. His parents did not notice any breaks in the skin or bruising. His parents deny seeing any rashes or swelling, pain, or redness of any other joints. He has not recently been ill and has never had symptoms like this in the past.

Finn is up to date on all of his vaccines, including his flu shot, which he received a few weeks ago at his 24-month health supervision visit. He has been meeting his developmental milestones and does not have any underlying health conditions. Finn attends child care but has not gone for the past few days since he started feeling ill. Finn and his family have not traveled recently, but they did have family members come to visit. None of the visitors had a fever or other signs of illness, and no one in the household has had an infection caused by MRSA. Finn has not had any tick exposures or insect bites and does not live in an area where Lyme disease is endemic. The family has one dog that is fully vaccinated and on flea and tick prevention medications.

Finn has not had any oral intake during the 4 hours he has spent in the ED. His history and review of systems are otherwise unremarkable.

Physical Examination

Q: What parts of the physical examination should you focus on for Finn?

- Complete set of vital signs
- General appearance and ability to arouse normally
- Head, eyes, ears, nose, and throat: signs of concomitant illness or dehydration
- Peripheral perfusion, including distal pulses, capillary refill time, and temperature of distal extremities
- Affected extremity, including the joints above and below the area of concern (when a specific area can be identified)
  - Voluntary movement of the extremity (referred to as *active movement*)
  - Pain or resistance when joint is moved by the examiner (referred to as *passive movement*)
  - Position in which the child holds the affected extremity
  - Edema, tenderness, warmth, or erythema
  - Joint effusion
- Gait and ability to bear weight
- Skin: lesions, such as excoriations, vesicles, puncture wounds, petechiae, erythroderma, or other rashes
- Enlarged lymph nodes or organomegaly

CASE FOCUS

Physical Examination

As you begin to examine Finn, you first make note of his vital signs. He is febrile with a temperature of 38.3 °C (100.9 °F), tachycardic with a heart rate of 158 beats/min, and tachypneic with a respiratory rate of 38 breaths/min. His oxygen saturation is normal, and his blood pressure is normal at 92/59 mm Hg.

On examination, Finn is lying on the bed next to his mother. He is fussy during the examination but consoles when not being touched. He has moist mucous membranes. No oral ulcers, rhinorrhea, or pharyngeal erythema are present. He has mild tachycardia with a regular rhythm and no murmur. His distal extremities are warm, radial and pedal pulses are normal, and capillary refill time is less than 2 seconds. He has tachypnea, but his pulmonary and abdominal examinations are otherwise normal without focal findings. There is no organomegaly or lymphadenopathy.

You begin the musculoskeletal examination and notice that Finn is holding his left lower extremity slightly externally rotated while lying in the bed. He does not want to move his left lower extremity. He cries with passive range of motion of the left hip and with flexion and extension of his left knee. Range of motion of the left ankle is normal. There is mild nonpitting edema and significant tenderness of the proximal left thigh, but no erythema is noted. You do not notice any effusions or erythema of the left knee. There are no breaks in the skin, and no rashes are noted anywhere on his body. The remainder of his examination is normal for age.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with acute-onset pain of a joint or extremity?

The differential diagnosis can be categorized into infectious and noninfectious causes, as shown in Box 23.1. For Finn, you are most concerned about infectious arthritis or osteomyelitis, but you would also like to consider pyomyositis, transient synovitis, or an oncologic process.

Box 23.1. Differential Diagnosis for a Child With Acute Onset of Lower Extremity Pain

Infectious etiologies	Noninfectious etiologies
• Cellulitis or erysipelas • Herpes zoster • Infectious arthritis, viral or bacterial (including Lyme disease)[a] • Necrotizing fasciitis • Osteomyelitis[a] • Pyomyositis	• Bone infarction related to sickle cell disease, Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), or Gaucher disease • Hematologic etiologies (eg, venous thrombosis, hemarthrosis) • Noninfectious inflammatory conditions — Acute rheumatic fever — Chronic recurrent multifocal osteomyelitis — KD — Poststreptococcal arthritis — Reactive arthritis — Rheumatologic conditions, such as JIA — Serum sickness-like reactions — Transient synovitis • Oncologic processes (eg, leukemia, Ewing sarcoma, osteosarcoma, Langerhans cell histiocytosis, metastatic disease)

(continued)

Box 23.1. Differential Diagnosis for a Child With Acute Onset of Lower Extremity Pain *(continued)*

Infectious etiologies	Noninfectious etiologies
	• Orthopedic conditions — Caffey disease (infantile cortical hyperostosis) — Nonmalignant bone lesions (eg, osteoid osteoma, bone cysts) — Overuse injuries, including "growing pains" — SCFE — Trauma-related etiologies (eg, compartment syndrome, fracture, hematoma, soft tissue injury, traumatic effusion) • Vitamin deficiencies (eg, scurvy, rickets)

Abbreviations: JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; SCFE, slipped capital femoral epiphysis.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with acute onset of pain of a joint or extremity?

As demonstrated by the differential diagnoses, joint or extremity pain in a child can be the presenting symptom for many conditions. Because Finn presented with acute onset of pain in association with fever, you are most concerned about first evaluating for acute infectious etiologies, such as septic arthritis and osteomyelitis. To evaluate the likelihood of these infections, rule out other possibilities on the differential diagnosis, and help identify the organism causing infection (when present), the following tests are recommended:

- Complete blood cell count (CBC) with differential: The white blood cell (WBC) count is commonly elevated with both septic arthritis and osteomyelitis, although a normal WBC count does not rule out these possibilities.
- Inflammatory markers, especially erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP): CRP appears to have a good negative predictive value for osteoarticular infections and is useful for monitoring response to treatment.
- Blood cultures: Blood cultures are positive in up to 50% of patients with osteomyelitis when drawn prior to the start of antibiotics and when sufficient volumes are collected.
- Plain radiographs: Plain radiographs are useful to evaluate for fractures and some bony tumors. Radiographs can also assess for evidence of subacute or chronic bone infections but are usually normal in the early stages of osteomyelitis. It is important to obtain frontal and lateral view radiographs of the area of concern and the joints above and below the site of pain, as pain may be referred.
- Magnetic resonance imaging (MRI): MRI of the affected extremity or joint is useful to evaluate for signs of bone, muscle, or joint disease. Because MRI lacks radiation and has a high specificity (95%) and sensitivity (92%) for detecting osteomyelitis, it is the preferred imaging modality for the diagnosis of bone and joint infections and performs better than computed tomography or bone scan. For most young children, an MRI is performed under sedation.
- Other tests to consider include the following:
  - Ultrasonography: Ultrasonography of the affected joint is useful to evaluate for the presence of a joint effusion.
  - Arthrocentesis: When there is strong evidence for septic arthritis, arthrocentesis should be performed to obtain synovial fluid for cell counts, Gram stain, and culture. Inoculation of synovial fluid into blood culture bottles can improve the yield of certain organisms. When available, polymerase chain reaction (PCR) testing of synovial fluid should be considered.
  - *Borrelia burgdorferi* antibody titers: Serologic testing should be ordered when there is concern for Lyme arthritis based on a relevant history.

— Tests for oncologic etiologies: To evaluate oncologic etiologies, initial tests to consider (in addition to CBC, ESR, CRP, blood culture, and radiographs) include a comprehensive metabolic panel, phosphorus level, reticulocyte count, peripheral smear, lactate dehydrogenase level, and uric acid level. Additionally, chest radiography may be useful in evaluating for adenopathy or metastatic disease. It is important for clinicians to know that normal serum laboratory test results do not rule out malignancy. Clinicians should consider consultation with a pediatric oncologist if there is suspicion for malignancy. An MRI of the involved bone and tissue samples may be needed.

CASE FOCUS

Diagnostic Evaluation

The ED physician ordered an initial diagnostic workup, the results of which are as follows:

Laboratory test	Result	Reference range
CBC		
WBC count	27,100/μL (27.1 × 10^9/L)	7,000–13,000/μL (7–13 x 10^9/L)
Hemoglobin	11.4 g/dL (114 g/L)	10.5–14 g/dL (105–140 g/L)
Hematocrit	34.1% (0.341)	32%–42% (0.32–0.42)
Platelet count	573 × 10^3/μL (573 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	70% (0.7)	23%–70% (0.23–0.7)
Lymphocytes	20% (0.20)	15%–67% (0.15–0.67)
Inflammatory markers		
CRP	15.2 mg/dL (152 mg/L)	<1 mg/dL (<10 mg/L)
ESR	65 mm/h	0–10 mm/h
Imaging		
Radiographs (anteroposterior and frog-leg views of pelvis)	No abnormalities	
Ultrasound, left hip	Small effusion	

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

An arthrocentesis was not performed in the ED, but a sedated MRI of Finn's left hip and femur has been ordered pending consultation with the orthopedic surgeon.

Arriving at a Diagnosis

Q: How do you develop an assessment for Finn?

As you think through Finn's case, you first decide to interpret his vital signs, as this will help determine if immediate treatments are needed and dictate triage for unit placement in the hospital. Next, you will interpret his history, examination findings, and diagnostic testing to develop a list of findings that will help narrow your differential diagnoses to the most likely etiology.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Finn has had 2 days of fever and 1 day of worsening left lower extremity pain with proximal thigh swelling. His pain has resulted in an inability to bear weight on his left lower extremity and refusal to move his

left hip. A few days earlier, he had a minor injury to that thigh on the playground. This injury did not require medical attention and may not be related to his current presentation. Finn is otherwise healthy and has no known infectious exposures, but he does attend child care.

- Physical examination: Finn has fever and tachycardia but a normal respiratory rate and oxygen saturation level. His tachycardia may be due to fever, pain, sepsis, and/or decreased oral intake. Finn's blood pressure is normal, and other findings to assess perfusion are also normal, including capillary refill, extremity temperature, and skin color. Overall, Finn's examination is normal except for his pain and left lower extremity findings, which point toward the hip and proximal thigh as the source of his pain and inflammation. The lack of skin erythema and induration indicates that the source of inflammation affects the deeper structures, making superficial/cutaneous etiologies unlikely.
- Diagnostic evaluation: Finn's laboratory test results demonstrate leukocytosis with a WBC count of 27,100/μL (27.1×10^9/L) and a predominance of neutrophils, suggestive of infection. The thrombocytosis on the CBC (573×10^3/μL [573×10^9/L]) is likely an indication of an inflammatory response to an active infection. His elevated ESR and CRP level further support the presence of an inflammatory process. Plain radiographs (anteroposterior and frog-leg views of pelvis) are normal without fracture or other bony abnormality, eliminating the possibility of a chronic osteomyelitis. Although a hip effusion was not seen on plain radiographs, it was detected on ultrasonography, suggesting nonspecific inflammation within the joint.
- Assessment for sepsis: In children, sepsis is defined as evidence of systemic inflammatory response syndrome (SIRS) in the setting of a suspected or documented infection. For a list of clinical criteria, refer to Section IV of the Appendix. Finn meets the definition of sepsis based on possible infection *and* the presence of all 4 age-based SIRS criteria, including fever (temperature > 38.5 °C [101.3 °F]), tachycardia (heart rate > 140 beats/min), tachypnea (respiratory rate > 22 breaths/min), and leukocytosis (WBC count > 15,500/μL [15.5×10^9/L]). At the present time, Finn does not have evidence of severe sepsis or septic shock.

2. Develop the list of findings.

- Left lower extremity pain, swelling, and decreased range of motion at or near the hip
- Small left hip effusion
- Thrombocytosis
- Elevated inflammatory markers (both ESR and CRP)
- Suspected sepsis (leukocytosis, fever, tachycardia, and tachypnea in the setting of a suspected infection)

3. Revisit the differential diagnosis.

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Finn's presentation?

- Based on Finn's symptoms, diagnostic evaluation, and list of findings, you are most suspicious of an acute infectious etiology, specifically acute hematogenous osteomyelitis and/or septic arthritis.
- Many other diagnoses are much less likely based on the degree of inflammation present, a lack of certain risk factors/exposures, an otherwise normal examination, and the apparent involvement of a single joint or the hip joint. Malignancy cannot be completely excluded but seems less likely based on Finn's history, examination, and diagnostic evaluation thus far. Although chronic recurrent multifocal osteomyelitis (a noninfectious inflammatory condition) can initially present in a similar manner to acute hematogenous osteomyelitis and cannot be removed from the differential quite yet, it is less likely to present with this level of acuity/severity and is usually only diagnosed once there are findings of multifocal disease unresponsive to antibiotics or recurrent episodes.

Q: How are septic arthritis and osteomyelitis diagnosed?

- Oftentimes, septic arthritis is suspected based on the findings of fever; joint pain, swelling, erythema, or warmth; and refusal to move the joint or bear weight. However, it is important for clinicians to know that fever is not invariably present. In children with septic arthritis of the hip (one of the most commonly affected joints), the child frequent holds the leg slightly abducted and externally rotated. The diagnosis of septic arthritis is confirmed by evidence of infection or severe inflammation in the synovial fluid.

- Osteomyelitis in children most commonly affects the metaphysis of long bones or small bones of the feet and presents with localized pain, fever, and signs of systemic and local inflammation. Similar to septic arthritis, fever is not universally present, and the associated cutaneous erythema and edema can be mistaken for cellulitis. The diagnosis of osteomyelitis is usually based on the presence of characteristic MRI findings but can be confirmed by evaluation of a surgical specimen or aspirate.
- Most cases of septic arthritis and osteomyelitis in children are hematogenous in origin, resulting from bacterial seeding of the bones or joints during episodes of transient bacteremia. Minor trauma to the area may predispose to the development of osteomyelitis, possibly through formation of a metaphyseal hematoma, but this theory is unproven. Less often, osteoarticular infections are the result of direct inoculation related to penetrating injury or a medical procedure. Additionally, both septic arthritis and osteomyelitis can result from an infection that spreads from contiguous areas.

Q: When symptoms are isolated to the hip, how are septic arthritis and transient synovitis differentiated?

- Septic arthritis and transient synovitis (a benign, self-limited condition) have overlapping symptoms, making differentiation between them difficult. For cases in which the 2 diagnoses cannot be easily distinguished, the Kocher criteria can be useful.
- Because Finn also has findings related to his upper thigh, the Kocher criteria should not be applied to his case. Additionally, the Kocher criteria should be used with caution in children of Finn's age.

BACK TO BASICS

The Kocher Criteria

- The Kocher criteria utilize 4 clinical and laboratory findings to estimate the probability of septic arthritis in children with hip pain. The criteria are as follows:
  - The patient is unable to bear weight.
  - The patient has a temperature greater than 38.5 °C (101.3 °F).
  - The patient's ESR is greater than 40 mm/h.
  - The patient's WBC count is higher than 12,000/μL (12×10^9/L).
- If the patient meets one criterion, there is a 3% probability of septic arthritis; 2 criteria correlate with a 40% probability; 3 criteria correlate with a 93% probability; and 4 criteria correlate with a 99% probability of septic arthritis.
- It should be noted that application of the Kocher criteria is restricted to the hip joint and that the original study did not include patients with arthritis related to *Kingella kingae*, limiting its utility in young children. Additionally, because osteomyelitis and septic arthritis share many common history, examination, and laboratory findings, 3 or 4 Kocher criteria may also be present in patients with osteomyelitis, with or without concomitant septic arthritis.

For Finn, you decide that he requires further investigation with orthopedic consultation and an MRI to clarify his diagnosis.

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with a suspected osteoarticular infection?

All patients with suspected osteoarticular infections require admission to the hospital for urgent evaluation, consideration of empiric intravenous (IV) antibiotics, consultation with orthopedic surgery, and close monitoring.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Finn is a 2-year-old boy presenting with fever, left lower extremity pain, and refusal to bear weight. He has leukocytosis, elevated inflammatory markers, thrombocytosis, a small hip effusion, and findings indicative of sepsis likely secondary to septic arthritis or osteomyelitis. Given the concern for these etiologies, Finn requires admission to the hospital for further diagnostic evaluation, treatment, and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing Finn's treatment plan, you review the literature to remind yourself about the treatment of osteomyelitis and septic arthritis in children. You decide to divide treatment considerations into the following components:

1. **Further diagnostic evaluation and specialist consultation**
   - For patients with suspected septic arthritis, arthrocentesis should be performed to obtain synovial fluid for cell counts, Gram stain, and culture. In cases with a strong suspicion of septic arthritis, therapeutic irrigation and drainage/debridement of the joint is indicated as well. When sufficient synovial fluid has been collected, further diagnostic testing (eg, PCR) can be performed on the sample.
   - MRI with contrast can be used to evaluate for osteomyelitis, pyomyositis, and to visualize other bone and joint abnormalities. When subperiosteal or intraosseous abscesses are present, surgical intervention is often required and can allow for specimen collection for culture.
   - Patients with suspected osteoarticular infections should be managed in conjunction with pediatric orthopedic surgeons. Additionally, clinicians should consider consulting pediatric infectious disease specialists, especially for patients with unusual pathogens, persistently positive blood cultures, multifocal infections, and complex medical comorbidities.
   - Because Finn has findings involving the left hip joint and the proximal left femur, you agree with the ED physician that an MRI of Finn's left hip and femur and arthrocentesis of his left hip will aid in his diagnostic evaluation. After discussions with the orthopedic surgeon, you will coordinate the timing of Finn's MRI with the availability of an operating room so that arthrocentesis and any other surgical intervention can occur under the same sedation. Given the osteoarticular infections protocol at your institution, you also plan to consult your pediatric infectious disease specialist to help determine if further testing is needed; assist with decisions about antibiotic selection, duration of treatment, and monitoring; and follow up with Finn after hospital discharge.
2. **Antibiotic therapy:** The goal of empiric antibiotic therapy is to treat for the most common organisms causing septic arthritis and osteomyelitis. Antibiotics can later be narrowed to treat the identified bacterial species, if possible. For patients who are clinically stable, it is reasonable to delay the initiation of antibiotics until intraoperative cultures have been obtained; however, it is also appropriate to initiate empiric therapy on admission if there is a delay to surgery or the patient is clinically unstable.
   - When choosing the empiric antibiotic therapy for a patient with osteomyelitis or septic arthritis, there are several factors that must be considered, as demonstrated in Table 23.1. In general, *S aureus* and *Streptococcus pyogenes* are the most common causes throughout childhood and adolescence; however, group B *Streptococcus* is a common cause in neonates and young infants, and *K kingae* is one of the most common causes in young children. *K kingae* is more likely to be associated with a subacute clinical course and is associated with child care attendance and recent stomatitis or upper respiratory tract symptoms.

- Because of the high prevalence of gram-positive organisms causing osteomyelitis and septic arthritis, empiric treatment options generally include oxacillin, clindamycin, or vancomycin, depending on the patient's clinical status, the local prevalence of community-acquired MRSA, and the local prevalence of clindamycin-resistant MRSA. When *K kingae* or other gram negative organisms are suspected, empiric treatment should also include use of a cephalosporin.
- Because Finn has signs of sepsis and there is a high prevalence of clindamycin-resistant *S aureus* in your area, you decide to start empiric vancomycin and ceftriaxone while awaiting his MRI and arthrocentesis.
- Antibiotics should be tailored based on culture results, when available.
- Between 20% and 50% of patients will have negative blood cultures, which may relate to insufficient blood volume, pretreatment with antibiotics prior to obtaining blood cultures, or viral or noninfectious etiologies. Additionally, synovial fluid cultures are often negative, but the use of PCR testing may help identify the etiology.

Table 23.1. Common Bacterial Pathogens Causing Osteoarticular Infections by Host Factor

Scenario	Common infectious organisms
Neonate or young infant (<2 months)	*Staphylococcus aureus* Group B *Streptococcus* Group A *Streptococcus* Gram-negative enteric rods
Otherwise healthy child (<4 years)	*S aureus* *Kingella kingae* Group A *Streptococcus* *Streptococcus pneumoniae* *Haemophilus influenzae*[a] *Neisseria meningitidis*
Otherwise healthy child (≥4 years)	*S aureus* Group A *Streptococcus* *S pneumoniae*[a] *N meningitidis* *K kingae*
Unimmunized child	In addition to the previously listed organisms for age: *H influenzae* *S pneumoniae*
Child with sickle cell disease	In addition to the previously listed organisms for age: *Salmonella* spp
Adolescent	*S aureus* Group A *Streptococcus* *Neisseria gonorrhoeae*

(continued)

Table 23.1. Common Bacterial Pathogens Causing Osteoarticular Infections by Host Factor *(continued)*

Scenario	Common infectious organisms
Immunocompromised patient	In addition to the previously listed organisms for age: *Candida* Other fungal species such as *Coccidioides*
Concern for vertebral osteomyelitis	In addition to the most common etiology, *S aureus*: *Bartonella henselae* *Mycobacterium tuberculosis* *Brucellosis* spp
Nail puncture wound to the foot through the shoe	*Pseudomonas aeruginosa*

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Not a common cause of septic arthritis in this age group.

Q: What is the duration of antibiotic therapy for osteomyelitis and septic arthritis?

- The average duration of therapy is typically 3 to 4 weeks for acute hematogenous osteomyelitis and 2 to 3 weeks for septic arthritis. The duration may differ in cases with unusual pathogens, concern for chronic infection, or a complicated clinical course.
- Most pediatric patients with uncomplicated acute hematogenous osteoarticular infections are good candidates for oral antibiotic therapy at home instead of prolonged IV antibiotics. In general, the decision to transition to oral antibiotics can be made when it is confirmed that the patient has an uncomplicated bone or joint infection and the patient has been afebrile for 24 to 48 hours, has received an adequate course of IV antibiotics (ie, >72 hours), and has a CRP that is consistently downtrending. Specific CRP thresholds tend to vary by institution, but the literature supports transitioning to oral antibiotics when the CRP is less than 2 to 3 mg/dL (20–30 mg/L).

3. **Laboratory monitoring:** The primary goal of laboratory monitoring is to ensure that the patient is receiving the appropriate antimicrobial therapy. Additionally, the long-term use of certain antimicrobials warrants periodic laboratory monitoring to evaluate for signs of toxicity or side effects of therapy.
   - ESR: For osteoarticular infections, the ESR should normalize within 3 to 4 weeks of initiation of appropriate antibiotics.
   - CRP: In general, CRP can be monitored every 48 hours while the patient is hospitalized, then periodically during outpatient antibiotic therapy until the antibiotic course is completed. CRP level should begin to decrease within 24 to 48 hours of initiation of appropriate antibiotics.
   - CBC: Leukocytosis and thrombocytosis should begin to improve within a few days of initiation of appropriate antibiotics. Occasionally, leukopenia or eosinophilia can develop as a side effect of prolonged antibiotic therapy and may be an indication to modify antibiotic therapy. Normocytic anemia commonly develops in severe inflammatory states such as osteoarticular infections; however, it is usually mild and generally resolves without treatment as the inflammation/infection improves. Occasionally, packed red blood cell transfusions may be needed.
   - Renal function and liver enzymes: Depending on the choice of antibiotics (eg, β-lactams, vancomycin), periodic monitoring of renal function and/or liver enzymes may be needed for the duration of antibiotic therapy.

4. Other monitoring and treatment considerations

- Monitoring for acute complications: Possible acute complications of osteoarticular infections include the development of severe sepsis, septic shock, avascular necrosis, pathologic fractures, deep vein thrombosis, septic pulmonary emboli, and the need for repeated surgical irrigation and drainage/debridement. An increased risk of more invasive disease and acute complications has been associated with methicillin-susceptible *S aureus* (MSSA) and MRSA isolates that secrete the virulence toxin Panton-Valentine leukocidin; however, routine testing for this toxin is not usually performed.
- Vital signs: Children admitted to the hospital with osteoarticular infections should undergo monitoring of their vital signs, with more frequent vital sign checks indicated for those in whom there is concern for sepsis. In addition to decreases in the CRP level, improvement in the child's heart rate and temperature curve can be other indicators of appropriate empiric antibiotics.
- Intake and output: Children with sepsis and dehydration should also undergo monitoring of their intake and output to ensure they are able to maintain their hydration and demonstrate evidence of adequate renal perfusion. IV fluids may be needed until children are taking sufficient fluids by mouth.
- Diet/nutrition: Clinicians should monitor the patient's nutritional status to ensure they are taking in adequate nutrients and calories.
- Pain: Osteoarticular infections commonly cause significant pain in the acute setting; therefore, clinicians and nursing staff should monitor pain with developmentally appropriate pain scales and treat pain with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids such as oxycodone or morphine.
- Rehabilitation: Prior to discharge home, many children with osteoarticular infections benefit from an evaluation by a physical therapist to help with rehabilitation and determining safe/appropriate methods of ambulation when needed.

CASE FOCUS

Plan for Treatment and Monitoring

- **Further evaluation and expert consultation:** You discuss Finn's case with the pediatric orthopedic surgery team and the infectious disease team, and they both agree with your plan to obtain an urgent MRI of Finn's left hip and femur. The surgeon plans to immediately review the MRI, perform an arthrocentesis, and proceed with any other necessary surgical intervention as indicated.
- **Empiric antibiotics:** Although it can be an appropriate option to temporarily withhold antibiotics for stable patients until after they undergo surgical drainage, Finn meets the criteria for sepsis. Because of this, you decide to start empiric IV ceftriaxone and vancomycin while awaiting the MRI, which is scheduled for later in the day. You choose vancomycin over clindamycin given the high rates of clindamycin-resistant MRSA in your community.
- **Laboratory monitoring:** You order a vancomycin trough to be drawn prior to the fourth dose and will order other laboratory tests when Finn's diagnosis is confirmed.
- **Other monitoring and treatment considerations:** You place Finn on nil per os (nothing by mouth) status and start maintenance IV fluids while awaiting his sedated MRI and possible surgery. You order acetaminophen, oxycodone, and IV morphine as needed for pain and will avoid NSAIDs while Finn is receiving vancomycin. You also order strict monitoring of intake and output, vital signs every 2 hours while sepsis is present, and frequent clinical reassessments. Once Finn's vital signs stabilize, you will space his vital sign checks to every 4 hours.

Case Resolution

Finn's MRI demonstrates edema and enhancement of the proximal left femur consistent with osteomyelitis, myositis in the left thigh, and a small left hip effusion without synovial enhancement. No drainable abscesses are present. Following the MRI, the orthopedic surgeon aspirates Finn's left hip joint, but the synovial fluid is not consistent with septic arthritis (as demonstrated in the following table) and is determined to represent a reactive effusion. The surgeon obtains a bone sample for culture, but further surgical intervention is not indicated.

Findings	Finn's synovial fluid	Septic (bacterial) arthritis	Transient synovitis	Normal joint
Color	Light yellow	Serosanguineous	Yellow	Yellow
Clarity	Clear	Turbid	Clear to cloudy	Clear
WBC count	2,000/μL (2 × 10^9/L)	> 50,000/μL (50 × 10^9/L)[a]	5,000–15,000/μL (5–15 × 10^9/L)	< 200/μL (< 0.2 × 10^9/L)
Neutrophils	20% (0.2)	>75% (0.75)	<25% (0.25)	<25% (0.25)
Culture	No growth	Positive in 70%–80% of cases	Negative	Negative
Glucose	100 mg/dL (5.55 mmol/L)	<40 mg/dL (2.22 mmol/L)	Equal to serum	Equal to serum

Abbreviation: WBC, white blood cell.

[a] This WBC count value is an approximation, as cases of septic arthritis can occur with lower values.

Initially, Finn is treated with IV vancomycin and ceftriaxone. After his blood culture demonstrates growth of MSSA, his antibiotics are narrowed to oxacillin. He is monitored every other day with laboratory tests to trend his CRP level. He initially requires opioids for pain control and IV fluids for hydration. He continues to have fever for 3 days, but his subsequent blood cultures remain negative. His bone culture ultimately grows MSSA, but his joint fluid remains negative.

Based on your institution's osteomyelitis protocol, Finn is discharged home on oral cephalexin once his CRP level is less than 2.0 mg/dL (20 mg/L), he is afebrile for more than 48 hours, and he shows clear clinical improvement. The infectious disease specialist plans to follow Finn as an outpatient to trend laboratory tests weekly, and he has follow-up scheduled with the orthopedic surgeon.

Discharge Criteria

Q: How do you know when Finn is ready to go home?

You can feel comfortable discharging your patient with osteomyelitis or septic arthritis when the following criteria are met:

- The patient has downtrending inflammatory markers and a CRP level less than 2 to 3 mg/dL (20–30 mg/L).
- The patient has been afebrile for more than 24 to 48 hours.
- If the patient had bacteremia, recent blood cultures should have no growth for approximately 48 hours.
- The patient has stable vital signs appropriate for age.
- The patient has improving physical examination findings.

- Appropriate follow-up appointments have been established with the primary care pediatrician, orthopedic surgeon, and infectious disease physician (as determined per institutional protocol).
- If being discharged on oral antibiotics, the patient can tolerate oral medication, and the medication is available from the pharmacy.

Anticipatory Guidance

Q: What instructions should you provide to Finn's caregivers upon discharge?

- Continue to monitor the site for redness, swelling, or warmth.
- Continue to monitor Finn's ability to bear weight and his willingness to use the affected extremity.
- Seek medical care if Finn's temperature is greater than 38 °C (100.4 °F).
- Notify Finn's pediatrician or infectious disease specialist if he is not able to tolerate oral antibiotics. It is important that Finn complete his entire course of antibiotics unless otherwise directed by the infectious disease physician.
- Based on severity of illness, long-term follow-up with Finn's orthopedic surgeon may be needed to monitor for the possibility of differences in leg length or other complications.

Clinical Pearls

- In children, bone pain or the limited use of an extremity are common presenting symptoms for a variety of diagnoses, including infection, an inflammatory process, malignancy, trauma, and ischemia.
- Acute hematogenous osteomyelitis typically presents in the long bones (particularly the femur, tibia, and humerus), and MRI is the most sensitive and specific diagnostic test for diagnosis.
- Consider individual patient factors and local susceptibility patterns when choosing empiric antibiotics. In an otherwise healthy school-aged child and where clindamycin resistance is not high in the region, clindamycin and ceftriaxone may be reasonable empiric options.
- Trending the patient's CRP level can help guide management and assist in discharge planning.

Documentation Tips

- Document sepsis, if present.
- Describe imaging findings, including the specific location of the infection and the presence of abscess or other indications for surgical intervention.
- Include the causative organism, if known.
- Document when there is a need for an extended course of IV antibiotics requiring peripherally inserted central catheter placement.

Suggested Reading

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Aubree, a 15-Year-Old Girl With Recurrent Abdominal Pain

CASE PRESENTATION

Aubree, a healthy 15-year-old girl, presented to the emergency department (ED) earlier today with recurrent abdominal pain and nausea that has not been controlled with acetaminophen at home. This is the third time in the last 4 months that Aubree has visited the ED with similar symptoms. Her mother decided to bring her to the ED today because her pain has increased in severity for the past 6 hours, and she was not tolerating liquids due to pain and nausea. In the ED, the team gave her an intravenous (IV) fluid bolus, acetaminophen, and ondansetron with minimal relief of her pain and nausea. The ED team also obtained a 2-view abdominal plain radiograph that did not demonstrate any free air or obstruction. Given her uncontrolled pain and intolerance of oral liquids, the ED physician calls you to evaluate Aubree for admission.

Patient History and Review of Systems

Q: What information should you collect from Aubree and her caregivers?

When patients present with chronic and recurrent symptoms, it is particularly important to obtain a thorough history that includes questions about previous episodes as well as the current episode.

- History of present illness
  - Timing and circumstances surrounding onset of symptoms
  - Quality/description of pain
  - Location of pain: diffuse or localized, whether pain has occurred in the same location or migrates or radiates
  - Severity of pain: pain level on a 0 to 10 scale, impact on daily activities
  - Timing of pain: episodic or constant; if episodic, length of each episode, time of day, and whether there is spontaneous resolution, including whether abdominal pain is related to menstrual cycle
  - Aggravating/alleviating factors (eg, diet, activity, stooling, medications)
  - Changes in weight; time period over which change has occurred
  - Stooling characteristics, including frequency, consistency, color, and presence of blood
  - Genitourinary symptoms, including changes in discharge or presence of lesions
  - Exposure history, including recent travel or any sick contacts
  - Dietary changes or changes in food availability, including screening for food security

- Associated symptoms, such as fevers, oral ulcers, hemorrhoids, joint pain, skin lesions, eye symptoms, headaches, or fatigue
- Medical history, including surgical history, menstrual history, immunization status, and any previous workup for current symptoms
- Medications, including prescription medications, supplements, and over-the-counter (OTC) medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs])
- Family history, specifically noting gastroesophageal reflux disease, eosinophilic esophagitis, celiac disease, inflammatory bowel disease (IBD), liver disease, pancreatic disease, or autoimmune disease
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment with specific focus on sexual activity, history of sexually transmitted infections and related testing, history of drug use (noting any cannabis use) or alcohol use, screening for eating disorders, and psychosocial history (refer to Section VII in the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

From your conversation with Aubree and her mother, you learn that Aubree's pain first started about 4 months ago. She describes it as diffuse, crampy, burning at times, and intermittent in character. The pain does not move or radiate. She has daily episodes of pain lasting from 30 minutes to 2 hours. The pain usually self-resolves, but she occasionally takes calcium carbonate chews (2 chews several times per week) or acetaminophen (325 mg several times per week but not daily). These medications lead to minimal improvement in her abdominal pain. The episodes occur at random times of the day and can be worse after eating (especially fatty foods) but not always. She states that her pain ranges in severity from 5 to 8 on a scale of 10, but today her pain has been a 9 out of 10. The pain is not associated with her menstrual cycle. Occasionally the pain wakes her from sleep. She has missed extracurricular events because of her symptoms but denies that the pain is worse with activity. She has associated nausea and anorexia, and she has lost approximately 3 kg in the past 3 months. She occasionally has episodes of nonbloody, nonbilious emesis. In addition, she reports bloating and early satiety.

On further questioning, she has occasional constipation but usually has 1 soft, nonbloody stool per day. She does not have abdominal pain associated with stooling. Additionally, her pain is not relieved by defecation. She reports frontal headaches that first started a few months ago and occur 3 to 4 times per week in the afternoons. She has also experienced fatigue over the past few months despite getting adequate sleep. She denies fevers, visible blood in her stool, hemorrhoids, back pain, heartburn, burning sensation in the back of her throat, mouth lesions, joint pain, skin lesions, or eye symptoms. In addition, she has not traveled recently and denies exposure to sick contacts.

Aubree has been diagnosed with anxiety and attends counseling once per week. This has helped her cope with her anxiety. She is otherwise healthy, developing normally, and is fully immunized. She has not undergone any previous workup for her abdominal pain. She had menarche at age 12 and has regular menstruation once monthly, typically lasting 4 to 5 days with mild cramping the first few days. She does not have any genitourinary symptoms. She denies body dysmorphia or a desire to lose weight. She reports no significant recent diet changes, and she screens negative for food insecurity. She has never had any abdominal surgeries. There is no family history of intestinal, biliary, urinary, autoimmune, or gynecological diseases. In addition to the acetaminophen and calcium carbonate chews, she takes a daily multivitamin but no other regular medications. She denies intake of NSAIDs.

You speak to Aubree by herself to conduct a HEADSS assessment. Aubree lives at home with her mother, father, and 2 siblings. She feels safe at home and enjoys school. She denies alcohol or drug use. Aubree identifies as heterosexual and denies current or past sexual activity of any kind. She endorses some anxiety symptoms but denies depression or suicidal ideation.

Physical Examination

Q: What parts of the physical examination should you focus on for Aubree?

- Complete set of vital signs
- Weight, height, and review of growth curves (if available)
- Skin: pallor, rashes, jaundice, turgor
- Head, eyes, ears, nose, and throat
  - Appearance of eyes (eg, sunken, icteric, injected)
  - Appearance of oropharynx
  - Mucous membranes (moist or dry; ulcerations)
  - Parotid gland enlargement
- Lymphadenopathy
- Abdomen
  - Appearance: distention, bruising, scarring
  - Auscultation: quantity and quality of bowel sounds
  - Palpation: tenderness, masses, guarding, rebound tenderness, assessment of liver and spleen
  - Specific signs (Murphy, Rovsing, psoas, obturator), tenderness at the McBurney point (refer to Back to Basics: Abdominal Examination in Case 10 for descriptions of specific signs)
- Costovertebral angle tenderness
- Visual examination of stool (if possible)
- Rectal: tags, fissures, hemorrhoids
- Genitourinary: inspection, pelvic examination (depending on history and physical examination findings)

CASE FOCUS

Physical Examination

Aubree's vital signs show that she is afebrile (36.7 °C [98.1 °F]). Her heart rate (80 beats/min) and respiratory rate (14 breaths/min) are within normal limits. She has a normal blood pressure for age (98/68 mm Hg), and her oxygen saturation is 99% on room air. Her weight is 50 kg (40th percentile for age), her height is 163 cm (60th percentile for age), and her body mass index (BMI) is 18.8 (35th percentile for age and height).

On examination, Aubree is tearful. She appears anxious and tired but is cooperative with the examination. Her skin and mucous membranes appear pale. Her eyes are clear, with no conjunctival erythema or scleral icterus. Her oropharynx and tonsils are without erythema or lesions. She has good dentition with moist mucous membranes. She does not have parotid gland enlargement. She has no appreciable lymphadenopathy in the cervical, supraclavicular, axillary, or inguinal regions. She has a normal respiratory and cardiac examinations. Her peripheral pulses are normal, and her capillary refill time is 1 to 2 seconds.

Her abdomen appears slightly distended. On auscultation, she has normoactive bowel sounds. She denies tenderness to light palpation, and no masses or organomegaly are appreciated. She reports tenderness to deep palpation in the periumbilical and epigastric areas and states that lying flat and deep palpation make her feel nauseated. There is no rebound tenderness, increased tenderness, or guarding at the McBurney point. Additionally, the Murphy, Rovsing, psoas, and obturator signs are all negative. There is no appreciable costovertebral angle tenderness. The external anal examination shows no abnormalities. Her skin is examination is normal.

A genitourinary examination is not performed because Aubree denies sexual activity or genitourinary symptoms.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent with chronic diffuse abdominal pain, vomiting, and weight loss?

The differential diagnosis for an adolescent with chronic diffuse abdominal pain, vomiting, and weight loss is shown in Table 24.1 and is divided into causes that seem more and less likely based on Aubree's presentation.

Table 24.1. Differential Diagnosis for an Adolescent With Chronic Diffuse Abdominal Pain, Vomiting, and Weight Loss

Diagnoses of highest suspicion	• Abdominal migraine • Functional abdominal pain, NOS • Functional dyspepsia • Gastritis/PUD, including from *Helicobacter pylori*[a] • IBD • IBS
Other diagnoses to consider	• Cannabis hyperemesis syndrome • Carbohydrate malabsorption • Chronic pancreatitis • Dysmenorrhea • Eating disorder (anorexia nervosa, bulimia, binge-eating disorder) • Endometriosis • Esophagitis/GERD, including eosinophilic esophagitis • Food allergy or intolerance, including IgE-mediated, non-IgE mediated (FPIES), and celiac disease • Foreign body/bezoar • Gallstones/chronic cholecystitis/choledochal cyst • Hereditary angioedema • Malignancy (rhabdomyosarcomas, neuroblastoma, lymphoma, gastrinoma) • Malrotation with or without volvulus • Musculoskeletal (hernia, hematoma, anterior cutaneous nerve entrapment syndrome) • Nephrolithiasis • Ovarian cysts or masses • Parasitic infection (giardiasis) • PID • Pregnancy • Rumination syndrome • SMA syndrome • Ureteropelvic junction obstruction • Rare causes: heavy metal poisoning (lead), porphyria

Abbreviations: FPIES, food protein–induced enterocolitis syndrome; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IgE, immunoglobulin E; NOS, not otherwise specified; PID, pelvic inflammatory disease; PUD, peptic ulcer disease; SMA, superior mesenteric artery.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for adolescents who present with chronic abdominal pain and vomiting?

- The diagnostic evaluation should start by evaluating the patient's history and physical examination for any "red flags," which, if present, may indicate an underlying organic etiology and necessitate a more in-depth workup.
  - "Red flag" historical features include weight loss, chronic/profuse/persistent diarrhea and vomiting, blood in the stool, pain localized to the right upper or right lower quadrants, slow or delayed growth, odynophagia, dysphagia, unexplained fever, arthritis, and family history of IBD or celiac disease.
  - "Red flag" examination findings include delayed puberty, oral or perianal lesions, localized abdominal tenderness, or hepatosplenomegaly.
- If symptoms are severe and/or persistent, or red flags are present, further diagnostic evaluation is warranted. Aubree's persistent abdominal pain and history of weight loss indicate a diagnostic workup is warranted.
- When there are no red flags and patients present with less severe waxing and waning symptoms, a functional abdominal pain disorder may be suspected, and outpatient monitoring may be most appropriate. Functional disorders are a diagnosis of exclusion, and further evaluation may be needed based on clinical judgment of presenting history and physical findings. However, if there are no red flags, the physical examination is reassuring, and clinical suspicion for a functional disorder is high, further diagnostic investigation is usually not necessary.

BACK TO BASICS

Functional Abdominal Pain Disorders

Functional abdominal pain disorders are common in children and adolescents and should always be considered when evaluating chronic, recurrent abdominal pain. There are several specific disorders under this general diagnostic term, including functional dyspepsia, irritable bowel syndrome, abdominal migraine, and functional abdominal pain not otherwise specified. Management of functional abdominal pain disorders starts with validation of patient concerns and educating patients and families about the pathophysiology of the disorder. Treatment modalities for these disorders include trigger identification, behavioral health assessment, counseling, dietary management, pharmacotherapy, and neuromodulation via complementary tools. In addition, a focus should be placed on goal-setting and targeting of therapies to improve clinical symptoms and health care–related quality of life.

- Based on Aubree's history and physical examination, you are most suspicious about peptic ulcer disease (PUD)/gastritis. Presenting symptoms of PUD are often poorly localized abdominal or epigastric pain, bloating, waterbrash taste, flatus, and early satiety. This diagnosis can also be associated with weight loss. When PUD is suspected, the workup includes the following:
  - Stool tests for occult blood, as ulcers can be associated with gastrointestinal (GI) bleeding.
  - Complete blood cell count with manual differential and iron studies, to assess for iron-deficiency anemia.
  - Comprehensive metabolic panel to assess for electrolyte abnormalities, acid-base disturbances, and transaminase levels.
  - Lipase level, to assess for pancreatitis.

- Testing for *Helicobacter pylori* is not typically performed in acute/ED settings; however, it may be completed in the hospital depending on availability of outpatient resources.
  - Indications for *H pylori* testing are as follows:
    - Evidence of gastric or duodenal PUD (if visualized during endoscopy).
    - Documented history of PUD without previous treatment for *H pylori.*
    - Refractory or unexplained iron-deficiency anemia.
    - Chronic use of NSAIDS.
  - Upper endoscopy with biopsies for Gram stain and culture for *H pylori* is considered the standard of reference for diagnosis of *H pylori* disease. Noninvasive testing (eg, *H pylori* stool antigen assay, urea breath test) is not recommended for the initial diagnosis of *H pylori,* except in cases where the patient would not otherwise require endoscopy (eg, when investigating causes of chronic immune thrombocytopenic purpura).
    - At least 6 biopsy specimens from the antrum and body of the stomach should be collected for the diagnosis of *H pylori*. A positive culture has 100% specificity for the diagnosis.
    - Alternatively, a combination of *H pylori* histopathologic findings *and* an additional biopsy-based test (eg, rapid urease, polymerase chain reaction [PCR]/fluorescence in situ hybridization) can confirm the diagnosis.
- In certain clinical scenarios, additional testing may be considered.
  - Pregnancy and ovarian masses can both present with bloating, nausea, vomiting, constipation, urinary frequency, or urinary retention. Therefore, a urine test for human chorionic gonadotropin should be obtained for any adolescent girl with concerning symptoms, regardless of reported sexual history. Additionally, pelvic ultrasonography should be considered for ovarian masses when suspected.
  - Presenting symptoms of IBD commonly include colicky abdominal pain, diarrhea (with or without blood), urgency, tenesmus, incontinence, weight loss, or poor growth. Patients may also have systemic symptoms (eg, fever, fatigue, perianal lesions, weight loss). In addition, extraintestinal symptoms may include joint pain, rashes, mouth sores, and symptoms of uveitis. If IBD is suspected, additional diagnostic testing may include a fecal calprotectin test, stool cultures or pathogen panel, stool staining for ova and parasites, GI pathogen PCR panel, stool PCR/antigen test for *Clostridioides difficile*, serum inflammatory markers, magnetic resonance enterography, and endoscopy and colonoscopy with biopsies. Consultation with a pediatric gastroenterologist can help guide the patient's diagnostic evaluation.
  - Superior mesenteric artery (SMA) syndrome is an unusual but important diagnosis on the differential. SMA syndrome is caused by compression of the third portion of the duodenum after loss of the mesenteric fat pad leads to narrowing of the space between the SMA and the aorta. This compression results in proximal intestinal obstruction. Rapid, significant weight loss is a common risk factor for this syndrome. SMA syndrome is often a diagnosis of exclusion but may be suggested by findings on abdominal radiographs or an upper GI series. Abdominal radiographs may demonstrate evidence of small bowel obstruction. An upper GI series with oral contrast may demonstrate a delay in passage of contrast from the duodenum into the distal small bowel.

CASE FOCUS

Diagnostic Evaluation

You first review the results of the laboratory tests obtained in the ED, which are as follows:

Laboratory test	Result	Reference range
CBC		
Hemoglobin	9 g/dL (90 g/L)	12–15 g/dL (120–150 g/L)
Hematocrit	28% (0.28)	35%–45% (0.35–0.45)
WBC count	6,000/μL (6×10^9/L)	4,000-10,500/μL ($4.0–10.5 \times 10^9$/L)
Platelet count	190×10^3/μL (190×10^9/L)	$150–400 \times 10^3$/μL ($150–400 \times 10^9$/L)
MCV	73 μm^3 (73 fL)	78–95 μm^3 (78–95 fL)
Other		
Fecal occult blood	Positive	Negative
Urine hCG	Negative	Negative

Abbreviations: CBC, complete blood cell count; hCG, human chorionic gonadotropin; MCV, mean corpuscular volume; WBC, white blood cell.

The 2-view abdominal plain radiograph does not reveal any free air, air fluid levels, or significant stool burden.

Arriving at a Diagnosis

Q: How do you develop an assessment for Aubree?

As you think through Aubree's case, you decide to review and interpret key elements of her history, physical examination and diagnostic workup.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Aubree's history is significant for chronic intermittent diffuse abdominal pain; nausea; occasional nonbloody, nonbilious emesis; bloating; early satiety; and recent 3 kg weight loss. Pertinent historical negatives include lack of fevers, hematochezia, mouth sores, arthritis, heartburn, genitourinary symptoms, cannabis use, and sexual activity.
   - Physical examination: Aubree's examination is significant for mild pallor and periumbilical and epigastric tenderness. Aubree appears well nourished on examination, and her BMI is in the 35th percentile; however, according to her reported 3 kg weight loss, she has lost 5.7% of her body weight. This degree of weight loss indicates mild malnutrition. Pertinent examination negatives include no evidence of localized abdominal pain, mouth/anal abnormalities, lymphadenopathy, or rashes.
   - Diagnostic evaluation: Aubree's complete blood cell count reveals microcytic anemia. She also has positive occult blood in her stool. Microcytic anemia in the setting of positive occult blood in stool is suspicious for a slow GI bleed. Her 2-view abdominal plain radiograph without free air or significant stool burden indicates low suspicion for bowel obstruction, perforation, or constipation.

2. **Develop the list of findings.**

Q: What major findings have you identified for Aubree?

- Acute worsening of chronic abdominal pain
- Nausea and nonbloody, nonbilious vomiting (intermittent)
- Weight loss/concern for mild undernutrition
- Intestinal blood loss
- Microcytic anemia

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Aubree's presentation?

Aubree has been having abdominal pain and GI issues for several months. The chronicity of her symptoms and the evidence of intestinal bleeding point toward PUD, with the possibility of *H pylori* infection. To confirm the diagnosis, she will need an upper endoscopy with biopsies.

Q: How does PUD typically present?

PUD is more common in adults, but its incidence in children is clinically significant. Presenting symptoms of PUD often vary by age. Younger children can present with irritability, vomiting, hemorrhage, and perforation, whereas older children and adolescents typically present with epigastric pain or diffuse abdominal pain, bloating, gas, nausea, and nocturnal awakenings due to pain.

Q: What causes PUD?

Peptic ulcers are a result of inflammation that leads to defects of the muscularis mucosae. The most common causes of peptic ulcers are medications (eg, NSAIDs, high-dose corticosteroids) and *H pylori* infection. Less common causes include hypersecretory states (Zollinger-Ellison syndrome), IBD, systemic mastocytosis, chronic renal failure, and hyperparathyroidism.

Aubree does not have a history of NSAID use. This raises your suspicion for *H pylori* infection as the cause of her symptoms. *H pylori* is a gram-negative bacillus that can cause a range of clinical findings from benign colonization to ulcers, gastric adenocarcinoma, and gastric lymphoma. *H pylori* is transmitted via the fecal-to-oral or oral-to-oral route, and the incidence of *H pylori* infection increases with age.

Q: What are possible complications of PUD?

PUD can lead to serious and even fatal complications if left untreated or detected late in the course. These complications can include intestinal perforation, hemorrhage, or gastric outlet obstruction. Patients experiencing complications of PUD may present with peritonitis, hematemesis, melena, or symptoms of anemia (fatigue, headaches, syncope). Although Aubree does have signs of an active slow GI bleed, she does not have signs of these more serious complications of PUD at this time.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with suspected PUD?

Most patients with PUD can be managed in the outpatient setting and do not require inpatient admission. There are, however, some instances when a patient may benefit from hospital admission, including the following:

- The patient's pain cannot be controlled at home with OTC medications.
- The patient is experiencing intractable vomiting or cannot maintain oral hydration.
- There is evidence of significant GI bleeding.
- The patient has signs of significant volume depletion or electrolyte disturbances.

Aubree meets the criteria for hospitalization based on her worsening abdominal pain, which was not controlled with OTC medications.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Aubree is a 15-year-old otherwise healthy girl who is here with fecal occult blood-positive stool, microcytic anemia, and mild undernutrition in the setting of 4 months of abdominal pain, likely due to PUD. Her pain has not been controlled at home with OTC medications, and she continues to have pain in the ED. She requires admission for further evaluation, including upper endoscopy and symptomatic treatment of her pain and nausea.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

After reviewing the literature regarding PUD management, you divide your treatment considerations into the following categories:

1. **Symptom management**
   - Pain management: For most patients presenting with PUD, pain control can be achieved with acetaminophen; however, severe pain may require the short-term use of opioids. It is important to avoid the use of NSAIDs, as they can cause further gastric irritation and mucosal breakdown.
   - Nausea: Ondansetron can be given for nausea and vomiting.
   - Hydration: Patients with PUD may develop dehydration (as a result of poor oral intake), nausea, and vomiting. Given Aubree's history of vomiting and her need to be nil per os (nothing by mouth) prior to endoscopy, she will need IV fluid hydration until she is able to maintain oral hydration after her procedure.
2. **Further diagnostic workup:** In patients with signs and symptoms suspicious for PUD, upper endoscopy with biopsies is indicated to confirm the diagnosis. This procedure is generally performed by a pediatric gastroenterologist. Aubree meets the criteria for endoscopy given her constitutional symptoms (abdominal pain, weight loss, fatigue, headache) and evidence of upper GI bleed. Preparation for upper endoscopy requires nothing by mouth for 8 hours prior to her endoscopy.
3. **Acid suppression:** Acid suppression facilitates ulcer healing in patients with PUD. When ulcerative disease is present, proton pump inhibitors (PPIs) are more effective and have fewer side effects than H2-receptor antagonists. Treatment with PPIs should be delayed, however, until after endoscopy is completed, because their administration can lead to false negative *H pylori* test results secondary to suppression of bacterial replication. PPIs should be started via IV in hospitalized patients and transitioned to oral formulation once patients are tolerating oral intake. The duration of treatment will vary depending on findings on endoscopy, but with appropriate treatment, most patients experience resolution of ulcers within 4 to 8 weeks. There are studies that show increased incidence of fractures, *C difficile*, chronic kidney disease, and GI infection with long-term use of PPIs in adults, but further studies need to be performed in children and adolescents. Given her symptoms, Aubree will most likely need to be started on an IV PPI following her endoscopy and then transitioned to an oral PPI as tolerated.

4. **Treatment of *H pylori* infection:** Patients with biopsies suspicious or confirmatory for *H pylori* should be started on treatment to eradicate the infection. Patients in which *H pylori* has been successfully treated have higher healing rates and lower PUD recurrence. Treatment should be based on culture results and local susceptibilities. If Aubree's endoscopic biopsies indicate that she has an *H pylori* infection, treatment should be initiated.
   - If there is no local resistance to clarithromycin or metronidazole, Aubree can be started on either
     - Amoxicillin and clarithromycin for 14 days.
     - Amoxicillin for 5 days, followed by clarithromycin and metronidazole for 5 days.
   - If there is local resistance to clarithromycin, she can be started on amoxicillin and metronidazole for 14 days.
   - If there is local resistance to clarithromycin and metronidazole, high-dose amoxicillin may be added.
   - Post-treatment *H pylori* eradication testing is performed with urea breath test or stool antigen at least 4 weeks after completion of therapy. It is important to note, however, that the use of PPIs or bismuth subsalicylate (eg, Pepto-Bismol) can affect the results of both tests and should be held prior to post-treatment eradication testing.
5. **Nutrition:** Patients with malnutrition should be seen by a registered dietician while hospitalized. Aubree's history of recent weight loss is concerning for undernutrition. Because of this, she should be seen by a registered dietitian for nutritional assessment. Growth curves from her primary care provider should be obtained, if possible. Further workup for malnutrition should be considered, including a comprehensive metabolic panel, trace mineral levels, and prealbumin.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment of pain:** You order scheduled oral acetaminophen for pain while Aubree is hospitalized. You anticipate rapid treatment of PUD will help alleviate her pain, but she may require short-term opioid use if her pain is not controlled by scheduled acetaminophen alone.
- **Hydration and vomiting:** You order that Aubree remain nil per os in preparation for endoscopy, and you order maintenance IV fluids with ondansetron as needed.
- **Acid suppression:** You order an IV PPI until Aubree is able to tolerate oral intake after her procedure.
- **Nutrition evaluation:** You order a nutrition consult to evaluate Aubree's nutritional status further. In addition, you will call Aubree's primary pediatrician to obtain her growth charts.
- **Consultations and further diagnostic testing:** You consult a gastroenterologist and plan for an esophagogastroduodenoscopy in the morning.

Case Resolution

Aubree undergoes an esophagogastroduodenoscopy the morning after admission and is found to have generalized gastritis and numerous small ulcers in her stomach and duodenum. Over the next 2 days, Aubree's pain improves, as does her appetite. She is preparing for discharge home with omeprazole when her biopsy results return positive for *H pylori*, and thus double antibiotic therapy with amoxicillin and clarithromycin is added to her discharge medications.

Discharge Criteria

Q: How do you know when Aubree is ready to go home?

Children and adolescents admitted with PUD without serious complications (perforation, hemorrhage, significant symptomatic anemia) usually do not require prolonged hospitalization. You can feel comfortable discharging your patient with PUD with an oral PPI and treatment regimen for *H pylori* (if positive) when the following criteria are met:

- The patient is tolerating adequate oral intake.
- Pain and nausea/vomiting are controlled with oral medications.
- There is no evidence of significant ongoing GI bleeding.
- There are no significant electrolyte derangements.

Anticipatory Guidance

Q: What instructions should you provide to Aubree's caregivers upon discharge?

- Pain should begin to improve upon initiation of a PPI and *H pylori* medications but can be also managed with acetaminophen as needed. Nausea can be managed with ondansetron as needed.
- Return to care for persistent vomiting, vomiting of blood, black or tarry stool, signs of dehydration, or acute, severe worsening of abdominal pain.
- Follow up with Aubree's primary care physician in 1 to 2 weeks. Follow up with a GI specialist for monitoring of medications and symptoms and to determine if noninvasive posttreatment testing for *H pylori* is indicated.

Clinical Pearls

- In a child or adolescent with chronic, recurrent abdominal pain and red flags on history (eg, constitutional symptoms, vomiting, blood in stool or emesis) or physical examination (eg, localized pain, delayed puberty, deceleration in linear growth, oral aphthous ulcerations), always consider additional evaluation for organic disorders.
- Functional abdominal pain disorders may be suspected when there are no red flags and the patient's pain is less severe and intermittent. These disorders are a diagnosis of exclusion, and further workup may be warranted based on history and physical examination findings.
- The reference standard for the diagnosis of *H pylori* disease is an upper endoscopy with biopsies for Gram stain and culture.
- SMA syndrome should be considered in patients with rapid, significant weight loss.

Documentation Tips

- In patients with weight loss, document the presence and severity of malnutrition.
- Document complications, including hemorrhage or perforation.
- When known, document the underlying etiology (eg, NSAIDs, high-dose corticosteroids, *H pylori* infection).

Suggested Reading

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CASE 25

Andy, a 9-Year-Old Boy With Respiratory Distress and Vomiting

CASE PRESENTATION

Andy is a 9-year-old boy with intermittent asthma who is brought to the emergency department (ED) by emergency medical services with acute-onset cough; shortness of breath; nonbloody, nonbilious emesis; and what his parents describe as "loud breathing." His symptoms started shortly after his arrival home from school and were not relieved by albuterol treatments by his parents or those given in the ambulance. In the ED, Andy receives a normal saline bolus, intravenous (IV) steroids, 2 nebulized albuterol treatments, and 1 dose of intramuscular (IM) epinephrine. His symptoms improve with these treatments; however, he is noted to have hypotension and persistent tachypnea and increased work of breathing. The ED physician orders another normal saline bolus and calls you to assess Andy for admission.

Patient History and Review of Systems

Q: What information should you collect from Andy and his caregivers?

- History of present illness
  - Significant preceding symptoms or events prior to symptom onset
  - Description of "loud breathing"
  - Risk for or history of foreign body aspiration
  - History of allergic reactions to medications and/or foods
  - Dietary intake in the hours prior to symptom onset, especially consumption of any possible or known allergens
  - Possible ingestion of nonfood substances
  - Exposure to environmental allergens such as pollen, dust, or cut grass
  - Insect bites or stings in the hour prior to symptom onset
- Associated symptoms, such as fever, cough, congestion, rash, nausea, flushing, or dizziness
- Medical history, including underlying health status, history of similar events, and detailed asthma history, including number and severity of exacerbations, steroid courses, and frequency of rescue inhaler use
- Medications, including recent use of antibiotics and over-the-counter medications

CASE FOCUS

History and Review of Systems

From speaking with Andy and his family, you learn that Andy was seen in a different ED more than 2 years ago for an asthma exacerbation. Since then, his asthma symptoms have been well controlled, and he rarely uses his rescue albuterol inhaler. He is allergic to almonds, which have caused an itchy full-body rash in the past. Because of this, Andy avoids all tree nuts.

Andy reports that prior to the onset of his current respiratory symptoms, he shared a candy bar with his friend on the bus coming home from school. He does not remember the name of the candy bar but states that he has never had this particular candy bar before. He and his family deny any other potential allergen exposure including foods, environmental allergens, or insect bites or stings. The bus ride home from school usually takes about 30 to 45 minutes. On arrival home, he noticed an itchy throat, had multiple episodes of vomiting, and began to cough and feel short of breath. His parents noted his "loud breathing," which they describe as a harsh vibrating noise when breathing. His family gave him an albuterol treatment without relief. They called emergency medical services because of how quickly his breathing was worsening.

Andy's family denies any preceding symptoms of illness including fever, congestion, or cough. They have not had any known sick contacts. They also deny any new stressors at home or at school, and Andy notes that he had an uneventful day at school that day. Andy says he has not taken any medications, drugs, or unknown substances and that he did not choke on any foreign bodies. Aside from his history of asthma, for which he uses albuterol as needed, Andy has no other chronic medical conditions. The family states that all prescription medications are locked at home.

Physical Examination

Q: What parts of the physical examination should you focus on for Andy?

- Complete set of vital signs
- Level of consciousness, ability to arouse normally, and obvious signs of distress
- Respiratory: tracheal deviation, rate and depth of respirations, accessory muscle use, auscultation for breath sounds and air movement, noting the presence of wheezing, stridor, grunting, or stertor
- Cardiac: rate and rhythm; point of maximal impulse (PMI); presence of murmurs, gallops, or rubs
- Peripheral perfusion: capillary refill time, temperature of extremities, quality of peripheral pulses
- Head, ears, eyes, nose, and throat: edema of the face, lips, or tongue; mucous membranes (moist, sticky, or dry)
- Abdomen: auscultation for bowel sounds; palpation for diffuse, focal, or rebound tenderness; organomegaly; signs of hernias or other abdominal wall protrusions
- Skin changes, including rashes or flushing

CASE FOCUS

Physical Examination

Andy's vital signs show that he is afebrile with a temperature of 36.6 °C (97.9 °F), tachycardic (resting heart rate: 140 beats/min while sitting up calmly), and tachypneic (respiratory rate between 40 and 50 breaths/min). His oxygen saturation is 95% on room air, and his blood pressure is 75/60 mm Hg.

On physical examination, Andy is sitting up in bed. He is alert and oriented to his surroundings and situation. He is flushed and appears to be in mild respiratory distress. You notice mild audible stridor and an intermittent dry cough. Examination of his head, eyes, ears, nose, and throat is unremarkable with no facial or oral edema noted. His oropharynx is clear with no evidence of erythema or exudate, and you do not visualize any airway obstruction. His mucous membranes are moist. On cardiovascular examination, Andy is tachycardic but otherwise has a normal rhythm with no rubs or gallops. His respiratory examination finds mild inspiratory stridor and moderately increased work of breathing, with tachypnea and subcostal and intercostal retractions. On auscultation, you hear expiratory wheezing diffusely but good air movement throughout his lung fields.

Andy's hands and feet are warm, his peripheral pulses are normal, and his capillary refill time is brisk. Examination of his abdomen is significant for hyperactive bowel sounds, but his abdomen is otherwise soft and nontender with no notable masses or organomegaly. Other than his flushed cheeks, no other rashes or lesions are found on a full skin examination. The remainder of his examination is normal, including a nonfocal neurological examination.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with acute onset of respiratory distress?

The differential diagnosis for a child with acute onset of respiratory distress is shown in Table 25.1 and is divided into causes that seem more and less likely based on Andy's presentation.

Table 25.1. Differential Diagnosis for a Child With Acute Onset of Respiratory Distress

Diagnoses of highest suspicion	• Anaphylaxis[a] • Angioedema • Asthma exacerbation • Croup • Foreign body aspiration • Lower respiratory tract infection (viral or bacterial)
Other diagnoses to consider	• Epiglottitis • Esophageal perforation • Hemothorax • Inhalational injury • Myocardial dysfunction or arrhythmia • Panic or anxiety attack • Pneumothorax • Pulmonary artery hypertension • Pulmonary embolism • Pulmonary hemorrhage • Vocal cord dysfunction

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with sudden onset of respiratory distress?

- As illustrated by the differential diagnosis, respiratory distress can be the presenting symptom for a broad range of conditions. For patients whose symptoms have no clear etiology after history and physical examination, upright 2-view chest radiography is useful. Additional imaging may follow depending on specific clinical concerns. When there is concern for impending or acute respiratory failure, an arterial, capillary, or venous blood gas test can be useful to evaluate adequacy of ventilation (and oxygenation, if arterial). Additionally, if there is concern for cardiac dysfunction or arrhythmia, an electrocardiogram with or without an echocardiogram and serum cardiac markers can be obtained.
- Refer to Table 25.2 for a list of clinical scenarios and their possible diagnostic evaluation.

Table 25.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Acute Onset of Respiratory Distress

Diagnosis	Possible clinical features	Diagnostic evaluation to consider
Anaphylaxis	Acute onset of symptoms following exposure to a known or suspected allergen. Symptoms include a combination of respiratory, gastrointestinal, cutaneous, or cardiovascular findings.	The diagnosis is clinical. Serum tryptase can be obtained if the diagnosis is in question, but results may take a number of days. Elevations of serum tryptase are not specific to anaphylaxis.
Angioedema	Edema of the larynx, oral mucosa, skin, or gastrointestinal tract	Ensure that the patient is not taking an ACE inhibitor. Serum tryptase level can identify an acute allergic process; allergy testing can be done on an outpatient basis. If there are concerns for hereditary angioedema, specific testing can be performed that may include complement studies and genetic testing.
Asthma exacerbation	Dyspnea, cough, tachypnea, expiratory or inspiratory wheezing, prolonged expiratory phase; decreased air entry and hypoxemia are common.	Diagnosis is usually clinical. Spirometry or peak flow can be employed, but they are usually not indicated in the acute setting. Consider chest radiograph in certain situations. Pediatric asthma scores can help assess severity and guide management (see Case 6).
Foreign body aspiration	Cough, tachypnea; distal airway foreign bodies may demonstrate focal area of diminished air entry of wheezing; laryngeal foreign bodies may present with stridor; recollection of choking episode is variable.	Inspiratory anteroposterior and lateral plain radiographs of neck and frontal chest radiograph to visualize radiopaque objects or signs of airway obstruction including hyperinflation, atelectasis, mediastinal shift, or pneumonia (distal to the obstructed airway). In younger children, bilateral lateral decubitus views may be required to demonstrate the presence of air trapping on the side of obstruction.

Table 25.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Acute Onset of Respiratory Distress *(continued)*

Diagnosis	Possible clinical features	Diagnostic evaluation to consider
Lower respiratory tract infection, including pneumonia	Onset of cough and tachypnea over hours to days Viral etiologies are most common in infants and young children. Upper respiratory tract symptoms and diffuse pulmonary findings are common. For typical bacterial etiologies, focal pulmonary findings and fever are common.	The diagnosis is clinical. Chest radiograph can be useful to confirm or rule out the suspected diagnosis as well as evaluate for possible complications.
Myocardial dysfunction (eg, viral myocarditis)	Symptoms of preceding or concomitant viral illness; most commonly a subacute presentation with malaise or fever prior to the onset of dyspnea, tachypnea, and tachycardia; a more fulminant, rapidly progressive course is possible.	ECG to assess rhythm; chest radiograph to assess cardiac silhouette; echocardiogram to assess anatomy and function; serum troponin and BNP levels
Pulmonary embolism	Variable presentation; acute onset of cough, dyspnea, pleuritic chest pain, tachypnea, tachycardia, and hypoxemia	Assess for coagulopathy risk; if low risk, consider D-dimer to further stratify. CT pulmonary angiography is the most sensitive diagnostic test. Wells score is not typically useful in children.
Vocal cord dysfunction	Respiratory distress, throat tightness, stridor; can be present in children with asthma and complicate their response to standard treatment	Laryngoscopy; pulmonary function tests

Abbreviations: ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; CT, computed tomography; ECG, electrocardiogram.

CASE FOCUS

Diagnostic Evaluation

For Andy, you decide no diagnostic evaluation is needed in this acute setting.

Arriving at a Diagnosis

Q: How do you develop an assessment for Andy?

In thinking through his case, you first decide to assess the stability of Andy's airway, breathing, and circulation. You then interpret this history, vital signs, and physical examination findings to develop a finding list that aids in narrowing your differential diagnosis to the most likely etiology. Afterward, admission criteria can be generated for your specific diagnosis.

1. **Assess airway, breathing, and circulation.**
   - Symptoms concerning for airway obstruction or impending respiratory failure may include inadequate respiratory effort, worsening stridor, or a change in level of consciousness. These symptoms may indicate the need for urgent intubation to protect the airway from obstruction and edema. Needle cricothyrotomy may be necessary if intubation is unsuccessful.
     - Andy is clearly demonstrating respiratory distress with tachypnea and some signs of upper and lower airway obstruction; however, he is maintaining appropriate oxygen saturation on room air and has good air movement on auscultation.
     - Based on your assessment of Andy's respiratory status, you decide to hold off on oxygen support and intubation for the time being.
   - Andy's most recent blood pressure reading is 75/60 mm Hg. Referring to Table 25.3, at an age of 9 years, Andy should have a minimum systolic blood pressure reading of 88 mm Hg; therefore, his current blood pressure classifies Andy as having hypotension.

Table 25.3. Hypotension, as Defined by Age

Age	Minimum systolic blood pressure (mm Hg)
Term neonate (0–28 days)	60
Infant (1–12 months)	70
Child (1–10 years)	70 + (2 × age in years)
Older than 10 years	90

2. **Interpret key findings from the history and examination.**
   - History: Andy's history is significant for rapid onset of respiratory distress and vomiting after ingestion of an unknown candy bar on the bus ride home from school. Andy has a known history of almond allergy and asthma. His symptoms did not improve with treatment of albuterol. All of this is concerning for anaphylaxis.
   - Physical examination: Andy's vital signs show hypotension and tachycardia, and his examination shows that he has evidence of respiratory distress with both stridor and wheezing; however, he appears to be oxygenating and ventilating appropriately and does not need emergent airway intervention.
3. **Develop the list of findings.**

Q: What major findings have you identified for Andy?

- Respiratory distress
- Stridor and wheezing
- Hypotension
- Vomiting
- Tachycardia
- History of asthma and almond allergy

4. Revisit the differential diagnosis.

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Andy's presentation?

- Severe asthma exacerbations can include vomiting as a symptom, and hypotension can be seen from albuterol toxicity; however, you are less suspicious for an asthma exacerbation given the presence of stridor and Andy's lack of response to multiple albuterol treatments and IV corticosteroids. A lower respiratory tract infection is less likely given his lack of fever and the fulminant onset of his symptoms. Additionally, an airway foreign body seems less likely given a lack of choking and the combination of upper and diffuse bilateral lower airway symptoms.
- With these etiologies eliminated, you conclude that anaphylaxis is the most likely cause of Andy's symptoms given the rapid onset and involvement of 3 organ systems (gastrointestinal, respiratory, and cardiac) in the setting of a suspected exposure to a known allergen. Refer to Box 25.1 for the diagnostic criteria for anaphylaxis.

Box 25.1. Diagnostic Criteria for Anaphylaxis

Anaphylaxis is likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritis or flushing, swollen lips-tongue-uvula) *and* at least one of the following:
   a. Respiratory compromise
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction such as hypotonia, syncope, or incontinence
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient:
   a. Involvement of the skin-mucosal tissue
   b. Respiratory compromise
   c. Reduced blood pressure or associated symptoms
   d. Persistent gastrointestinal symptoms
3. Reduced blood pressure after known allergen exposure as demonstrated by either of the following findings in infants and children:
   a. Low systolic blood pressure for age
   b. Greater than 30% decrease in baseline systolic blood pressure

Adapted with permission 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.

- Based on Box 25.1, you find that Andy meets criteria number 2 for anaphylaxis because he presented with (1) respiratory compromise as illustrated by his tachypnea, wheezing, and stridor; (2) hypotension; and (3) persistent gastrointestinal symptoms (vomiting) within 1 hour after eating a new candy bar that is likely to contain the implicated allergen. As demonstrated in Table 25.4, urticaria and angioedema are the most common symptoms of anaphylaxis, but these symptoms are not required for the diagnosis.

Table 25.4. Frequency of Signs and Symptoms of Anaphylaxis

Symptom	Frequency (%)
Cutaneous	
• Urticaria and/or angioedema	85–90
• Flushing	45–55
• Pruritus without rash	2–5
Respiratory	
• Dyspnea, wheeze	45–50
• Upper airway edema	50–60
• Rhinitis	15–20
Cardiovascular	
• Dizziness, syncope, hypotension	30–35
Gastrointestinal	
• Nausea, vomiting, diarrhea, cramping	25–30
Miscellaneous	
• Headache	5–8
• Substernal pain	4–6
• Seizure	1–2

- Food allergens account for 30% of fatal cases of anaphylaxis. The most commonly implicated foods are peanuts, tree nuts, fish, shellfish, cow milk, soy, and egg. Given that Andy has had an allergic reaction to almonds in the past, his risk of other tree nut allergies is higher. Tree nuts include pecans, walnuts, macadamia nuts, cashews, Brazil nuts, pistachios, and hazelnuts.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with anaphylaxis?

- Because of the risk of biphasic reactions, a minimum observation period of 4 to 6 hours after treatment of anaphylaxis is advised. Overall, biphasic reactions can occur in 1% to 23% of cases of anaphylaxis and tend to occur within 8 to 10 hours after the treatment that resulted in resolution of the initial symptoms. However, biphasic manifestations can occur up to 72 hours after initial symptoms. In biphasic reactions, initial presenting symptoms recur and are often more severe.
- Patients with signs of hypotension, airway obstruction, or respiratory distress should be admitted for close monitoring and continued management.
- Patients who require multiple doses of epinephrine for protracted symptoms should be observed for a longer period, as they are at higher risk for biphasic reactions. However, there is no consensus for the minimum period of observation, as this should be tailored to each patient.

You determine that Andy meets the criteria for hospital admission based on the presence of hypotension and respiratory distress 45 minutes after IM epinephrine was administered.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Andy is a 9-year-old boy with a medical history significant for intermittent asthma and almond allergy who presented to the ED with anaphylaxis shortly after suspected allergen exposure. He remains hypotensive and in respiratory distress after 1 dose of IM epinephrine, nebulized albuterol, and dexamethasone, but his symptoms have notably improved since presentation. He requires admission to the inpatient pediatric unit for further treatment and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The acute management of anaphylaxis is primarily focused on immediate stabilization of the patient's respiratory and cardiovascular status, monitoring for symptom recurrence, providing education for allergen avoidance, and developing an outpatient management plan. You decide to divide your treatment and monitoring plan into the following components:

6. **Stabilization of airway, breathing, and circulation:** Airway protection in the form of intubation may be necessary if laryngeal edema compromises the airway. Isotonic IV fluid boluses should be considered in the setting of persistent hypotension after the administration of epinephrine. Although Andy is demonstrating some signs of respiratory distress with wheezing and stridor, you decide that his airway is protected and that he is ventilating appropriately on room air. However, given his hypotension, you order another normal saline bolus.
7. **Administration of epinephrine:** Immediate administration of IM epinephrine is the treatment of choice for anaphylaxis. The IM epinephrine should be administered to the anterolateral thigh and can be given every 5 minutes as needed until symptoms improve. The use of epinephrine during anaphylaxis has been shown to decrease mortality, morbidity, and the incidence of biphasic reactions. A delay in administration of epinephrine is an important risk factor for death and is seen in 80% to 87% of fatal cases. Given Andy's hypotension and respiratory symptoms, you decide to administer another dose of IM epinephrine.
8. **Removal of inciting allergen(s):** In the case of a suspected medication allergy, discontinuing the culprit is important. For suspected food allergies, counseling on future avoidance of the allergen as well as potential for cross-reactivity is important. For Andy, you plan to enter both "almond" and "tree nut" allergies into the electronic medical record to avoid accidental exposure.
9. **Adjunct therapies:** Adjunct therapies such as histamine blockers, inhaled bronchodilators, and steroids should only be considered after the patient has been stabilized and IM epinephrine has been administered. These medications can be used to help alleviate symptoms during hospitalization such as pruritus, urticaria, angioedema, wheeze, cough, and dyspnea; however, there is no evidence that these medications reduce the incidence of biphasic reactions or decrease the patient's risk of death.
    - Histamine H1-receptor antagonists such as diphenhydramine can be helpful with continued cutaneous symptoms of anaphylaxis such as urticaria or pruritis when present. Histamine blockers such as famotidine and ranitidine can theoretically help with gastrointestinal symptoms; however, these are considered second-line therapies, as they have no role in the acute treatment of cardiopulmonary compromise.

- Inhaled bronchodilators such as albuterol can be used for bronchospasm refractory to epinephrine.
- There is a lack of evidence about the role of steroids in the treatment of anaphylaxis, although theoretically steroids may help decrease the risk or severity of biphasic reactions.
- For Andy, you decide to order nebulized albuterol to help with his wheezing. You also order a dose of dexamethasone.

10. **Monitoring:** It is important to monitor vital signs including blood pressure and pulse oximetry closely in patients with anaphylaxis until symptoms have resolved. Reassessment of the patient's airway, breathing, and circulation as well as response to treatment is important to detect a biphasic reaction.
11. **Consultations:** Suspected allergens causing anaphylaxis should be confirmed with allergen testing done by an allergist as an outpatient.
12. **Discharge planning:** Discharge planning for patients hospitalized due to anaphylaxis should include the following:
    - Prescription for epinephrine autoinjector (eg, EpiPen) and instruction on its use.
    - Education about avoidance of triggers and what symptoms would necessitate administration of epinephrine.
    - A written anaphylaxis emergency management plan provided to the family, which should include the common signs and symptoms of anaphylaxis as well as instructions on how to administer epinephrine.
    - For Andy, you advise avoidance of all tree nuts until allergy testing can be performed on an outpatient basis.

CASE FOCUS

Plan for Treatment and Monitoring

- **Airway, breathing, and circulation:** To improve Andy's respiratory and circulatory status, you immediately initiate the following orders:
  - IM epinephrine to be administered immediately and repeated every 5 minutes as needed for persistent respiratory symptoms and hypotension. If Andy's anaphylaxis is not resolving with use of IM epinephrine, he may require the initiation of an epinephrine drip and transfer to the pediatric intensive care unit.
  - Oxygen as needed to maintain saturations above 92%.
  - IV isotonic fluid bolus of 20 mL/kg.
- **Adjunct therapies:** Because Andy does not have urticaria or pruritus, you do not order any antihistamines at this time; however, you do decide to provide an albuterol treatment concurrent with administration of epinephrine and order an additional dose of IV dexamethasone.
- **Monitoring:** You order hourly reassessment of Andy's airway, breathing, and circulation and vital sign monitoring, with blood pressure measurements, until Andy is stable. You also order continuous pulse oximetry to assess Andy's oxygenation and strict monitoring of intake and output to assess his fluid status and renal function.
- **Removal of suspected allergen:** You enter almond and tree nut allergies into Andy's electronic medical record as guidance for when he is able to resume his diet.
- **Determining etiology:** You order referral to an outpatient allergist for allergen testing on discharge.
- **Discharge planning:** You prescribe an epinephrine autoinjector. Ideally, this medication should be in hand prior to discharge. You also plan to provide education on anaphylaxis and trigger avoidance and will create an anaphylaxis plan for home and school.

Case Resolution

After administration of a normal saline bolus, another dose of IM epinephrine, and an albuterol treatment, Andy's blood pressure and respiratory status improve. He is observed overnight and does well during that time, with no evidence of symptom recurrence. The following morning, he is discharged home after he and his family are provided with education about allergen avoidance, the signs of anaphylaxis, and the use of his epinephrine autoinjector. In addition, a written anaphylaxis emergency management plan is developed and reviewed with Andy and his family. Andy has his new epinephrine autoinjector in hand before discharge, and his family is provided with a referral to an allergist for further testing.

Discharge Criteria

Q: How do you know when Andy is ready to go home?

You can feel comfortable discharging your patient with anaphylaxis when the following criteria are met:

- There is resolution or notable improvement of symptoms.
- The patient is hemodynamically stable.
- There are no signs of respiratory distress or airway compromise.
- A reasonable period of observation is completed without recurrence of symptoms. The time interval between the initial reaction and the onset of biphasic reaction symptoms ranges from 1 to 72 hours; however, most biphasic reactions are shown to occur within 8 to 10 hours. As such, the recommended period of observation is a minimum of 4 to 6 hours.
- Education about proper use and storage of prescribed epinephrine is provided with understanding demonstrated by the family and patient. In one study, only approximately 30% of patients or their health care professionals could demonstrate proper use of an epinephrine autoinjector.
- Prescribing physicians should recognize that cost and availability are common obstacles that families must overcome to obtain an epinephrine autoinjector for outpatient use. Ideally, the patient should be discharged from the hospital with this rescue medication in hand. Consultation with a social worker may be helpful in reaching this goal.

HEALTH EQUITY FOCUS

Health Care Access to Pharmaceuticals

An important component of health care access includes the ability of patients to obtain medications on discharge from the hospital. Cost is a significant obstacle for many families in obtaining potentially lifesaving medications.

Physicians should learn about the most common cost-prohibitive medications that they prescribe. They should educate themselves on generic alternatives and patient assistance programs that can help patients obtain these medications.

Anticipatory Guidance

Q: What instructions would you provide to Andy's caregivers on discharge?

- All caregivers and Andy's school should understand and have access to the anaphylaxis emergency management plan. (See the Suggested Readings section for an emergency action plan template.)
- Epinephrine autoinjectors should be carried by Andy (or the caregiver present with him) at all times.
- If Andy has a severe allergic reaction that results in the use of IM epinephrine, it is important to immediately call 911 for medical assistance and transportation to the nearest ED.
- Follow up with an allergist for allergen testing.
- Avoid the suspected allergen and related foods.

Clinical Pearls

- Anaphylaxis is a clinical diagnosis and prompt recognition can be lifesaving.
- The incidence of anaphylaxis is difficult to determine for a variety of reasons, including underdiagnosis and variable clinical definitions; however, its incidence appears to be increasing, particularly in the pediatric and young adult populations.
- Peanuts are the most common cause of food-induced anaphylaxis in the United States. Tree nuts are another common cause. Frequently, peanuts and tree nuts are inadvertently ingested, as they are commonly used as ingredients in food items.
- IM epinephrine should be administered as quickly as possible in cases of anaphylaxis, as it is the only treatment that has been shown to decrease the morbidity and mortality associated with anaphylaxis.
- Cutaneous and respiratory symptoms may be absent in up to 15% and 50% of anaphylaxis cases, respectively.
- Cost and availability are significant and common obstacles to obtaining epinephrine autoinjectors for outpatient use. These obstacles should be recognized by the prescribing physician and ideally resolved prior to discharge. Consultation with a social worker may be helpful.

Documentation Tips

- Document interventions required and supportive care provided.
- Document the patient's clinical response to interventions.

Suggested Readings

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CASE 26

Janice, an 11-Year-Old Girl With Prolonged Menses

CASE PRESENTATION

Janice, an 11-year-old previously healthy girl, presents to the emergency department (ED) with dizziness and fatigue. In the ED, she reports that she is currently menstruating, and today she has been saturating 1 pad nearly every hour. In the ED she is given a normal saline (0.9%) bolus and started on maintenance intravenous (IV) fluids containing dextrose. The ED physician is concerned about the volume of her bleeding and calls you to request that you evaluate Janice for admission.

Patient History and Review of Systems

Q: What information should you collect from Janice and her caregivers?

- History of present illness
  - Detailed history of current menses, including duration of bleeding, presence of clots, how often pads/tampons are changed, the size of pads/tampons used, and whether leaks occur
  - Detailed menstruation history, including age at menarche, typical menstrual cycle interval, length of typical menses, presence of clots, how often pads/tampons are changed, the size of pads/tampons used, and whether leaks occur often
  - History of similar episodes of heavy bleeding
  - Associated symptoms, such as light-headedness, syncope, pallor, abdominal/pelvic pain, nausea, vomiting, fatigue, fever, changes in vaginal discharge, headaches, vision changes, or weight changes
- Medical and surgical history, including prior evaluation or treatment of heavy menses; symptoms of a bleeding disorder, including excessive bleeding with surgical or dental procedures, easy bruising, petechiae, frequent nose bleeds, or gingival bleeding
- Dietary history with specific attention to hydration and any indicators of disordered eating
- Current or recent medications, including oral contraceptive pills (OCPs), nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and over-the-counter medications or supplements
- Family history, especially noting history of endocrine or bleeding disorders
- Social history, including complete HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, including sexual activity, history of sexually transmitted infections (STIs), and history of genital trauma (refer to Section VII of the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

From your conversation with Janice and her parents, you learn that Janice has been having vaginal bleeding every day for the past 4 weeks. She had menarche 9 months ago, and her menses often last up to 3 weeks at a time. She normally has 1 to 2 weeks in between her menses and uses normal-sized pads. During menstruation, she normally changes her pads at least 3 to 4 times a day, and this has been consistent for the last 3 weeks, but over the past few days, she has needed to change pads once every few hours. Today, she has needed to change her pad hourly. She has not noticed any blood clots, but she has on several occasions bled through her pad overnight during the last week. She has not been evaluated for heavy menstrual bleeding in the past.

Janice reports feeling fatigued over the past 2 weeks and has been told by her family and teachers that she appears pale. Over the past 3 days, she has developed lightheadedness at rest, fatigue, and nausea. She has never had symptoms like this before. Because of these new symptoms, she told her mother about her prolonged menses and her mother brought her directly to the ED. Her dietary intake has remained unchanged and she has no history of modifying her diet to alter her weight. She denies syncope, abdominal or pelvic pain, fever, change in her baseline vaginal discharge, bruises, headaches, temperature intolerance, gingival bleeding when brushing her teeth, vision changes, excessive body hair, or significant weight changes.

Both parents are at her bedside, and her mother mentions that both she and Janice's maternal grandmother have a history of heavy menstrual bleeding with irregular cycles in the years after menarche. Janice's parents deny any family history of excess bleeding with surgical or dental procedures, easy bruising, or sudden vision changes. There is no other significant family medical history.

Janice has had no recent illnesses and denies changes to her diet. She takes no medications or oral contraceptives. She is fully immunized per the Centers for Disease Control and Prevention schedule. She has never had any surgeries and denies prolonged bleeding after a tooth extraction 3 years ago. The family has been keeping her home from school for the past few days because of her fatigue and dizziness. They have been treating her with rest and fluids to keep her comfortable.

You ask Janice's parents to step out of the room so that you can obtain a confidential HEADSS assessment directly from Janice. From this conversation, you learn that she feels safe at home and lives with her parents and 2 siblings. She is in the fifth grade, enjoys school where she has 2 close friends, and denies bullying. She reports that she tried a sip of alcohol once but has never used tobacco or other drugs. She has never dated or kissed anyone, has never been sexually active, and denies any sexual or physical abuse. She denies any suicidal ideation or genital trauma.

Physical Examination

Q: What parts of the physical examination should you focus on for Janice?

- Complete set of vital signs
- Level of consciousness
- Overall appearance (body habitus, nutritional status)
- Head, eyes, ears, nose, and throat: mucous membranes (any buccal or palatal ecchymosis or petechiae), neck (thyroid enlargement or nodules), visual field testing, fundus examination

- Cardiac: heart rate, presence of a flow systolic murmur
- Peripheral perfusion: capillary refill time, peripheral pulses, temperature of extremities
- Skin: presence of ecchymoses, petechiae, pallor, acanthosis nigricans, acne, hirsutism, changes in pigmentation
- Abdomen: tenderness, guarding, masses
- Sexual maturity rating of breasts
- Genitourinary: appearance of genitalia, sexual maturity rating of pubic hair, signs of sexual abuse/trauma, vaginal discharge, confirmation of blood at the vaginal introitus

CASE FOCUS

Physical Examination

Janice's vital signs show that she is afebrile with tachycardia (heart rate: 115 beats/min). She has a normal respiratory rate (20 breaths/min) and oxygen saturation on room air (98%). Her blood pressure for age is borderline low at 101/45 mm Hg, with normal orthostatic vitals. Her height and weight upon arrival to the ED are 155 cm and 49 kg, respectively. Her age adjusted body mass index is 20.4 (79th percentile).

On examination, Janice appears well nourished but tired and endorses feeling lightheaded while sitting up. She is alert, oriented, and appropriately responsive to questions. She appears pale but without bruising, petechiae, or abnormal pigmentation. She has minimal acne and no signs of hirsutism or acanthosis nigricans. She has normal visual fields and no blurring of the optic discs on ophthalmologic examination. There is no thyroid enlargement or palpable nodules on neck examination. She has abdominal pain in the lower quadrants but no guarding, rebound tenderness, or palpable masses. Her peripheral pulses are normal with a capillary refill time of less than 3 seconds, and her extremities are warm to the touch. Her breasts and pubic hair are at Tanner stage 4. Her genitourinary examination shows normal genitalia and perineum with confirmation of blood at the vaginal introitus and no vaginal discharge. The remainder of her examination is normal.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an older child or adolescent with abnormal vaginal/uterine bleeding?

The differential diagnosis for an older child or adolescent with abnormal vaginal/uterine bleeding is shown in Table 26.1 and is divided into causes that seem more and less likely based on Janice's presentation.

Table 26.1. Differential Diagnosis for an Older Child or Adolescent With Abnormal Vaginal/Uterine Bleeding

Diagnoses of highest suspicion	• Anovulatory cycle[a] • Bleeding disorder (such as platelet function disorders, vWD, coagulation factor deficiencies)
Other diagnoses to consider	• Anatomical abnormality of the reproductive tract • Cervicitis • Eating disorder • Endometriosis • Foreign body • Genital tract malignancy • Medications (hormonal contraceptives, anticoagulants, platelet inhibitors, antipsychotics) • PCOS • PID • Pituitary adenoma • Pregnancy complication (ectopic pregnancy, threatened/incomplete abortion) • Sexual abuse • Thrombocytopenia • Thyroid disease • Trauma • Uterine polyp • Vaginitis

Abbreviations: PCOS, polycystic ovary syndrome; PID, pelvic inflammatory disease; vWD, von Willebrand disease.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What evaluation is needed for patients who present with abnormal vaginal/uterine bleeding and have associated symptoms (eg, tachycardia, dizziness)?

In order to appropriately evaluate patients with abnormal vaginal/uterine bleeding, it is important to first classify the abnormal bleeding as specifically as possible.

- A normal menstrual cycle occurs every 21 to 35 days. Menstruation typically lasts between 3 and 7 days, with menstruation of 8 days or longer considered prolonged. Normal menstruation involves the loss of 30 to 40 mL of blood per cycle, which should require the use of 3 to 6 pads or tampons per day or 10 to 15 soaked pads or tampons per cycle.
- Abnormal uterine bleeding can be defined as any deviation from normal menstruation in frequency, regularity, duration, or volume. Based on this definition, Janice has abnormal uterine bleeding. Abnormal menstrual bleeding is further subdivided into heavy menstrual bleeding and intermenstrual bleeding.

- Janice fits the definition of heavy menstrual bleeding. Heavy menstrual bleeding requires further diagnostic evaluation for the presence of anemia and to determine if there is any identifiable underlying etiology. Diagnostic testing for patients with heavy menstrual bleeding may include the following:
  - Complete blood cell count (CBC) and reticulocyte count: It can be difficult to accurately determine the presence of anemia and estimate its degree based on symptoms, physical examination findings, and vital signs; therefore, a CBC is necessary to diagnose and quantify the degree of a patient's anemia, if present. It is also helpful in evaluating for thrombocytopenia. A reticulocyte count is useful to assess the patient's bone marrow response when anemia is present.
  - Pregnancy test: Pregnancy should always be ruled out in any older child or adolescent presenting with vaginal bleeding regardless of her reported sexual activity. Not only is pregnancy an important etiology to identify early, but ectopic pregnancy may require emergent intervention.
  - Type and screen: If clinicians are considering blood transfusion, it is imperative to urgently obtain a type and screen.
  - Testing for bleeding disorders: Clinicians should consider evaluating older children and adolescents with heavy menstrual bleeding for a bleeding disorder. Studies show that approximately 20% of patients in the United States presenting with heavy menstrual bleeding have an underlying bleeding disorder. Von Willebrand disease (vWD) is the most common cause, followed by coagulation disorders in general.
    - A menstrual history concerning for a bleeding disorder may include bleeding lasting longer than 7 days, soaking 1 pad or tampon every hour, passing clots larger than 1 in (2.54 cm) in diameter (the size of a quarter), or leaks that soak through clothing.
    - If a patient has sufficient bleeding to necessitate a blood transfusion, this is another indication to rule out a bleeding/coagulation disorder.
    - Tests for bleeding disorders should be collected prior to initiating hormonal therapy because estrogen can elevate vWD studies and provide falsely reassuring results.
    - The workup for a bleeding disorder includes prothrombin time, partial thromboplastin time, fibrinogen level, von Willebrand panel (von Willebrand factor [vWF] antigen, ristocetin cofactor assay, factor 8 assay), and platelet function assay.
  - Thyroid function tests: Free thyroxine and thyroid-stimulating hormone should be obtained for patients in whom there are signs, symptoms, or history concerning for thyroid disease.
  - Bimanual and speculum examination: With patient and parental consent, this examination may be helpful to evaluate for pelvic inflammatory disease, masses, or trauma/lacerations.

Table 26.2 highlights additional clinical scenarios that may prompt further diagnostic evaluation.

Table 26.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Patients With Abnormal Vaginal/Uterine Bleeding

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
STI/PID	Sexually active patient, vaginal discharge with or without fever, abdominal/pelvic pain, cervical motion tenderness	*Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* testing Urine nucleic acid amplification testing (or vaginal swabs if speculum examination is performed) Further testing as indicated by history and physical examination
Genital tract malignancy, uterine polyp	Presence of abdominal or adnexal mass	Pelvic US
Anovulatory cycles	Older child or adolescent within 4 years of menarche	FSH level, LH level
PCOS or late-onset congenital adrenal hyperplasia	Obesity, hirsutism, moderate to severe inflammatory acne, acanthosis nigricans, skin pigmentation changes	Serum total and free testosterone, dehydroepiandrosterone sulfate, LH, FSH, 17-hydroxyprogesterone
Pituitary adenoma	Headaches, galactorrhea, visual field defects, papilledema	Prolactin level, which will help determine whether further testing or imaging is needed
Coagulation disorder	Presence of ecchymoses or petechiae	CBC, platelet count, PT, PTT, fibrinogen level, von Willebrand panel (vWF antigen, ristocetin cofactor activity, factor 8 assay) Consultation with hematology/oncology specialist to help guide further testing (eg, platelet function tests, clotting factor tests)

Abbreviations: CBC, complete blood cell count; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; PID, pelvic inflammatory disease; PT, prothrombin time; PTT, partial thromboplastin time; STI; sexually transmitted infection; US, ultrasonography; vWF, von Willebrand factor.

CASE FOCUS

Diagnostic Evaluation

When placing Janice's IV line, the physician in the ED obtained serum laboratory tests. The results are as follows:

Laboratory test	Result	Reference range
WBC count	7,000/μL (7×10^9/L)	4,000–10,500 /μL ($4.0–10.5 \times 10^9$/L)
RBC count	2.7×10^6/μL (2.7×10^{12}/L)	$4.1–5.1 \times 10^6$/μL ($4.1–5.1 \times 10^{12}$/L)
Hemoglobin	7.2 g/dL (72 g/L)	12–15 g/dL (120–150 g/L)
Hematocrit	20.2% (0.202)	35%–43% (0.35–0.43)
MCV	73 μm^3 (73 fL)	78–91 μm^3 (78–91 fL)
MCH	24 pg/cell	26–32 pg/cell
MCHC	32 g/dL (320 g/L)	32.5–35.2 g/dL (325–352 g/L)
RDW	18.3%	11.4%–13.5%
Platelet count	250×10^3/μL (250×10^9/L)	$175–400 \times 10^3$/μL ($175–400 \times 10^9$/L)
MPV	9.7 fL	6.6–9.8 fL
Neutrophils	64% (0.64)	54%–62% (0.54–0.62)
Lymphocytes	29% (0.29)	25%–33% (0.25–0.33)
Monocytes	5% (0.05)	3%–7% (0.03–0.07)
Eosinophils	1% (0.01)	1%–3% (0.01–0.03)
Basophils	1% (0.01)	0%–1% (0–0.01)
Reticulocyte count	1% (0.01)	0.5%–1.5% (0.005–0.015)

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell.

Despite Janice reporting no sexual activity, you explain to her that you still need to confirm that she is not pregnant. Janice gives consent to obtain a urine pregnancy test, and the test is negative.

You are concerned that Janice may need a packed red blood cell (pRBC) transfusion and decide to obtain a blood type and screen, prothrombin time, partial thromboplastin time, fibrinogen level, and von Willebrand panel (vWF antigen, ristocetin cofactor assay, factor 8 assay).

Laboratory test	Result	Reference range
Blood type	O+	
Antibody	Negative	
PT	12.5 s	11.7–14.7 s
PTT	31.0 s	25–35 s
Fibrinogen	310 mg/dL (3.1 g/L)	200–400 mg/dL (2–4 g/L)

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Janice?

Using her history, vital signs, examination findings, and diagnostic evaluation, you first assess Janice's hemodynamic stability to guide initial interventions and then develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology (or etiologies). You can then generate admission criteria for your specific diagnosis.

1. **Assess airway, breathing, and circulation:** Janice is showing evidence of being symptomatic from her blood loss given her reported fatigue and dizziness. Objectively, her vital signs and physical examination can give clues to her body's ability to compensate for the blood loss and help you determine if she is in hypovolemic shock from the blood loss, which would require emergent interventions. Her vital signs reveal tachycardia (heart rate: 115 beats/min) but only borderline low blood pressure for age (101/45 mm Hg). She also remains alert and oriented with normal peripheral pulses and capillary refill. This suggests that her body is compensating for the decreased circulating blood volume; thus, she is maintaining end-organ perfusion and is in compensated hypovolemic shock. However, with ongoing blood loss, she still remains at risk for progressing to decompensated hypovolemic shock (secondary to hemorrhagic shock); therefore, addressing her volume status remains critically important as does determining the underlying etiology of her blood loss.
2. **Interpret key findings from the history and physical examination.**
   - History: Janice denies sexual activity, abuse, or recent trauma. This history, along with a negative pregnancy test, make any pregnancy complications or STI-related bleeding less likely. Her lack of galactorrhea and history of frequent (as opposed to absent) menses make prolactinoma an unlikely diagnosis. She is not currently taking any medications and has never been on OCPs, making medication side effects unlikely.
   - Physical examination: Janice's physical examination shows no clinical signs of thyroid dysfunction or polycystic ovary syndrome, and she reports no history of changes in vaginal odor or discharge, making a foreign body or infection unlikely. Anatomical anomalies of the reproductive tract are very rare in Janice's age range and are pursued once more common diagnoses are ruled out. The absence of significant fluctuations in her weight or recent changes to her diet makes an eating disorder less likely.
3. **Interpret key findings from the diagnostic evaluation.**
   - Laboratory test results: Janice's laboratory test results show a significantly decreased hemoglobin level, a decreased mean corpuscular volume (MCV), and an elevated red blood cell distribution width.
   - In the setting of anemia without other cytopenias and with ongoing bleeding, it is important to evaluate red blood cell indices, such as MCV and reticulocyte count, to help identify an underlying etiology or concurrent diagnosis. Ongoing blood loss may present as normocytic anemia, but chronic blood loss more commonly presents as microcytic anemia (MCV < 80).
   - The constellation of microcytic anemia (MCV < 80) with an elevated red blood cell distribution width in an older child with a known risk factor (heavy menstrual bleeding) indicates that, in addition to ongoing blood loss, iron deficiency may be contributing to Janice's anemia.
4. **Develop the list of findings.**

Q: What major findings you have identified for Janice?

- Microcytic anemia
- Acute blood loss
- Compensated hypovolemic shock
- Abnormal uterine bleeding with heavy menstrual bleeding

5. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Janice's presentation?

- You suspect that abnormal uterine bleeding secondary to anovulatory cycles is the most likely cause of Janice's symptoms. This is the most common cause of abnormal uterine bleeding in older children and adolescents within 4 years of menarche.
- During anovulatory cycles, the ovaries produce continuous levels of estrogen and, without ovulation or progesterone secretion, the endometrium proliferates unopposed. Without progesterone to stabilize the endometrium, the endometrium breaks down, leading to incomplete shedding and irregular, often heavy, menses.
- One of the causes of anovulatory cycles is an immature hypothalamic-pituitary-ovarian axis, which is common in older children and adolescents. Older children and adolescents may experience irregular menses for the first 2 to 3 years following menarche due to this immature axis.

6. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with abnormal uterine bleeding?

- The patient has ongoing heavy bleeding with the need for close monitoring for cessation of bleeding.
- Signs of hemodynamic instability (syncope, dizziness, lightheadedness, hypotension, delayed capillary refill) are present.
- The patient has symptomatic or severe anemia requiring a pRBC transfusion.

You determine that Janice meets criteria for hospital admission based on her ongoing heavy bleeding, symptomatic anemia, and signs of hemodynamic instability.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Janice is an 11-year-old previously healthy girl presenting with severe microcytic anemia and compensated hypovolemic shock from abnormal uterine bleeding related to suspected anovulatory cycles. She is symptomatic from her anemia with ongoing blood loss and therefore requires hospitalization for ongoing treatment and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

To prepare to treat Janice's symptoms, you review the literature to remind yourself about the treatment of abnormal uterine bleeding in older children and adolescents. You decide to divide treatment considerations into the following components:

1. **Stabilization of airway, breathing, and circulation:** In patients with signs of hemodynamic instability, prompt intervention is required. Janice has evidence of compensated hypovolemic shock and severe anemia as demonstrated by her tachycardia, orthostatic hypotension, dizziness, and delayed capillary refill. She also is experiencing ongoing bleeding. Therefore, a pRBC transfusion should be considered.
2. **Cessation of bleeding:** As Janice's bleeding is ongoing, it is important to control the current episode of heavy uterine bleeding. Hormonal therapy is the mainstay of treatment. Estrogen has a twofold effect: procoagulation, which promotes better hemostasis, and uniform growth of the endometrial lining, which limits heavy and painful menses. Progestins help stabilize the endometrium and prevent irregular shedding and menstruation.
   - Mild bleeding: If the hemoglobin level is normal (>12 g/dL [>120 g/L]) and there is mild to no active bleeding, the patient can be managed with reassurance and observation; no acute hormonal therapy is indicated.
   - Moderate bleeding: If there is ongoing bleeding or mild anemia (hemoglobin level 10–12 g/dL [100–120 g/L]), hormonal therapy should be introduced. A combined OCP that contains ethinyl estradiol and an androgenic progestin such as norgestrel or levonorgestrel is a common regimen.
     - Estrogen-containing treatment is contraindicated in certain patients, such as those who smoke or have a history of blood clots, uncontrolled hypertension, or migraines with aura. Detailed information on contraindications can be found online at the Centers for Disease Control and Prevention's US Medical Eligibility Criteria for Contraceptive Use site: https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html.
     - In patients in whom estrogen is contraindicated, use of progestin-only therapy is indicated, such as medroxyprogesterone acetate or norethindrone acetate.
   - Severe bleeding: If there is excessive or prolonged bleeding with significant anemia (hemoglobin <10 g/dL [<100 g/L]), hormonal treatment with higher doses of estrogen should be started.
     - Higher-dose estrogen treatment can be accomplished with combined OCPs given every 4 to 6 hours until the bleeding slows or stops.
     - For patients who are unable to tolerate oral medications or who are hemodynamically unstable, IV-conjugated estrogen can be given every 4 to 6 hours for up to 48 hours to control bleeding. Once bleeding is controlled and the patient is stabilized, the patient can be changed to a combined OCP given 2 or 3 times daily, which is then tapered to once daily dosing.
     - If high-dose hormonal therapy does not stop the acute bleeding, consultation with a gynecologist is important, as the patient likely requires further evaluation and may need surgical management.
3. **Treatment of iron deficiency:** Patients presenting with symptomatic abnormal uterine bleeding are at high risk for having concurrent iron deficiency. Patients who are starting hormonal therapy for abnormal uterine bleeding should also be started on iron supplementation to replenish iron stores. Iron therapy should be initiated with elemental iron. A CBC should be rechecked in 4 weeks to assess clinical improvement and therapeutic efficacy.
4. **Antiemetics:** To minimize nausea and vomiting caused by high-dose estrogen therapy, consider starting an antiemetic. In children, ondansetron is the antiemetic of choice, given the relatively benign side effect profile (avoid use in patients with long QT syndrome, and use with caution in those taking other QT-prolonging agents or serotonergic drugs).

5. **Analgesia:** Acetaminophen and NSAIDs can be used as needed. NSAIDs have been shown to help decrease menstrual bleeding by blocking prostaglandin production and causing vasoconstriction. NSAIDs would be contraindicated in patients who have a known bleeding disorder or are undergoing further workup to rule out such a disorder.
6. **Inpatient specialty consultation**
   - A gynecology or adolescent medicine specialist should be consulted in cases of severe uterine bleeding despite 24 to 48 hours of hormonal treatment, especially when estrogen-containing therapies are contraindicated. Consultation should also be considered for assistance with a tapering schedule for OCP treatment.
   - A hematology specialist should be consulted when there is a known history or strong suspicion for an underlying coagulopathy.
7. **Monitoring:** In patients admitted for abnormal uterine bleeding, it is appropriate to monitor pad counts, obtain vital signs every 4 hours, and repeat a CBC as indicated, depending on the severity of ongoing blood loss.
8. **Follow-up and preventive treatment:** Once acute bleeding is stabilized and the patient is ready for discharge, the patient should continue hormonal treatment as an outpatient to prevent recurrent bleeding. In addition to seeing their pediatrician, patients should follow up with either an adolescent medicine or gynecology specialist, who will help determine the length of hormonal treatment.

CASE FOCUS

Plan for Treatment and Monitoring

- **Airway, breathing, and circulation and treatment of anemia:** Based on Janice's hemoglobin level of 7.2 g/dL (72 g/L) and ongoing significant bleeding, you decide to give her a pRBC transfusion. You already collected a type and screen and further testing to rule out a bleeding/coagulation disorder.
- **Bleeding:** Given Janice's severe bleeding and anemia along with tachycardia and borderline hypotension, you decide to start IV-conjugated estrogen to control bleeding. As her bleeding decreases, you plan to transition to an oral OCP. An oral OCP taper is planned to be completed following discharge.
- **Iron deficiency:** Because Janice is at high risk for iron deficiency, you start elemental iron supplementation to help replenish her iron stores, which will be continued following her discharge.
- **Antiemetics:** You start ondansetron as needed to minimize nausea and vomiting caused by high-dose estrogen therapy.
- **Analgesia:** You order acetaminophen and ibuprofen as needed for pain.
- **Consultations:** You decide to monitor Janice's initial treatment response before deciding to consult any specialists.
- **Monitoring:** You order vital signs, including blood pressure, every 4 hours, daily weights, and strict monitoring of intake and output, including the number of soaked pads/tampons.

Case Resolution

Following her admission, Janice tolerates a pRBC transfusion well and reports her initial symptoms of fatigue and dizziness have completely resolved. Her uterine bleeding slows dramatically over the next 24 hours after starting IV-conjugated estrogen. You transition Janice to oral estrogen and determine that she is stable for discharge. She is subsequently discharged with a plan to complete her estrogen taper and follow up with her pediatrician and, as needed, an adolescent medicine or gynecology specialist.

Discharge Criteria

Q: How do you know when your Janice is ready to go home?

You can feel comfortable discharging your patient with symptomatic anemia secondary to abnormal uterine bleeding when the following criteria are met:

- Vaginal bleeding has stopped or significantly slowed.
- The patient is hemodynamically stable.
- The patient is tolerating oral hormonal therapy and has access to OCPs following discharge.
- Reliable outpatient follow-up with a primary care doctor, and specialists if needed, is established.

Anticipatory Guidance

Q: What instructions should you provide to Janice and her caregivers upon discharge?

- Monitor the length of menstrual cycles and the amount of bleeding with each cycle. Return for care if pad/tampon use exceeds more than 3 to 4 pads/tampons per day, if Janice soaks 1 pad or tampon every hour, passes clots larger than 1 in (2.54 cm) in diameter (the size of a quarter), or if bleeding soaks through clothing.
- Return for care for inability to take oral hormonal therapy, worsening dizziness or fatigue, persistent or worsening abdominal pain, or any new concerns.
- Taper off hormonal therapy as instructed and continue iron therapy.

Clinical Pearls

- Abnormal uterine bleeding due to anovulatory cycles remains a diagnosis of exclusion. Clinicians should rule out pregnancy, STIs, pregnancy-related complications, and endocrine disease.
- Anovulatory cycles from hypothalamic-pituitary-ovarian axis immaturity are the most common cause of abnormal uterine bleeding in children and adolescents within 4 years of menarche.
- A comprehensive history and physical examination are important to evaluate for any underlying medical etiologies.
- A pregnancy test is highly recommended in the evaluation of any older child or adolescent presenting with abnormal uterine bleeding regardless of sexual history.
- Treatment of abnormal uterine bleeding is determined by the underlying pathology, extent of bleeding, and degree of anemia.

Documentation Tips

- Document the presence of and the type of the patient's anemia.
- Document whether hemorrhagic shock is present due to bleeding/anemia.

Suggested Readings

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CASE 27

Amaia, a 16-Year-Old Girl With Hematemesis

CASE PRESENTATION

Amaia is a 16-year-old girl who presented to the emergency department (ED) earlier today with 2 days of forceful vomiting. Her emesis has become bloody today. In the ED, she appears dehydrated and has several witnessed episodes of bright red emesis that are guaiac positive. The ED physician caring for her obtains intravenous (IV) access and draws blood for laboratory tests, including a complete blood cell count (CBC), comprehensive metabolic panel, prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), urine pregnancy test, and blood type and crossmatch. The ED physician also gives Amaia a 20-mL/kg normal saline bolus and IV doses of ondansetron and a proton pump inhibitor (PPI). Amaia's laboratory test results are significant for a hemoglobin level of 8.8 g/dL (88 g/L), and the ED physician contacts you to evaluate Amaia for admission.

Patient History and Review of Systems

Q: What information should you collect from Amaia and her caregivers?

- History of present illness
  - Timeline of symptoms, including onset and frequency of vomiting
  - Symptoms of anemia, such as dizziness, pallor, or palpitations
  - Symptoms of dehydration, such as decreased urine output, increased thirst, or dizziness
  - Ability to tolerate oral intake (both solids and liquids)
- Associated symptoms, such as fatigue, diarrhea, melena, fever, rash, throat pain, trouble swallowing, change in mental status, or abdominal pain
- Medical and surgical history, including history of excessive bruising or bleeding
- Medications or supplements taken or available in the home
- Family history, especially noting bleeding disorders
- Travel history, activity history, and exposures, including animal interactions (eg, farm, petting zoo), sick contacts, or contaminated water
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, especially noting drug or alcohol use (refer to Section VII in the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

On your arrival to the ED, you find Amaia and her parents in the room. As you speak with her and her parents, you learn that Amaia had an acute onset of nausea and forceful vomiting and retching yesterday morning. The vomiting started approximately 12 hours after eating a meal of leftover sushi for dinner the night before. Amaia's parents took her to see her pediatrician, who diagnosed her with acute gastroenteritis and recommended supportive management at home. The vomiting continued with at least 10 episodes overnight. Amaia states that she thought she noticed "specks of blood" in her vomit yesterday, but she notes that today the blood was "kind of a lot," which is why she came to the ED. She states that the blood is bright red in color. In the last 24 hours, she has also had 2 episodes of diarrhea. She did not see any blood in her stool. Since her symptoms started, she has only been able to tolerate a few sips of water. She does not remember if she has urinated today.

Amaia describes some mild crampy abdominal pain as well as fatigue, but otherwise her review of systems is negative.

Amaia is a healthy and typically developing adolescent girl with no chronic medical conditions. Amaia has never had similar symptoms in the past, and she has never had surgery. She takes ibuprofen for occasional headaches and for menstrual cramps but does not take any other medications. She denies any known sick contacts, recent travel history, exposure to contaminated water, or interactions with animals other than the family dog. Her family history is noncontributory. A HEADSS assessment with Amaia alone is remarkable for a history of intermittent condom use with male sexual partners and a chlamydia infection last year, which was appropriately treated. She uses an implanted progestin rod for contraception. She denies alcohol or drug use.

While reviewing her electronic medical record, you note Amaia has been seen annually for her health supervision visits, is up to date with preventive health care (vaccinations, including seasonal flu vaccine, and sexually transmitted infection testing) and has infrequent sick visits or ED visits.

Physical Examination

Q: What parts of the physical examination should you focus on for Amaia?

- Complete set of vital signs
- General: level of consciousness; ability to arouse and interact appropriately
- Appearance of eyes: conjunctival pallor, sunken, injected, icteric
- Mucous membranes: moist, sticky, dry
- Oropharynx: leukoplakia or ulcers
- Peripheral perfusion: capillary refill time, temperature of extremities, quality of peripheral pulses
- Cardiac: presence of murmurs or gallops
- Abdomen: visual inspection, tenderness, guarding, masses, quantity and quality of bowel sounds
- Skin: lesions (eg, petechiae, purpura), turgor, pallor
- Visual examination of vomitus, if available

CASE FOCUS

Physical Examination

Amaia's vital signs reveal that she is afebrile (36.6 °C [97.9 °F]). Her heart rate (98 beats/min) and respiratory rate (15 breaths/min) are within normal limits. She has a normal blood pressure (90/65 mm Hg) for age and a normal oxygen saturation on room air (99%).

On examination, she appears uncomfortable but not toxic and answers your questions appropriately. Her eyes are clear with anicteric sclerae and no conjunctival inflammation. Her oropharyngeal examination shows her oral mucosa is slightly dry but otherwise clear, without erythema, ulcers, or other lesions. Her nares are clear, with pale turbinates and no evidence of blood. She has normal cardiac and respiratory examinations. Her extremities are warm, and her peripheral pulses are normal with 3-second capillary refill.

Her abdomen appears nondistended, without scars or bruising. On auscultation, bowel sounds are present and hyperactive. Her abdomen is soft, and no masses or organomegaly is noted. She does not have any abdominal tenderness on palpation. There is no appreciable costovertebral angle tenderness. The rest of her examination, including her neurologic and skin examinations, is normal.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent with hematemesis?

The differential diagnosis for an adolescent with hematemesis is shown in Table 27.1 and is divided into causes that seem more and less likely based on Amaia's presentation.

Table 27.1. Differential Diagnosis for an Adolescent With Hematemesis

Diagnoses of highest suspicion	• Gastritis • MWS[a] • PUD
Other diagnoses to consider	• Blood from outside the GI tract (eg, epistaxis, hemoptysis, dental bleeding) • Boerhaave syndrome (transmural esophageal tear) • Bowel obstruction • Coagulopathy — Acquired (eg, DIC, thrombocytopenia, multisystem organ failure) — Congenital/hereditary (factor deficiencies) • Crohn disease • Esophageal varices • Esophagitis — Autoimmune — Caustic ingestion — Erosive (due to foreign body, such as a pill or battery) — Infectious

(continued)

Table 27.1. Differential Diagnosis for an Adolescent With Hematemesis *(continued)*

Other diagnoses to consider *(continued)*	• Hemobilia • Hereditary hemorrhagic telangiectasia • Hiatal hernia • Streptococcal pharyngitis • Trauma (eg, iatrogenic trauma from instrumentation, such as a nasogastric tube) • Vascular lesions (eg, Dieulafoy lesion, angiodysplasia, aortoenteric fistula, arteriovenous malformation, bleeding hemangiomas) • Vasculitis, such as IgA vasculitis

Abbreviations: DIC, disseminated intravascular coagulation; GI, gastrointestinal; IgA, immunoglobulin A; MWS, Mallory-Weiss syndrome; PUD, peptic ulcer disease.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with hematemesis?

- The differential for hematemesis in a pediatric patient includes a variety of etiologies, from benign to life-threatening. The most important first step for any bleeding patient is to stabilize the patient's airway, breathing, and circulation. Some of the actions taken to stabilize a patient can also offer diagnostic clues.
- Once the patient has been stabilized, the next step is to identify the source of the bleeding. If blood is originating from sources outside of the gastrointestinal (GI) tract (eg, epistaxis or bleeding from oral cavity), this is often apparent on history and physical examination. In instances such as this, when the etiology of hematemesis is apparent based on history and physical examination, or when there is no evidence of ongoing bleeding, a thorough history and physical examination is often sufficient to confirm the diagnosis, and no further evaluation is warranted.
- When an obvious cause outside of the GI tract cannot be identified based on history and examination, an upper GI bleed should be considered. Hematemesis, with or without melena, is a common presenting symptom of an upper GI bleed. The patient's history and physical examination may provide important clues to help localize the source of bleeding along the GI tract. When an upper GI tract bleed is suspected and the etiology is not apparent from history alone, it is reasonable to consider the following diagnostic studies:
  - CBC: It can be challenging to evaluate the degree of a patient's blood loss based on physical examination, vital signs, and history alone; therefore, obtaining hemoglobin and hematocrit levels can be helpful to identify the presence of anemia and to quantify the degree of the anemia when present. A CBC can also be used to assess the patient's platelet count and determine if thrombocytopenia is contributing to the hematemesis.
  - Type and screen: Patients with upper GI bleeding may require packed red blood cell (pRBC) transfusion if they are experiencing symptomatic anemia, hemodynamic instability, or hemorrhagic shock as a result of blood loss. As clinical deterioration can progress rapidly in patients with acute upper GI bleeding, a type and screen should be ordered preemptively to avoid delays in treatment in the event that a pRBC transfusion is needed.

  - PT/INR and PTT: These studies assess how long it takes for the blood to clot and can be helpful to evaluate for bleeding disorders.
  - Hepatic function panel: This series of tests can be used to evaluate for liver inflammation and synthetic function, which may indicate liver disease.
- Nasogastric tube lavage: In patients with suspected upper GI bleeding, nasogastric tube lavage (with room temperature water or normal saline) can be used to confirm the upper GI tract as the location of the bleeding and to determine whether the bleeding is ongoing. Nasogastric lavage is particularly helpful for suspected vascular bleeds (eg, varices) and will remove particulate matter, fresh blood, and clots to facilitate endoscopy and decrease the risk of aspiration. When varices are suspected, consultation with a gastroenterologist may be helpful, as there is risk of worsening bleeding with nasogastric tube placement. Note that lavage may not be positive for fresh blood or "coffee ground" blood if bleeding has ceased or has an origin distal to a closed pylorus. Coffee ground blood results from upper GI bleeding that has slowed or stopped, with conversion of bright hemoglobin to dark hematin by acid in the stomach.
- Esophagogastroduodenoscopy (EGD): Many causes of hematemesis require direct visualization via EGD to look for the source of bleeding. This procedure is often performed by a pediatric gastroenterologist or surgeon.
- If the source of bleeding is not apparent on EGD, additional studies such as a nuclear medicine scan, angiography, or capsule endoscopy may be utilized. The decision to perform these studies should be guided by a pediatric gastroenterologist.

CASE FOCUS

Diagnostic Evaluation

You review the full results from Amaia's ED laboratory evaluation, which are as follows:

Laboratory test	Result	Reference range
CBC with differential		
WBC count	7,000/μL (7 × 10^9/L)	4,000–10,500/μL (4.0–10.5 × 10^9/L)
RBC count	3.2 × 10^6/μL (3.2 × 10^{12}/L)	3.8–5.0 × 10^6/μL (3.8–5.0 × 10^{12}/L)
Hemoglobin	8.8 g/dL (88 g/L)	11.2–15 g/dL (112–150 g/L)
Hematocrit	27% (0.27)	35%–45% (0.35–0.45)
MCV	82 μm^3 (82 fL)	78–95 μm^3 (78–95 fL)
MCH	30.2 pg/cell	26.0–32.0 pg/cell
MCHC	31.1 g/dL (311 g/L)	32–36 g/dL (320–360 g/L)
RDW	15.2% (0.152)	11.4%–13.5% (0.114–0.135)
Platelet count	275 × 10^3/μL (275 × 10^9/L)	150–450 × 10^3/μL (150–450 × 10^9/L)
Neutrophils	65% (0.65)	54%–62% (0.54–0.62)
Lymphocytes	29% (0.29)	25%–33% (0.25–0.33)
Monocytes	4% (0.04)	3%–7% (0.03–0.07)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
CBC with differential *(continued)*		
Eosinophils	1% (0.01)	1%–3% (0.01–0.03)
Basophils	1% (0.01)	0%–1% (0–0.01)
Reticulocyte count	1.3% (0.013)	0.5%–2.0% (0.005–0.02)
Additional hematologic studies		
Blood type	B+	
Antibody	Negative	
PT	13.5 s	12.2–15.5 s
PTT	31.0 s	26.5–35.5 s
INR	1.1	0.8–1.2

Abbreviations: CBC, complete blood cell count; INR, international normalized ratio; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell.

In addition, a comprehensive metabolic panel shows normal albumin, bilirubin, aspartate aminotransferase, and alanine aminotransferase, and a urine pregnancy test is negative. Amaia's serum lipase level is within normal limits.

Arriving at a Diagnosis

Q: How do you develop an assessment for Amaia?

1. **Assess airway, breathing, and circulation:** Patients with upper GI bleeding are at risk for rapid deterioration from uncompensated hemorrhagic shock. Therefore, assessing their airway, breathing, and circulation is the first step. Amaia is speaking normally, and she does not have any signs of respiratory distress, indicating that her airway is not compromised. Amaia has normal vital signs and she is not exhibiting any signs of hypovolemic shock, such as lethargy or confusion. Because of this, you determine that she is currently hemodynamically stable and does not require any urgent interventions at this time.
2. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Amaia's history reveals a previously healthy, normally growing and developing adolescent girl with recent diagnosis of acute gastroenteritis who developed an acute onset of hematemesis after multiple episodes of forceful vomiting. This history is most consistent with Mallory-Weiss syndrome (MWS).
   - Physical examination: Amaia's physical examination is significant for slightly dry mucous membranes and slightly delayed capillary refill, suggesting moderate dehydration.
   - Diagnostic evaluation: Amaia's laboratory test results are notable for anemia; however, her normal vital signs make massive blood loss unlikely. She does not require urgent transfusion at this time, however, given the signs of ongoing bleeding (continued vomiting of blood in the ED), upper endoscopy is warranted within the next 24 to 48 hours to identify the source of bleeding and potentially halt the bleeding. However, if at any point she becomes unstable, an urgent gastroenterology consult with endoscopy is warranted to stop the acute bleeding. Amaia's normal synthetic liver function and coagulation tests make a hepatic cause of her symptoms unlikely.

3. **Develop the list of findings.**

Q: What major findings you have identified for Amaia?

- Moderate dehydration
- Hematemesis
- Moderate anemia
- Acute gastroenteritis

4. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Amaia's presentation?

- In reviewing the differential diagnoses in light of Amaia's history, physical examination, and diagnostic evaluation, you narrow the source of Amaia's bleeding to her upper GI tract. Common etiologies in this age group include MWS, gastritis associated with nonsteroidal anti-inflammatory drugs, and peptic ulcer disease.
- Given the acute onset of Amaia's vomiting and hematemesis that started *after* her vomiting, in the setting of a diagnosis of acute gastroenteritis, you decide that MWS is the most likely cause of Amaia's symptoms. An upper endoscopy is needed to confirm this diagnosis.

Q: What is MWS?

MWS is characterized by longitudinal superficial lacerations in the mucosa of the esophagus and upper stomach that often lead to bleeding from the submucosal arteries and veins. One of the leading causes of MWS is the increased intra-abdominal pressure associated with vomiting or retching. MWS typically presents with acute hematemesis in patients who first experience nonbloody vomiting or retching. MWS can also develop as a result of other causes of increased intra-abdominal pressure, such as coughing. The forceful vomiting Amaia experienced as a result of her acute gastroenteritis likely precipitated MWS.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with hematemesis?

- The patient has ongoing bleeding with the need for close monitoring.
- The patient has signs and/or symptoms of hemodynamic instability (eg, syncope, dizziness, lightheadedness, hypotension, tachycardia, delayed capillary refill).
- The patient has symptomatic or severe anemia requiring a pRBC transfusion.
- The patient is experiencing severe pain that requires monitoring and IV medications.
- The patient has dehydration, with inability to tolerate oral intake, and requires IV hydration.

Amaia meets criteria for admission based on dehydration and the inability to tolerate oral intake. You also have concerns for ongoing bleeding given the episodes of hematemesis Amaia experienced in the ED.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Amaia is a previously healthy 16-year-old girl with hematemesis and dehydration in the setting of acute gastroenteritis. Her hematemesis is most likely from a Mallory-Weiss tear given the acute onset of hematemesis following forceful vomiting. Amaia requires admission for further evaluation, hydration, and close monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goals of Amaia's treatment plan are to ensure hemodynamic stabilization, identify and treat the underlying cause of hematemesis, monitor for and treat episodes of further bleeding, and provide supportive care for her vomiting and dehydration.

1. **Management of anemia:** There is no definitive hemoglobin level at which a transfusion is necessary for anemia, but red blood cell transfusion should be considered in patients with hemoglobin of less than 8 g/dL (80 g/L) who are symptomatic or have ongoing blood loss.
2. **Management of hematemesis**
   - Nasogastric tube lavage: As previously stated, nasogastric tube lavage can be helpful in removing particulate matter, fresh blood, and clots to facilitate endoscopy. Nasogastric tube lavage may also be helpful in preventing aspiration. Whether or not nasogastric tube lavage is performed, it is prudent to give the patient nothing by mouth until the bleeding stops. As Amaia will likely need an EGD, a nasogastric tube lavage should be considered.
   - Medications: There are several pharmacologic interventions to consider in patients with upper GI bleeding.
     - PPIs: PPIs are used empirically in hospitalized patients with suspected upper GI bleeds. These medications are helpful if ulcers are the underlying etiology of hematemesis, given their effects on acid suppression, and they may also help with hemostasis in patients with upper GI bleeding from other etiologies. Physicians should start IV PPIs in patients with ongoing vomiting and then transition to an oral version once the patient is tolerating oral intake. In patients with MWS, oral PPIs are often continued following discharge to help promote mucosal healing. Given her continued vomiting and your concern for ongoing bleeding, it is appropriate to initiate IV PPIs for Amaia.
     - Somatostatin and octreotide: These medications inhibit vasodilatory hormone release and decrease intestinal blood flow. Somatostatin and octreotide can be particularly useful in patients with suspected variceal bleeding or other bleeds that are difficult to control. As Amaia is currently hemodynamically stable and her signs and symptoms are not consistent with variceal bleeding, these medications are not immediately indicated. When considering these medications, it is reasonable to consult a gastroenterologist for guidance.
     - Stopping anticoagulant/antiplatelet agents: These agents are less commonly used in healthy children, but clinicians should evaluate patients' current medication lists for any anticoagulants/antiplatelet medications. These medications should be stopped for any patient with a suspected bleed.
3. **Supportive management**
   - Pain control: In patients who are also experiencing pain, acetaminophen and opioids are appropriate analgesics. Nonsteroidal anti-inflammatory drugs should be avoided until the etiology of hematemesis has been further evaluated.
   - Antiemetics: MWS is most often associated with forceful vomiting; therefore, antiemetics are an important component of management. Given her diagnosis of acute gastroenteritis, ondansetron is an appropriate antiemetic for Amaia's ongoing nausea and vomiting.
   - Hydration: Patients with moderate dehydration may benefit from initial fluid replacement via boluses of isotonic fluid, such as normal saline or lactated Ringer solution. Because Amaia is still not tolerating oral intake, you can anticipate ongoing fluid losses, which require maintenance IV hydration at a minimum. If ongoing fluid losses significantly exceed Amaia's IV fluid intake, she may require fluids at more than the maintenance rate. Repeated assessments of her hydration status using physical examination findings (mucous membranes, capillary refill time) and urine output will help guide this decision.
   - Refer to Case 1 for further discussion regarding the management of acute gastroenteritis.

4. **Further diagnostic evaluation:** EGD is usually required to determine the underlying etiology of hematemesis. In the case of MWS, endoscopic therapy can be used to stop active bleeding. Therefore, the amount of bleeding on presentation will determine the urgency of the procedure. If the patient has stable vital signs and hemoglobin level, it is reasonable to schedule the procedure within 1 to 2 days to be performed by a pediatric gastroenterologist. In the event that the patient is actively bleeding on endoscopy, the proceduralist can intervene directly at the location of the bleed.
5. **Consultations**
   - A gastroenterology consult is needed for ongoing hematemesis to help determine the need for diagnostic EGD and perform the procedure. A pediatric gastroenterologist can also help guide further diagnostic testing in the event that the bleeding source is not identified with an EGD.
   - Rarely, a surgical or interventional radiology consultation may be warranted if the bleeding is massive and cannot be controlled with endoscopic therapy.
6. **Monitoring:** Patients with upper GI bleeding are at risk for acute decompensation from rapid blood loss; therefore, vital signs should be monitored closely for signs of hemodynamic instability. Additionally, intake and output, including volume and frequency of hematemesis, should be closely monitored. Although scheduled checks of hemoglobin and hematocrit are not indicated, these levels should be rechecked if Amaia develops symptoms of anemia.

CASE FOCUS

Plan for Treatment and Monitoring

- **Management of anemia:** Amaia does not show signs of hemodynamic compromise, and although her hemoglobin level is slightly low, it is not low enough to warrant urgent transfusion. Once the source of her bleeding is identified and controlled and she is tolerating oral intake, her anemia is expected to resolve on its own.
- **Management of hematemesis**
  - Nasogastric tube lavage: Nasogastric tube lavage is performed with room temperature saline in the ED and returns fresh blood without a coffee ground appearance. You plan to keep the nasogastric tube in place. Amaia should receive nothing by mouth until after endoscopy.
  - Medications: You start Amaia on an IV PPI on admission, with plans to transition to an oral PPI once her bleeding has subsided and she is able to tolerate oral intake.
- **Supportive care**
  - Medications: You also start Amaia on the IV antiemetic ondansetron until her vomiting subsides. You plan to order acetaminophen if Amaia begins to experience pain.
  - Hydration: After her fluid bolus in the ED, you start Amaia on maintenance fluids containing dextrose and an isotonic fluid.
- **Further diagnostic evaluation and consultations:** You plan to consult gastroenterology to complete an endoscopic evaluation.
- **Monitoring:** You order vital signs every 4 hours and strict monitoring of intake and output.

Case Resolution

Amaia's nausea and vomiting significantly improve following ondansetron administration. She has only 1 episode of emesis overnight, which contains a moderate amount of blood. Amaia undergoes EGD the next morning, and she is noted to have a red, longitudinal tear in the esophageal mucosa, with some oozing of blood from the site on EGD consistent with a Mallory-Weiss tear. Her bleeding is successfully stopped during endoscopy using hemoclips. After recovery from endoscopy, Amaia has no further episodes of vomiting, and her diet is slowly advanced from nil per os (nothing by mouth) to clear liquids and then to a regular diet. Amaia is discharged home on an oral PPI with plans to follow up with the gastroenterologist in 2 weeks.

Discharge Criteria

Q: How do you know when Amaia is ready to go home?

The duration of hospitalization for children admitted for hematemesis depends primarily on the ability to control the blood loss and the patient's ability to tolerate oral intake. If the bleeding is persistent enough to warrant admission, it is likely that determining the etiology of the bleeding will be necessary to help contain it. You can feel comfortable discharging your patient with an upper GI bleed when the following criteria are met:

- The patient is hemodynamically stable with appropriate vital signs for age and without signs of symptomatic anemia (dizziness, syncope, or pallor).
- The patient is tolerating adequate oral intake.
- There are no signs of continued GI bleeding, such as hematemesis or symptomatic anemia.

Anticipatory Guidance

Q: What instructions should you provide to Amaia and her caregivers upon discharge?

- Continue taking the oral PPI for acid suppression and to facilitate mucosal healing until the follow-up appointment with the gastroenterologist.
- Return to care for recurrence of bleeding, pain, inability to tolerate oral intake, or signs of symptomatic anemia (dizziness, syncope, or pallor).

Clinical Pearls

- In any child with apparent upper GI bleeding, the most important first steps are to evaluate for uncompensated hemorrhagic shock and assess airway, breathing, circulation, and vital signs.
- Most children with significant upper GI bleeding will benefit from EGD for both diagnosis and possible intervention. In cases where the child is hemodynamically stable, this can be done on a nonemergent basis within 24 to 48 hours of admission.

Documentation Tips

- Document the location (upper or lower) and cause of GI bleed (eg, MWS, coagulopathy, thrombocytopenia) when known.
- Document presence of any complications (eg, anemia, hemorrhagic shock) due to bleeding.

Suggested Readings

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CASE 28

Chandler, a 7-Year-Old Boy With Eye Swelling

CASE PRESENTATION

Chandler is a 7-year-old boy who presents to the emergency department (ED) for evaluation of fever and redness, swelling, and pain around his left eye. In the ED, initial analgesia with oral acetaminophen and ibuprofen is provided, blood work is obtained, and he is given a dose of intravenous (IV) clindamycin for a suspected skin infection. His blood work is notable for mild leukocytosis. Due to his significant periorbital edema and erythema, you are asked to evaluate Chandler for admission so that he can undergo continued monitoring while receiving IV antibiotics.

Patient History and Review of Systems

Q: What information should you collect from Chandler and his caregivers?

- History of present illness
  - Onset and duration of symptoms, including maximum temperature
  - Recent trauma to the eye or surrounding skin
  - Recent illnesses, specifically upper respiratory tract infections (URTIs), sinusitis, allergies, skin infections, and dental infections
  - Associated symptoms, such as headache, proptosis, vomiting, malaise, blurry vision, change in vision, pain with eye movement, or eye discharge
- Medical history, including underlying health status, past sinus or dental disease, prior eye surgery, immunodeficiency, and immunization status, specifically *Haemophilus influenzae* type B (Hib) and pneumococcal conjugate vaccines
- Personal or family history of recurrent skin and soft tissue infections or thyroid disease
- Sick contacts
- Medications, including recent use of antibiotics or over-the-counter medications

CASE FOCUS

History and Review of Systems

During your conversation with Chandler and his family, you learn that Chandler was in his normal state of good health until 7 days ago, when he began to have a runny nose, cough, and congestion. On his third day of illness, he was seen by his pediatrician and diagnosed with a viral URTI. His mother states that his left eye was fine until last night, when she noticed a small amount of redness along his upper eyelid. At the time, Chandler did not seem bothered by the redness, so she did not think much of it. This morning, Chandler woke up crying, with a temperature of 38.9 °C (102 °F). At that time, he was noted to have pronounced redness, swelling, and tenderness around his left eye, prompting the trip to the ED.

At the time of your evaluation, Chandler rates his pain as a 5 on a scale of 0 to 10. He says, "It feels like something is pushing on my eye, and it hurts to look around." Chandler and his mother deny that he has had headache, vomiting, trauma to the eye, altered mental status, or seizure-like activity. He does not have any eye drainage but is unable to see because of his eyelid swelling. You elicit no history of previous skin or soft tissue infections for Chandler or his family members, and Chandler has never had sinus or dental surgery. His medical history is notable for eczema and allergic rhinitis, but he and his mother deny any facial eczema. He takes cetirizine seasonally for his allergic rhinitis. He takes no other medications and has no known drug allergies. There have been no known sick contacts, although he does attend school. His vaccines are up to date. His parents do not have a history of thyroid disease.

Physical Examination

Q: What parts of the physical examination should you focus on for Chandler?

- Complete set of vital signs
- Overall appearance (acute distress, malaise, consolability)
- Orbital
  - Unilateral versus bilateral findings
  - Periorbital erythema, edema, or discharge
  - Tenderness to palpation in periorbital region, including sinuses
  - Visual acuity changes
  - Pain with eye movement
  - Conjunctivitis or chemosis (edema of the conjunctiva)
  - Ophthalmoplegia (paralysis of eye muscles)
  - Proptosis
- Neurologic: signs of central nervous system (CNS) involvement
- Oropharyngeal: signs of dental caries or odontogenic infections
- Thyroid: tenderness, enlargement, cysts, nodules
- Skin: presence of rash

CASE FOCUS

Physical Examination

Chandler's vital signs show that he is febrile and tachycardic, with a temperature of 39.1 °C (102.4 °F) and a heart rate of 135 beats/min. His respiratory rate and blood pressure are within normal range for age.

On examination, Chandler appears to be in a mild amount of distress related to discomfort. He begins to cry and guard his left eye when you start to prepare for the examination. After a minute of talking, he is consoled, which allows you to elicit a normal cardiac, respiratory, and abdominal examination. Peripheral pulses are normal with brisk capillary refill. There are no murmurs or gallops. You perform a full skin examination, which is largely unremarkable aside from some eczematous patches on his hands and feet.

On his eye examination, Chandler's right eye appears unaffected. His left eye, however, has significant periorbital edema with surrounding erythema that extends to both the upper and lower eyelids, preventing him from being able to fully open his eye. This area is moderately tender to palpation. His visual acuity and extraocular movement are difficult to assess due to the severity of the swelling, but he reports pain with eye movement. There is no apparent conjunctivitis, chemosis, discharge, or proptosis. You see no obvious signs of trauma, insect bite, eczema, or foreign body.

Examination of his oropharynx and thyroid gland is normal. His neurologic examination is limited, but he is able to ambulate normally and can grab objects with both hands.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with periorbital edema and erythema?

There are many causes of periorbital edema and erythema in children; however, these causes can be easily narrowed based on a complete history and thorough physical examination. Table 28.1 demonstrates the differential diagnosis for periorbital erythema and edema, separated into diagnoses that appear more or less likely for Chandler. From this list, you are most concerned for orbital or periorbital cellulitis.

Table 28.1. Differential Diagnosis for a Child With Periorbital Edema and Erythema

Diagnoses of highest suspicion	• Cavernous sinus thrombosis • Conjunctivitis (bacterial, viral, chemical, allergic) • Orbital cellulitis (postseptal cellulitis), including subperiosteal abscess or orbital abscess[a] • Preseptal cellulitis (periorbital cellulitis)[a] • Sinusitis
Other diagnoses to consider	• Allergic reaction • Blepharitis • Carotid cavernous fistula • Chalazion • Dacryoadenitis • Dacryocystitis • Dacryocystocele • Hordeolum (ie, a *stye*) • Idiopathic inflammation (orbital myositis, orbital pseudotumor, granulomatosis with polyangiitis) • Impetigo • Neoplasm (rhabdomyosarcoma, retinoblastoma) • Nephrotic syndrome • Periocular dermoid cyst • Shingles or HSV infection • Thyroid-associated orbitopathy (Graves disease) • Trauma (corneal abrasion, insect bite, intraorbital foreign body, orbital fracture)

Abbreviation: HSV, herpes simplex virus.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What is the diagnostic evaluation for a child with periorbital erythema and edema?

- Many of the aforementioned diagnoses can be diagnosed clinically and do not require a diagnostic evaluation. For others, the diagnostic evaluation will vary based on the suspected etiologies.
- When considering a diagnostic evaluation for suspected infections involving the eye, it is important to first determine whether the site of infection is anterior or posterior to the orbital septum, as the infection sites have significantly different clinical implications.
  - Infections anterior to the orbital septum, such as preseptal cellulitis (periorbital cellulitis), are typically milder. They can be diagnosed clinically and are usually treated in the outpatient setting.
  - Infections posterior to the orbital septum, such as orbital cellulitis (postseptal cellulitis), are considered medical emergencies, requiring hospitalization for further evaluation and treatment.

Q: What is the orbital septum?

The orbital septum (Figure 28.1) is a thin membrane that extends from the orbital rims to the eyelids, demarcating the anterior boundary of the orbit. It forms a barrier between the superficial eyelid and the deeper orbital structures. In doing so, the orbital septum protects the delicate components of the orbit from external insults, such as the spread of infection.

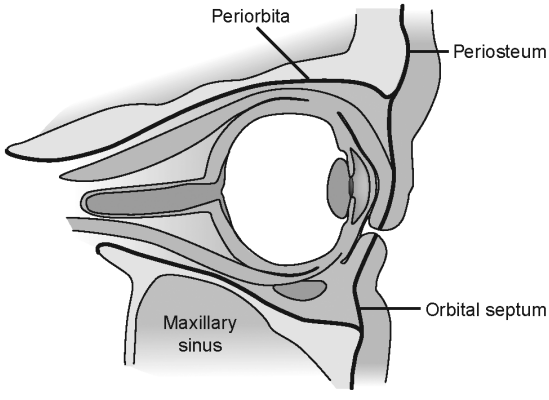

Figure 28.1. Illustration of the orbital septum.

Reprinted with permission from Wald E. Preseptal and orbital cellulitis. In: McInerny TK, Adam HM, Campbell DE, DeWitt TG, Foy JM, Kamat DM, eds. *American Academy of Pediatrics Textbook of Pediatric Care*. 2nd ed. American Academy of Pediatrics; 2017:2537–2543.

Q: Are serum laboratory tests necessary when orbital cellulitis is suspected?

- The utility of an extensive laboratory workup for infections involving the orbit is limited. Although elevated white blood cell count and inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) may be helpful in differentiating orbital cellulitis from the more superficial preseptal cellulitis, or in trending inflammatory response (C-reactive protein), these laboratory tests should not be used to make a definitive diagnosis.

- Cultures
  - Ocular discharge, as well as surgically collected fluid from the orbit, sinuses, or underlying abscess, can be cultured with relatively high yield to identify causative infectious organisms. Although obtaining cultures is not the primary indication for surgery, cultures should be collected in cases where surgery is needed.
  - Blood cultures, on the other hand, have a lower yield in identifying causative organisms and do not need to be routinely collected in all cases. One recent study of pediatric orbital cellulitis cited blood culture positivity around 7%. In patients with severe disease or systemic signs of sepsis, blood cultures have greater utility, as they are more likely to be positive.

Q: When should imaging be considered?

If orbital cellulitis is suspected, imaging should be strongly considered. In addition to confirming a diagnosis of orbital cellulitis, proper imaging can also identify emergent complications, such as an underlying abscess. Imaging may also identify other processes requiring surgical intervention, such as tumors.

Q: What is the preferred imaging modality?

- Contrast-enhanced computed tomography (CT) scan and magnetic resonance imaging (MRI) are both appropriate modalities for the identification of orbital cellulitis and its complications. CT scan of the orbits and sinuses is the preferred initial imaging modality due to its ready availability and shorter acquisition time. MRI is superior for monitoring the progression of soft tissue diseases over time and has the benefit of limiting radiation, but it often requires sedation in younger children due to prolonged acquisition time.
- If complications such as intracranial extension or cavernous sinus thrombosis are suspected, further imaging with CT venography or MRI/MR venography (MRV) should be considered due to increased sensitivity compared to CT imaging.

CASE FOCUS

Diagnostic Evaluation

You review the complete blood cell count obtained in the ED and see that the results are within normal limits, other than a white blood cell count of 16,400/μL (16.4×10^9/L). The ED physician also sent a blood culture prior to antibiotic administration, and these results are pending.

Because orbital cellulitis is high on your differential, you move forward with imaging. A contrast-enhanced CT scan of Chandler's orbits and sinuses reveals prominent periorbital edema and left-sided inflammation of the extraocular muscles with mild anterior displacement of the globe. A 4-mm medial subperiosteal abscess is present. Moderate opacification of the ethmoid and maxillary sinuses is also noted.

On reexamination, you notice that Chandler now has a mild amount of white-tinged discharge draining from the affected eye. You collect a sample of the discharge and send it for culture.

Arriving at a Diagnosis

Q: How do you develop an assessment for Chandler?

In thinking through Chandler's case, you should first interpret the findings from his history, vital signs, examination, and diagnostic evaluation, evaluate for sepsis criteria, and develop a list of his major findings. From there, you will establish his final diagnosis and consider the relevant admission criteria.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History, vital signs, and examination findings: Chandler presented with acute signs and symptoms most consistent with preseptal or orbital cellulitis that developed in the setting of a recent URTI. He has no history of trauma or injury to the skin. In the ED, he was febrile and tachycardic. His physical examination is remarkable for significant left-sided periorbital edema and erythema, with mild tenderness to palpation. Although visual acuity and extraocular movements are difficult to assess due to swelling, Chandler reports pain with eye movement, which increases your concern for an orbital infection. His examination is negative for severe orbital symptoms, such as proptosis, vision alteration, or neurologic changes. Additionally, his examination findings eliminate any concern for other ocular or periorbital pathology, such as conjunctivitis, hordeolum, chalazion, blepharitis, impetigo, or herpes zoster.
   - Diagnostic evaluation: Chandler's laboratory test results reveal leukocytosis. Contrast-enhanced CT imaging of the sinuses and orbits shows left-sided sinus disease and extension of inflammation into the orbital space including the extraocular muscles. He also was noted to have a small subperiosteal abscess with resulting anterior displacement of the globe.
   - Assessment for sepsis: Chandler is currently febrile and tachycardic with leukocytosis on laboratory evaluation. These findings are consistent with sepsis, but he does not have any findings of severe sepsis or septic shock. Refer to Section IV in the Appendix for definitions of sepsis, severe sepsis, and septic shock.
2. **Develop the list of findings.**

   ### Q: What major findings have you identified for Chandler?

   - Periorbital edema, erythema, and pain with eye movement
   - Opacification of the left-sided maxillary and ethmoid sinuses
   - A small subperiosteal abscess
   - Inflammation of the left-sided extraocular muscles with anterior displacement of the globe
   - Sepsis
3. **Revisit the differential diagnosis.**

   ### Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Chandler's presentation?

   Before Chandler's diagnostic evaluation, your 2 leading diagnoses were preseptal and orbital cellulitis. Although not diagnostic, his examination and laboratory values are supportive of the diagnosis of orbital cellulitis. His imaging results have established a definitive diagnosis of orbital cellulitis complicated by a small subperiosteal abscess. His CT scan also demonstrates findings consistent with sinusitis, which is where the infection originated before extending into the orbit. Although there is evidence of periorbital soft tissue edema on examination and CT scan, this edema is likely reactive and not the nidus of Chandler's infection.

   ### Q: How can preseptal cellulitis and orbital cellulitis be differentiated clinically?

   - Both preseptal cellulitis and orbital cellulitis can present with eyelid swelling, erythema, fever, and ocular pain. In addition to these findings, orbital cellulitis may display additional signs and symptoms, such as ophthalmoplegia, pain with eye movement, proptosis, or chemosis. Table 28.2 compares the differences in presentation of the 2 processes.

Table 28.2. Comparison of Preseptal and Orbital Cellulitis

Criterion	Preseptal cellulitis	Orbital cellulitis
Definition	An infection of the eyelid and surrounding structures anterior to the orbital septum	An infection of the contents within the orbit (fat and ocular muscles) posterior to the orbital septum, excluding the globe
Population affected	Occurs more commonly in children, with higher incidence than orbital cellulitis	Occurs more commonly in children, often in winter months due to association with viral respiratory illnesses/sinusitis
Pathogenesis	Infection of facial soft tissues following local trauma, insect bites, or foreign bodies	Complication of acute paranasal (ethmoid) sinusitis Less commonly from orbital/odontogenic surgery, facial trauma, or hematogenous spread
Clinical features	Eyelid swelling Erythema With or without fever and ocular pain	Eyelid swelling Erythema Fever Ocular pain With or without ophthalmoplegia, pain with eye movements, proptosis, and chemosis

- Preseptal cellulitis is usually caused by a direct insult to the skin and soft tissues surrounding the orbit. Common examples include trauma or insect bites. It can also occur secondary to infections of the lid structures, such as blepharitis or dacryocystitis (Figure 28.2), as an extension of cheek cellulitis related to an odontogenic infection or as a complication of sinusitis. Preseptal cellulitis can develop from hematogenous seeding, but this is uncommon in the era of Hib vaccination.

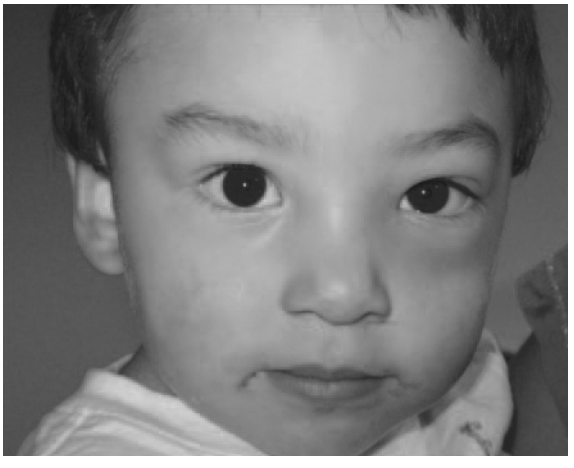

Figure 28.2. Child with preseptal cellulitis.

Reprinted with permission from Hauser A, Fogarasi S. Periorbital and orbital cellulitis. *Pediatr Rev*. 2010;31(6):242–249.

- In the vast majority of cases, orbital cellulitis develops as a complication of rhinosinusitis with direct extension of infection into the orbit. Ethmoid sinusitis is the most common source given the thin lamina papyracea that separates the ethmoid sinus and the medial aspect of the orbit (Figure 28.3). Less often, orbital cellulitis develops from hematogenous seeding or orbital extension of a preseptal infection. Rarely, orbital cellulitis has been described as resulting from odontogenic infections.

Figure 28.3. Child with orbital cellulitis.

Reprinted with permission from Wright KW. Eyelid and orbital masses. In: *Pediatric Ophthalmology for Primary Care*. 3rd ed. American Academy of Pediatrics; 2008:223–241.

Q: What is the possibility of an accompanying cavernous venous thrombosis?

This diagnosis seems unlikely based on Chandler's examination findings and lack of abnormal intracranial findings on CT scan; however, if there is significant concern, an MRI/MRV would be warranted.

4. **Consider admission criteria.**

Q: What are admission criteria for a patient with orbital cellulitis?

Because orbital cellulitis represents a severe and vision-threatening complication of sinusitis, all patients with this diagnosis require hospitalization for the initiation of IV antibiotics, urgent surgical consultation, and close clinical monitoring.

Based on this knowledge, you agree that Chandler requires hospitalization.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Chandler is a 7-year-old boy with history of eczema, seasonal allergies, and recent diagnosis of URTI who is here with acute onset of left orbital cellulitis and a subperiosteal abscess secondary to left-sided maxillary and ethmoid sinusitis. His combination of laboratory test results and vital signs are consistent with sepsis; however, he is clinically stable, with adequate pain control, and is tolerating oral intake without difficulty. He requires hospitalization for treatment and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The treatment of orbital cellulitis generally involves a multidisciplinary team and is focused on prompt initiation of broad-spectrum IV antibiotics, determining the need for surgical intervention, and monitoring for possible complications.

1. **Consultation of specialists**
   - A coordinated multidisciplinary team is the standard approach for management of orbital cellulitis. This team most commonly includes the pediatric hospitalist, a pediatric ophthalmologist, and a pediatric otolaryngologist.
   - Further consultation with an infectious disease specialist, a neurologist, and other surgical subspecialists (eg, oculoplastic specialist, neurosurgeon) may be considered on a case-by-case basis or in accordance with institutional protocol.
   - For Chandler, you decide to consult both a pediatric ophthalmologist and pediatric otolaryngologist.
2. **Determining the need for surgical intervention:** Although most patients with orbital cellulitis can be managed medically, including those with small orbital abscesses, some patients do require operative intervention. These interventions are performed to drain abscesses, relieve increased orbital pressure, or obtain samples for culture.

Q: Which patients require surgical drainage?

- Patients that present with complete ophthalmoplegia, displacement of the globe/proptosis, or significant impairment of vision require urgent evaluation for prompt operative drainage of the abscess and paranasal sinuses. These symptoms indicate severe, vision-threatening disease.
- Studies have shown that surgical intervention is more likely to be needed in the following scenarios:
  - Large abscesses (typically defined as > 10 mm)
  - Nonmedial abscesses (eg, those extending from frontal sinuses)
  - Small abscess or orbital inflammation that is refractory to antibiotic therapy
  - Extraocular movement restriction
  - Age older than 9 years
- Commonly performed surgical procedures include paranasal sinus surgery and external orbitotomy. For medial abscesses, intranasal endoscopic drainage may be an option that allows the patient to avoid an external incision.

3. **Selecting antimicrobial therapy:** Before deciding on appropriate antimicrobial therapy for orbital cellulitis, it is important to first review the most common causative organisms.

Q: What are the common infectious etiologies of orbital cellulitis?

- The most commonly identified pathogens in orbital cellulitis include *Staphylococcus aureus* (methicillin-susceptible *S aureus* and methicillin-resistant *S aureus* [MRSA]) and *Streptococcus* species (eg, *Streptococcus pneumoniae*, group A β-hemolytic streptococcus, and *Streptococcus anginosus*).
- Although infections due to Hib have decreased since the introduction of the Hib vaccine, nontypeable *H influenzae* remains a major cause of sinus and orbital infections.
- Although less common, anaerobes, such as *Eikenella* and *Fusobacterium*, have also been reported. In immunocompromised patients or those in diabetic ketoacidosis, fungal sources also should be considered.
- Infections can be polymicrobial, particularly in older children and adolescents.

Q: What antimicrobial treatment should be used for patients with orbital cellulitis?

- Empiric IV antimicrobial therapy should be chosen to provide broad-spectrum coverage against gram-positive, gram-negative, and anaerobic bacteria.
- Coverage for MRSA should also strongly be considered. The specific agent should be based on local prevalence, regional sensitivities, and personal patient history.
- When community prevalence of clindamycin-resistant *S aureus* is low, an example initial antibiotic regimen is clindamycin *plus* a third-generation cephalosporin, such as ceftriaxone.
- For patients with severe symptoms or concern for clindamycin-resistant *S aureus* or highly resistant *S pneumoniae*, a regimen of vancomycin *plus* a third-generation cephalosporin, such as ceftriaxone, with or without metronidazole for anaerobic coverage is recommended.
- CNS penetration is not typically needed for orbital cellulitis unless there is concern for intracranial extension or other CNS complication. Apart from the retina, the orbit itself is not considered CNS space.
- Antibiotics can be transitioned from IV to oral once the patient has shown significant improvement in symptoms and examination of the affected eye returns to near normal. If definitive culture results are available, antibiotic coverage can be narrowed as appropriate. Empiric oral coverage can be achieved by clindamycin *or* trimethoprim-sulfamethoxazole *plus* either amoxicillin, amoxicillin-clavulanate, or cefdinir.
- Patients who do not begin to show improvement within 24 to 48 hours of initiating appropriate therapy should be considered for repeat imaging and reevaluation of their antibiotic regimen.
- Orbital cellulitis typically requires antibiotic therapy for a total of 2 to 3 weeks.

4. **Monitoring for complications**

Q: What complications should you watch for in a patient with orbital cellulitis?

- Increasing orbital pressure from edema, abscess, or other causes can damage the optic nerve, resulting in vision impairment or blindness. Increased pressure can present as worsening pain, proptosis, ophthalmoplegia, or vision change. Such symptoms should prompt emergent surgical intervention.
- CNS complications may include cavernous sinus thrombosis and intracranial extension of infection, including subdural empyema, abscess, or meningitis. Further imaging with MRI or MRV should be considered emergently if such CNS complications are suspected, as they can lead to vision loss, permanent blindness, or death.
- Serial examinations of the orbit should be conducted on a regular basis. Such examinations can affirm improvement or provide early recognition of disease progression that may require surgical intervention.
- Individuals at higher risk for complications include patients with late presentation, those who are immunocompromised, and those with inadequate medical or surgical treatment. It is worth noting that complications can also arise despite appropriate, timely, and aggressive intervention.
- Patients who have suspected sepsis should be monitored closely for clinical changes and to trend their heart rate and blood pressure.

5. **Additional therapies**

- Analgesia is important for patient comfort and may assist with the patient's ability to tolerate eye examination. Typically, this can be achieved with nonsteroidal anti-inflammatory drugs, though sometimes opioids are required. Reassessment is important, as worsening pain can be a sign of progressive disease.
- The utility of nasal decongestants, steroids, and antihistamines continues to be debated in the literature, and their use is typically directed by local expert opinion.

CASE FOCUS

Plan for Treatment and Monitoring

- **Consultations and decisions about surgical intervention:** After consulting pediatric ophthalmology and pediatric otolaryngology specialists, you determine that Chandler does not warrant emergent surgery based on his current examination and the small size of the abscess. As a multidisciplinary team, you agree that initially, he should be treated medically.
- **Anti-infectives:** You start Chandler on empiric IV antibiotic coverage with clindamycin and ceftriaxone. You anticipate antibiotic coverage for a total of 2 to 3 weeks with a plan to transition to oral antibiotics once he has shown substantial improvement.
- **Other therapies:** You order nonsteroidal anti-inflammatory drugs as needed for pain and fever.
- **Monitoring:** Chandler will be monitored closely, including serial vision assessments, to detect worsening symptoms or complications, which could prompt further imaging and reevaluation of his antibiotic regimen. Close monitoring of his vital signs is also warranted to ensure there are no signs of worsening sepsis, which could require a broadening of his antimicrobial coverage or fluid resuscitation.

Case Resolution

Chandler is treated in the hospital with IV antibiotics for 4 days while his symptoms gradually improve. He does not require surgical intervention. His eye culture grows multiple bacterial species, including *S pneumoniae*. On hospital day 4, he is discharged home on oral antibiotics to complete his 3-week antibiotic course. Chandler's family is given strict anticipatory guidance regarding return precautions, and Chandler is scheduled for outpatient follow-up with his pediatrician in 2 days and with pediatric ophthalmology and pediatric otolaryngology 1 week after discharge. He ultimately has full resolution of his symptoms and no residual complications.

Discharge Criteria

Q: How do you know when Chandler is ready to go home?

You can feel comfortable discharging your patient with orbital cellulitis when the following criteria are met:

- The patient's symptoms have substantially improved on antibiotics and their examination has returned to normal or near normal.
- Antibiotics have successfully been transitioned from IV to oral administration.
- The patient is tolerating oral intake.
- The patient's caregivers understand the importance of continued antibiotic therapy and have ensured follow-up.

Anticipatory Guidance

Q: What instructions should you provide to Chandler's caregivers upon discharge?

- Be sure to complete the full course of antibiotics.
- Follow up with Chandler's pediatrician as scheduled.
- Follow up with specialists as scheduled.
- Return to the ED for altered mental status, severe headache, facial numbness, neck stiffness, intractable vomiting, changes in vision, limited eye movements, or general worsening of fever, pain, redness, or swelling.

Clinical Pearls

- Preseptal cellulitis is a soft tissue infection that occurs anterior to the orbital septum. It is a relatively mild condition that is diagnosed clinically and treated on an outpatient basis with oral antibiotics.
- Orbital cellulitis is a soft tissue infection that occurs posterior to the orbital septum. It is a medical emergency that is definitively diagnosed with CT or MRI and treated on an inpatient basis with IV antibiotics.
- Suspicion for orbital cellulitis should be increased if a patient presenting with unilateral eye pain, redness, or swelling also has proptosis, ophthalmoplegia, or pain with eye movements.
- Patients diagnosed with orbital cellulitis should be admitted for broad-spectrum IV antibiotics. Clindamycin plus ceftriaxone is an appropriate initial regimen in most areas. Pediatric ophthalmology and pediatric otolaryngology should be consulted for further evaluation and to help determine if surgical intervention is needed in addition to medical management.
- If diagnosed early and treated appropriately, the majority of patients with orbital cellulitis recover fully without long-term complications.

Documentation Tips

- Include the failure of outpatient treatment, when applicable.
- Document findings of pain with extraocular eye movement, proptosis, or vision changes.
- Document findings of CT or other imaging, if available, including whether an abscess is present.
- Include whether bacteremia or sepsis is present.

Suggested Reading

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CASE 29

Philip, a 7-Year-Old Boy With Intermittent Abdominal Pain

CASE PRESENTATION

You are called to evaluate a 7-year-old previously healthy boy, Philip, who presented to the emergency department (ED) with diffuse abdominal pain that has worsened over the past few days. Upon arrival to the ED a couple of hours earlier, Philip was doubled over and clutching his abdomen. The physician in the ED obtained a comprehensive metabolic panel, an abdominal ultrasound, and an abdominal radiograph. Abdominal ultrasonography showed a normal appendix, and per the ED physician's review, the abdominal radiograph revealed no acute findings. A dose of ibuprofen does not seem to alleviate Philip's discomfort. The ED physician is concerned that his level of pain warrants further workup and monitoring. She calls you to evaluate Philip for admission.

Patient History and Review of Systems

Q: What information should you collect from Philip and his caregivers?

- History of present illness
  - Characteristics of the abdominal pain, including onset and duration, location, quality, severity, progression, aggravating and alleviating factors (including association with eating or drinking), whether the pain interferes with activity or interrupts sleep, and any associated weight loss
  - Tolerance of oral intake, including timing of last oral intake and details regarding what was consumed
  - Changes in urinary output
  - Typical diet and recent dietary modifications
  - Frequency of bowel movements, consistency and diameter of stool, presence of blood in stool
  - Recent trauma
- Associated symptoms, such as fever, vomiting, diarrhea, constipation, dysuria, stool or urinary incontinence, rashes, joint pain, cold intolerance, hair loss, weight gain, daytime tiredness, polyuria, or polydipsia
- Medical history, including history of constipation, timing of the passage of meconium following birth, trends in height and weight, and surgical history
- Medications, including nonsteroidal anti-inflammatory drugs, laxatives, and recent antibiotics
- Family history of gastrointestinal (GI) illnesses, including colorectal cancer, inflammatory bowel disease, irritable bowel syndrome (IBS), and celiac disease
- Detailed social history including living situation, potential lead exposure, screening for food insecurity, presence of stressors at home or school, screening for abuse (ie, exposure to violence, history of physical injury)

CASE FOCUS

History and Review of Systems

In the ED, you find an anxious-appearing child sitting next to his mother on the hospital bed. During your conversation with Philip and his mother, you learn that Philip's abdominal pain worsened 4 days ago, but he has had mild pain for the past 3 months. The pain is intermittent, usually occurring 4 to 5 times per week and lasting 30 to 60 minutes at a time. Because the pain was mild and each episode quickly self-resolved, his mother planned to discuss this at his next health supervision visit but had not sought additional evaluation. In the last 4 days, however, the pain has occurred daily. When asked more details about his pain, Philip gestures to his abdomen and states that his pain is "all over" but then points to the left lower quadrant, where he indicates that the pain is the worst. He describes the pain as "crampy" and says that it comes and goes. Philip and his mother are unsure whether there is any association of the pain with eating or drinking. The pain does not awaken Philip from sleep, but his mother does note that it sometimes prevents him from wanting to play outside.

Philip's mother says that he has "not been very hungry" over the last couple of days. He ate a small bowl of cereal with milk this morning but did not eat any lunch. He has been drinking normally. He has had no recent changes in his urinary output. He has not been sick recently. Philip has taken ibuprofen daily over the past 3 days for the abdominal pain. Philip's mother states that he has had irregular bowel movements and constipation for "a long time." She does not remember the exact timing of meconium passage following birth but does not believe it was abnormal. She estimates that his stools range from once daily to once every 6 to 7 days, but she is not entirely sure, as he uses the bathroom on his own. When you ask Philip, he describes his stools as "hard little balls, but sometimes it's like water." He indicates that defecation is a little painful. He has not noted any blood or mucous in his stool, and he thinks his last bowel movement was roughly 1 week ago.

You learn that he has begun soiling himself recently. The accidents first started around 4 weeks ago, initially only at night or early morning and occurring approximately once every few days; however, they have become more frequent and he is soiling himself at school, causing great embarrassment. His mother also worries that he is being bullied at school because of this. He is a picky eater and mostly eats meat, burgers, pizza, and french fries. He drinks 1 cup of milk and 2 cups of juice or soda daily. His height has always tracked along the 50th percentile. Philip's weight has been greater than the 85th percentile for as long as his mother can remember, and it has been consistently greater than the 99th percentile for the last 2 years.

You conduct a review of symptoms, which is positive only for generalized fatigue. Family history reveals that Philip's father has celiac disease.

You inquire more about Philip's medical history. Other than obesity, he has no other medical diagnoses. He does not take any regular medications, and he has not taken laxatives or recent antibiotics. He has never had any surgeries. His mother reports that "while he seems normal to me, he has always been anxious around people outside of the family." His mother reports that his teachers say that he is "quiet, sensitive, and slow to warm up" but is also a "sweet and well-mannered young man." He interacts with and plays appropriately with the other children in his class. However, his teachers have noticed that over the last few weeks he has become more irritable, moody, and distracted.

Detailed social history reveals that Philip lives with his mother and maternal grandparents. His parents were divorced 6 months ago, and he sees his father every other weekend. The separation was amicable, and both parents remain equally involved in Philip's care. However, his mother states that Philip has been coping poorly with their separation and recently started seeing a counselor. His lead exposure screening is negative. There is no concern for food insecurity, and Philip's mother denies any history of domestic violence.

Physical Examination

Q: What parts of the physical examination should you focus on for Philip?

- Complete set of vital signs
- Weight and height, with comparison to previous measurements if available
- General: overall appearance, level of distress
- Head: hair thinning
- Neck: thyroid examination
- Cardiovascular: heart rate and rhythm, pulses, capillary refill
- Abdomen: distension, tenderness, bruising, rigidity or guarding, quality of bowel sounds, hepatosplenomegaly, masses, McBurney point tenderness, psoas sign, obturator sign, Rovsing sign (refer to Back to Basics: Abdominal Examination in Case 10 for descriptions of specific signs)
- Testicles: pain, scrotal edema, cremasteric reflexes
- Neurologic: sensory loss, lower extremity weakness, hypotonia, hyporeflexia
- Musculoskeletal: nonpitting edema
- Skin: turgor, hyper- or hypopigmentation, dryness or scaling, palpable purpura, ulcers, rashes, nodules
- Rectal: anal fissures, skin tags, lesions, hemorrhoids, sphincter tone, presence of fecal impaction, occult bleeding, stool expulsion
- Psychiatric: mood, affect, interactions with caregiver

CASE FOCUS

Physical Examination

Philip's vital signs show that he is afebrile (36.7 °C [98.1 °F]). His heart rate (84 beats/min) and respiratory rate (16 breaths/min) are within normal limits. He has a normal blood pressure for age (98/59 mm Hg) and a normal oxygen saturation on room air (99%). He weighs 46 kg and is 131 cm tall (body mass index: 27, >99th percentile). He is comfortable and in no acute distress, but you notice that he does not make much eye contact with you and speaks quietly. You ask him how he feels, and he states that his "stomach does not hurt as much right now."

On examination, Philip appears clinically well hydrated with brisk capillary refill. His abdomen is slightly distended, and he complains of mild discomfort with moderate palpation equally throughout all quadrants. There is no McBurney point tenderness. There is no guarding or rigidity. Psoas, obturator, and Rovsing signs are all negative. You are able to palpate stool in the left lower quadrant of his abdomen. You do not appreciate any hepatosplenomegaly or abdominal masses. He has hypoactive bowel sounds.

Philip has a normal hair pattern. On neck examination, there are no masses or goiter. Philip's lungs are clear to auscultation bilaterally. On cardiac examination, there is a regular heart rate and rhythm with no murmur present. Philip's extremities are without swelling or deformity. You do not see any skin rashes, nodules, or other abnormalities. A neurologic examination reveals 5/5 strength and intact sensation of bilateral lower extremities. He has 2+ patellar reflexes. On examination of his genitalia, there is no scrotal edema or tenderness, and there is a normal cremaster reflex bilaterally. You consider a digital rectal examination, but given the patient's distress and anxiety, you decide to hold off for the time being.

Differential Diagnosis

Q: What is the differential diagnosis for a child with chronic abdominal pain and irregular stooling pattern?

The differential diagnosis for a child with chronic abdominal pain and an irregular stooling pattern is shown in Table 29.1 and is divided into causes that seem more and less likely based on Philip's presentation.

Table 29.1. Differential Diagnosis for a Child With Chronic Abdominal Pain and Irregular Stooling Pattern

Diagnoses of highest suspicion	• Celiac disease • Functional constipation[a] • Hypothyroidism
Other diagnoses to consider	• Acute gastroenteritis with postinfectious ileus • Anal achalasia • Bowel obstruction • CF • Hirschsprung disease (short segment) • IBD • Intestinal obstruction • Intra-abdominal mass • Lead poisoning • Medication side effect: opioids, anticholinergic agents • Neuromuscular disorders (cauda equina, autonomic neuropathy, tethered cord) • Other functional gastrointestinal disorder (ie, IBS, functional abdominal pain NOS, abdominal migraine, and functional dyspepsia) • Pseudoobstruction

Abbreviations: CF, cystic fibrosis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NOS, not otherwise specified.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with chronic abdominal pain and irregular stooling pattern?

- Many etiologies on the differential diagnosis for chronic abdominal pain with an irregular stooling pattern can be considered less likely after obtaining a thorough history, physical examination, and review of the child's growth curves. For example, a normal neurologic examination and typical development decreases the likelihood of neuromuscular disorders and lead poisoning. A thorough history can help eliminate medication side effects and disorders that usually present with symptoms in infancy (eg, Hirschsprung disease). Additionally, many of the differential diagnoses related to malabsorption (eg, celiac disease) and altered metabolism (eg, hypothyroidism) can impact both linear growth and weight while causing constipation and abdominal pain. Because Philip's height and weight have been tracking without significant changes, these diagnoses are less likely.

- Functional constipation remains highest on the list of differential diagnoses for Philip, although there is not one specific study to confirm this diagnosis. IBS or functional abdominal pain may also be contributing to Philip's presentation, but likewise, there are no specific diagnostic tests to confirm these diagnoses. Diagnosis of IBS or functional abdominal pain is made based on history, physical examination, and the exclusion of other etiologies.
- Abdominal radiograph is a low-cost, low-risk study that is useful to evaluate fecal impaction, especially in a child who has obesity or who is unable to tolerate a rectal examination. It may also provide a general visualization of the degree of stool retention and screen for bowel obstruction; however, the presence of stool on radiograph overall has a poor correlation with clinical constipation.
- Laboratory testing should be considered if there are aspects of history and physical examination concerning for systemic disease. Concerning elements of history and physical examination may include signs of malnutrition, bloating, distension, vomiting, diarrhea, family history of celiac disease, or a history of autoimmune disease.
  - For patients with family history of celiac disease, or a history of autoimmune disease, consider evaluating for celiac disease (serum immunoglobulin [Ig] A to tissue transglutaminase, total IgA).
  - For patients presenting with cold intolerance, fatigue, weight gain, or growth decline, consider workup for thyroid abnormalities (thyroid-stimulating hormone [TSH] level, free thyroxine level).
  - The presence of neurocognitive deficits, irritability, or living in a residence built before 1978 (especially when there is a recent history of home remodeling) should warrant consideration of lead poisoning and evaluation of venous blood lead level.
- Magnetic resonance imaging of the spine should be considered in the presence of concerning neurologic signs/symptoms, including lower extremity weakness or loss of sensation, or loss of bowel/bladder control.
- If concern for Hirschsprung disease exists, a barium enema may aid in the initial evaluation. For diagnosis, rectal biopsy is necessary to confirm the absence of ganglion cells in the rectum and sigmoid colon.
- Anorectal manometry and anal sphincter electromyography can assess for appropriate relaxation of the internal anal sphincter and the rectal sensory threshold and evaluate activity of the external anal sphincter and puborectalis muscles. Abnormal results could increase suspicion for Hirschsprung disease or a motility issue.
- A sitz marker study involves swallowing radiopaque markers that are tracked radiographically through the GI tract. This study can be used to assess for colonic transit abnormalities.

CASE FOCUS

Diagnostic Evaluation

Philip's evaluation in the ED includes a normal comprehensive metabolic panel. His right lower quadrant abdominal ultrasonography shows a normal appendix, and his abdominal radiograph reveals a moderate to large amount of scattered stool within a nondilated colon and rectum.

Although functional constipation remains high on your differential for Philip, you consider important elements from his history to guide your diagnostic evaluation elements. For now, you decide to expand the workup to include TSH level, free thyroxine level, tissue transglutaminase IgA antibody, and total serum IgA. The results are as follows:

Laboratory test	Result	Reference range
TSH	1.33 mIU/mL	0.5–4.5 mIU/mL
Free T4	1.2 ng/dL (15.45 pmol/L)	0.7–2.0 ng/dL (9.01–25.74 pmol/L)
Tissue transglutaminase IgA antibody	0.2 U/mL	0–4 U/mL
Total serum IgA	94 mg/dL (0.94 g/L)	33–236 mg/dL (0.33–2.36 g/L)

Abbreviations: CBC; complete blood cell count; IgA, immunoglobulin A; T4, thyroxine; TSH, thyroid-stimulating hormone.

Arriving at a Diagnosis

Q: How do you develop an assessment for Philip?

To arrive at a diagnosis, you first review Philip's history, examination, and diagnostic evaluation to develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology. Afterward, admission criteria can be generated for your specific diagnosis.

1. **Interpret key findings from the history and physical examination:** Philip's abdominal pain, encopresis, decreased appetite, painful defecation, and infrequent passage of hard stool are highly suspicious for either functional constipation or IBS, especially in the absence of "red flag" symptoms such as fever, weight loss, or nighttime awakening due to pain. The presence of palpable stool in the left lower quadrant of the abdomen and the fact that he has not had a bowel movement in a week indicates fecal impaction. His physical examination findings of generalized abdominal tenderness, palpable stool, and hypoactive bowel sounds without signs of peritonitis are consistent with these diagnoses also. If the pain were to improve upon treatment of his constipation, this would indicate functional constipation. If not, this would suggest IBS.
2. **Interpret diagnostic studies:** The laboratory evaluation is all within normal limits, making thyroid abnormalities and celiac disease less likely. On abdominal radiograph, there is no evidence of an obstruction. There is a moderate to large stool burden present; however, this finding alone is not sufficient to diagnose constipation or rule out an alternative diagnosis. Radiographic evidence of stool retention is seen as frequently in clinically constipated children as compared with those who are not clinically constipated.

3. **Develop the list of findings.**

Q: What major findings have you have identified for Philip?

- Chronic constipation with encopresis and concern for fecal impaction
- Chronic/recurrent abdominal pain
- Stressful family circumstances and concern for associated anxiety
- Obesity
- High-calorie/low-fiber diet
- Decreased oral intake

4. **Revisit the differential diagnosis.**

Q: How are organic and functional constipation differentiated?

Constipation is loosely defined as the painful and infrequent passage of hard stool. It is therefore important to consider the normal stooling patterns for different age groups (Table 29.2).

Table 29.2. Average Stooling Frequency in Children, by Age

Age group	Normal stooling pattern
Infants	Highly variable based on diet (human [breast] milk vs formula), although average is 3–4 stools per day
2–3 years	1–2 stools per day
4 years and older	Variable; 3 times per day to 3 times per week

- Organic constipation: In children, fewer than 5% of cases of constipation have an underlying organic cause. Organic causes most commonly occur in younger infants with red flag symptoms (eg, fever, vomiting, bloody diarrhea, ribbon-like stool, constipation since birth, delayed passage of meconium beyond 48 hours, malnutrition, urinary incontinence). Organic causes of constipation include the following:
  - Hirschsprung disease is commonly diagnosed in early infancy; however, short and ultra-short segment disease may present later in life. Patients with short and ultra-short Hirschsprung disease most often have a history of poor growth and chronic constipation without fecal incontinence. This is not consistent with Philip's history, making Hirschsprung disease less likely.
  - Neurologic disease can lead to bowel dysfunction and subsequent constipation. Given the absence of pertinent neurologic history and a normal neurologic examination, etiologies such as spinal cord trauma, cauda equina, spinal dysraphism, cerebral palsy, and sacral masses are unlikely.
  - Cystic fibrosis (CF) can cause constipation due to the abnormal composition of intestinal fluid, pancreatic insufficiency, and pseudoobstruction of the ileocecum, otherwise known as *distal intestinal obstruction syndrome*. Although the newborn screen immunoreactive trypsinogen/DNA assays detect CF with excellent sensitivity, missed cases do occur, and late diagnoses are possible. Features that argue against CF in Philip's history are the lack of respiratory symptoms or sinus disease, and absence of malnutrition.
  - Hypothyroidism can present with constipation. Patients may also have sluggishness, poor concentration, cold intolerance, weight gain, dry skin, and brittle hair. Although Philip has exhibited some of these symptoms, his normal thyroid function tests indicate that he does not have hypothyroidism.

- Lead poisoning presents with neurocognitive deficits, fatigue, anemia, and constipation. Philip has exhibited some of these symptoms, but his lead exposure screening was negative; thus, this is lower on your differential diagnosis.
- Celiac disease can present at any age with bloating, abdominal pain, constipation, diarrhea, weight loss, and dermatitis herpetiformis rash. Philip's clinical presentation combined with his family history of celiac disease is sufficient to have warranted testing. His normal serum IgA to tissue transglutaminase and total IgA make this diagnosis less likely.

- Functional constipation: The majority of cases of constipation in healthy children are due to idiopathic, or functional, constipation (also known as *functional fecal retention* or *withholding*). The Rome criteria (Box 29.1) are used to make the diagnosis.
  - Functional constipation may be triggered by stressful or uncomfortable changes in the patient's environment.
  - Behavioral and neurodevelopmental disorders, such as autism spectrum disorder, are often associated with functional constipation.
  - Dietary changes in children or infants, such as transition from breast milk to cow milk or transition to solid foods, can trigger functional constipation.
  - Anal fissures, external hemorrhoids, or other causes of rectal pain may lead to stool-withholding behavior.
  - Low "self-efficacy" for defecation is the avoidance of defecation out of fear that one cannot accomplish the task of defecation without pain or discomfort. Low self-efficacy for defecation is associated with functional constipation.

Box 29.1 Rome IV Criteria for the Diagnosis of Functional Constipation in Infants and Children

Children 4 years and older
Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for diagnosis of IBS: • 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years • At least 1 episode of fecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of large diameter stools that may obstruct the toilet In addition, after appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Abbreviation: IBS, irritable bowel syndrome.

Adapted with permission from Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional disorders: children and adolescents. *Gastroenterology*. 2016;150(6):1456–1468.e2.

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Philip's presentation?

Based on your assessment and statistical likelihood, you are now reasonably confident that functional constipation is the cause for Philip's symptoms. There have been no concerning physical examination findings, laboratory test results, imaging, or historical red flags that would suggest an alternate cause for his constipation and encopresis. Additionally, you have done your due diligence to rule out hypothyroidism and celiac disease.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with functional constipation?

Functional constipation is frequently treated on an outpatient basis with osmotic, lubricant, or stimulant-based laxatives. Chronic constipation can sometimes lead to fecal impaction, which describes significant blockage by stool in the distal GI tract and is generally palpable on abdominal or rectal examination. In these cases, evacuation of the bowels, or a "cleanout," is required before initiating maintenance therapy, as outpatient treatments do not suffice. Polyethylene glycol (PEG) is the osmotic laxative of choice, and large volumes are generally required to achieve successful evacuation. The oral route is preferred and, if tolerated, may be attempted on an outpatient basis. However, in the pediatric population, oral administration of PEG is sometimes not well tolerated, and nasogastric tube insertion and hospital admission may be necessary. Scenarios in which inpatient hospitalization for bowel cleanout are indicated include:

- Failure of outpatient management
  - Inability to tolerate prescribed bowel regimen due to associated pain, nausea, vomiting, or aversion to the volume of PEG required
  - Continued fecal impaction and encopresis despite treatment
- Inability to tolerate oral intake

You suspect that Philip has a fecal impaction based on the presence of palpable stool on his abdominal examination, the presence of encopresis, and his radiographic findings. Philip requires a bowel cleanout, but you are uncertain whether this can be done on an outpatient basis. You consider the previously noted criteria for outpatient bowel cleanout, noting that his pain is not yet resolved. Furthermore, he has underlying stressful family circumstances, anxiety, and dietary concerns that may benefit from inpatient behavioral health and dietician consults. After discussing your concerns with Philip and his mother, you decide that it is reasonable to admit him.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Philip is a 7-year-old boy who presents with chronic abdominal pain and encopresis secondary to fecal impaction from functional constipation. Given the severity of his impaction, current level of pain, and poor oral intake, he requires hospitalization for a bowel cleanout.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goals of managing fecal impaction from functional constipation include symptomatic relief while treating the acute impaction and creating a management plan for chronic constipation. You decide to divide treatment considerations into the following categories:

1. **Acute pharmacologic treatment**
   - PEG: Evidence-based guidelines from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommend high-dose oral PEG for a maximum of 6 days as first-line treatment for children presenting with fecal impaction. It has been found to be more effective than lactulose, milk of magnesia, mineral oil, or placebo. PEG with electrolyte solution can be given by nasogastric tube if needed. Although practice varies between institutions, PEG is generally administered at a rate of 25 to 40 mL/kg/h with a maximum rate of 400 mL/h until stool is clear. You think Philip would benefit from PEG as a first-line treatment.
   - Enema: Alternatively, an enema can be given once daily for up to 6 days. Although equally efficacious as high-dose PEG, enemas are invasive and often more distressing to the patient. However, literature suggests that enemas are associated with less frequent fecal incontinence during treatment of fecal impaction and more immediate relief of pain when compared with PEG treatment. Saline, mineral oil, glycerin, or sodium phosphate enemas may achieve more rapid disimpaction. Some providers choose to administer an enema in combination with PEG for severe cases. Because of the potential distress this intervention may cause, you plan to wait and assess the effectiveness of PEG before moving to this intervention.
2. **Symptom management**
   - Antiemetics: If the patient is experiencing nausea, vomiting, or abdominal distension while receiving PEG with electrolyte solution via nasogastric tube, the infusion should be decreased to a slower rate. Additionally, ondansetron is safe and well tolerated in children experiencing nausea.
   - Analgesics: Functional constipation can cause significant abdominal pain, which is often the presenting symptom. In one pediatric emergency medicine study, nearly a quarter of pediatric patients with abdominal pain presenting to the ED had a discharge diagnosis of functional constipation. Pain relief is normally achieved with evacuation of stool. If Philip experiences continued pain during evacuation, acetaminophen or ibuprofen are appropriate analgesics for first-line use. Opioid analgesics are not recommended, as they can exacerbate constipation.
3. **Maintenance pharmacologic therapy**
   - Patients should continue on a maintenance regimen of oral laxatives to prevent reaccumulation of stool and reimpaction. A smaller, daily dose of PEG titrated to maintain daily, soft stools is first-line chronic management. Per expert opinion, maintenance therapy should be continued for a minimum of 2 months following impaction and at least 1 month following resolution of all constipation-related symptoms.
   - Stimulant laxatives (eg, senna, bisacodyl) can be used intermittently and can be added as a second-line maintenance therapy. They are not routinely used as pharmacologic management of fecal impaction, as they may cause abdominal cramping due to their stimulant effect on colonic smooth muscle.
   - Probiotics have been suggested as a treatment modality for functional constipation; however, they have not been shown to regulate defecation frequency or alleviate pain.
4. **Diet**
   - Despite its popular practice, increasing fiber intake beyond the recommended daily amount has not been definitively shown to help acute or chronic constipation.
   - Increasing fluid intake has also not been shown to treat constipation and should only be encouraged if the patient is dehydrated.

- Inpatient dietician consultation may be helpful to encourage a balanced diet and identify solutions for patients, like Philip, who have been identified as having a diet that does not meet the recommended daily amount of fiber or other nutrients.
- It is important to screen for and address any identified food insecurity, as variable access to healthy options will have a significant impact on the child's diet.

5. **Activity:** There is no significant evidence to show that increasing physical activity stimulates bowel activity, though this is often recommended.
6. **Consultations**
   - Behavioral health: There may be benefits to identifying and addressing psychosocial and behavioral barriers to healthy stooling patterns in the management of functional constipation, although studies have not demonstrated that the addition of behavioral therapy to laxative treatment is more effective than laxative treatment alone.
   - Gastroenterology: Although consultation with a gastroenterology specialist is not typically needed for functional constipation, it may be considered when initial interventions are unsuccessful or when there are concerns for an alternative diagnosis that may require further workup.

CASE FOCUS

Plan for Treatment and Monitoring

- **Pharmacologic treatment:** You explain options for disimpaction to Philip's mother. She prefers a PEG with electrolyte solution cleanout via nasogastric tube. She worries that an enema will cause significant distress to Philip, and she does not believe he will be able to tolerate the large volume of solution by mouth. You order the PEG with electrolyte solution to be delivered at an initial rate of 100 mL/h and increased by 100 mL every hour to a goal rate of 400 mL/h.
- **Antiemetics:** If Philip experiences vomiting, you will slow the rate of PEG with electrolyte solution infusion. You also order ondansetron as needed.
- **Analgesia:** Philip continues to experience intermittent abdominal pain. You order acetaminophen as your first-line analgesic. You allow ibuprofen for breakthrough pain.
- **Diet:** Philip states that he is now hungry. You find it reasonable to allow a clear liquid diet.
- **Activity:** You place no restrictions on physical activity.
- **Consults:** Given Philip's typical daily diet, you decide to consult the on-call dietician. Given his underlying anxiety, shame, parents' divorce, and behavioral concerns at school, you think he would benefit from a behavioral health evaluation and intervention, as psychosocial distress and constipation often co-occur. You decide to wait to consult a gastroenterologist, but you will do so if your intervention does not go as planned or other alarming symptoms emerge.
- **Monitoring:** You order strict monitoring of intake and output, vital signs every 4 hours, and daily weights.

Case Resolution

Upon his arrival to the floor, Philip tolerates nasogastric tube placement well and PEG is started. The rate is slowly increased overnight and he soon begins to have large volume stools. He has some mild abdominal cramping initially, which improves over the next 24 hours. The dietician sees Philip and his mother and helps them generate a plan for a more balanced diet at home. The behavioral health team sees Philip, teaches him some age-appropriate stress-alleviating techniques, and connects him with an outpatient therapist to continue to work through the stress he is experiencing at home. Thirty-six hours after admission, his stool is clear and has a liquid consistency. His pain is resolved, and he is tolerating oral intake. You decide Philip is ready for discharge home with a plan for daily PEG and close follow-up with his pediatrician.

Discharge Criteria

Q: How do you know when Philip is ready to go home?

You can feel comfortable discharging your patient with functional constipation and fecal impaction when the following criteria are met:

- Stool is clear, watery, and pale yellow.
- Pain is adequately controlled.
- The patient is tolerating oral intake without emesis.

Anticipatory Guidance

Q: What instructions should you provide Philip's caregivers upon discharge?

- Start maintenance regimen of daily PEG. If this is unsuccessful, it is reasonable to trial one or more alternative laxatives, such as other osmotic laxatives (eg, lactulose, magnesium hydroxide). Stimulant laxatives (eg, senna) and stool softeners (eg, mineral oil, docusate) may be useful additions to the bowel regimen.
- Closely monitor consistency and frequency of stools. A reasonable goal is at least 3 bowel movements per week without encopresis or pain on defecation.
- Provide a positive and supportive home environment during treatment. Avoid blaming or shaming Philip.
- Encourage a balanced diet with adequate fiber, whole grains, vegetables, and fruits, and 32 to 64 fl oz of water daily for maintenance of general health.
- Return to care for worsening abdominal pain, frequent emesis, inability to eat or drink, rectal bleeding, or any new concerns.
- Follow up with Philip's primary pediatrician for posthospitalization assessment and ongoing management.

Clinical Pearls

- The majority of cases of constipation are functional. Chronic constipation can lead to fecal impaction, abdominal pain, and vomiting.
- The mainstays of treatment for functional constipation include enteric laxatives or rectal enemas for disimpaction and maintenance therapy. Psychosocial support and a balanced diet should be encouraged.
- Most cases of functional constipation can be managed on an outpatient basis; however, inpatient admission may be required in cases of failed outpatient management or for patients who cannot tolerate oral intake or do not have the ability to follow up regularly.

Documentation Tips

- Include number of days since last stool.
- Include home treatments attempted to alleviate constipation.

Suggested Readings

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CASE 30

Alex, a 9-Year-Old Boy With Edema and Hematuria

CASE PRESENTATION

You are working an overnight shift when your attending physician asks you to evaluate a direct admission patient who just arrived as a transfer from an outside hospital's emergency department (ED). You are told that the patient, named Alex, is a 9-year-old boy who presented to that ED with dark urine, fatigue, and eye swelling. At the outside ED, his urine dipstick was positive for the presence of blood; therefore, the ED physician requested transfer to your hospital so that Alex's symptoms could be further evaluated at a children's hospital.

Patient History and Review of Systems

Q: What information should you collect from Alex and his caregivers?

- History of present illness
  - Onset, duration, and progression of symptoms
  - Urine description: color (eg, yellow, brown, pink, red), general appearance (eg, clear, cloudy, foamy), odor
  - Recent voiding history: amount; frequency; presence of any dysuria, urgency, or flank/suprapubic pain
  - Other areas of edema and any recent changes in weight
  - Recent abdominal or back trauma
  - Recent illnesses (especially respiratory, skin, or gastrointestinal [GI])
  - Prior episodes of dark urine
  - Recent travel or sick contacts
  - Associated symptoms, such as fever, headache, nausea, vomiting, diarrhea, constipation, abdominal distention, abdominal or flank pain, shortness of breath, chest pain, cough, skin changes (rashes, bruising, petechiae, jaundice), joint swelling or pain, or myalgias
- Medical history, including overall state of health, growth, and surgical history
- Medications, including recent use of antibiotics and over-the-counter medicine (eg, nonsteroidal anti-inflammatory drugs)
- Family history: kidney disease, transplant, dialysis, or stones; hearing loss

CASE FOCUS

History and Review of Systems

Upon arrival to Alex's room, you meet him and his parents. Alex's parents report that he is generally healthy, growing well, and fully vaccinated, but they explain that both he and his sister were sick with a sore throat and fever 2 weeks ago. At that time, his highest temperature was 38.8 °C (101.8 °F). He returned to baseline health status within a week, and no medications other than antipyretics were given.

Over the last 3 days, Alex's parents have noticed that he has had a decreased appetite and fatigue. Last night and this morning, Alex told them he had brown-colored urine, which they attributed to not drinking sufficient fluids. Alex did not notice any odor or foam in his urine. This morning, his mother noticed swelling around his eyes. He has never had swelling like this before and does not have a history of allergies; his mother gave him diphenhydramine but does not think it helped. His parents have not noticed any swelling in other parts of his body. He has had only 1 small void today.

Alex has not had any fevers since his illness 2 weeks ago, and he denies headache, chest pain, shortness of breath, palpitations, nausea/vomiting, abdominal pain, constipation, dysuria, urinary urgency, skin changes, joint pain, or back pain. He frequently plays outside with his friends and is on an after-school basketball team, but he denies any recent trauma. The family has not recently traveled, and they are unaware of any family members with kidney diseases or conditions, renal stones, or hearing abnormalities. Other than his sister's recent illness, he is not aware of any sick contacts. Alex has not had any surgeries and has never had prior similar episodes. Alex's mother checked his online health portal and found that his weight at a routine pediatrician visit 3 months ago was 28.3 kg (48th percentile).

Physical Examination

Q: What parts of the physical examination should you focus on for Alex?

- Complete set of vital signs
- Weight, with comparison to most recent weight
- Overall appearance
- Appearance of eyes (icteric, sunken, periorbital edema)
- Mucous membranes (moistness, lesions, hypertrophy)
- Oropharynx (exudates, erythema, palatal petechiae)
- Lymphadenopathy
- Cardiovascular: signs of pericardial effusion or heart failure (accessory heart sounds, rubs, gallops, distended neck veins), tachycardia, peripheral pulses, capillary refill time
- Respiratory: signs of pulmonary fluid overload (tachypnea, decreased breath sounds, work of breathing, crackles, hypoxia), shortness of breath, improvement of respiratory effort (sitting vs supine)
- Abdomen: distension, quantity and quality of bowel sounds, tenderness, guarding, hepatosplenomegaly, masses, fluid wave
- Flank: costovertebral angle tenderness, bruising, masses
- Back: sacral edema

- Peripheral edema, location and presence or absence of pitting
- Skin: color, turgor, rashes, bruising, bleeding
- Joint swelling and range of motion
- Genitals: scrotal edema or evidence of urethritis
- Visual examination of urinary specimen (if possible)

CASE FOCUS

Physical Examination

On your evaluation, Alex is afebrile. He is hypertensive with a blood pressure of 128/89 mm Hg (verified by repeat measurement). His heart rate, respiratory rate, and oxygen saturations are normal. His weight is 30.1 kg (55th percentile), and his height is 135 cm (50th percentile).

On examination, Alex appears tired but is nontoxic. He is alert, oriented, and converses appropriately. You note moderate periorbital edema without conjunctival injection or discharge. His mucous membranes are moist, and his oropharynx is normal without exudate, injection, or palatal petechiae. His neck is supple without lymphadenopathy. His cardiac and respiratory examinations are unremarkable. His capillary refill time is 2 seconds with brisk peripheral pulses. No jugular venous distention is noted. Alex's abdomen is soft, nontender, and without hepatosplenomegaly. There is no fluid wave noted. There is no costovertebral angle tenderness or suprapubic pain. You also notice mild bilateral pitting edema of his lower extremities. There is an indentation of the skin from his socks and his underwear. The genital examination reveals mild scrotal edema. His bilateral testes are palpable within the scrotum. The remainder of the examination is unremarkable. Visualization of a urine specimen reveals light brown urine without cloudiness or sediment.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with edema, oliguria, and hematuria?

This combination of features is highly suggestive of renal pathology, the different causes of which are listed in Table 30.1. Of these, you are most concerned about a type of glomerulonephritis (GN).

Table 30.1. Differential Diagnosis for a Child With Edema, Oliguria, and Hematuria

Diagnoses of highest suspicion	• GN, specifically the following types: — Alport syndrome — Goodpasture syndrome (anti–glomerular basement membrane disease) — Granulomatosis with polyangiitis (formerly called *Wegener's granulomatosis*) — IgA nephropathy (also called *Berger's disease*)[a] — Membranoproliferative GN — Postinfectious GN, including PSGN[a] — Rapidly progressive GN[a] — SLE nephritis[a]
Other diagnoses to consider	• Acute tubular necrosis related to heme- or myoglobin-induced injury • GN, other types: — Endocarditis-associated GN — IgA vasculitis — Shunt infection-related GN • HUS • Interstitial nephritis related to medications, infection, or systemic disease • Renal vein thrombosis

Abbreviations: GN, glomerulonephritis; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; PSGN, poststreptococcal glomerulonephritis; SLE, systemic lupus erythematosus.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with hematuria, oliguria, and edema?

For patients in whom there is concern for hematuria, oliguria, and fluid overload, a diagnostic evaluation is indicated. Initial testing should include the following:

- Blood pressure measurement (if not previously obtained).
- Urinalysis and microscopy to confirm hematuria and evaluate for proteinuria or other abnormalities.
  - A urine dipstick that is positive for blood can indicate the presence of hematuria, myoglobinuria, or hemoglobinuria. To distinguish among these 3 possibilities, the sediment from a centrifuged urine specimen should be evaluated by microscopy. Urine microscopy can confirm the presence of red blood cells (RBCs), quantify the number of RBCs present, and evaluate for casts, crystals, bacteria, or other cells. The presence of RBC casts is indicative of glomerular disease.
  - For heme-positive urine without the presence of RBCs on microscopy (ie, a false-positive dipstick), a serum creatine kinase level, reticulocyte count, and complete blood cell count (CBC) should be considered to evaluate for myoglobinuria or hemoglobinuria.
- Serum chemistry panel to evaluate kidney function and electrolyte status.
- Serum albumin level to assess for hypoalbuminemia when proteinuria or peripheral edema is present.
- CBC with a peripheral smear to evaluate for signs of infection/inflammation, anemia, thrombocytopenia, or abnormal cell morphology.

- If hematuria is confirmed by urinalysis, complement levels (C3 and C4) should be obtained to help in the evaluation of possible GN; based on interpretation of C3 and C4 levels and elements from the patient's history, other testing may be needed.
  - For patients with a history of a preceding respiratory or skin infection, serum antistreptolysin O (ASO) and antideoxyribonuclease (anti-DNase) B levels should be considered. Elevated levels may indicate a recent infection by *Streptococcus pyogenes,* a common causative agent in postinfectious GN.
  - In the setting of a recent diarrheal illness, or when the CBC findings are concerning for hemolytic uremic syndrome, a stool culture should be obtained to evaluate for Shiga toxin–producing *Escherichia coli*.
  - In patients with a low C4 level, an antinuclear antibody (ANA) screen should be ordered to differentiate between lupus-related nephritis or membranoproliferative GN (type 1).
  - When complement levels are normal, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis or Goodpasture syndrome should be considered. Testing for these etiologies may include a serum ANCA and antiglomerular basement membrane antibodies.
- Clinicians should also consider obtaining a renal ultrasound to evaluate renal anatomy and exclude urinary tract obstruction; if a renal vein thrombosis is suspected, the addition of Doppler ultrasonography can assess vascular blood flow.
- Occasionally, a renal biopsy may be needed in the evaluation of patients with renal abnormalities, especially if renal function is worsening, when the etiology is unclear based on serum studies, or when a biopsy is needed for diagnostic confirmation or disease staging.

CASE FOCUS

Diagnostic Evaluation

You first review Alex's laboratory test results from the outside ED. The results of these tests are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	133 mEq/L (133 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	106 mEq/L (106 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	17 mEq/L (17 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	10 mEq/L (10 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	11.5 mg/dL (4.1 mmol/L)	5–18 mg/dL (1.8–6.4 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)	0.3–0.6 mg/dL (26.5–53.0 µmol/L)
Glucose	73 mg/dL (4.1 mmol/L)	60–100 mg/dL (3.3–5.6 mmol/L)
Albumin	3.6 g/dL (36 g/L)	3.6–5.2 g/dL (36–52 g/L)
CBC		
WBC count	11,200/µL (11.2 × 10^9/L)	4,000–13,000/µL (4–13 × 10^9/L)
Hemoglobin	10.8 g/dL (108 g/L)	11.5–14.5 g/dL (115–145 g/L)
Hematocrit	30% (0.3)	33%–43% (0.33–0.43)
MCV	84.5 µm^3 (84.5 fL)	76–90 µm^3 (76–90 fL)
Platelet count	390 × 10^3/µL (390 × 10^9/L)	150–400 × 10^3/µL (150–400 × 10^9/L)
Peripheral smear	Normal	Normal

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Urinalysis[a]		
Color	Amber	Yellow
Clarity	Clear	Clear
pH	6.6	4.5–8
Specific gravity	1.015	1.005–1.030
Bilirubin	Small	Negative
Urobilinogen	Negative	Negative
Blood	2+	Negative
Protein	3+	Negative
RBC count	10–15/HPF	≤5/HPF
WBC count	0–2/HPF	≤5/HPF
Squamous epithelial cell	0–2/HPF	≤2/HPF
RBC casts	10/HPF	≤2/HPF

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; HPF; high-power field; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

[a] Urinalysis: negative for glucose, ketones, nitrites, leukocyte esterase; no crystals on microscopy.

Because these results confirm the presence of hematuria with evidence of glomerular disease, you decide to order the following studies:

Laboratory test	Result	Reference range
C3	24 mg/dL (0.24 g/L)	77–195 mg/dL (0.77–1.95 g/L)
C4	31 mg/dL (0.31 g/L)	7–40 mg/dL (0.07–0.40 g/L)
ASO	417 Todd units	<330 Todd units
Anti-DNase B	590 Todd units	<640 Todd units
Serum IgA	145 mg/dL (1.45 g/L)	33–236 mg/dL (0.33–2.36 g/L)
Rapid strep (throat swab)	Negative, culture pending	–
ANCA	Negative	–
ANA (ELISA)	Negative	Negative
ANA (immunofluorescence)	<1:40	<1:40
Renal ultrasound with Doppler	Normal	

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-DNase, antideoxyribonuclease; ASO, antistreptolysin O; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A.

Arriving at a Diagnosis

Q: How do you develop an assessment for Alex?

To determine the underlying etiology of Alex's symptoms and develop a treatment plan that fully addresses all of his symptoms, you first think through his history, vital signs, examination, and diagnostic studies to create a list of findings that can help you narrow his differential diagnosis.

1. **Interpret key findings from the history, vital signs, and physical examination:** According to his history, Alex has acute onset of fatigue, poor oral intake, oliguria, and hematuria following a recent febrile illness characterized by pharyngitis, which may have been streptococcal pharyngitis. He has had a recent weight gain of approximately 1.8 kg, peripheral edema on examination, and elevated blood pressure, all of which suggests fluid overload.

Q: How do you classify Alex's elevated blood pressure?

- For children younger than 13 years, classification of blood pressure is based on the blood pressure percentiles shown in Table 30.2. For blood pressure percentiles by age, height, and sex, refer to the 2017 American Academy of Pediatrics (AAP) "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents."
- When an elevated blood pressure reading is identified (≥ 90th percentile), the reading should be verified by 2 repeat measurements (ideally with a manual cuff using auscultatory technique). To ensure proper technique, clinicians should check that the blood pressure cuff is appropriately sized, that the patient is positioned properly, and that the patient is free of pain or anxiety at the time of the measurement, whenever possible. For a full discussion of proper blood pressure measurement in children and the management of abnormal blood pressure readings, refer to the 2017 AAP "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents."

Table 30.2. Blood Pressure and Hypertension Staging

Definition	Children aged 1 to < 13 years	Children aged ≥ 13 years of age
Normal	< 90th percentile	< 120/< 80 mm Hg
Elevated BP	≥ 90th percentile to < 95th percentile or 120/80 mm Hg to < 95th percentile (whichever is lower)	120/< 80 mm Hg to 129/< 80 mm Hg
Stage 1 HTN	≥ 95th percentile to < 95th percentile + 12 mm Hg, or 130/80 mm Hg to 139/89 mm Hg (whichever is lower)	130/80 mm Hg to 139/89 mm Hg
Stage 2 HTN	≥ 95th percentile + 12 mm Hg, or ≥ 140/90 mm Hg (whichever is lower)	≥ 140/90 mm Hg

Abbreviations: BP, blood pressure; HTN, hypertension.

Reprinted with permission from Flynn JT, Kaelber DC, Baker-Smith CM, et al; 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.

- Acute severe hypertension (ie, hypertensive crisis): When a child's blood pressure meets the definition of stage 2 hypertension, clinicians should consider whether or not the child is having a hypertensive crisis, which is defined as an acute elevation in the blood pressure that can result in immediate end-organ damage. Hypertensive crisis is uncommon at systolic blood pressures less than the 95th percentile + 30 mm Hg. There are 2 classifications used to define a hypertensive crisis.
  - Hypertensive urgency: Hypertensive urgency is defined as an elevated blood pressure without signs of acute target organ damage, although symptoms such as headache and nausea may be present.
  - Hypertensive emergency: Hypertensive emergency is defined as an elevated blood pressure with signs of acute target organ injury (eg, central nervous system, renal, or cardiovascular effects). Central nervous system manifestations may include hypertensive encephalopathy with severe headache, altered mental status, visual changes, seizure, focal neurological deficits, and even coma. Renal manifestations can include proteinuria and edema. Cardiac manifestations can include heart failure, chest pain, exertional dyspnea, and palpitations.
- For Alex, his blood pressure is verified on repeat measurement to meet the definition of stage 2 hypertension; however, he does not have any features concerning for hypertensive emergency.

2. Interpret findings from the diagnostic evaluation.

- Alex's renal panel shows mild hyponatremia, nongap metabolic acidosis, and elevated creatinine for age consistent with an acute kidney injury (AKI). In pediatric patients, AKI is commonly defined as an increase in serum creatinine by at least 0.3 mg/dL (26.5 µmol/L) or 50% from baseline. Although a baseline creatinine level for Alex is not available, it is reasonable to assume that based on his size, his baseline creatinine level is less than 0.6 mg/dL (53.0 µmol/L).
- His laboratory test results also show a normal serum albumin level, making nephrotic-range proteinuria less likely. His CBC shows a mild normocytic anemia but without signs of hemolysis.
- His urinalysis confirms the presence of hematuria and demonstrates proteinuria and dysmorphic RBC casts, suggesting glomerular injury.
- His additional laboratory tests found a low C3 with a normal C4, a negative ANA, and a negative ANCA. His high ASO level is consistent with a recent pharyngitis from group A streptococcus (*S pyogenes*).
- His normal renal ultrasound with Doppler decreases suspicion of renal vein thrombosis.

Q: What is the difference between microscopic and macroscopic (ie, gross) hematuria?

When urine microscopy confirms hematuria by the presence of RBCs, hematuria can then be further classified as *microscopic* (urine appears normal) or *macroscopic* (visible blood in the urine).

- Microscopic hematuria: This type of hematuria is generally defined as more than 2 to 3 RBCs per high-power field. In the absence of systemic symptoms, transient causes can be exercise or acute febrile illnesses. Other common etiologies include urinary tract infections, nephrolithiasis, or glomerular diseases. Anatomic or hematologic diseases can also cause persistent hematuria.
- Macroscopic (gross) hematuria: Macroscopic hematuria is defined as pink, red, or brown urine that is confirmed to contain blood by urine dipstick and microscopy. When gross hematuria originates from the glomerulus, the urine is brown in color (cola- or tea-colored).

3. **Develop the list of findings.**

Q: What major findings have you identified for Alex?

- Hypervolemia, as evidenced by edema, hypertension, and weight gain
- Stage 2 hypertension without hypertensive emergency
- Macroscopic hematuria with dysmorphic RBC casts
- Oliguria
- Mild nonanion gap metabolic acidosis
- AKI
- Hypocomplementemia, specifically C3
- Serologic evidence of a recent *S pyogenes* infection
- Hyponatremia
- Anemia

4. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Alex's presentation?

- In considering the renal etiologies of Alex's constellation of findings, you can easily eliminate acute tubular necrosis given the absence of risk factors. Additionally, his risk for drug-induced acute interstitial nephritis is low, and he does not have any white blood cells casts in his urine, which would be characteristic. He does have mild anemia but does not have other CBC findings consistent with hemolytic uremic syndrome. His history and renal ultrasonography results are not consistent with renal vein thrombosis. Based on this, you are confident that a GN is most likely.
- GN is characterized by hematuria, oliguria, and fluid overload (usually manifested by hypertension and/or edema); Alex has all 3 of these findings. The next step in Alex's assessment is to determine the underlying etiology of his GN.

Q: What is GN, and how is its cause identified?

- GN is a condition of immune-mediated renal inflammation that is diagnosed by the presence of a combination of clinical features: glomerular hematuria, proteinuria, oliguria, and evidence of fluid overload (ie, edema and/or hypertension). GN may also present with findings of rapidly worsening renal function.
- In most cases, glomerular bleeding is macroscopic, resulting in cola- or tea-colored urine. In these cases, the urine will also contain protein (>100 mg/dL via dipstick, but usually less than nephrotic range) and have certain urinary microscopic findings (RBC casts and deformed urinary RBCs).
- The key to evaluating the underlying etiology of GN lies in the interpretation of patient serum complement levels, specifically C3 and C4.
  - Low C3, normal C4: Transient, first-time nephritic syndrome with a low C3 and normal C4 is consistent with a postinfectious GN, which includes poststreptococcal GN (PSGN). A decline in C3 levels often precedes clinical symptoms and should return to near baseline within 8 weeks. Persistently depressed C3 should prompt further evaluation for less common causes, such as membranoproliferative GN or C3 glomerulopathy.
  - Low C3, low C4: This pattern is typically seen with lupus renal involvement, especially when associated with corresponding clinical features or autoantibodies. Additional etiologies that can cause this pattern of complement abnormalities include membranoproliferative GN and GN related to endocarditis or a shunt infection.

- Normal C3, normal C4: Etiologies of GN with normal complement levels include immunoglobulin A (IgA) nephropathy, ANCA-associated vasculitides (microscopic polyangiitis, granulomatosis with polyangiitis), hemolytic uremic syndrome, IgA vasculitis, and Alport or Goodpasture syndrome. Clinical clues will help delineate these etiologies, as most will have systemic findings. Fevers, rash, GI symptoms, and/or arthralgias point to vasculitides such as IgA vasculitis, polyarteritis nodosa, or granulomatosis with polyangiitis. A family history of hearing problems and kidney disease should raise the concern for Alport disease. Concurrent pharyngitis with hematuria (*synpharyngitic hematuria*) would point towards IgA glomerulonephropathy, the most common GN.

- Alex's low C3 and normal C4 are consistent with a postinfectious GN. Although there are many infections that can cause postinfectious GN, Alex's high-ASO titer is consistent with PSGN.
- PSGN is the most common type of GN in children.
  - The burden of PSGN is highest in the developing world. Worldwide, the incidence is decreasing, possibly related to earlier treatment of streptococcal skin infections and pharyngitis with antibiotic therapy, which reduces the spread of nephritogenic strains. The true incidence of PSGN is likely underestimated, however, because many cases of PSGN are subclinical and go undetected.
  - The underlying pathogenesis of PSGN relates to immune complex deposition, which leads to glomerular inflammation and damage. This then causes a reduction in glomerular filtration that results in the retention of sodium, water, and other electrolytes.
  - Edema and hypertension occur in the vast majority of pediatric patients with PSGN, with hypertension requiring treatment in approximately half of those cases. Edema, hypertension, and gross hematuria usually spontaneously resolve within 10 days of onset, though microscopic hematuria may persist for much longer. Other symptoms may include oliguria, nausea, malaise, and flank pain. For the majority of children, there are no long-lasting effects on renal function, with their creatinine level returning to baseline within a few weeks.
  - PSGN most commonly affects children between the ages of 4 and 12 years and occurs, on average, 1 to 2 weeks after streptococcal pharyngitis and 3 to 6 weeks after streptococcal skin infections. PSGN is more common after skin infections than following pharyngitis and has an increased incidence in the summer.
  - To prove the relationship of a patient's postinfectious GN with a recent streptococcal infection, streptococcal serology testing may be considered. Although there are multiple serum antibodies against streptococcal antigens, the most commonly available are ASO and anti-DNase B.
    - ASO rises about 1 week after streptococcal pharyngitis and peaks in about 4 weeks. ASO is less likely to rise following skin infections.
    - Anti-DNase B rises 2 weeks after skin infections, peaking at about 7 weeks, and also is elevated after streptococcal pharyngitis.
  - Other common laboratory findings in PSGN include the following:
    - CBC: Mild anemia and mild leukocytosis.
    - Electrolyte abnormalities: Because of fluid overload, patients will often have a relative hyponatremia. Mild hyperkalemia, metabolic acidosis, and elevated blood urea nitrogen and creatinine are common but of variable severity, depending on the degree of renal injury.

Q: Does treatment of streptococcal infections decrease the risk of subsequent PSGN?

Although timely and adequate treatment of group A streptococcus infection decreases a patient's risk of acute rheumatic fever and strep-related suppurative complications (eg, acute otitis media, abscesses), the same cannot be said for a patient's risk of developing GN. At this time, the role of antibiotics in preventing PSGN is unproven; however, as previously stated, timely treatment of streptococcal infections can prevent the spread of nephritogenic strains.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with suspected PSGN?

Many children with newly diagnosed PSGN require hospitalization to monitor their blood pressure, edema, and renal function and provide treatment when indicated. Specific indications for hospitalization may include the following:

- There is concern for hypertensive emergency.
- The patient has symptomatic fluid overload, as evidenced by symptoms such as shortness of breath, hypoxemia, or respiratory distress.
- The patient has AKI, defined as creatinine greater than 50% above baseline.
- The patient has oliguria, defined as persistent urine output less than 1 mL/kg per hour.

For Alex, you determine he requires hospitalization to monitor his blood pressure, edema, oliguria, AKI, and electrolyte abnormalities.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Alex is a 9-year-old boy with a recent history of pharyngitis who presents with acute onset of macroscopic hematuria, AKI, oliguria, edema, and hypertension. These symptoms and his complement levels are consistent with PSGN. Alex requires hospitalization for close monitoring of his hypertension, fluid overload, and oliguric AKI.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The overall goal in treatment of patients with PSGN is to provide supportive care by promoting diuresis and treating other disease manifestations, such as hypertension or hyperkalemia. For Alex, you divide his treatment considerations into the following components:

1. **Management of fluid overload**
   - Diuretics: Diuretics are the mainstay of therapy for fluid overload.
     - Loop diuretics: Loop diuretics are very efficacious for postinfectious GN to help with both fluid overload and hypertension. They are typically used alone and result in a brisk response; however, they can be paired with other diuretics for additional efficacy. Loop diuretics also lower serum potassium through their inhibition of the sodium/potassium/chloride cotransporter in the thick ascending limb, which can be an additional benefit in patients with GN.
     - Thiazide diuretics: Thiazide diuretics also are often used for fluid overload. Literature shows that they are not very helpful in the setting of severe kidney involvement, specifically at glomerular filtration rates less than 30 mL/min per 1.73 m^2.
     - Potassium-sparing diuretics: Generally, this type of diuretic should be avoided because of the risk of hyperkalemia.

- Antihypertensives: Calcium channel blockers (CCBs) and beta blockers can serve as adjunct medications to diuretics. Criteria for treatment are persistently increasing blood pressure despite supportive measures and blood pressure greater than the 90th percentile for age, height, and sex.
  - CCBs: CCBs can cause worsening peripheral edema related to an increased vascular permeability; therefore, they should be used in combination with a loop diuretic.
  - Beta blockers: For best results, beta blockers should be used in combination with a diuretic. Because of a risk of hyperkalemia with beta blocker use, clinicians should consider monitoring serum potassium levels.
  - Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers: These medications are used very cautiously in patients with high potassium because of their side effect profile, which includes hyperkalemia and renal impairment. This risk is greatest for patients with poor glomerular filtration rates or renal artery stenosis.
- Dietary restrictions: Salt and fluid restrictions are needed while oncotic pressures normalize and diuresis takes place. Fluid boluses should be avoided.
- Because Alex has signs of edema and hypertension, you plan to initiate diuresis with furosemide, a loop diuretic. If he remains hypertensive despite furosemide, you will also start an oral CCB.

2. **Further streptococcal testing and antibiotic therapy**
   - Because an inciting infection usually precedes the onset of GN, throat or skin cultures are positive in less than 30% of patients at time of presentation with GN.
   - Unless the patient is identified as having evidence of an active streptococcal infection, antibiotic therapy is not indicated.
   - Testing of household contacts should be considered to decrease the spread of nephritogenic strains.
   - No antimicrobials are indicated for Alex given the postinfectious nature of his GN; however, you do recommend streptococcal testing for his close contacts to prevent spread of nephritogenic strains.
3. **Monitoring**
   - Renal function: The goal of supportive treatment is to stabilize kidney function while promoting diuresis. If the patient's serum creatinine level is greater than 50% above baseline (consistent with AKI), creatinine should be monitored every 8 to 12 hours until stabilization or improvement is noted. Serum creatinine levels may take weeks to return to their prenephritic baseline and do not need to be completely normal for discharge.
   - Electrolyte derangements: The most common electrolyte anomaly is a relative hyponatremia related to fluid retention. Hyponatremia tends to improve with diuresis. Additionally, hyperkalemia is common, and a mild gap acidosis may be present, depending on the duration of nephritic symptoms.
   - Volume status: To ensure diuresis and improvement in hypervolemia, once or twice daily weights and frequent monitoring of the patient's intake and output and blood pressure is required.
4. **Specialist consultation**
   - Some children with PSGN develop renal failure refractory to medical management, which necessitates hemodialysis or continuous renal replacement therapy. Early consultation with pediatric nephrology should be considered when GN is suspected.

- Dialysis and/or transfer to a critical care unit may be required in the following situations:
  - The patient's blood pressure is greater than the 99th percentile despite interventions.
  - A hypertensive emergency exists.
  - The patient has oliguria (urine output < 1 mL/kg/h) that is unresponsive to diuretics.
  - Significant uremia (blood urea nitrogen > 90 mg/dL [32.1 mmol/L]) or electrolyte (potassium > 6.5 mEq/L [6.5 mmol/L]) abnormalities exist.
  - The patient has other signs of severe fluid overload, including pathologic heart sounds or an increasing oxygen requirement.
- Renal biopsy may be indicated for some patients, especially if their creatinine level continues to increase despite treatment. Persistently abnormal or worsening renal function should prompt investigation for rapidly progressive GN. This is a potentially fatal condition that requires urgent diagnosis and treatment.

CASE FOCUS

Plan for Treatment and Monitoring

- **Management of hypertension, edema, and fluid overload**
  - **Diuretics: You decide to order intravenous furosemide and assess Alex's response by monitoring the volume of his urine output in the hours following administration. If there is no response, you will repeat furosemide at an increased dose or switch to a thiazide diuretic.**
  - **Antihypertensives: You decide on oral isradipine to be used as needed for blood pressures greater than the 90th percentile. If Alex's blood pressure continues to be elevated despite diuresis, you will consider starting scheduled amlodipine.**
  - **Diet/hydration: You limit Alex's fluid intake to one-third of the maintenance rate using the standard "4–2–1 rule" and place a low-salt restriction on his diet.**
- **Antimicrobials: None indicated. You will recommend streptococcal testing for Alex's close contacts.**
- **Monitoring: You plan to monitor Alex's potassium, sodium, and renal function by obtaining a repeat basic metabolic panel in 12 hours. You will monitor his urine output with strict monitoring of intake and output, obtain blood pressures every 4 hours, and measure his weight twice daily.**
- **Consultations: You will consult pediatric nephrology to assist with Alex's management.**

Case Resolution

During the first 48 hours of Alex's hospital stay, he receives a total of 3 doses of furosemide and 2 doses of antihypertensives to achieve adequate diuresis and stabilize his blood pressure. By the third day of his hospitalization, he no longer has clinical signs of fluid overload, and his gross hematuria is improving. He is monitored for another night off diuretics, and his blood pressure and urine output remain stable. Over the course of his hospitalization, his creatinine level downtrends to a final value of 0.5 mg/dL (44.2 µmol/L), and his electrolytes normalize. On the fourth day of admission, Alex is discharged home off all medications and with close follow-up at his pediatrician's clinic ensured.

Discharge Criteria

Q: How do you know when Alex is ready to go home?

You can feel comfortable discharging your patient with PSGN when the following criteria are met:

- Blood pressure is controlled. The goal is for the patient's blood pressure to be less than the 90th percentile (through use of medication, if necessary).
- Creatinine level is downtrending and urine output is greater than 1 mL/kg/h.
- Weight should be downtrending and near baseline.
- Electrolytes are stable.
- Close follow-up with a pediatrician and/or nephrologist is scheduled.

Anticipatory Guidance

Q: What instructions should you provide to Alex's caregivers upon discharge?

- More than 95% of pediatric patients with PSGN recover from their illness. In the months following an episode of PSGN, approximately 5% of patients will have residual protein or blood in their urine, and about 3% of patients will have mild hypertension.
- Household contacts should be evaluated for evidence of streptococcal infection. Any contacts with sore throat or similar symptoms should be promptly evaluated.
- Alex should return to care for new dark urine, inability to tolerate oral fluids, headache, or new facial swelling/fluid overload.
- Close follow-up with Alex's pediatrician is important. A repeat C3 level should be obtained in 8 weeks to ensure normalization.

Clinical Pearls

- The combination of hematuria and fluid overload (as evidenced by edema or hypertension) is concerning for GN.
- Complement levels are helpful to delineate the etiology of GN.
- PSGN is the most common type of GN in children but is rare in children younger than 3 years of age.
- It is unclear whether early identification and treatment of streptococcal infections reduces the risk and severity of renal sequelae, although treatment of group A streptococcus infections does decrease the spread of nephritogenic strains.
- Treatment of PSGN is often supportive and targeted toward edema and blood pressure control.
- Rapidly worsening oliguria or renal function panels are worrisome and should prompt aggressive treatment and urgent nephrology consultation.
- C3 levels should be repeated 8 weeks after postinfectious GN. Persistently depressed levels should prompt consideration of a renal biopsy.

Documentation Tips

- Document the presence of hypertension, respiratory compromise, AKI, oliguria, or heart failure.
- Include the severity of hypertension (including degree of increase > 95th percentile for age, height, and sex, if known).
- Document acute or worsening target organ damage secondary to hypertension (eg, encephalopathy, AKI, heart failure, seizure, papilledema, retinal hemorrhage).

Suggested Reading

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CASE 31

Ella, an 8-Year-Old Girl With 2 Weeks of Fever

CASE PRESENTATION

A pediatrician in your community calls to request a direct admission for Ella, an 8-year-old girl who has had 2 weeks of fever in the setting of recent international travel. Her pediatrician reports that Ella has been having daily fevers to 40 °C (104 °F), prompting 2 visits to the office during that time. Ella has also had intermittent, crampy abdominal pain for the last 2 or 3 days. Ella's pediatrician ordered outpatient laboratory tests last week, but her family was unable to have them done because of transportation barriers. The pediatrician asks you to admit Ella to expedite the evaluation of her fever of unknown origin (FUO).

Patient History and Review of Systems

Q: What information should you collect from Ella and her caregivers?

- History of present illness, including the following:
  - Date of fever onset
  - Method of fever measurement (rectal, axillary, oral, temporal)
  - Height of fever
  - Duration and time of day the fevers occur
  - Whether there is any pattern to the fevers (intermittent, remittent, continuous, hectic, relapsing)
- Exposure history, including the following:
  - Sick contacts or tuberculosis (TB) exposure
  - Dietary changes, especially consumption of unpasteurized dairy products, undercooked poultry or eggs, or game meat
  - Arthropod or animal exposures
  - Water exposure
  - Recent travel history, including any prophylactic vaccines and/or medications
  - Time spent in migrant or refugee camps or detention centers
  - Occupational or environmental exposures
- Associated signs and symptoms, such as weight loss, rhinorrhea, cough, chest pain, joint swelling, diarrhea, jaundice, pallor, or rash
- Medical history, including prior episodes of prolonged febrile illnesses, growth and development milestones, and immunization status

- Medication use
- Family history, including autoimmune disease, immunodeficiencies, and familial fever syndromes
- Social concerns/barriers (eg, ability to obtain prescribed medications, transportation to follow-up appointments)

CASE FOCUS

History and Review of Systems

After Ella arrives at the hospital, you obtain further history from her and parents. Her parents confirm that Ella's fevers have occurred daily for 2 weeks to a maximum temperature of 40 °C (104 °F). They have been measuring her temperature orally and note that her fevers occur mostly during evening hours. For the last 2½ days, Ella has also been experiencing vomiting, diarrhea, and intermittent, crampy abdominal pain. There is no blood or mucus noted in her stools, nor do the stools appear abnormally dark. She does not have a runny nose, cough, chest pain, joint swelling, jaundice, or rash. Ella's parents suspect that she has lost some weight and note decreased urination for the past few days. When you ask about the laboratory testing ordered by Ella's pediatrician, her parents explain that they do not own a car. The family took the city bus to Ella's laboratory appointment last Friday afternoon as directed by their pediatrician but arrived too late to be seen. They have been unable to schedule another appointment because the laboratory was closed for a holiday weekend.

Both Ella's medical history and family history are unremarkable. There were no concerns about her growth or development prior to these fevers. She is up to date on her vaccinations. There is no history of ill contacts or known TB exposure. Ella does not take any regular medications, nor has she taken any over-the-counter or prescription medications for her current symptoms. A few days prior to the onset of her fever, she returned home from a 3-month visit with extended family in a rural area of Vietnam. She did not receive any prophylactic immunizations or medications prior to the trip because her insurance had lapsed when her father lost his job, and her parents were unable to have insurance reinstated in time to see her pediatrician before they departed for Vietnam. Her parents deny any consumption of unpasteurized dairy products, undercooked poultry or eggs, or game meat. The family all drank only bottled water while in Vietnam. They consumed the same diet as Ella on the trip, and they have not been ill. Ella had no illnesses while in Vietnam. She did experience many mosquito bites during her time in Vietnam but did not have any other animal or arthropod exposures.

Physical Examination

Q: What parts of the physical examination should you focus on for Ella?

- Complete set of vital signs
- Weight, with comparison to most recent weight(s); review of growth charts, if available
- General appearance: body habitus, level of alertness, signs of distress
- Hydration status: mucous membranes (moist, sticky, dry), presence or absence of tears, capillary refill
- Head, eyes, ears, nose, and throat: conjunctiva (injection or pallor), sclera (icterus), oropharynx (ulcers, erythema, exudates)
- Neck: masses or meningismus
- Cardiac: murmurs, gallop
- Respiratory: work of breathing, adventitious lung sounds
- Abdominal: tenderness, organomegaly, masses
- Skin: rashes, bruises, other lesions
- Lymph nodes: palpation of occipital, preauricular, cervical, supraclavicular, axillary, epitrochlear, and inguinal regions
- Neurologic: mental status, motor weakness, sensory deficits, ataxia, brisk reflexes

CASE FOCUS

Physical Examination

Ella's vital signs reveal that she is febrile, with a temperature of 39.5 °C (103.1 °F). Her heart rate is elevated at 144 beats/min, and she is slightly tachypneic at 22 breaths/min. She is normotensive, with a blood pressure of 104/68 mm Hg. Her weight is 21 kg (10th percentile), which represents a 1.4 kg weight loss over 10 days, using weights recorded at her pediatrician's office.

On examination, Ella appears thin and is moderately ill appearing. Ella is not in acute distress. Her conjunctiva are not injected, her sclera are anicteric, and her fundoscopic examination is normal. Her mucous membranes are dry. Her oropharynx is without erythema, ulcers, or exudates. Her neck is supple and without lymphadenopathy, thyromegaly, or meningismus. On cardiovascular examination, she is tachycardic with a regular rhythm and a II/VI systolic ejection murmur at the left lower sternal border, which is loudest when lying flat. She has a normal S1 and S2, you do not hear a gallop, and her precordium is hyperdynamic but otherwise normal. On her respiratory examination, she is breathing comfortably, and her lungs are clear to auscultation with good air entry. Ella's abdomen has mild diffuse tenderness to palpation but without guarding, organomegaly, or masses. No lymphadenopathy is noted. Her extremities are warm with good pulses throughout and with a capillary refill time of 3 seconds. Her skin is without jaundice, rashes, or other lesions. Her neurologic examination is normal.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with FUO?

The definition of FUO has evolved over time and varies in different references, but for the purposes of this case, FUO is defined as a fever greater than or equal to 38 °C (100.4 °F) lasting at least 8 days without a known etiology. It is important to remember that FUO is often an uncommon presentation of common diseases, with infectious etiologies predominating. In a returning traveler, such as Ella, it is also necessary to consider infections endemic to that region. It can be helpful to organize the differential diagnoses into infectious and noninfectious etiologies, as shown in Table 31.1.

Table 31.1. Differential Diagnosis for a Child With Fever of Unknown Origin

Diagnoses of highest suspicion	Infectious etiologies (most likely)	• Localized infections – Abscesses, including intra-abdominal, hepatic, and central nervous system – Adenitis – Endocarditis – Mastoiditis – Osteomyelitis – Pneumonia – Pyelonephritis – Sinusitis • Systemic infections – Bacterial: *Bartonella henselae*, *Brucella* spp, *Francisella tularensis*, *Mycobacterium tuberculosis*, *Yersinia* spp, *Streptobacillus moniliformis* (rat-bite fever), *Borrelia burgdorferi*, *Leptospira* spp, rickettsia, *Salmonella typhi*, *Mycoplasma pneumoniae* – Fungal: coccidiomycosis, blastomycosis, histoplasmosis – Parasitic: malaria, toxoplasmosis, cryptosporidium – Viral: EBV, CMV, arboviruses, hepatitis, HIV, SARS-CoV-2

(continued)

Table 31.1. Differential Diagnosis for a Child With Fever of Unknown Origin *(continued)*

Diagnoses of highest suspicion	Infectious etiologies (most likely) *(continued)*	• Infections endemic to Vietnam: TB, malaria, HAV, HBV, *S typhi*, diphtheria, Japanese encephalitis, measles, chikungunya, dengue, Zika virus, hand-foot-and-mouth disease, H5N1 avian influenza, and rabies • Pseudo-FUO
Other diagnoses to consider	Rheumatologic/ autoimmune etiologies	• Acute rheumatic fever • Autoinflammatory syndromes (periodic fever syndromes) • IBD • JIA • Juvenile dermatomyositis • KD • MIS-C • SLE
	Oncologic etiologies	• HLH • Leukemia • Lymphoma • Neuroblastoma
	Miscellaneous etiologies	• Addison disease • Drug fever • Factitious fever • Pancreatitis • Poisoning • Thyrotoxicosis

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; FUO, fever of unknown origin; HAV, hepatitis A virus; HBV, hepatitis B virus; HLH, hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; SLE, systemic lupus erythematosus; TB, tuberculosis.

Diagnostic Evaluation

Q: What is the initial diagnostic evaluation for patients who present with FUO?

There is no reference standard for the initial workup for FUO. Clinical judgment is used to determine the initial evaluation, based upon findings from the history and physical examination and the local or travel-area disease prevalence.

- Commonly, an initial diagnostic evaluation may include a complete blood cell count with differential, blood culture, basic metabolic panel, liver function tests, and urinalysis.
- Directed imaging studies can be obtained, such as chest radiography for patients with pulmonary signs and/or symptoms.
- Patients with diarrhea should have their stool sent for cultures, ova and parasites, and possible *Clostridioides difficile* testing.
- For patients with neurologic symptoms, clinicians should consider obtaining head imaging and/or performing lumbar puncture for cerebrospinal fluid studies.
- Figure 31.1 outlines additional tests and imaging that may be considered based on key findings from the patient's history and examination as well as resource availability.

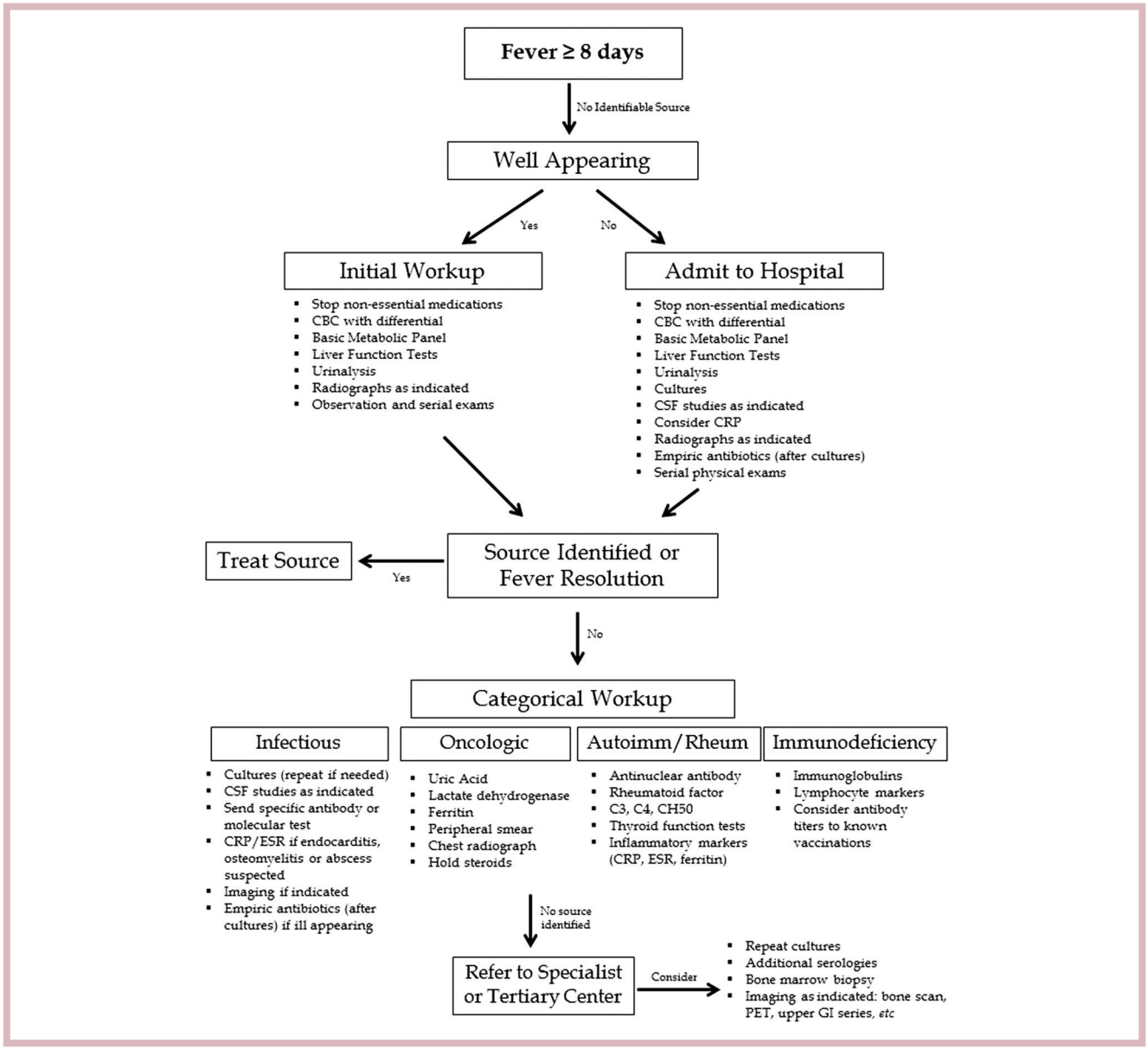

Figure 31.1. Algorithm for evaluation of fever of unknown origin.

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; PET, positron emission tomography.

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Diagnostic Evaluation

Based on Ella's travel history and symptoms, you decide to start her evaluation with a complete blood cell count with differential, an erythrocyte sedimentation rate and C-reactive protein, a comprehensive metabolic panel, chest radiograph, and urinalysis. A urine culture, blood culture, interferon-gamma release assay (IGRA) for TB, stool studies, and blood smears for parasites are also collected and are pending. The results immediately available are as follows:

Laboratory test	Result	Reference range
CBC		
WBC count	4,200/μL (4.2 × 10^9/L)	4,000–13,000/μL (4–13 × 10^9/L)
Hemoglobin	12.6 g/dL (126 g/L)	11.5–14.5 g/dL (115–145 g/L)
Hematocrit	37% (0.37)	33%–43% (0.33–0.43)
Platelet count	228 × 10^3/μL (228 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	74% (0.74)	35%–55% (0.35–0.55)
Bands	1% (0.01)	0%–1% (0–0.01)
Lymphocytes	22% (0.22)	25%–33% (0.25–0.33)
Inflammatory markers		
ESR	94 mm/h	0–10 mm/h
CRP	13.7 mg/dL (137 mg/L)	< 1.0 mg/dL (< 10 mg/L)
Serum chemistries		
Sodium	138 mEq/L (138 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.1 mEq/L (4.1 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	103 mEq/L (103 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	11 mEq/L (11 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	7 mEq/dL (2.5 mmol/L)	5–18 mEq/dL (1.8–6.4 mmol/L)
Creatinine	0.4 mg/dL (35.4 μmol/L)	0.3–0.6 mg/dL (26.5–53.0 μmol/L)
Glucose	80 mg/dL (4.44 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
ALT	32 U/L (0.53 μkat/L)	13–35 U/L (0.22–0.58 μkat/L)
AST	30 U/L (0.50 μkat/L)	10–35 U/L (0.17–0.58 μkat/L)

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Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Urinalysis		
Color	Amber	Pale-amber
Clarity	Clear	Clear-turbid
pH	6.2	4.5–8
Specific gravity	1.025	1.005–1.025
Bilirubin	Negative	Negative
Urobilinogen	Negative	Negative
Glucose	Negative	Negative
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Blood	0	<1+
Protein	0	≤1+
RBC count	0/HPF	≤5/HPF
WBC count	0/HPF	≤5/HPF
Imaging		
Chest radiograph	Normal	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HPF, high-power field; RBC, red blood cell; WBC, white blood cell.

Arriving at a Diagnosis

Q: How do you develop an assessment for Ella?

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Ella's history is notable for 2 weeks of daily fever to 40 °C (104 °F) after returning from a 3-month visit to Vietnam. In addition, she has recently developed abdominal pain, vomiting, and diarrhea, and has had a weight loss of 1.4 kg. She is previously healthy, up to date on her routine immunizations, and has not had any known sick contacts. It is notable that Ella had multiple mosquito bites on her trip and did not receive any travel-related vaccinations or malaria prophylaxis. Her history is also notable for barriers to access to medical care due to limited transportation and health insurance coverage.
   - The timeline of Ella's symptoms as related to her travel and her mosquito exposure is most consistent with an infectious etiology of FUO. Her symptoms are less consistent with some localized infections (eg, sinusitis, urinary tract infection, osteomyelitis, pneumonia). Pseudo-FUO, or different infections over a short period of time that are confused with one prolonged infection, cannot be ruled out; however, pseudo-FUO is also

unlikely given that Ella has had no sick contacts. Although less likely based on her history, noninfectious inflammatory diseases (eg, multisystem inflammatory syndrome in children, inflammatory bowel disease) cannot be ruled out.

- Physical examination: On your examination, Ella is somewhat ill appearing and dehydrated. She is febrile, tachycardiac, and tachypneic, and you are concerned she is at risk for sepsis. Her normal head, eyes, ears, nose and throat, and lung examinations decrease suspicion for sinusitis and pneumonia. Her cardiac examination, with a systolic ejection murmur with qualities suggestive of a benign murmur, may be related to her febrile state, although endocarditis cannot be eliminated. Her normal neurologic examination decreases concern for a central nervous system pathology. Her abdominal examination notable for diffuse tenderness but without guarding or peritoneal signs suggests urgent surgical intervention is not required. She has no rashes. Her lack of abdominal masses, organomegaly, and lymphadenopathy decreases your suspicion for oncologic conditions.
- Diagnostic evaluation: Ella's laboratory evaluation is fairly nonspecific. She has a mild leukopenia with a neutrophil predominance and elevated inflammatory markers. Her chest radiograph is normal.

2. **Develop the list of findings.**

Q: What major findings have you identified for Ella?

- 2 weeks of daily fever to 40 °C (104 °F)
- Recent travel to Vietnam without travel-related vaccinations or use of malaria prophylaxis
- Concern for sepsis
- Weight loss
- Dehydration
- Anemia
- Abdominal pain
- Diarrhea
- Vomiting
- Barriers to care access (transportation and health insurance coverage)

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Ella's presentation?

Although you cannot yet narrow the cause Ella's symptoms to a single diagnosis, her recent travel makes an infectious disease more likely than other categories of disease. Infections endemic to Vietnam should be explored first.

Q: What infectious agents seem most likely as the etiology of Ella's symptoms based on her recent travel?

- Based on Ella's recent travel to Vietnam, you suspect that she is at increased risk of certain pathogens, including *Salmonella typhi*, malaria, dengue, hepatitis A and B, measles, Japanese encephalitis, chikungunya, Zika virus, and *Mycobacterium tuberculosis*.
- Ella does not have symptoms consistent with encephalitis and was previously vaccinated against hepatitis and measles; therefore, you think that these etiologies are unlikely.
- See Table 31.2 for risk factors, presenting symptoms, and diagnostic evaluations of the remaining infections to consider for Ella.

S typhi (typhoid fever) and malaria are the most likely infectious etiologies in Ella's case, based on her travel history and symptom presentation.

Table 31.2. Risk Factors, Presenting Symptoms, and Diagnostic Evaluation for Select Infections

Disease	Risk factors for transmission	Presenting symptoms	Diagnostic evaluation
Malaria	Mosquito bites, travel to endemic area	Symptoms can develop over weeks to months after exposure and commonly include high fevers, chills, and an influenza-like illness. Anemia, thrombocytopenia, and jaundice may be found in severe disease.	Visualization of parasites on stains of peripheral blood films (blood smear microscopy) is diagnostic. Smears should be repeated if they are negative and clinical suspicion is high. PCR testing or rapid diagnostic antigen testing can also be used, although rapid diagnostic tests require peripheral smear confirmation.
Typhoid fever (enteric fever)	Ingestion of contaminated food or water, travel to endemic area	An incubation period of up to a month is possible. Symptoms may include high fevers, chills, headache, malaise, anorexia, abdominal pain, vomiting, diarrhea/constipation. Some patients have a transient maculopapular rash known as *rose spots*.	Blood and stool cultures
TB	Contact with person(s) with confirmed TB, recent travel to high-risk areas, or exposure to at-risk populations (incarcerated; experiencing homelessness)	FUO can be a presentation of extrapulmonary TB in children. Symptoms of TB commonly include fevers, cough, and weight loss or failure to thrive.	TB can be diagnosed with a high index of clinical suspicion or via positive tuberculin skin test or IGRA.
Chikungunya	Arthropod bites, travel to endemic area	Acute onset of high fever and arthralgias (bilateral and symmetric). Other symptoms may include a maculopapular rash, headache, myalgia, arthritis, conjunctivitis, and nausea/vomiting. Neurologic complications can occur.	Reverse-transcription PCR or viral serology is diagnostic. Supportive laboratory findings may include leukopenia, thrombocytopenia, AKI, and transaminitis.
Dengue	Arthropod bites, travel to endemic area	Most infections are asymptomatic. A nonspecific febrile illness is common with infection and may include headache, retro-orbital pain, nausea/vomiting, rash (macular, maculopapular, or petechial), myalgias/arthralgias, facial erythema, and leukopenia.	Diagnosis is primarily clinical. Laboratory test results during the febrile phase of illness may include leukopenia and evidence of hemoconcentration from vascular leakage. Thrombocytopenia may be seen during progression to severe disease.

(continued)

Table 31.2. Risk Factors, Presenting Symptoms, and Diagnostic Evaluation for Select Infections *(continued)*

Disease	Risk factors for transmission	Presenting symptoms	Diagnostic evaluation
Zika	Arthropod bites, travel to endemic area	The majority of infections are asymptomatic or mildly symptomatic. Symptoms can include fever, headache, arthralgias, pruritic maculopapular rash, arthralgia, myalgias, vomiting, lymphadenopathy, peripheral edema, and conjunctival hyperemia. Neurologic complications including Guillain-Barré syndrome have been reported.	Real-time reverse-transcription PCR or viral serology is diagnostic. Supportive laboratory findings may include leukopenia, thrombocytopenia, and transaminitis.

Abbreviations: AKI, acute kidney injury; FUO, fever of unknown origin; IGRA, interferon-gamma release assay; PCR, polymerase chain reaction; TB, tuberculosis.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with FUO?

Well-appearing patients with FUO can often be evaluated and monitored on an outpatient basis until a diagnosis is made or the fever resolves. There are some scenarios, however, where admission to the hospital is indicated for a patient with FUO, including the following:

- There is concern that the patient is clinically unstable.
- The patient is unable to maintain their hydration.
- There is evidence that the patient is unable to complete the FUO workup in the outpatient setting. Reasons for this may include a lack of laboratory testing resources in the outpatient setting or obstacles impacting access to care.

Ella meets criteria for hospital admission based upon her clinical instability, her risk of sepsis, and the need for an expedited evaluation in the setting of limited access to outpatient resources.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Ella is a previously healthy 8-year-old girl with a 2-week history of daily spiking fevers, weight loss, abdominal pain, vomiting, and diarrhea following a 3-month visit to Vietnam. Based on her travel history, *S typhi* or malaria are the most likely etiologies. Ella therefore requires admission for further evaluation, monitoring, and empiric treatment initiation.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

For patients in whom the underlying disease or disorder is clear, treatment and monitoring should be individualized based on their diagnosis. For Ella, however, the focus of her admission will be medical stabilization and empiric antimicrobial treatment while concurrently monitoring her symptom progression and further evaluating for alternative causes of her FUO. Additionally, and specifically applicable to Ella, another important component of many patients' inpatient care is to address any social determinants of health leading to barriers that may have contributed to their admission.

1. **Further diagnostic evaluation:** When an etiology is not discovered through initial diagnostic workup, clinicians should broaden their evaluation to include less common etiologies of FUO. For Ella, further workup may include testing for multisystem inflammatory syndrome in children and an echocardiogram, among others; however, it is prudent to first await her malaria smear, IGRA for TB, blood culture, and stool studies before pursuing other testing. If new symptoms develop during Ella's hospitalization, further laboratory tests and imaging can be tailored toward her new symptomatology.
2. **Empiric antimicrobials:** Often it is preferable to avoid empiric treatment in a well-appearing patient with FUO, as it may mask symptoms and delay diagnosis. It is reasonable, however, to begin empiric antimicrobial treatment when a life-threatening diagnosis is suspected or if the child is unstable or ill appearing. For Ella, it is prudent to initiate empiric antibiotic coverage given her ill appearance and her risk of sepsis. Given her differential diagnosis, ceftriaxone is an appropriate first-line choice.
3. **Monitoring:** Patients with FUO should be monitored closely for symptom progression or signs of hemodynamic instability. For Ella, care should include close monitoring of her hydration status and fever curve in addition to serial physical examinations that may reveal new or progressing symptomatology. Because her vital signs and physical examination lead you to believe Ella is at risk for sepsis, it is appropriate to initiate frequent vital sign checks until she demonstrates clinical improvement.
4. **Specialist consultation:** Clinicians should consider consulting an infectious disease specialist for assistance with the patient's evaluation and management, when available. In Ella's case, if she continues to have gastrointestinal symptoms without a known diagnosis, consultation with a gastroenterologist should be considered as well.
5. **Supportive care:** Patients hospitalized with FUO should also receive supportive care directed at their specific symptoms. This may include hydration support and treatment to reduce symptoms, such as pain and fever. Given the concern about Ella's hydration status and your concern that she is at risk for sepsis, it is reasonable to initiate rapid intravenous (IV) hydration. Following initial IV fluid boluses, it is reasonable to start IV fluids at her maintenance rate until she is able to maintain her hydration orally. Additionally, antipyretics can be used as needed for discomfort related to fever.
6. **Social determinants of health:** The conditions in which children live have a significant impact on overall health. These conditions, referred to as *social determinants of health*, should be carefully considered in all patients. Any identified barriers to care should be addressed while the patient is still hospitalized, if at all possible. It is clear from her history that Ella faced significant barriers that have limited her access to timely and adequate medical care. It is possible that with consistent health insurance coverage and reliable transportation, Ella could have obtained a laboratory workup as an outpatient. Treatment then could have been initiated as an outpatient and hospitalization might have been avoided. Providing resources to help Ella and her family access care in the future will be important, and a social worker should be consulted to assist in providing information regarding these community resources.

CASE FOCUS

Plan for Treatment and Monitoring

- **Further diagnostic evaluation:** You will follow up on Ella's pending blood smears for parasites, IGRA for TB, blood culture, urine culture, stool culture, and stool testing for ova, parasites, and *C difficile.*
- **Empiric antimicrobials:** You initiate IV ceftriaxone and plan to narrow coverage, if possible, when Ella's diagnosis is confirmed.
- **Monitoring:** You order vital signs to be obtained every hour initially and plan to space to every 4 hours when Ella's vital signs begin to normalize. You plan for serial physical examinations and strict monitoring of intake and output.
- **Specialist consultation:** You consult the infectious disease team to help prioritize Ella's workup and optimize her treatment plan as you work through the differential diagnosis.
- **Supportive care:** To improve Ella's hydration status, you start with a 20 mL/kg bolus of IV fluids, and you will then start maintenance IV fluids. You order antipyretics to be given as needed.
- **Social determinants of health:** You plan to consult a social worker to help provide Ella's family with resources for transportation and to assess for any additional barriers to further care that might be present.

Case Resolution

Soon after admission, Ella's peripheral blood smear returns negative for malaria parasites, and her blood culture demonstrates growth of gram-negative rods. On a repeat physical examination, you note a new finding of 2- to 3-mm blanching pink macules on her trunk and extremities. You think this rash is consistent with the "rose spots" seen in *S typhi*, which further increases your confidence in your diagnosis. You decide to start oral azithromycin in addition to the ceftriaxone for empiric treatment of *S typhi*. Later in the day, Ella's urine culture shows no growth at 24 hours, and her stool testing for ova, parasites, and *C difficile* is negative.

Over the following days, Ella's IGRA for TB is negative, and both her stool and blood cultures confirm the presence of *S typhi.* At that time, you continue IV ceftriaxone and oral azithromycin while sensitivities are pending. The hospital social worker meets with Ella and her family and reaffirms that transportation and lapse of health insurance are significant barriers to care for Ella. The social worker provides resources regarding your state's medical transportation program and assists Ella's family with applying for state health insurance, for which Ella is eligible. This program provides free nonemergency medical transportation services. After multiple subsequent negative blood cultures and significant clinical improvement, including resolution of her fever, Ella is discharged home to complete a 14-day course of amoxicillin based on her *S typhi* sensitivity testing.

Discharge Criteria

Q: How do you know when Ella is ready to go home?

The discharge criteria for patients with FUO vary depending on their ultimate diagnosis and clinical course. However, in general, you can feel comfortable discharging your patient with FUO when the following criteria are met:

- The patient is clinically stable, and acutely life-threatening etiologies have been ruled out.
- The patient is showing signs of clinical improvement and/or laboratory improvement on the initiated treatment.
- Any barriers to the completion of outpatient treatment and follow-up care have been fully addressed.

Anticipatory Guidance

Q: What instructions should you provide to Ella's caregivers upon discharge?

- Good hand hygiene is important to prevent the spread of infection to other household members.
- Close follow-up with Ella's pediatrician within 2 to 3 days after discharge is important. Update the pediatrician if any new signs or symptoms develop or if Ella has persistence of her vomiting, abdominal pain, and diarrhea.
- Return to care for severe abdominal pain, a change in mental status, or signs of dehydration.
- For future international travel, discuss the latest Centers for Disease Control and Prevention recommendations for vaccination and medical prophylaxis with Ella's pediatrician or a travel medicine specialist at least 4 to 6 weeks prior to departure.

Clinical Pearls

- In pediatrics, most cases of FUO represent uncommon presentations of common diseases.
- Although FUO was previously defined as fever for at least 3 weeks, many contemporary pediatric references define it as an unexplained daily fever lasting 8 days or longer.
- The differential diagnosis for FUO is broad, and the diagnostic evaluation should be prioritized based on specifics from the patient's history and examination.
- The underlying diagnosis determines the prognosis and management; however, for undiagnosed patients, most cases (approximately 75%) spontaneously resolve and mortality is low.

Documentation Tips

- Document sepsis or concern for sepsis, if present.
- Document the duration and the height of fever.
- When an empiric treatment is started, it is important to state what you are empirically treating for even if the diagnosis is not yet confirmed.

Suggested Reading

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Maria, a 15-Year-Old Girl With Lower Extremity Weakness

CASE PRESENTATION

A 15-year-old previously healthy girl, Maria, is brought to the emergency department (ED) by emergency medical services for rapidly progressing left lower extremity weakness. Maria has been experiencing left leg weakness for the last 2 weeks after injuring her left ankle while playing basketball, but when she suddenly was unable to stand on her left leg, her father became alarmed and called 911. Upon Maria's arrival to the ED, the ED physician obtains an immediate computed tomography (CT) scan of her head, which shows no abnormality. Radiographs of the left lower extremity from the hip to foot are also obtained and are normal. The ED physician is concerned about an underlying neurologic cause for Maria's symptoms and calls you to ask that you evaluate her for admission.

Patient History and Review of Systems

Q: What information should you collect from Maria and her caregivers?

- History of present illness
  - Detailed history of the weakness, including onset, severity, evolution, ability to bear weight, and involved sites
  - Complete trauma history, including local trauma and trauma to the head, neck, and spine
  - Other neurologic symptoms (eg, incontinence, loss of consciousness, headaches, abnormal movements, seizures)
  - Any illnesses in the weeks prior, especially diarrheal or respiratory illnesses
  - Recent changes in behavior (eg, emotional lability, irritability)
  - Travel history and sick contacts
- Associated symptoms, including pain, swelling, decreased range of motion, or sensory changes
- Complete review of systems, especially focused on any constitutional, musculoskeletal, or hematologic symptoms
- Medical history, especially developmental history, history of bleeding or clotting disorders, bone or joint pains, or psychiatric diagnoses
- Medications, including recent use of antibiotics, oral contraceptives, over-the-counter medications, or supplements
- Family history, including migraines, epilepsy, cerebrovascular accident, neurologic or genetic conditions, mental illness, and periodic paralysis syndromes
- Full HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, including illicit drug or alcohol use, sexual history, abuse, or other stressors (refer to Section VII in the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

You meet Maria and her father in the ED and learn that she was in her normal state of health, with no recent illnesses, until 2 weeks ago when she fell and "rolled her left ankle" during a basketball game. She had associated pain along the medial malleolus but no swelling, bruising or difficulty bearing weight at the time of injury. She immediately iced her ankle and took a 400-mg dose of ibuprofen at the time of injury and the following morning. The pain resolved within 24 hours, but since then, she has been intermittently complaining of "heaviness" of the left foot. Yesterday, she acutely began dragging her left foot when walking. Since this morning, she has been unable to bear any weight on her left leg. When asked why she cannot stand up, she replies, "My leg is too weak. I just fall." She denies any sensory changes in the leg.

Maria has no chronic medical or psychiatric diagnoses and takes no daily medications. She has a normal developmental history, and her immunizations are up to date, including a recent influenza immunization. She has never had surgery, and she has no history of bleeding or clotting disorders. Maria lives with her mother, father, and younger brother. Her family history is unremarkable. She has not had any recent animal bites or unusual exposures. She has no history of recent travel or known sick contacts.

A complete review of systems is negative aside from the symptoms described with this illness. Maria denies headaches, abnormal movements/seizures, or numbness/tingling. She has no history of bone or joint pains prior to the injury 2 week ago.

When asking about any recent changes in Maria's behavior, her father reveals that Maria is currently failing multiple classes in school, despite having excellent grades the prior semester. He notes that if her grades do not improve in the next couple of weeks, she will be suspended from the basketball team. Her best friend has stopped coming by the house in the last 2 months, and Maria has started to refuse attending church on Sunday.

During a HEADSS examination without her father present, Maria denies alcohol use or illicit/prescription drug use. She shrugs when asked about preferences for romantic or sexual partners and denies sexual activity. She reports that she feels safe at home but becomes quiet when asked about school and states "I don't want to talk about school right now." She denies suicidal ideation.

Physical Examination

Q: What parts of the physical examination should you focus on for Maria?

- Complete set of vital signs
- Head, eyes, ears, nose, and throat: signs of head trauma
- Neurologic: mental status, cranial nerve examination, reflexes (including clonus and Babinski sign), sensation (eg, pain, proprioception, vibration, temperature), coordination (eg, finger to nose, dysdiadochokinesia), gait, muscular bulk and tone, and strength, including Hoover's test
- Musculoskeletal: tenderness (especially in extremities or along spine) or muscular atrophy, active and passive range of motion of all extremities
- Psychiatric: general observations regarding appearance, speech, behavior, affect, orientation, memory, insight, and judgment

BACK TO BASICS

Hoover's Test

A detailed physical examination is required to determine if a patient's signs and symptoms may be explained by neurologic disease. Demonstration of internal inconsistency on physical examination is one way to demonstrate that clinical findings are inconsistent with neurologic disease and may help support a nonneurologic diagnosis. Hoover's test is a physical examination technique that may elicit internal inconsistency when a patient presents with lower extremity weakness.

Hoover's test is conducted by having the patient lay supine on the bed. The examiner then places their hands under the heels of the patient and asks the patient to push down their heels. If there is weakness of one leg during this portion of the examination, the examiner asks the patient to raise the contralateral leg. No pressure would be expected on the side of the weak extremity during this portion of the test. If there is pressure felt, this would indicate a positive Hoover's sign.

CASE FOCUS

Physical Examination

Maria's vital signs show she is afebrile (37.3 °C [99.1 °F]), with an age-appropriate blood pressure (112/81 mm Hg), heart rate (94 beats/min), respiratory rate (20 breaths/min) and adequate oxygen saturation (98%) on room air.

On examination, Maria is sitting in her bed in no acute distress, though she appeared anxious throughout the history and review of systems and had seemed restless during the HEADSS examination you conducted earlier. Her head, eyes, ears, nose, and throat; cardiac; respiratory; abdominal; and integumentary examinations are normal. A genitourinary examination is deferred per her request. All 4 extremities are warm and well perfused. She has no joint effusion. No musculoskeletal tenderness is appreciated. You do not find any evidence of muscle atrophy.

On her neurologic examination, she is able to follow commands. All of her cranial nerves are intact. She has normal reflexes (including bicep, tricep extensor digitorum, patellar, ankle, and downgoing Babinski), passive range of motion, and sensation in all extremities. No spinal abnormalities are appreciated; however, her left lower extremity strength is 1 on a scale of 0 to 5 (visible muscle contraction, but no movement). She does, however, have a positive Hoover's sign. She has evidence of a coordination deficit during heel to shin testing of the left lower extremity, but otherwise her coordination is normal. Because she cannot bear weight on her leg, Maria is unable to participate in any gait testing or maneuvers involving standing. Her strength is notably 5 on a scale of 0 to 5 in all other extremities.

Maria is alert and oriented, with normal registration and recall. She has good insight into the reasons surrounding her hospitalization and answers hypothetical scenarios with good judgment. When asked how she is feeling, she responds "I'm okay, but I don't know what is happening to my leg."

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent with acute-onset unilateral lower extremity weakness?

Based on what you know so far, you think Maria may have functional neurological symptom disorder (FNSD; also known as *conversion disorder*). Because this is a diagnosis of exclusion, you decide to systematically organize a detailed differential diagnosis, as shown in Table 32.1.

Table 32.1. Differential Diagnosis for an Adolescent With Acute-Onset Unilateral Lower Extremity Weakness

Category	Etiology
Diagnosis of highest suspicion	
Somatic symptoms and related disorders	FNSD[a]
Other diagnoses to consider	
Intracranial/spinal etiologies	• AFM • ALS • Autoimmune encephalitis (eg, ADEM, NMDA-receptor encephalitis) • Hemiplegic migraine • Hemorrhage • Mass (eg, neoplasm) or lesion • MS • Poliomyelitis • TM • Todd paralysis • Vascular ischemia/infarct
Peripheral neuropathy	• Acute demyelinating illness (eg, Guillain-Barré syndrome) • Charcot-Marie-Tooth disease • Neurotoxin (eg, botulinum, snake venom)
Bone/soft tissue etiologies	• Myopathy (eg, dermatomyositis, rhabdomyolysis, MD) • Septic arthritis • Skeletal fracture • Tendinopathy • Transient synovitis
Other etiologies	• Amplified musculoskeletal pain syndrome • Factitious disorder • Lambert-Eaton myasthenic syndrome • Leukodystrophies • Malingering • Myasthenia gravis • Periodic paralysis disorder

Abbreviations: ADEM, acute disseminated encephalomyelitis; AFM, acute flaccid myelitis; ALS, amyotrophic lateral sclerosis; FNSD, functional neurological symptom disorder; MD, muscular dystrophy; MS, multiple sclerosis; NMDA, *N*-methyl-D-aspartate; TM, transverse myelitis.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with acute-onset unilateral lower extremity weakness?

- Sudden onset of focal weakness can be an indication of emergent diagnoses, such as an ischemic infarct or hemorrhage of the central nervous system. It is important to be methodical in the diagnostic evaluation, first focusing attention to rule out emergent etiologies.
  - Head CT scan without contrast is helpful to assess for any acute intracranial abnormality requiring emergent intervention, including hemorrhage, hydrocephalus, or other causes of intracranial mass effects.
  - Magnetic resonance imaging (MRI) with diffusion-weighted imaging and magnetic resonance angiography (MRA) of the brain and spine can help rule out ischemia, hemorrhage, or other inflammatory or infectious lesions.
- When a patient expresses that they are experiencing "weakness," it is important to differentiate among neuropathic weakness, restricted range of motion, or hesitation related to pain, as the former may indicate neurologic pathology, whereas the latter 2 may point more toward structural or mechanical etiologies (eg, soft tissue injuries, fractures).
  - Focal deficits in strength testing indicate weakness secondary to neuronal involvement/impairment.
  - Impairments in passive range of motion point to possible joint structure pathology (eg, tendinopathy, synovitis, arthritis).
  - Signs of pain (eg, grimacing, crying) during examination raise suspicion for soft tissue (eg, myopathy) or osseous pathologies (eg, fracture) as the primary source for the subjective concern of weakness rather than a true deficit in strength.
- Prodromal infectious symptoms (eg, fever, rhinorrhea, cough, diarrhea, vomiting) increase concern for diagnoses like poliomyelitis or Guillain-Barré syndrome. Constitutional symptoms (eg, fever, weight loss, fatigue, night sweats) raise concern for chronic inflammatory pathologies like neoplasm or paraneoplastic syndromes (eg, Lambert-Eaton). A complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein level can be helpful initial indicators of inflammatory or infectious etiologies. Because Maria does not have any of these symptoms, infection and inflammation are less likely.
- Associated symptoms can be helpful clues in making a diagnosis in patients with weakness and should be carefully considered. Headaches or seizures may raise concern for intracranial lesions (eg, hemorrhage, brain mass); different patterns of behavioral changes may suggest encephalitis, intracranial lesions, or psychiatric etiologies; sensory deficits may suggest neuronal lesions, such as those present in multiple sclerosis (MS) or Guillain-Barré syndrome (which may be associated with neuropathic pain in children and adolescents).
- Specific characteristics and timing of weakness can be helpful in narrowing the differential diagnosis. Guillain-Barré syndrome typically presents with a bilateral ascending weakness. MS typically has remitting/relapsing weakness. Myasthenia gravis usually presents with weakness that is worse later in the day and improves by morning. When there is suspicion for such diagnoses, cerebrospinal fluid studies (including cell counts, protein, glucose, and oligoclonal studies) can be helpful in affirming neuropathies like MS and Guillain-Barré syndrome. Nerve conduction studies and electromyography can be useful in identifying patterns of denervation and muscle injury in myopathies and peripheral neuropathies. Muscle tenderness may indicate a fracture or infection. Internal inconsistency at examination, such as is seen with a positive Hoover's sign, may provide evidence that symptoms are a result of a functional neurologic diagnosis.
- Maria's symptomatology does not appear to fit squarely into the presentation for typical neurologic, infectious, or musculoskeletal etiologies of weakness. Her weakness is acute, unilateral, and worsening. She also has a positive Hoover's sign. Without evidence of primary or secondary gain from the illness, FNSD appears the most likely diagnosis. Learning more about Maria's mood and stressors is important while completing your workup and continuing to monitor for signs and symptoms that may indicate an alternative diagnosis. FNSD is often considered a diagnosis of exclusion, but when suspected, FNSD should be discussed with families early in the evaluation process, concurrently with other diagnoses on the differential. In Maria's case, ruling out emergent diagnoses will be helpful in affirming the diagnosis.

CASE FOCUS

Diagnostic Evaluation

After reviewing the normal head CT scan and lower extremity radiographs obtained in the ED, you decided to obtain an MRI of the brain and spine. The results are as follows:

MRI with contrast and MRA of the brain and spine: Normal scan. No acute or chronic lesions appreciated.

Arriving at a Diagnosis

Q: How do you develop an assessment for Maria?

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Maria had a left ankle injury 2 weeks ago and since then, has indicated that she is experiencing weakness. Her weakness acutely worsened just before her presentation. Her history suggests possible social stressors but is otherwise unremarkable. Maria's atypical history of weakness does not fit into classic organic neurologic presentations. She has not had any associated symptoms, including headaches, seizures, prodromal upper respiratory infection or gastroenteritis symptoms, sensory symptoms, or constitutional symptoms to suggest common neurologic, infectious, or musculoskeletal pathologies.
   - Physical examination: Maria has focal left lower extremity weakness; her strength is 1 on a scale of 0 to 5, but she has no other neurologic deficits. Maria's normal passive range of motion with the absence of swelling and tenderness lowers the likelihood of a local inflammatory process. Her normal reflexes decrease the likelihood of typical peripheral and central motor neuropathies. Though focal deficits can occur with peripheral neuropathies like Guillain-Barré syndrome, this is atypical. Her psychiatric examination is unremarkable aside from her anxious demeanor.
   - Diagnostic evaluation: Maria's head CT scan is normal and her MRI/MRA of the brain and spine is normal. Her negative CT scan and MRI are reassuring against acute intracranial or spinal lesions. Her normal left extremity radiographs indicate no fracture or other gross osseous abnormalities.
2. **Develop the list of findings.**

Q: What major findings have you identified for Maria?

- Left lower extremity weakness, nonprogressing
- Significant social stressors
- Hoover's sign

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Maria's presentation?

Maria's examination findings, coupled with her unremarkable workup and significant social stressors, raise concern for FNSD, commonly known as *conversion disorder*.

Q: What is FNSD?

- FNSD falls under the umbrella of somatic symptoms and related disorders (SSRDs), a category of psychogenic somatization diagnoses, including (but not limited to) functional gastrointestinal disorder, amplified pain syndromes, and nonepileptiform seizures. SSRDs may account for as many as 10% of primary care visits in children, and SSRDs are the second leading cause for consultation of child and adolescent psychiatric services in children's hospitals.

- FNSD describes a constellation of neurologic manifestations, including weakness/paralysis, sensory deficits, and seizures, without any attributable organic or physical causes and often precipitated by a psychological trigger.
- According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), diagnostic criteria for FNSD include the presence of one or more voluntary motor or sensory function symptoms that are not explained by another diagnosis, and clinical evidence that symptoms are incompatible with recognized neurologic or other medical conditions.
- FNSD has an association with maladaptive personality traits, stressful life events, or a history of a neurologic disease that causes similar symptoms. There is a higher incidence of FNSD in adolescents compared to prepubertal children. FNSD is also more prevalent in girls and women for unknown reasons. Additionally, FNSD often presents after an illness or physical injury, which may initially make diagnosis more challenging. Older classifications and diagnostic criteria of conversion disorder required a psychosocial trigger; in the most recent DSM-5 criteria for diagnosis, this is not a requirement.
- When the triggering stressor can be promptly identified and addressed, the prognosis for full recovery is very good. Relapse or the development of new psychosomatic symptoms in the future is common; however, prompt recognition and early treatment by an interdisciplinary team may lead to quicker recovery times.

Q: What challenges might you anticipate in making the diagnosis of FNSD?

- The path to diagnosis of FNSD can be difficult for providers, patients, and families alike. In an effort to isolate an explanation for symptoms, it is not uncommon for patients to undergo extensive workup and evaluation by multiple specialty/subspecialty providers. Pressures to identify an organic etiology can lead to overtesting and, in turn, prolonged hospital stays, iatrogenic injuries, increased healthcare costs, and heightened economic or emotional burdens on families.
- Patients and families may be uncomfortable with the diagnosis, often due to the stigma associated with mental health diagnoses. Families may also presume this diagnosis suggests their child's or adolescent's illness is fabricated or fear that the medical team may be missing a rarer or more life-threatening diagnosis. Thus, it is helpful to begin conversations regarding mind-body connection and somatization early in the diagnostic process. Further, early involvement of behavioral health consulting services in the diagnostic process can help families become familiar with and develop trust in the mental health team. What is more, interventions for FNSD are largely benign, so trialing treatments may have potential benefit without risk of harm.
- In addition to consulting mental health providers, consultation with additional subspecialty providers and rehabilitative providers can be helpful both in the diagnosis and management of FNSD. Because of the multidisciplinary nature of diagnosis and management of FNSD, communication with families can become overwhelming and prone to disjointed messages. Interdisciplinary meetings, along with the use of some scripted messaging, may help communicate a clear and unified message and help emphasize the complicated nature of SSRDs. When executed successfully, coordinated interdisciplinary communications are associated with improved treatment adherence, outpatient engagement, and improved patient outcomes.

Table 32.2 offers sample scripts to assist clinicians with discussions about the underlying etiology of somatic or functional disorders and the importance of mental health providers in the patient's evaluation and treatment.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with suspected FNSD?

The diagnosis of FNSD can often be made in the ED and outpatient treatment can be initiated. Because of this, patients with FNSD typically do not need to be admitted to the hospital. There are, however, some situations in which the patient may benefit from hospitalization:

- There is a need for serial neurologic examinations to confirm the diagnosis when other etiologies cannot be excluded.
- There is a potential psychogenic stressor or safety concern in the outpatient environment that cannot be immediately addressed.
- There is a need for subspecialist consultation, such as evaluation by a neurologist to help evaluate when an atypical presentation of an organic etiology is suspected.

Table 32.2. Sample Scripts for Introducing Functional Neurological Symptom Disorder to Families

Concept	Sample language
Introducing the mind-body connection	*"The brain and body are connected and communicate through nerves, hormones, and chemicals. We call this the mind-body connection. Sometimes it's hard to understand how the mind-body connection contributes to symptoms, so we want to explain that. The body automatically sends information to the brain, and at the same time, the brain automatically sends information to the body to communicate feelings, such as fear and pain."* *"You may have heard of the 'fight-flight-freeze' response. When we sense danger, the brain tells the body to stay on alert using electrical and chemical signals. The body starts doing things to help us survive; for example, lungs breathe faster and shallower, and [the] heart beats faster and harder to get more oxygen to the brain and muscles. Muscles tense up, getting ready to fight or run. All of these reactions happen quickly and automatically, without us even thinking about it. Later, when the danger is gone, the brain tells the body to calm down, but the experience can leave a physical toll on the body. This is our body's response to stress, also known as the physiology of stress."* *"Stress can be positive or negative, and although we may not consider something 'dangerous' or stressful, our bodies can experience the effects of stress through physical symptoms. In this way, we can view the physical symptoms as the body telling us it is feeling distressed or that we are feeling the emotion or stress in our bodies."*
Introducing behavioral health and other consulting teams	*"We are going to review all the tests and treatments you've done so far to determine what has been helpful, what needs to be repeated, and what new tests and consultations are needed. We see many children with symptoms similar to what your child has and have a standard multidisciplinary approach to care that includes different consultants from medical specialties, surgical specialties, physical and/or occupational therapy, social work, psychiatry and/or psychology, etc. This comprehensive approach will help us better understand the nature of your child's symptoms and the impact on all areas of his or her life and will also help us develop an effective management plan."*

Adapted with permission from Ibeziako P, Brahmbhatt K, Chapman A, et al. Developing a clinical pathway for somatic symptom and related disorders in pediatric hospital settings. *Hospital Pediatrics*. 2019;9(3):147–155.

- Education and coordination of therapy is needed and not available in the outpatient setting. Treatment of FNSD is often a long-term process requiring communication with multiple providers in the outpatient setting and a clear understanding of goals of care. Families must be empowered with the understanding and tools to be successful, and this may, in some cases, be expedited by coordinated care in the inpatient setting. Additionally, when functional limitations like difficulty with ambulation or activities of daily living exist, especially in older children and adolescents who cannot easily be physically supported through these limitations at home, inpatient rehabilitation services become crucial.

Although hospital admission may allow the time to confirm the diagnosis of FNSD, more definitively rule out other diagnoses, and empower families with the necessary knowledge and resources for outpatient care, it is imperative to patient recovery that patients transition to outpatient services as soon as possible. Therefore, admission for observation, rather than a full inpatient admission, may be appropriate.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Maria is a 15-year-old previously healthy girl presenting with acute-onset left leg weakness in the setting of underlying stress most consistent with FNSD. She requires admission for a period of observation and further evaluation.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The treatment plan for patients who have FNSD depends in large part on the specifics of the contributing psychological stressors and the presenting physical symptoms (eg, weakness, blindness, stuttering, seizures); however, the goals of therapy are to engage mental health resources, improve physical functionality, successfully transition to outpatient care, and return to typical daily living.

1. **Mental health consultation and intervention:** When a contributing psychogenic stressor can be identified, addressing the source is as important as addressing the manifesting somatization. Data from children is limited; however, extrapolating from adult data, when the stressor is promptly identified and removed, the prognosis for recovery from FNSD is very good. Mental health consultation and intervention should begin concurrently with the ongoing workup when FNSD is suspected. Early consultation of mental health professionals helps families become familiar with the multifactorial nature of SSRDs and feel more confident in the diagnosis and in the patient's quality of care. Mental health providers can also assist with the evaluation and treatment of any co-occurring psychiatric diagnoses (eg, depression and anxiety).
2. **Rehabilitation:** When symptoms of FNSD significantly affect activities of daily living, inpatient rehabilitative services may be indicated. Appropriate therapies depend on the functional impairments from somatic symptoms (eg, speech therapy for stutter or physical and occupational therapy for focal weakness) with the overarching goal of returning physical functionality. For Maria's symptoms, physical and occupational therapy consults should be considered.
3. **Further diagnostic evaluation:** Further workup for patients hospitalized with FNSD includes definitively ruling out any emergent diagnoses that remain on the differential and looking for confirmatory evidence of FNSD.
   - Having ruled out emergent etiologies and with low suspicion for alternative etiologies of extremity weakness, you can move toward a period of observation and evaluation for Maria.
   - Although not every case of FNSD has an identifiable stressor, conducting a more thorough HEADSS examination for Maria is necessary. An initial HEADSS assessment can be incomplete, especially given the sensitivity of the questions, minimal rapport, and the stressful environment of the ED. However, identifying and addressing contributing stressors can be both reassuring of the diagnosis and important for the prognosis and treatment of FNSD. Therefore, returning to the bedside to develop a physician-patient relationship and engaging in repeat, focused HEADSS examinations is crucial.
4. **Monitoring:** Patients with FNSD should be monitored closely for any clinical changes that allow the physician to rule out more atypical presentations of other etiologies and affirm the diagnosis of FNSD. Given the nature of her symptoms, serial neurologic examinations are particularly important in Maria's evaluation. A progressively worsening clinical examination would be expected in certain diseases (eg, Guillain-Barré syndrome), whereas a more variable worsening can be seen in other diseases (eg, myasthenia gravis). Additionally, FNSD symptoms can be inconsistent, and serial examinations allow the physician the opportunity to identify these inconsistencies.

5. **Outpatient transition**
   - Patients benefit from continued outpatient mental health services to monitor their mental health progress and assist in developing healthy social environments and coping strategies. These may include family therapy or individual behavioral therapy. Treatment also includes connecting patients to the appropriate support services for any identified social stressors (eg, food insecurity, homelessness, bullying).
   - Many patients will also benefit from continued outpatient rehabilitative therapies, which patients should be connected to prior to hospital discharge.
6. **Psychosocial support:** Return to typical daily life (to the supports and familiarity of home, school, family, and friends) is a key part of the treatment process. Families play a large role in the continued treatment, and thus helping families understand and accept the importance of patients returning to their typical routines at home is crucial. It is critical that clinicians work in partnership with the patient's family to understand the specific obstacles the patient is facing in returning to typical daily life and help the patient and their family overcome these obstacles.

CASE FOCUS

Plan for Treatment and Monitoring

You discuss your concern for FNSD with Maria and her family, explaining the mind-body connection and the importance of involving pediatric neurology and behavioral health teams to better characterize Maria's illness, understand how her symptoms are affecting her life, confirm the diagnosis, and treat her acute weakness.

- **Mental health consultation: You plan to consult the child and adolescent psychiatry team to assist with your evaluation for comorbid psychiatric illness.**
- **Rehabilitation: You will consult physical and occupational therapists to evaluate Maria's weakness and provide any necessary physical rehabilitation. Additionally, you will order crutches for Maria to use while she regains functionality in her left leg.**
- **Further diagnostic evaluation: You plan to repeat a HEADSS examination now that Maria is out of the busy and stressful environment of the ED. You also will consult a pediatric neurologist to complete a neurologic evaluation of Maria.**
- **Monitoring: You plan to continue serial neurologic examinations and ask Maria's bedside nurse to take note of any symptom evolution.**
- **Outpatient transition: You plan to reach out to Maria's primary care pediatrician and discuss her suspected diagnosis and begin planning her eventual outpatient transition.**
- **Psychosocial support: You plan for an interdisciplinary family meeting with the primary care pediatrician and the consult teams following completion of Maria's evaluations to help determine how to best address any barriers identified to Maria's return to typical daily life.**

Discharge Criteria

Q: How do you know when Maria is ready to go home?

You can feel comfortable discharging your patient with FNSD when the following criteria are met:

- Other acute pathologies have been ruled out.
- The patient has established care with all providers needed to complete symptom-appropriate therapies (eg, physical therapy for weakness).
- The patient has connected with continued outpatient therapy providers and a plan for follow-up care has been confirmed.

Case Resolution

Soon after Maria is admitted, her bedside nurse records in a note that "the patient remains afebrile with stable vitals. Intermittently kicking off her blanket with her left leg in varied positions while napping, however unable to move her leg when awake." To you, this suggests a subconscious capacity to move her left lower extremity. This inconsistency is supportive of the diagnosis of FNSD.

Maria's repeat neurologic examination reveals collapsing weakness of the left lower extremity, without deficits in passive range of motion, reflexes, or sensation (consistent with her initial evaluation). She does not develop progressive involvement in other focal sites, including extremities, trunk, and cranial nerves. When encouraged to stand, Maria is able to bear weight for up to 3 seconds before collapsing onto the bed. To you, the presence of "collapsing weakness," or an ability to briefly resist before the onset of weakness, suggests a psychogenic process. Her brief ability to bear weight is inconsistent with organic causes of weakness and affirms your suspicion for FNSD.

You repeat a HEADSS assessment when Maria is alone and discover that at the beginning of the semester, Maria confided in her best friend, Amelia, that she is attracted to male and female partners. Afterward, Amelia started cancelling plans and withdrawing. Maria noticed her other friends stopped inviting her to social events, so she began to worry that Amelia had shared her secret. Maria feels guilty about hiding her sexuality from her mother and father but is nervous to discuss it with them because she believes they would be disappointed. She also worries that her poor grades will affect her future application to college and participation on the basketball team but is struggling to focus on school since her discussion with Amelia. She reports no alcohol or illicit drug use. She denies current or prior romantic partners or sexual activity. She says she feels safe and otherwise supported at home. Despite reporting feeling frequently anxious about her secret, she denies anhedonia or hopelessness and she has no active or prior suicidal ideation.

Following their assessment, the pediatric neurology team agrees with your diagnosis of FNSD and does not suspect an alternative neurologic etiology of Maria's weakness. The child and adolescent psychiatry team also sees Maria and does not believe she meets clinical criteria for major depressive disorder or anxiety but recommends family therapy and personal therapy to help address the previously described stressors. The inpatient physical and occupational therapy teams meet with Maria and perform an initial assessment to create a longitudinal therapy plan.

Alone with Maria, you discuss your concerns that her stress around sexuality is manifesting as weakness, paying careful attention to legitimize both her symptoms and her stressors. After some discussion, Maria decides she will start her healing process by coming out to her aunt, a trusted adult in her family.

With her family, you discuss Maria's case in an interdisciplinary meeting with her inpatient teams and outpatient pediatrician. You focus on psychogenic stressors like scholastic pressures, fears surrounding basketball suspension, and her college application. Her parents are appropriately concerned and agree to participate in family therapy and to engage Maria in independent behavioral therapy to help address her anxieties.

You place a referral for continued physical and occupational therapy for Maria. Prior to her discharge, you identify both a personal therapist and a family therapist to follow Maria and her family on an outpatient basis.

Anticipatory Guidance

Q: What instructions or guidance should you provide to Maria and her caregivers upon discharge?

- The recovery process continues outside of the hospital setting and is dependent on continued efforts and engagement with mental health providers, rehabilitative therapies, subspecialists, and continued family and/or social supports.

- The goal of returning to the familiarity of daily routines requires all members of the family to work to resolve stressors and/or to develop healthy coping mechanisms. This may involve seeking family counseling or other resources for family members.
- Nearly one-quarter of patients with resolved FNSD will relapse or develop new psychosomatic symptoms in the future. Therefore, any new symptoms should be discussed with the outpatient treatment team as soon as possible to rule out new alternative diagnoses and to reinitiate treatment to avoid progression of psychosomatic symptoms.

Clinical Pearls

- SSRDs are often viewed as diagnoses of exclusion. Instead, simultaneously pursuing both a medical and mental health evaluation early helps minimize unnecessary testing and assists with transitions of care.
- Including the primary care pediatrician and other key outpatient providers in the interdisciplinary meetings not only helps add a voice of familiarity to the conversation but can also help families to accept and understand the diagnosis while helping to facilitate the transition to continued outpatient care.

Documentation Tips

- Document the type of functional disorder (eg, functional paralysis or weakness, functional sensory disorder, functional cognitive disorder).
- Document interdisciplinary interventions required.
- Document any findings demonstrating internal inconsistency on physical examination.

Suggested Reading

Ibeziako P, Brahmbhatt K, Chapman A, et al. Developing a clinical pathway for somatic symptom and related disorders in pediatric hospital settings. *Hosp Pediatr*. 2019;9(3):147–155 PMID: 30782623 https://doi.org/10.1542/hpeds.2018-0205

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CASE 33

Juan, a 16-Year-Old With Shoulder Pain

CASE PRESENTATION

Juan is a 16-year-old transgender male adolescent, with no significant medical history other than gender dysphoria, who presents to an urgent care clinic with right shoulder pain. He reports no known injuries but has recently increased his workouts as part of his football training. At the urgent care clinic, radiographs of his right upper arm and shoulder are unremarkable. He is given acetaminophen and ibuprofen but is still in significant pain. The urgent care physician calls to ask if you will consider admitting Juan for pain control and further evaluation.

Patient History and Review of Systems

Q: What information should you collect from Juan and his caregivers?

- History of present illness
  - Onset and timing, whether pain is intermittent or constant, and if intermittent, the duration and frequency of episodes
  - Location: diffuse or localized
  - Intensity of the pain, interference with activities, and progression over time
  - Quality (eg, stabbing, burning, aching, sore)
  - Aggravating or alleviating factors
  - History of trauma or recent injuries
  - Associated symptoms, such as weakness, edema, skin changes, numbness/tingling, fever, decreased urine output, changes in urine color, upper respiratory symptoms, or gastrointestinal symptoms
- Medical history, including prior similar episodes
- Medication use, including prescription medications, over-the-counter medications, or supplements
- Social history, specifically for HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment and self-injury (refer to Section VII of the Appendix for an example of a complete HEADSS assessment)
- Family history, most notably for similar symptoms or a myopathy

HEALTH EQUITY FOCUS

Gender Inclusive Care

Health care providers commonly encounter transgender patients in the hospital setting. It is important for providers to be knowledgeable about and sensitive to issues surrounding gender identity.

Many electronic medical records (EMRs) allow a patient's medical record to include a gender other than the gender assigned at birth, as well as other names. Other EMRs have ways to alert healthcare professionals of gender incongruence in the patient's medical record.

- Be mindful that the patient's name and gender in the EMR may not match the name and gender identity of the person in front of you.
- Introduce yourself to patients by including your pronouns: "Hi, I'm Dr. Brown, I use she/her pronouns. What do you like to be called? What pronouns do you use?"
- Use the pronouns and name given to you by the patient. If you make a mistake, quickly apologize, correct yourself, and move on.
- For transgender patients who are receiving hormonal therapy, some of their laboratory values may no longer fall within the reference ranges for the patient's sex assigned at birth. For example, the serum hemoglobin concentration of a transgender male adolescent receiving testosterone will align with the hemoglobin value for cisgender male adolescents.

CASE FOCUS

History and Review of Systems

When Juan arrives at your hospital, you meet him and his parents in his room. You note that the EMR lists Juan with a different name and gender than his presenting name and gender. When asked for Juan's pronouns and name, Juan says that he uses he/his pronouns and goes by Juan.

From these questions, you learn that Juan is a football player at his high school, where his coaches have recently instituted "two-a-day" workouts in preparation for the upcoming season. For the past 3 days, Juan has increased his training both on and off the field. As part of his new routine, Juan has been intensifying his weight training and added in 200 push-ups each day. He is unsure of any specific injury, but he does have full contact practices.

He states that his pain has been constant and progressively worsening, and he describes it as aching and burning. It began 1 day ago and forced him to sit out of practice. He notes pain in both shoulders, upper chest, and upper arms, with the pain in his right shoulder being most severe at a 7 on a scale of 0 to 10. He reports that his shoulders also feel "tight and swollen." The only medication he takes is intramuscular (IM) testosterone, 100 mg weekly, as part of his gender-affirming care. He has been taking testosterone for the past 2 years. He rotates his injection site and does not inject into his arms.

On his review of systems, he notes some nausea but no emesis. He has been tolerating a regular diet. He states that his urine seems more concentrated but denies any dark-colored urine. He denies any similar episodes in the past. His HEADSS assessment is negative for any illicit drug or alcohol use. He states he does not have issues with bullying and is supported at home and at school. He reports that his increase in workouts was not due to poor body image but increased effort in trying to make the varsity team. Juan is generally healthy, without chronic medical conditions, and he denies any past similar episodes. No one in his family has had muscle concerns.

Physical Examination

Q: What parts of the physical examination should you focus on for Juan?

- Complete set of vital signs
- Presence of edema (periorbital, pedal, genital, muscular)
- Musculoskeletal: presence of limb deformity, muscle tenderness, joint range of motion
- Lungs: tachypnea, adventitious sounds
- Abdomen: tenderness
- Neurologic: reflexes, sensation, muscle strength
- Skin: erythema, warmth, swelling, rash
- Visual examination of urine, if possible
- Peripheral perfusion: pulses and capillary refill time

CASE FOCUS

Physical Examination

Juan's vital signs show that he is afebrile (37.1 °C [98.8 °F]). His respiratory rate (16 breaths/min), oxygen saturation (98% on room air), and blood pressure (110/71 mm Hg) are within normal limits. He does have mild tachycardia, with a heart rate of 105 beats/min. He weighs 73.2 kg.

On examination, Juan is sitting in his hospital bed in no obvious discomfort. He is able to converse easily and answer your questions. You notice that his right upper arm and shoulder appear larger than his left. There are no signs of trauma or skin changes to either upper extremity. You start by examining his left arm and shoulder more closely. There is fullness and mild tenderness to palpation over this left deltoid, biceps, triceps, and pectoralis major, but he tolerates your examination and range of motion without difficulty. His left upper extremity has 5/5 strength and normal reflexes. His left arm appears warm and well perfused, with a strong radial pulse and brisk capillary refill. You move to examine Juan's right arm, which he has been keeping still. You note that his right deltoid and biceps appear fuller and firmer than his left deltoid and biceps. On light palpation of his right deltoid and biceps, Juan grimaces and pulls away. He also has tenderness over his right triceps and pectoralis major muscles. He is unable to cooperate with strength or range of motion testing with his right upper extremity because of pain. He reports being unable to lift his right arm off the bedrail where it is resting. He is able to squeeze your fingers with good strength. The right upper extremity has normal sensation and is well perfused. The remainder of his physical examination is unremarkable.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent with extremity pain and swelling?

There are many causes of extremity pain and swelling; however, the etiologies can be narrowed based on a complete history and thorough physical examination. Table 33.1 demonstrates a differential diagnosis for these symptoms and has been separated into diagnoses that appear more or less likely for Juan.

Table 33.1. Differential Diagnosis for an Adolescent With Extremity Pain and Swelling

Diagnoses of highest suspicion	• Compartment syndrome • Musculoskeletal injury, including overuse injuries • Myopathies, especially rhabdomyolysis[a] (eg, exertional,[a] viral, traumatic, metabolic, seizure) • Viral illness with associated myositis
Other diagnoses to consider	• Bone, soft tissue, or vascular tumors • Musculoskeletal infection (eg, osteomyelitis, pyomyositis, or septic arthritis) • Skin infections (eg, cellulitis or herpes zoster) • Venous thrombosis

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with extremity pain and swelling?

- The diagnostic evaluation for any child or adolescent with extremity pain and swelling should be guided by the patient's history and physical examination findings. Refer to Table 33.2 to identify the recommended tests based on the clinical scenario.
- The clinician should be particularly mindful to consider (and exclude) etiologies that would require urgent evaluation and treatment, such as open fracture or compartment syndrome.

BACK TO BASICS

Compartment Syndrome

Compartment syndrome occurs when the IM compartmental pressure is elevated to such an extent that it compromises the function of structures within the compartment, including nerves and blood vessels. Although the most common underlying etiology is trauma, there are multiple known causes, including rhabdomyolysis, IM injections, envenomation, prolonged limb compression, and intravenous (IV) fluid extravasation. The presence of compartment syndrome may be suggested by pain out of proportion to apparent injury, the development of paresthesias that may progress to numbness or pulselessness, with pulselessness being a late finding. Other findings may include pain with passive stretch, muscle weakness, and a firm or "wood-like" feeling of the affected compartment. The diagnosis of compartment syndrome is based on the measurement of muscle compartment pressures, which requires surgical consultation. Compartment syndrome is a surgical emergency, and the treatment is urgent fasciotomy.

- For Juan, you are most concerned for rhabdomyolysis but also need to consider myositis, compartment syndrome, and an injury such as overuse injury. Infectious etiologies (eg, osteomyelitis, septic arthritis) appear unlikely based on his bilateral findings. Refer to Table 33.2 for the diagnostic evaluation of these possible etiologies.

Table 33.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children and Adolescents With Limb Pain and Swelling

Diagnosis	Possible clinical features	Diagnostic evaluation to consider
Compartment syndrome	Pain out of proportion to injury; paresthesia, numbness, or pulselessness	Measurement of intracompartmental pressures
Musculoskeletal injury or overuse syndrome	Recent injury or strenuous physical activity Point tenderness or focal area of swelling may be present. For tendon rupture or displaced fracture, examination may show obvious deformity.	Examination may be diagnostic in some cases; for others, imaging (eg, radiographs, MRI) may be required.
Myositis, viral	Muscle pain and swelling, most commonly involving the legs; weakness of the involved muscle groups; concomitant or recent viral symptoms (eg, fever, respiratory tract symptoms)	CMP, UA with microscopy, and CK Consider testing for underlying etiology such as influenza.
Osteoarticular infections (eg, osteomyelitis, septic arthritis)	Focal area of pain and swelling Fever usually present Inability to bear weight or move extremity	Blood culture, CBC, and inflammatory markers Imaging (eg, radiographs, joint US, MRI of the extremity)
Rhabdomyolysis	Pain and swelling of extremity Absence of skin changes Weakness of the involved muscle groups; otherwise, normal neurologic examination Dark urine	CMP, UA with microscopy, and CK Investigation into the underlying etiology may be required if not evident on history (eg, urine drug screen, testing for influenza).

Abbreviations: CBC, complete blood cell count; CK, creatine kinase; CMP, comprehensive metabolic panel; MRI, magnetic resonance imaging; UA, urinalysis; US, ultrasonography.

CASE FOCUS

Diagnostic Evaluation

To help establish Juan's diagnosis, you order a chemistry panel, complete blood cell count, creatine kinase (CK) level, and urinalysis (UA) with microscopy. The results of these tests are as follows:

Laboratory test	Result	Reference range[a]
Serum chemistries		
Sodium	139 mEq/L (139 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	6 mEq/L (6 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	106 mEq/L (106 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	22 mEq/L (22 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	11 mEq/L (11 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	20 mg/dL (7.14 mmol/L)	6–20 mg/dL (2.14–7.14 mmol/L)
Creatinine	1.5 mg/dL (132.6 µmol/L)	0.5–0.9 mg/dL (44.2–79.6 µmol/L)
Glucose	92 mg/dL (5.11 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Calcium	8 mg/dL (2 mmol/L)	9.2–10.5 mg/dL (2.3–2.6 mmol/L)
CK	37,234 U/L (621.8 µkat/L)	30–145 U/L (0.5–2.4 µkat/L)
Urinalysis		
Color	Straw	Yellow
pH	6.0	4.5–8
Specific gravity	1.020	1.005–1.030
Blood	Moderate	Negative
RBC count	2–3/HPF	0–2/HPF
CBC		
WBC count	9,500/µL (9.5×10^9/L)	4,000–10,500/µL ($4.0–10.5 \times 10^9$/L)
Hemoglobin	13 g/dL (130 g/L)	12.5–16.1 g/dL (125–161 g/L)
Hematocrit	41% (0.41)	36%–47% (0.36–0.47)
Platelet count	220×10^3/µL (220×10^9/L)	150–400 $\times 10^3$/µL (150–400 $\times 10^9$/L)

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; CK, creatine kinase; HPF, high-power field; RBC, red blood cell; WBC, white blood cell.

[a] Because Juan is receiving testosterone treatment, reference ranges reflect those for cisgender male adolescents.

After reviewing Juan's potassium results, you order an electrocardiogram (ECG), which shows sinus rhythm with no peaked T waves or other findings consistent with cardiac effects from hyperkalemia.

Arriving at a Diagnosis

Q: How do you develop an assessment for Juan?

To arrive at Juan's diagnosis, you will interpret the findings from his history, examination, and diagnostic evaluation and develop a list of findings. Then, admission criteria can be generated based on the suspected diagnosis.

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History and physical examination: Juan presents with swelling, tenderness, and pain in the bilateral deltoid, pectoralis major, triceps, and biceps muscle groups, as well as right upper extremity weakness. The pain and tenderness in his right upper extremity is greater than in his left, particularly the right deltoid and biceps. These findings developed in the setting of recently increasing his workouts in preparation for the upcoming football season. Juan is noted to have no overlying skin findings, normal peripheral perfusion, and normal sensation of the involved extremities. There are no current findings concerning for compartment syndrome. Juan has no other associated symptoms or risk factors for muscle injury other than his recent exercise.
   - Diagnostic evaluation: Juan had radiographs prior to his admission that were negative for any fractures. Juan reports normal color urine, but his laboratory results show hyperkalemia, hypocalcemia, elevated creatinine (consistent with acute kidney injury [AKI]), and an elevated CK level, which greatly narrows your differential. His UA shows moderate blood but only 2 to 3 red blood cells per high-power field. In the setting of a normal hemoglobin and increased CK, urine hemoglobin out of proportion to red blood cells on urine microscopy is consistent with myoglobinuria.
2. **Develop the list of findings.**

Q: What major findings have you identified for Juan?

- Swelling, pain, and tenderness of the bilateral deltoid, pectoralis, biceps, and triceps
- Right upper arm weakness
- Elevated CK with myoglobinuria
- AKI
- Hyperkalemia
- Hypocalcemia

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Juan's presentation?

You think that Juan's recent exercise history, upper body pain and weakness, and elevated CK level are suggestive of muscle injury leading to rhabdomyolysis.

Q: What is rhabdomyolysis, and how is it diagnosed?

- Rhabdomyolysis is a disorder of muscle cell necrosis that results in the leakage of muscle-cell contents into the peripheral circulation. These cellular contents include electrolytes and proteins such as myoglobin, CK, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase. Rhabdomyolysis is diagnosed based on measurement of serum CK levels.
- Consensus criteria for the diagnosis of rhabdomyolysis in the pediatric population is lacking, but the most commonly used definition is a CK level greater than 5 times the upper limit of normal, or greater than 1,000 U/L (16.7 μkat/L). In rhabdomyolysis, CK typically peaks after a few days and may take 7 to 10 days to normalize.
- Because the myoglobin level rises before the CK level rises, and because myoglobin has a half-life of 1 to 3 hours (compared to >1 day for CK), the presence of myoglobinuria on the UA is not required for the diagnosis of rhabdomyolysis.

Q: What are the possible etiologies of rhabdomyolysis?

- The list of etiologies for rhabdomyolysis is extensive. The most common causes are included in Box 33.1. The patient's history and physical examination findings should aid in identifying the trigger for rhabdomyolysis.
- Based on Juan's history, you suspect excessive/strenuous activity is the cause of his muscle injury. An additional evaluation could be considered if suggested by the following findings on history:
  - If there is an association with other symptoms that could be representative of viral illness, clinicians may consider testing for influenza or other viruses.
  - If there is a concern of illicit drug use, especially in an adolescent, clinicians should obtain a urine drug screen.
  - Recurrent episodes of rhabdomyolysis, exercise intolerance, or an elevated baseline CK level should prompt evaluation for an underlying disorder.

Q: What are some of the potential complications associated with rhabdomyolysis?

- Electrolyte abnormalities, including the following:
  - Hyperkalemia: Potassium levels frequently rise with release from damaged muscles and decreased clearance through the kidneys, particularly in patients with AKI.
  - Hypocalcemia and hypercalcemia: Hypocalcemia is frequently seen initially as a result of calcium precipitation in the damaged muscles. As the patient recovers, calcium will mobilize from the damaged muscles and may lead to hypercalcemia later in the clinical course.
  - Hyperphosphatemia: Hyperphosphatemia can contribute to the development of hypocalcemia, but mild hyperphosphatemia associated with rhabdomyolysis is generally asymptomatic and resolves as muscle injury and renal function both improve.
- Acute renal injury: Renal injury is a common sequela of rhabdomyolysis and can occasionally progress to kidney failure with need for dialysis support, particularly in rhabdomyolysis due to other causes like diabetic ketoacidosis or neuroleptic malignant syndrome. The etiology of AKI and acute renal failure in rhabdomyolysis is multifactorial but is partly related to intravascular volume depletion and myoglobin precipitation in the renal tubules. It can further be confounded by prehospital use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain control, often in inadequately hydrated patients, which is of particular concern with teens suffering from exertional rhabdomyolysis. AKI is more likely with higher CK levels and unlikely at levels below 5,000 U/L (83.5 µkat/L). Juan's creatinine level is elevated at 1.5 mg/dL (132.6 µmol/L), which suggests the presence of AKI.
- Arrhythmias: Patients with severe rhabdomyolysis may present with arrhythmias secondary to electrolyte abnormalities, particularly in the setting of an elevated serum potassium level. Juan is presenting with hyperkalemia, which could have fatal consequences; however, his ECG does not show any of the common changes that you would expect from hyperkalemia. At a serum potassium level of 5.5 to 6.5 mEq/L (5.5–6.5 mmol/L), isolated peaked T waves may be seen, although additional changes (eg, shortened T waves, shortened QT intervals, widened QRS complexes) typically are not seen in children until the serum potassium is above 6.5 mEq/L (6.5 mmol/L).
- Compartment syndrome: Patients with severe rhabdomyolysis are at risk for compartment syndrome, as the damaged muscles cause localized edema. The risk of compartment syndrome is higher following fluid resuscitation, as muscle edema increases. Signs of compartment syndrome can be challenging to distinguish from the symptoms caused by the rhabdomyolysis itself but may include pain out of proportion to the degree of edema, paresthesia, numbness, pallor of the area, and pulselessness (a late finding).
- Disseminated intravascular coagulation: Released cell contents from injured muscles can lead to disseminated intravascular coagulation as a potential late complication. This condition carries a high morbidity and mortality and must be recognized and treated promptly.

Box 33.1. Causes of Pediatric Rhabdomyolysis

Acquired etiologies	Inherited or immune-mediated disorders
• Exertion or trauma — Compartment syndrome — Crush injury — Seizure — Strenuous activity • Illicit drugs — Amphetamines — Cocaine — Heroin — Marijuana • Infections — Bacterial ■ Malaria ■ Mycoplasma ■ Salmonella — Viral ■ CMV ■ EBV ■ Influenza • Medications — Anesthesia agents causing malignant hyperthermia — Colchicine — Neuroleptics — Statins • Metabolic — DKA — Thyroid disease • Toxins — Carbon monoxide — Ethanol — Hornet stings — Snake venom	• Inborn errors of metabolism — Fatty-acid oxidation defects — Glycogen storage diseases — Mitochondrial disorders • Inflammatory myopathies — Dermatomyositis — Polymyositis — Sarcoidosis • MDs — Duchenne or Becker — Dysferlinopathy — *FKRP*-related

Abbreviations: CMV, cytomegalovirus; DKA, diabetic ketoacidosis; EBV, Epstein-Barr virus; *FKRP*, fukutin-related protein; MD, muscular dystrophy.

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with exertional rhabdomyolysis and associated AKI and hyperkalemia?

- The goal of treatment of rhabdomyolysis is to avoid common complications like electrolyte imbalances or AKI.
- Most patients with rhabdomyolysis are admitted for close clinical and laboratory monitoring and IV hydration.

Juan meets criteria for admission based on the presence of rhabdomyolysis, AKI, and electrolyte abnormalities.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Juan is a 16-year-old previously healthy transgender male adolescent admitted with acute right upper extremity pain and weakness in the setting of excessive muscle use. His laboratory test results demonstrate AKI, hypocalcemia, and hyperkalemia, which are secondary to his underlying diagnosis of exertional rhabdomyolysis. He requires hospitalization for aggressive fluid hydration and electrolyte monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goals of care for patients with rhabdomyolysis are to prevent or treat renal injury and electrolyte abnormalities, mostly through use of aggressive hydration. Close monitoring is required to ensure dangerous electrolyte abnormalities, acute renal failure, or other complications do not develop. You approach Juan's treatment with the following considerations:

1. **Fluid resuscitation:** The mainstay of treatment of rhabdomyolysis is fluid resuscitation, which is critical to initiate rapidly; however, there is not clear consensus on the type of fluid, rate of administration, or duration of IV fluid treatment.
   - IV fluid type: Isotonic fluids (eg, normal saline, lactated Ringer solution) should be administered. Although normal saline has traditionally been used in cases of rhabdomyolysis, studies have shown that normal saline and lactated Ringer solution are equally efficacious at lowering CK levels and preventing AKI.
   - IV fluid rate: Aggressive fluid hydration is key to treating and preventing AKI. This is accomplished by increasing renal perfusion to decrease ischemic injury and to increase the urine flow rate to limit intratubular cast formation. For pediatric patients, it is reasonable to start with twice the maintenance rate with adjustment based on urine output. The first 6 hours following the diagnosis are the most critical for treating and preventing AKI with fluid hydration. Therefore, normal saline bolus administration may be considered at the initiation of fluid resuscitation if not completed in the emergency department or if the patient clinically appears volume depleted.
   - Ensuring adequate urine output: All patients with rhabdomyolysis should have strict monitoring of intake and output. It is reasonable to use a urine output of 3 to 4 mL/kg/h (to a maximum of 200–300 mL/h) as a target for adequate diuresis.
   - Juan already has evidence of AKI and an elevated potassium level; therefore, you plan to immediately provide a normal saline bolus and then start his IV fluids at twice his maintenance rate. You will then titrate his IV fluid rate to achieve a goal urine output of at least 200 mL/h. In the setting of AKI, urine output does not always rise as expected. Therefore, Juan's fluid status will need to be monitored closely during this period of hyperhydration. If his urine output does not rise as expected and he develops signs of volume overload, consultation with a nephrologist may be beneficial. In this case, adjunctive therapies may be warranted.
2. **Adjunctive therapies**
   - Sodium bicarbonate: Based on the proposed mechanisms of AKI in rhabdomyolysis, the addition of sodium bicarbonate to IV fluids is advocated by some experts, but a clear clinical benefit has not been established in trials. Its use, therefore, remains controversial and is typically reserved for critically ill patients or patients with significant acidosis.

- Mannitol: It has been theorized that by improving diuresis, mannitol may have a role to play in preventing AKI. It may be of use in situations where adequate diuresis cannot be achieved with IV fluid alone, but it also remains controversial and should not be a routine part of care. Mannitol can be beneficial in the management of volume overload in patients with rhabdomyolysis complicated by AKI. It is important to note that mannitol can worsen hypocalcemia, and its use requires careful monitoring, usually in consultation with a nephrologist.
- You determine that these additional therapies are not needed for Juan at this time.

3. **Monitoring for complications**
   - Arrhythmias: Serial ECG or telemetry monitoring may be needed for patients with electrolyte derangements.
   - Serum laboratory tests: Initially, CK, creatinine, and electrolyte levels should be measured at least twice a day until CK levels begin to downtrend, AKI resolves, and electrolytes have normalized. Some patients may need more frequent monitoring, depending on the severity and rate of rise of CK, presence of AKI, and degree of electrolyte derangements. Hyperkalemia should be treated as needed. Treatment for hypocalcemia is usually not needed unless patients are symptomatic. Infrequently, dialysis is required for acute renal failure or severe electrolyte disturbances.
   - Compartment syndrome: Patients should be monitored for signs of compartment syndrome, including worsening pain, paresthesia, numbness, pallor, and pulselessness. If suspected, the patient should have emergent surgical consultation.
   - Given that Juan has hyperkalemia and AKI, you will start immediate telemetry monitoring and obtain repeat electrolyte, blood urea nitrogen, and creatinine levels after his normal saline bolus. If his potassium level is increasing or if he is developing ECG changes consistent with hyperkalemia, you will initiate specific therapies for hyperkalemia, including calcium gluconate, insulin with dextrose, and a potassium binder. Although Juan does not currently have evidence of compartment syndrome, you will perform serial assessments to monitor for any concerning signs or symptoms.
4. **Pain management:** Because patients with rhabdomyolysis are at risk for AKI, NSAIDs should be avoided because they are known to be nephrotoxic. Additionally, opioids should be used cautiously in patients with AKI because of the risk of poor clearance of opioid metabolites, leading to altered mental status or respiratory depression. For Juan, you will start with scheduled acetaminophen and use opioids sparingly if needed.
5. **Activity:** It is recommended that patients with rhabdomyolysis minimize their activity, particularly with regard to use of the affected area, to reduce continued muscle injury. You will ensure Juan is placed on bedrest until he is improving significantly.
6. **Consultations:** Nephrology consultation should be considered for severe AKI, worsening renal function, or if adequate diuresis cannot be achieved with aggressive IV hydration. Patients with severe hyperkalemia, volume overload, or azotemia may require dialysis. For Juan, you plan to consult nephrology if his hyperkalemia or AKI worsens.
7. **Further diagnostic evaluation:** Patients with recurrent episodes of rhabdomyolysis, family history of myopathy, and a personal history of myalgias or exercise intolerance warrant further investigation for underlying myopathy. The majority of this evaluation will be completed on an outpatient basis, but it is reasonable to initiate neurology and genetic consultations during admission to facilitate the process. Further evaluation for underlying myopathy is not indicated for Juan at this time, as this is his first occurrence of rhabdomyolysis, he has no personal history of myalgias, and he has no family history of myopathies.

CASE FOCUS

Plan for Treatment and Monitoring

- **Fluid resuscitation:** You order a 1-L IV normal saline bolus for Juan, followed by IV normal saline at 200 mL/h. You will titrate IV fluids to a goal urine output of 200 mL/hr.
- **Adjunctive therapies:** No adjunctive therapies are indicated for Juan at this time.
- **Monitoring:** You order telemetry monitoring, strict monitoring of intake and output, and repeat electrolytes, blood urea nitrogen, and creatinine to be drawn within 2 hours. You will decide on a subsequent laboratory monitoring schedule based on these results but anticipate initially performing monitoring of Juan's electrolytes and kidney function every 6 hours and his CK level twice daily. You will conduct repeat physical examinations to ensure there are no signs of compartment syndrome.
- **Pain management:** You order 650 mg of oral acetaminophen every 6 hours as needed for pain. You will avoid NSAIDs and minimize the use of opioids should Juan's pain worsen.
- **Activity:** You order bed rest for Juan, aside from walking to the bathroom.
- **Consultations:** No consultations are indicated at this time.
- **Further diagnostic evaluation:** Juan does not appear to have any risk factors for a myopathy, so no further testing is indicated at this time.

Case Resolution

Over the course of his hospitalization, Juan's repeat laboratory tests demonstrate improving creatinine, CK, and serum electrolyte levels. His AKI resolves by hospital day 2, at which point his laboratory tests are spaced to every 12 hours. At that time, he is also drinking sufficient fluids to have his IV fluid rate decreased to his maintenance fluid rate. On the fourth day of hospitalization, Juan's CK level is less than 5,000 U/L (83.5 µkat/L), and his CK level remains stable off IV fluids. He has no complications during his hospital stay. Based on his symptomatic and laboratory improvement as well as his adequate oral intake, he is discharged home later that day.

Discharge Criteria

Q: How do you know when Juan is ready to go home?

You can feel comfortable discharging your patient with rhabdomyolysis when the following criteria are met:

- The patient's pain is well controlled on oral analgesics.
- The patient's electrolytes have normalized.
- Normal kidney function has resumed as evidenced by normalized creatinine.
- The patient is tolerating adequate oral intake to maintain good urine output (eg, >2 mL/kg per hour).
- The patient's CK level is downtrending and ideally is less than 5,000 U/L (83.5 µkat/L). Based on adult data, this is the lowest level that has been associated with renal injury.

Anticipatory Guidance

Q: What instructions should you provide to Juan and his caregivers upon discharge?

- Follow up with Juan's pediatrician 2 to 3 days after discharge to ensure continued clinical improvement. Patients with AKI are at increased risk for future chronic kidney disease, hypertension, and proteinuria, and therefore require ongoing monitoring for these findings.
- Work with Juan's pediatrician to determine when it is safe for him to resume regular activity and return to play. It is reasonable to wait until Juan is asymptomatic with normalized CK levels. Return to play should be cautiously advanced, with initial avoidance of eccentric activities, as these exercises may be more likely to cause rhabdomyolysis.
- Juan needs to slowly increase his exercise intensity in the future. He should also take care to avoid excessive heat and drink sufficient fluids to prevent dehydration.

Clinical Pearls

- Rhabdomyolysis should be considered in the differential diagnosis for patients with localized pain.
- There are many potential etiologies for rhabdomyolysis, including exertional, infectious, medication-related, and inherited conditions.
- Patients with rhabdomyolysis are at risk for AKI and electrolyte derangements and should be monitored closely for these issues and potential sequelae.
- Aggressive and timely fluid hydration to maintain urine output of at least 200 mL/h is the mainstay of treatment to prevent and treat renal injury. For children, a goal urine output of 3 to 4 mL/kg/h is appropriate.
- After discharge, patients should cautiously reintroduce activity to avoid worsening muscle breakdown.
- Patients with recurrent episodes of rhabdomyolysis, a family history of myopathy, or personal history of myalgias/exercise intolerance should undergo further evaluation for underlying myopathy.

Documentation Tips

- Document the need for IV fluids and the frequency of laboratory monitoring required.
- Interpret abnormal electrolyte findings (eg, document "hyperkalemia" instead of stating the potassium value).
- Document symptoms of electrolyte disturbances and the measures required to correct electrolyte abnormalities.
- Define AKI as "acute kidney injury" first, because AKI is not an approved abbreviation for coding.
- Do not use "acute kidney injury" interchangeably with "acute renal insufficiency" in documentation, as these terms are not synonymous in coding guidelines.
- Acute tubular necrosis can be documented as an additional finding when the creatinine level is elevated for at least 3 days. This signals increased AKI complexity and morbidity.

Suggested Reading

Szugye HS. Pediatric rhabdomyolysis. *Pediatr Rev*. 2020;41(6):265–275 PMID: 32482689 https://doi.org/10.1542/pir.2018-0300

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Bernard, a 15-Year-Old Boy With Abdominal Pain and Diarrhea

CASE PRESENTATION

Bernard is a 15-year-old boy with no significant medical history who presents to the emergency department (ED) with abdominal pain and diarrhea that he has had for about 2 weeks. The ED physician calls you because she is concerned about his pain and hydration status and would like you to evaluate him for possible admission. She also mentions that Bernard has noticed blood in his stool for the past 2 to 3 days. In the ED, Bernard received a 1-L intravenous (IV) bolus of normal saline (0.9%) for tachycardia and dehydration and 1 dose of IV morphine for his abdominal pain, which is a 7 on a scale of 10. After speaking to the ED physician, you begin your patient evaluation.

Patient History and Review of Systems

Q: What information should you collect from Bernard and his caregivers?

- History of present illness
  - Further characterization of his abdominal pain, including location/radiation, severity, timing, and quality; exacerbating or alleviating factors; and patterns (eg, relationship to meals, interruption of sleep)
  - Description of diarrhea, including number of daily episodes and estimated diarrheal volumes; stool characteristics (eg, watery, mucoid, loose); presence of blood in stool (streaks, bright red, or melanotic); presence of urgency or tenesmus
  - Any correlation of symptoms to dairy consumption, gluten, or other foods
  - Indicators of hydration status (eg, daily fluid intake; urine color, volume, and frequency)
  - Any history of similar episodes
  - Potential exposures: organophosphates, heavy metals, well water, raw or undercooked meats or seafood
  - Recent travel and activity history: foreign travel, water-related activities, animal exposures, camping trips
  - Associated symptoms, such as fevers, fatigue, headache, dizziness, weight loss, vomiting, joint pain, vision changes, mouth sores, skin lesions, or rashes
- Medical history, including underlying health status and growth history (ie, change in weight or height percentiles)
- Current and recent medications, including selective serotonin reuptake inhibitors, antibiotics, laxatives, and supplements
- Dietary history: typical daily nutrition and diet
- Family medical history, including celiac disease, inflammatory bowel disease (IBD), and autoimmune illnesses

- Social history, including sick contacts, caregiver/parent occupations, and pets in the home
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, specifically related to sexual history, illicit drug use, suicidal ideation, and medication ingestion (refer to Section VII of the Appendix for an example of a HEADSS assessment)

History and Review of Systems

In the ED, you meet Bernard and his father. From your questions, you learn that Bernard has significant cramping pain (characterized as 6 on a scale of 10) below the umbilicus that is most prominent in the right lower quadrant. He has had at least 7 to 8 episodes of small-volume, watery diarrhea daily for approximately 2 weeks. Additionally, he has noticed bright red blood in his stool over the last few days. He reports that his pain is worse prior to defecation and slightly improved following elimination. He does not correlate his symptoms with the consumption of dairy or gluten.

Bernard has been drinking and eating less because of his abdominal pain and nausea and has had decreased urinary frequency and volumes. His dietary history seems typical for age, although reduced in quantity recently related to his pain and nausea. He has also had occasional episodes of nonbilious and nonbloody vomiting. His father reports that Bernard seems to have less energy recently and will often nap after school, which is not typical for him. He does endorse feeling sad recently but denies poor body image or the use of laxatives.

A few days ago, he visited his pediatrician for his symptoms, and she ordered stool studies. At that visit, she also noted that Bernard had lost over 15 lb (6.8 kg) since his visit 6 months prior.

Bernard denies any recent travel or exposures, and he has not noticed any changes to his skin or vision. He also does not recall fevers or joint pain. He does not have any chronic medical conditions, but when you ask, he remembers some intermittent diarrhea and abdominal discomfort over the past few months. He is not currently taking any medications, denies illicit drug use, and has not recently taken antibiotics. He is not actively seeking to lose weight and denies any body image issues. Bernard's father has no significant medical history, and his mother has hypertension and arthritis. His older sibling does not have any medical diagnoses. Bernard's mother is a veterinarian, and his father is a teacher. He has no known sick contacts. He and his family have 2 indoor dogs.

Physical Examination

Q: What parts of the physical examination should you focus on for Bernard?

- Complete set of vital signs
- General appearance and nutritional status
- Eyes: visual acuity and gross abnormalities (conjunctival injection and photophobia)
- Mouth: oral ulcers or abscesses, parotid gland enlargement
- Cardiovascular: murmurs, peripheral perfusion
- Abdomen: distension, quantity and quality of bowel sounds, tenderness, peritoneal signs, guarding, presence of masses or organomegaly
- Musculoskeletal: swollen, erythematous, or tender joints, extremities, or digits; presence of digital clubbing
- Rectal: presence of fissures, abscess, skin tags, fistulas
- Skin: evidence of pallor, jaundice, rashes, other lesions
- Visual examination of stool, if possible

CASE FOCUS

Physical Examination

Bernard's vital signs show that he is afebrile. The tachycardia present in the ED (heart rate: 130 beats/min) improved after his initial fluid bolus but persists (current heart rate: 105 beats/min). He has a normal blood pressure for age and a normal oxygen saturation. His height and weight upon arrival to the ED are 65 in (165.1 cm) and 106.7 lb (48.4 kg), respectively. His body mass index (BMI) is 15th percentile for age, with a *z* score of −1.03.

On examination, Bernard is nontoxic, alert, and responsive, but he appears fatigued and uncomfortable lying in bed. He appears thin. You notice slight cracking of his lips and sticky oral mucosa. No oral ulcers or parotid gland enlargement are noted. His pupils are round and reactive without any gross abnormalities. On cardiovascular examination, you note tachycardia and a II/VI systolic murmur auscultated at the right upper sternal border. He has normal peripheral pulses and a capillary refill time that is mildly prolonged at 2 to 3 seconds. His hands and feet are slightly cool to the touch. His lungs are clear with no abnormalities.

On his abdominal examination, no abnormalities are noted on visual inspection. His bowel sounds are hypoactive but present. There is diffuse abdominal tenderness that is worse in the bilateral lower quadrants with some guarding but no peritoneal signs. His abdomen is soft, though there is some fullness appreciated in the right lower quadrant.

There is no costovertebral angle tenderness. Bernard's skin appears pale on examination, but no rashes are present. There are no abnormalities noted on his musculoskeletal examination. On the rectal examination, there is blood in the rectal vault; however, no fissures, masses, fistulas, abscess, or skin tags are seen.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent with abdominal pain and prolonged, persistent, or chronic diarrhea with blood?

The differential diagnosis for abdominal pain is discussed separately in Case 10. For Bernard, you are most interested in considering the causes of his bloody diarrhea.

Table 34.1 shows the many causes for prolonged (>7–13 days), persistent (14–29 days), and chronic (30+ days) diarrhea. Of these etiologies, you are most concerned that Bernard may have IBD or an acute infectious gastroenteritis.

Table 34.1. Differential Diagnosis for Prolonged, Persistent, and Chronic Diarrhea in Children and Adolescents

Diagnoses of highest suspicion	• Acute infectious gastroenteritis (viral, bacterial, parasitic)[a] • Celiac disease (gluten-sensitive enteropathy) • IBD[a] • IBS
Other diagnoses to consider	• Allergic enteropathy • Antibiotic-associated diarrhea • CF • Environmental exposure • Excessive juice or caffeine intake • Factitious diarrhea or laxative use • Hepatobiliary disease • Hyperthyroidism • Lactose intolerance • Neuroendocrine tumors • Pancreatic insufficiency or malabsorption • ZES

Abbreviations: CF, cystic fibrosis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; ZES, Zollinger-Ellison syndrome.

[a] Diagnoses that seem most likely based on your patient's presentation.

Q: What are common causes of bloody stools in an adolescent?

The presence of blood in stool could indicate an upper or lower gastrointestinal (GI) tract bleed. The blood in Bernard's stool is more likely to be originating from the lower GI tract, given its bright red appearance. Although most of the following diagnoses do not explain Bernard's entire clinical picture, they could be complicating one of the previously listed etiologies of diarrhea. Table 34.2 shows the causes of bloody stool in children and adolescents. Based on the entirety of Bernard's clinical picture, you are again most suspicious of an infectious or inflammatory colitis.

Table 34.2. Causes of Bloody Stool in Children and Adolescents

Category	Common presenting symptoms	Etiology
Upper GI tract bleeding	Hematemesis and/or melena	• Esophageal varices • Esophagitis • Mallory-Weiss tear • PUD or gastritis • Upper respiratory tract bleeding
Lower GI tract bleeding	Hematochezia	• Anal fissures • Bowel ischemia (eg, volvulus or intussusception) • Infectious colitis[a] • Inflammatory colitis[a] • Intestinal AVM • Juvenile polyps • Meckel diverticulum (usually presents in early childhood)

Abbreviations: AVM, arteriovenous malformation; GI, gastrointestinal; PUD, peptic ulcer disease.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is required for patients with abdominal pain, persistent diarrhea, and bloody stools?

- The diagnostic evaluation of persistent or chronic diarrhea in adolescents may vary based on certain clinical features (refer to Table 34.3 for possible diagnostic evaluations based on suspected etiology).
- For patients with a prolonged, persistent, or chronic diarrheal illness of suspected infectious or inflammatory etiology, the following testing should be considered:
  - Complete blood cell count (CBC) to assess for anemia or other abnormalities
  - Serum electrolytes, blood urea nitrogen (BUN) level, and creatinine level, especially if there is concern for dehydration, electrolyte disturbances, or malnutrition
  - Stool studies
    - Fecal occult blood
    - Stool leukocytes and fecal calprotectin to evaluate intestinal inflammation
    - Infectious testing with a stool culture, *Clostridiodes difficile* antigen and/or polymerase chain reaction (PCR), and stool microscopy for ova and parasites; alternatively, a stool pathogen panel by PCR can be used if it has a rapid turnaround time
  - Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein level)
  - Two-view abdominal radiographs to assess for partial or total bowel obstruction
  - Thyroid function tests to assess for thyroid abnormalities, if suspected
  - Review of growth curves

Table 34.3. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Adolescents With Prolonged, Persistent, or Chronic Diarrhea

Diagnosis	Possible clinical features	Diagnostic evaluation to consider
Acute infectious gastroenteritis (viral, bacterial, parasitic)	Acute onset of diarrhea and vomiting; bloody stool, fever, and abdominal pain are common in bacterial infections.	Testing is not necessary except in cases that are atypical, prolonged, or are accompanied by bloody stools; in those cases, infectious testing of the stool may be indicated.[a]
Antibiotic-associated diarrhea	Recent antibiotic use	*Clostridiodes difficile* stool testing[a]
Allergic enteropathy	Symptoms associated with the consumption of certain foods	Elimination trial of suspected dietary trigger; consider evaluation by a gastroenterologist and allergist.
Celiac disease	Poor weight gain, diarrhea, constipation, abdominal pain, or bloating; family history of celiac disease	Tissue transglutaminase IgA antibody (with or without endomysial antibody); histology from small bowel; IgA level (to ensure IgA deficiency is not present)
Factitious diarrhea or laxative use	Inconsistent or unexpected clinical history	Plasma osmolality, stool osmolality (stool sodium, stool potassium), thorough social history
Hyperthyroidism	Weight loss, palpitations, restlessness, anxiety, hyperreflexia, enlarged thyroid	TSH, free T4

(continued)

Table 34.3. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Adolescents With Prolonged, Persistent, or Chronic Diarrhea *(continued)*

Diagnosis	Possible clinical features	Diagnostic evaluation to consider
IBD	Diarrhea (with or without hematochezia); weight loss or poor growth; extraintestinal signs include rashes, changes to vision, and joint pain	CBC, CMP, ESR, CRP level, FOBT (normal laboratory test results do not rule out IBD) Stool studies to rule out infection Consider fecal calprotectin and fecal leukocytes; diagnosis is made by endoscopy and colonoscopy with biopsies.
IBS	Abdominal pain that resolves following defecation; alternating bouts of constipation and diarrhea; typically no other concerning symptoms	History and examination may be diagnostic. Consider CBC, CMP, ESR, CRP level, FOBT, plasma osmolality and stool osmolality, fecal calprotectin and leukocytes, abdominal radiographs, and stool studies for infection.[a]
Lactose intolerance	Symptoms associated with dairy consumption	Hydrogen breath test or blood glucose test
Neuroendocrine tumors	Palpitations, flushing, skin changes, or difficulty breathing	Serum VIP, fasting gastrin, and PGE2 levels, along with 24-hour urine collection for 5-hydroxyindoleacetic acid
Pancreatic insufficiency or malabsorption	Poor weight gain; history of respiratory infections (for patients with CF); greasy stools; diarrhea, especially with fatty foods	Stool elastase, chymotrypsin, fecal fat; sweat test if concerned for cystic fibrosis
ZES	Burning epigastric pain; nausea or vomiting; weight loss; family history of GI ulcers	CBC, BMP, gastrin level, secretin stimulation test, gastric acid secretion studies, endoscopy

Abbreviations: BMP, basic metabolic panel; CBC, complete blood cell count; CF, cystic fibrosis; CMP, comprehensive metabolic panel; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FOBT, fecal occult blood test; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IgA, immunoglobulin A; PGE2, prostaglandin E2; T4, thyroxine; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal peptide; ZES, Zollinger-Ellison syndrome.

[a] Refer to Case 1 for stool testing recommendations.

CASE FOCUS

Diagnostic Evaluation

The ED physician obtained serum laboratory tests when Bernard's IV line was placed, and the laboratory test results are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	142 mEq/L (142 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.2 mEq/L (3.2 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	108 mEq/L (108 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	19 mEq/L (19 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	24 mg/dL (8.57 mmol/L)	6–20 mg/dL (2.14–7.14 mmol/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)	0.5–0.9 mg/dL (44.2–79.6 µmol/L)
Glucose	92 mg/dL (5.11 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Alkaline phosphatase	100 U/L (1.67 µkat/L)	100–390 U/L (1.67–6.51 µkat/L)
ALT	50 U/L (0.84 µkat/L)	10–55 U/L (0.17–0.92 µkat/L)
AST	17 U/L (0.28 µkat/L)	10–40 U/L (0.17–0.67 µkat/L)
Albumin	2.5 g/dL (25 g/L)	3.6–5.2 g/dL (36–52 g/L)
Lipase	12 U/L (0.20 µkat/L)	4–39 U/L (0.07–0.65 µkat/L)
Direct bilirubin	0.2 mg/dL (3.42 µmol/L)	0–0.2 mg/dL (0–3.42 µmol/L)
CBC		
WBC count	15,000/µL (15×10^9/L)	4,000–10,500/µL ($4–10.5 \times 10^9$/L)
RBC count	3.4×10^6/µL (3.4×10^{12}/L)	$4.3–5.7 \times 10^6$/µL ($4.3–5.7 \times 10^{12}$/L)
Hemoglobin	9.8 g/dL (98 g/L)	12.5–16.1 g/dL (125–161 g/L)
Hematocrit	28% (0.28)	36%–47% (0.36–0.47)
MCV	68 µm³ (68 fL)	78–95 µm³ (78–95 fL)
RDW	16% (0.16)	11.4%–13.5% (0.114–0.135)
Platelet count	560×10^3/µL (560×10^9/L)	$150–400 \times 10^3$/µL ($150–400 \times 10^9$/L)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell.

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

In addition to these studies, you obtain an erythrocyte sedimentation rate, a C-reactive protein level, stool occult blood test, fecal calprotectin test, fecal leukocytes, and the results of Bernard's stool studies from his pediatrician's office. You also order a 2-view radiograph. These results are as follows:

Laboratory test	Result	Reference range
ESR	30 mm/h	<15 mm/h
CRP	5.9 mg/dL (59 mg/L)	<1 mg/dL (<10 mg/L)
Fecal calprotectin	200 µg/g	10–50 µg/g
Fecal leukocytes	Many	None
Stool pathogen panel by PCR (ordered by Bernard's pediatrician a few days prior)	Negative for all pathogens, including parasites, *Yersinia enterocolitica*, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, and *Clostridiodes difficile*	None detected
Stool occult blood	Positive	Negative
Imaging		
Abdominal radiographs	Nonobstructive bowel gas pattern. No free air.	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction.

Given the earlier laboratory results showing a low mean corpuscular volume consistent with microcytic anemia, you order iron studies, which show a low serum iron, elevated ferritin, decreased total iron binding capacity, decreased transferrin, and a decreased transferrin saturation.

You contact Bernard's pediatrician, who confirms that his weight 6 months ago was 53.4 kg (5 kg greater than his current weight). His growth curves also show that his height velocity appears to have slowed over the past year, with his height for age dropping from the 25th percentile to approximately the 20th percentile.

Arriving at a Diagnosis

Q: How do you develop your assessment for Bernard?

You decide to first review the key elements of Bernard's history and examination and assess his hydration status. Next, you will evaluate his nutritional status and summarize the key findings from his diagnostic evaluation. This will help to develop a finding list that aids in narrowing your differential diagnosis to the most likely etiology. Afterward, admission criteria can be generated for your specific diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History and examination: Bernard has had months of intermittent diarrhea and abdominal pain, both of which have worsened over the previous 2 weeks, accompanied by weight loss and new-onset hematochezia. Review of systems also revealed malaise, decreased urination, and vomiting. His examination demonstrates abdominal tenderness, a cardiac murmur (likely related to his anemia), and signs of dehydration.
   - Assessment of hydration status: Because of Bernard's history of chronic diarrhea and intermittent vomiting, you want to closely evaluate for dehydration. On examination, you confirmed the tachycardia observed in the ED and noted that he had a slightly prolonged capillary refill, dry lips, and sticky oral mucosa. Although Bernard's anemia and pain might also contribute to his tachycardia, based on his examination findings and his overall clinical picture, you determine that he meets the Centers for Disease Control and Prevention's criteria for mild to moderate dehydration. Refer to Table A.2 in the Appendix for more information about classifying dehydration.
   - Assessment of nutritional status: You suspect malnutrition given Bernard's significant weight loss, and you are concerned for nutritional deficiencies as a result of his prolonged diarrhea. Although there are different methods used to classify malnutrition, as shown in Table 34.4, your institution uses unintentional weight loss or BMI *z* scores for simplicity. *Z* scores represent the number of SDs away from the mean, with negative numbers representing the number of SDs below the mean. Classification of Bernard's nutritional status based on his weight loss (9.4%) and BMI *z* score of −1.03 shows that Bernard has mild to moderate malnutrition.

Table 34.4. Classification of Malnutrition

Method	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Weight for height % of median	80%–89%	70%–79%	<70%
Weight for height *z* score	–1 to –1.9	–2 to –2.9	<–3
BMI for age *z* score	–1 to –1.9	–2 to –2.9	<–3
Weight loss % of usual body weight	5%–7.4%	7.5%–9.9%	≥10%

Abbreviation: BMI, body mass index.

- Diagnostic studies
  - Serum laboratory tests
    - Electrolytes: Bernard's laboratory test results show a low bicarbonate level (metabolic acidosis) with an elevated anion gap, suspicious for starvation ketoacidosis. He likely also has bicarbonate losses from his diarrhea that are contributing to his acidosis. Refer to Box 1.1 in Case 1 for the various causes of metabolic acidosis.
    - Renal function: The elevated BUN and creatinine levels for his age and body habitus and a BUN/creatinine ratio greater than 20 are suggestive of a prerenal azotemia and an acute kidney injury (AKI). These findings are most suggestive of dehydration.
    - CBC: Based on Bernard's low hemoglobin, red cell indices, and iron studies, you suspect a combination of iron deficiency from intestinal blood loss and anemia of chronic disease. Refer to Case 19 for discussion of anemia.
  - Stool studies
    - The stool fecal occult blood test is positive, confirming blood in Bernard's stool.
    - The stool pathogen panel by PCR sent by Bernard's pediatrician is negative, decreasing your suspicion for infectious colitis.
    - The fecal calprotectin level is 200 µg/g and fecal leukocytes are positive, indicating inflammation in the GI tract.
  - Imaging: You are reassured that there are no signs of bowel obstruction. You had low clinical suspicion for this, given that Bernard was still passing stool and his vomiting was nonbilious.

2. **Develop the list of findings.**

Q: What major findings have you identified for Bernard?

- Persistent diarrhea
- Evidence of intestinal inflammation without evidence of infection
- Nausea and vomiting
- Hematochezia
- Mild to moderate dehydration
- Mild to moderate malnutrition
- Abdominal pain
- Elevated anion gap metabolic acidosis related to ketoacidosis and stool bicarbonate losses
- Anemia from iron deficiency and chronic inflammation
- AKI
- Mild hypokalemia

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Bernard's presentation?

IBD is the leading diagnosis to consider in this adolescent with chronic diarrhea with evidence of blood, a negative infectious evaluation, weight loss, and elevated systemic and fecal inflammatory markers.

Q: What are the 2 classifications of IBD, and what distinguishes them from each other?

IBD can be classified into 2 types: Crohn disease and ulcerative colitis. The diagnosis and classification of IBD is dependent upon gross appearance on endoscopy/colonoscopy and pathological findings on histology from biopsies; however, there are clinical manifestations that can help guide diagnosis (see Table 34.5).

Table 34.5. Comparison of Crohn Disease and Ulcerative Colitis

	Crohn disease	Ulcerative colitis
Presentation	• Presenting symptoms include abdominal pain, diarrhea, poor growth, and weight loss, as the small intestine can be affected by the disease process, leading to malabsorption • Stools may contain blood but may also appear normal or watery	• Presenting symptoms include diarrhea, bright blood in the stool, and abdominal pain • Fevers and weight loss are not as common
Affected location	• Skip lesions throughout the GI tract (from the oral mucosa to the anus, with intermittent areas that are unaffected); ileocolonic involvement is common	• Involvement limited to the large bowel
Endoscopic findings	• Skip lesions • Transmural inflammation • Perianal involvement (fistulas, fissures, and tags) • Cobblestone appearance of the intestinal mucosa	• Continuous area of involvement to the rectum
Histological findings	• Presence of inflammatory cells (eg, lymphocytes, basal cells, and giant cells within the lamina propria); crypt atrophy; and epithelial metaplasia • Noncaseating granulomas in 30%–50% of patients	• Presence of inflammatory cells (eg, lymphocytes, basal cells, and giant cells within the lamina propria); crypt atrophy; and epithelial metaplasia • Crypt neutrophilia

Abbreviation: GI, gastrointestinal.

- Though there are differences between the 2 types of IBD, sometimes it is not possible to distinguish between them. When this is the case, there is a third type of classification that can be assigned: IBD unclassified.
- Although Bernard does not appear to have any extraintestinal manifestations or perianal disease, these findings are common in patients with IBD. Examples of extraintestinal manifestations include uveitis, autoimmune hepatitis, primary sclerosis cholangitis, arthritis, arthralgias, erythema nodosum, and pyoderma gangrenosum. Extraintestinal manifestations can occur in both Crohn disease and ulcerative colitis. Perianal disease, which occurs most commonly in Crohn disease, can include fissures, fistulas, abscesses, and skin tags.

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with suspected new-onset IBD?

- The patient has symptomatic anemia or the need for blood transfusion.
- The patient is unable to keep up with stool losses.
- The patient is experiencing significant abdominal pain and/or vomiting.
- Electrolyte abnormalities are present.
- The patient has severe malnutrition.

You decide that Bernard meets the criteria for hospitalization, given his electrolyte abnormalities, significant abdominal pain, and anemia with ongoing blood loss.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Bernard is a 15-year-old previously healthy boy who is in the ED with persistent diarrhea associated with hematochezia, mild to moderate malnutrition and dehydration, and abdominal pain, which are suspected to be caused by IBD. His laboratory evaluation indicates he has anemia, a nonanion gap metabolic acidosis, and mild hypokalemia. At the time of evaluation, he does not have signs of an acute abdomen. He requires hospitalization for treatment of his electrolyte abnormalities, pain, and malnutrition. He also requires consultation with a GI specialist, further diagnostic evaluation, and clinical improvement prior to discharge.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In developing a treatment plan for Bernard, you review references related to the treatment of dehydration, malnutrition, and IBD. You decide to divide treatment considerations into the following components:

1. **Rehydration and maintenance of hydration:** Many patients with mild to moderate dehydration can undergo rehydration orally or via nasogastric tube; however, IV fluids may be needed for patients with lethargy, persistent nausea or vomiting, or significant abdominal pain. Additionally, a patient's hydration should be maintained by providing their hourly fluid requirements in accordance with the Holliday-Segar method. To maintain a patient's hydration, it is also important to keep up with their ongoing fluid losses; therefore, replacement fluids should be provided for each episode of emesis and diarrhea. For more information about treatment of dehydration and maintenance of hydration, including the Holliday-Segar method, please refer to Case 1.
2. **Correction and monitoring of electrolyte abnormalities:** Patients with severe or prolonged GI losses are at risk for electrolyte abnormalities. For example, patients with severe, recurrent vomiting may experience a hypochloremic metabolic alkalosis, and patients with significant diarrhea commonly experience a metabolic acidosis. Hypokalemia is commonly present in both recurrent vomiting and significant diarrhea. To prevent the complications associated with severe electrolyte abnormalities, oral or IV electrolyte replacement may be required. Periodic monitoring of serum electrolytes is needed for some patients.
3. **Diet and treatment of malnutrition**
   - The most important treatment of malnutrition is the initiation of adequate nutrition, either enterally or intravenously, depending on the patient's circumstances. For patients with moderate to severe malnutrition, monitoring for refeeding syndrome may be required.
   - Patients with malnutrition (especially when related to intestinal malabsorption, such as is seen in Crohn disease) are also at risk of micronutrient deficiencies. For patients with malabsorption, clinicians should consider monitoring vitamin levels (A, C, D, E, and K), calcium, and zinc.
   - Ideally, a dietician will be available to assist in creating a diet with supplemental nutrition specific to patient needs.

4. **Anemia:** Anemia is a common complication of IBD. In IBD, the etiology of the patient's anemia is frequently multifactorial, caused by a combination of poor dietary iron intake related to anorexia and abdominal pain, poor intestinal iron and micronutrient absorption, an inflammatory state (ie, anemia of chronic disease), and intestinal blood loss. For patients with hemodynamic instability, significant ongoing blood loss, or a hemoglobin level of less than 7 g/dL (70 g/L), packed red blood cell transfusion should be considered. When iron deficiency is present, oral or IV iron therapy should be started. For IBD patients with anemia, clinicians should also consider assessing serum folate and vitamin B_{12} levels.
5. **Supportive measures**
   - IV or oral ondansetron can be used in patients with nausea or vomiting.
   - In patients with suspected IBD, gastric prophylaxis with an H2-receptor antagonist is reasonable.
   - Patients with intestinal bleeding and suspected IBD should avoid use of nonsteroidal anti-inflammatory drugs because of concerns about the potential exacerbation of IBD and gastritis. Acetaminophen is a better option for mild pain, and hyoscyamine can be used for cramping pain. Low-dose opioids can be used for breakthrough pain, but opioids should be used sparingly whenever possible.
6. **Monitoring:** Patients hospitalized with dehydration, diarrhea, and hematochezia should undergo close monitoring of their intake and output, vital signs, and intestinal blood loss.
7. **Further evaluation and treatment:** Because the definitive diagnosis of IBD is made by endoscopy and colonoscopy, it is important to consult with a pediatric gastroenterologist early in the patient's hospital stay.
   - Induction of remission: If the diagnosis of IBD is confirmed, the mainstay of treatment for induction has traditionally been with the use of systemic corticosteroids. Some patients and providers may decide to forgo steroid induction and proceed directly to biologics, such as anti–tumor necrosis factor agents. Another option for induction in patients with Crohn disease is exclusive enteral nutrition, which is achieved by the patient consuming only formula supplements for 8 to 12 weeks. This dietary change is as successful at inducing remission as systemic steroids while avoiding their side effects. Aminosalicylates are another therapeutic option for induction therapy in patients with mild ulcerative colitis.
   - Maintenance of remission
     - Medication options for maintenance therapy include aminosalicylates, enteric-coated corticosteroids (not preferred), immunomodulators (eg, thiopurine or methotrexate), and antitumor necrosis factor agents. Maintenance therapy may change over time depending on the patient's response.
     - Complementary and alternative medications and therapies are commonly used by patients with IBD, and there is evidence that many patients with IBD report improvement in their symptoms with regular use of certain strains of probiotics. Unfortunately, there is a lack of robust data about the efficacy of many complementary and alternative treatments or certain dietary changes (eg, dairy or gluten elimination, specific carbohydrate diet, diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAP]) in maintaining remission.
   - Role of surgery: For severe or poorly controlled ulcerative colitis, colectomy is often considered. Surgical intervention is less common for Crohn disease, because it involves different aspects of the intestinal tract; however, surgery may be indicated for fistulas or abscesses or for resection of areas with stricturing.

CASE FOCUS

Plan for Treatment and Monitoring

- **Hydration therapy:** You note that Bernard's tachycardia is slightly improved following the normal saline bolus in the ED. Given his nausea, vomiting, and persistent diarrhea, you decide to provide an additional IV normal saline bolus and start maintenance fluids of 5% dextrose in normal saline with 20 mEq of potassium chloride at 100 mL/h based on his weight. You will monitor his intake and output and daily weights and provide additional fluids intravenously if he is unable to keep up with his GI losses by mouth.
- **Correction and monitoring of electrolyte derangements:** Because Bernard has mild hypokalemia and is not taking much food by mouth, you decide to provide 2 oral doses of 20 mEq potassium chloride, separated by a few hours to prevent GI upset. To ensure there is no further worsening of his hypokalemia, AKI, and metabolic acidosis, you plan to obtain a repeat electrolyte and renal function panel in 12 hours. If his acidosis is worsening, he may require bicarbonate replacement orally or by the addition of acetate to his IV fluids.
- **Diet and malnutrition:** You have concerns for malabsorption given the inflammation within Bernard's bowel and would like to give him an opportunity for bowel rest. You therefore order a clear liquid diet. Additionally, you plan to consult a registered dietician for further recommendations about his required caloric intake and will consider initiation of nasogastric tube feeds if Bernard's appetite remains poor.
- **Anemia:** Bernard's CBC shows signs of anemia, with symptoms including tachycardia, fatigue, and pallor but without signs of hemodynamic instability; therefore, you choose to not transfuse at this time. If he continues to have hematochezia, you plan to obtain a repeat CBC within 24 to 48 hours. Once Bernard is tolerating oral intake, you will start oral iron therapy, which will be continued on an outpatient basis.
- **Supportive care:** You order IV ondansetron as needed for nausea and vomiting and IV famotidine twice daily for gastric protection. You order monitoring of Bernard's pain status and acetaminophen and hyoscyamine as needed. You will consider adding IV morphine if needed for breakthrough pain.
- **Monitoring:** In addition to monitoring Bernard's intake and output, your order vital sign monitoring every 4 hours and serial abdominal examinations.
- **Further evaluation:** You plan to consult a pediatric gastroenterologist and anticipate Bernard will soon undergo an endoscopy and colonoscopy to confirm his diagnosis.

Case Resolution

You consult a pediatric gastroenterologist is who recommends a cleanout for an endoscopy and colonoscopy for Bernard. The endoscopy and colonoscopy show terminal ileitis, mild gastritis, and cobblestone appearance at various spots throughout the colon. Biopsies confirm active chronic inflammation with occasional noncaseating granulomas, which is consistent with Crohn disease. Bernard's gastroenterologist plans to obtain a magnetic resonance enterography to evaluate the extent of Bernard's small bowel disease and discuss treatment options with Bernard and his family, including systemic steroids, exclusive enteral nutrition, and biologics. The dietician meets with Bernard and recommends he start formula supplements to correct his malnutrition.

Discharge Criteria

Q: How do you know when Bernard is ready to go home?

You can feel comfortable discharging your patient with new-onset IBD when the following criteria are met:

- The patient demonstrates improvement in stool losses.
- The patient's electrolytes are stable.
- The diagnosis has been confirmed, although this is not always necessary if close outpatient follow-up with a gastroenterologist is ensured.
- The patient is tolerating oral intake.
- Pain is well controlled with oral medications.
- There is decreased volume of blood in the stool and/or stable hemoglobin.
- The patient's hemodynamics are stable.
- Adequate follow-up is ensured.

Anticipatory Guidance

Q: What instructions should you provide to Bernard's caregivers upon discharge?

- Provide additional oral fluids for each episode of vomiting or diarrhea at home.
- Monitor the amount of diarrhea and monitor stool for the presence of blood.
- Return to care for lethargy, increasing blood in the stool, fever, dizziness, worsening abdominal pain, or inability to tolerate oral intake.
- Continue medication regimen as recommended by the gastroenterologist.
- Continue following nutrition recommendations to improve malnutrition.
- Because of the risk of ocular manifestations in patients with IBD, it will be important for Bernard to establish care with an ophthalmologist for periodic eye examinations.

Clinical Pearls

- In an adolescent, persistent or chronic diarrhea with weight loss has a broad differential, but IBD must be ruled out as an etiology.
- Although serum and stool testing can help support the diagnosis of IBD, endoscopic evaluation is required for the diagnosis.
- Treatment is based on immunosuppression, but use of exclusive enteral nutrition is a nonpharmacologic option for some patients.

Documentation Tips

- Document the severity of abdominal pain when present, including any need for IV pain medications or supplemental IV fluids.
- Document the degree of malnutrition, if present, and the need for supplemental tube feeding or parenteral nutrition.
- Mention the presence of secondary anemia and if a transfusion is needed.
- Include findings of endoscopy/colonoscopy, if performed.
- Document initiation of new treatments or changes to any existing outpatient treatment regimen.

Suggested Reading

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CASE 35

Ricky, a 3-Year-Old Boy With Shaking

CASE PRESENTATION

Ricky is a 3-year-old boy with no significant medical history who is brought to the emergency department (ED) by emergency medical services (EMS) for an episode of shaking and unresponsiveness at home. EMS reports that on their arrival, Ricky was observed having whole body stiffening and shaking lasting approximately 5 minutes, for which he received 1 dose of intramuscular midazolam. From the descriptions of Ricky's parents and EMS, the ED physician determines that the episode is consistent with a seizure. Ricky has been observed in the ED for approximately 3 hours without further seizure activity. Though still drowsy, he does sit up briefly and takes a few sips of juice before falling back asleep. The ED physician contacts you to request that you evaluate Ricky for admission.

Patient History and Review of Systems

Q: What information should you collect from Ricky's caregivers?

- History of present illness
  - Episode onset (witnessed or unwitnessed) and any immediately preceding event(s)
  - Detailed description of the event, including whether one part or all of the body was affected at onset, patient's level of awareness during the event, characterization of movements (eg, stiffening, loss of muscle tone, shaking), eye deviation, episode duration, ability of observer(s) to suppress the movements during the event by applying gentle pressure, loss of bowel and/or bladder continence (if able to determine), and central cyanosis or apnea
  - Mental status following the event (confused, irritable, drowsy) and the duration of any variation from neurologic and/or cognitive baseline
  - Areas of focal weakness (Todd paralysis) after the event
  - Presence of fever prior to, during, or immediately following the episode
  - Symptoms of preceding illness (eg, nasal congestion, cough, vomiting, diarrhea, rash)
  - Concerning neurologic history surrounding time of the event (eg, headache, facial asymmetry, focal weakness of extremities, confusion, altered mental status, abnormal eye movements)
  - Recent changes in behavior or mood
  - History of trauma
- Developmental history, especially any delays or regression in milestones

- Medical history, including birth history, newborn screen results, growth (weight, height, head circumference), underlying medical conditions (specifically history of febrile seizures, traumatic brain injury, or meningitis), vaccination status, and medications
- Prior episodes of abnormal movements or impaired awareness
- Medications, supplements, or illicit substances in the home and patient's ability to access them
- Family history of seizures, metabolic disorders, cardiac arrhythmias, or neurologic disorders

CASE FOCUS

History and Review of Systems

From your conversation with Ricky's family, you learn that Ricky's presumptive seizure was witnessed by his mother as she was putting him down for a nap. She was holding him, rocking him to sleep, when she felt his entire body stiffen and his eyes rolled back. He then proceeded to have rhythmic shaking of all 4 extremities. He was not crying before the event. During the shaking, she is unsure if he was breathing but says he "looked pale" and had blue discoloration around his lips and "foaming of the mouth." She called out to her husband, and he dialed 911. The episode continued for about 5 minutes. When EMS arrived, they gave Ricky an injection that stopped the shaking. Shortly after the injection, Ricky seemed to look around the room briefly, though he was drowsy and intermittently crying. EMS transported Ricky to the ED for further evaluation.

His mother reports that Ricky has had mild nasal congestion for the last 2 to 3 days but denies fever, cough, vomiting, diarrhea, or skin rashes. She also denies any fussiness or irritability other than immediately following the seizure. Ricky had slightly decreased oral intake today but otherwise had been playful and acting like himself. Since having the seizure, he has not been awake enough to drink more than a few sips of liquid. Ricky's mother notes that he last urinated more than 6 hours ago.

Ricky has never had a seizure before. He is not currently taking any medications at home. His vaccinations are current, including his seasonal influenza vaccine. His birth history was unremarkable; he was born full-term with no complications, and both newborn screens were normal. He has no chronic medical conditions. His developmental history is normal, and his pediatrician has never expressed any concerns. Ricky lives at home with his parents and 5-year-old sister. He attends child care, where his mother reports multiple classmates have runny noses. There is no family history of seizures, cardiac problems, or neurologic disorders.

Physical Examination

Q: What parts of the physical examination should you focus on for Ricky?

- Complete set of vital signs
- Weight, height, and length
- General appearance, level of consciousness, fussiness, or irritability
- Head: evidence of trauma
- Neck: range of motion, nuchal rigidity, meningismus
- Appearance of eyes, including pupillary reactivity, extraocular movements, and any eye deviation
- Evidence of facial asymmetry
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Abdomen: any focalities
- Respiratory: any focalities or respiratory depression

- Skin: rashes or findings concerning for neurocutaneous syndromes (eg, cafe au lait spots, ash leaf spots, facial port-wine stain)
- Neurologic: comprehensive examination, including level of consciousness and ability to arouse; cranial nerve examination; strength; muscle tone; deep tendon reflexes; cerebellar signs (eg, nystagmus, ataxia, abnormal coordination); and assessment of appropriate developmental milestones for gross motor, fine motor, and speech

CASE FOCUS

Physical Examination

Ricky is afebrile with a normal heart rate (100–110 beats/min) when sleeping, which increases to 130 beats/min when he awakens and becomes fussier. He has a normal blood pressure and respiratory rate for age, and his oxygen saturation is 99% on room air. His weight is 13.9 kg (20th percentile). Based on previous measurements documented in his electronic medical record, all his growth parameters are tracking appropriately.

On examination, Ricky appears nontoxic and is initially sleeping in his mother's arms. When aroused, he cries appropriately and easily calms when soothed by his mother. He intermittently falls back asleep. His head is atraumatic. His pupils are equal and reactive to light and no deviation of the eyes is noted. He has full range of motion of his neck without meningismus. His face is symmetric, and his mucous membranes are slightly sticky. He has a normal cardiac and respiratory examination when calm. His peripheral pulses and capillary refill time are normal. His abdominal examination is benign, and his skin turgor is normal.

Ricky's neurologic examination initially shows a drowsy child, but he does awaken and cry appropriately with the examination. His father can soothe him with his stuffed animal. Ricky tracks you as you move around the room, and his extraocular movements appear intact without nystagmus. His strength appears normal and symmetric as he pushes away from you with both arms and kicks both legs. His muscle tone is normal. The deep tendon reflexes of his lower extremities are normal but are difficult to assess in his upper extremities, as he becomes agitated with the examination. You do not detect any ankle clonus. When briefly awake, he sits on his mother's lap without any evidence of truncal ataxia. His gait is not assessed. During the examination, you note that when awake, Ricky reaches for a sippy cup of juice with both hands without any tremor. He holds the cup to his mouth, taking a few sips without difficulty before falling back asleep. He has no rashes or skin lesions.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a young child with possible new-onset seizure?

When thinking about the causes of possible new-onset seizures, it is important to first consider etiologies with respect to the patient's age, the presence or absence of fever, and/or underlying illness. Within the seizure events category, etiologies can be further divided into provoked versus unprovoked seizures. This is an important distinction, as many causes of provoked seizures require more emergent diagnostic evaluation. Careful consideration should also be given to seizure mimics, as these may be overlooked given their likeness to actual seizure events. The comprehensive differential diagnosis for a seizure event in a child is shown in Box 35.1, but a more focused differential diagnosis should be tailored to the patient according to age and presentation. You are confident that Ricky experienced a seizure. Given his neurotypical developmental status and recent illness without fever, you are most suspicious for hypoglycemia, electrolyte disturbances, and new-onset epilepsy as possible etiologies.

Box 35.1. Differential Diagnosis for Seizure Event in a Child

Seizure		Seizure mimics
Provoked	**Unprovoked**	
• Anoxia • CNS infection (meningitis, encephalitis) • Congenital brain malformation • Drug or toxin ingestion • Electrolyte abnormality[a] • Fever • Hypoglycemia[a] • Intracranial mass/tumor • Perinatal hypoxic ischemic brain injury • Stroke (hemorrhagic or ischemic) • TBI (eg, nonaccidental trauma)	• First presentation of epilepsy[a] — Genetic — Immune — Infectious — Metabolic — Structural — Unknown • Unknown etiology[a]	• Breath-holding spell (pallid or cyanotic type) • Cardiac arrhythmia • Paroxysmal movement disorders • Syncope • Tics

Abbreviations: CNS, central nervous system; TBI, traumatic brain injury.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for a child with new-onset seizures?

For a first-time nonfebrile seizure presentation, diagnostic testing will be guided by the patient's age, history, clinical appearance, physical examination, and the description of the seizure event, including the duration of the seizure. The evaluation of first-time febrile seizures is discussed separately in Case 16.

- **Evaluation of first-time nonfebrile seizure:** For the evaluation of first-time nonfebrile seizures (not status epilepticus [SE]), it is recommended that patients receive a routine referral to neurology and that the following diagnostic tests are considered:
  - Electroencephalogram (EEG): A routine EEG is recommended for all children after their first unprovoked seizure and may be obtained nonurgently if the child returns to neurologic/cognitive baseline.
  - Serum studies: The patient's individual clinical history and examination should be considered when deciding on the need for laboratory testing. A history of vomiting or diarrhea, evidence of dehydration, concern for ingestion/intoxication, or a failure to return to baseline alertness may be indications for further testing.
  - Neuroimaging: Neuroimaging is not routinely obtained for first-time, nonfebrile, generalized seizure; however, if neuroimaging is performed, magnetic resonance imaging (MRI) is preferred to other modalities. MRI is more sensitive and specific than computed tomography (CT) scan in identifying brain abnormalities; however, pediatric patients often require sedation to complete an MRI, which may limit its use in the emergent or urgent setting.

- Indications for emergent neuroimaging include the following:
  - Presence of a postictal focal deficit (ie, Todd paralysis) that is not quickly resolving
  - Failure to return to neurologic baseline within several hours of the seizure
- Nonemergent neuroimaging should be considered in the following situations:
  - Children with underlying cognitive or motor impairment of unknown etiology
  - Unexplained, nonacute abnormalities on the neurologic examination
  - Seizure of focal onset
  - Children younger than 1 year

— Electrocardiogram (ECG): Because cardiac arrythmias can present as syncope or generalized seizure, many clinicians recommend obtaining an ECG for patients with a first-time nonfebrile generalized seizure.

- **Evaluation of first-time seizure in SE**

— Because the recommended evaluation of first-time seizures is different based on seizure duration, it is prudent to first define SE. In the past, SE was defined as a seizure lasting 30 minutes or longer; however, for treatment purposes, SE is commonly defined as a continuous seizure lasting longer than 5 minutes or a series of epileptic seizures over a period of 30 minutes during which function is not regained between ictal events.

— The diagnostic evaluation of pediatric patients presenting with SE is different from the evaluation of first-time seizures without SE, and more extensive testing is usually performed. Refer to Table 35.1 for a summary of the recommended studies for patients with new-onset seizures in SE compared with those without SE.

Table 35.1. Diagnostic Evaluation of Patients Presenting With New-Onset Seizure

	New-onset seizures in SE	New-onset seizures without SE
Recommended testing	Electrolytes EEG Neuroimaging (CT or MRI)[a]	Electrolytes EEG
Testing to consider	Urine or serum toxicology Genetic/metabolic testing Lumbar puncture[b]	Urine or serum toxicology Neuroimaging (CT or MRI)[a]
Additional considerations for febrile seizures	CBC Lumbar puncture	CBC Lumbar puncture
Additional considerations for refractory seizures or persistent encephalopathy	Video EEG monitoring	Video EEG monitoring

Abbreviations: CBC, complete blood cell count; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; SE, status epilepticus.

[a] Neuroimaging may be performed nonemergently if the patient returns to neurologic/cognitive baseline.

[b] Although lumbar puncture may be considered in the absence of fever, data do not support routine lumbar puncture in afebrile children in SE.

CASE FOCUS

Diagnostic Evaluation

When reviewing Ricky's chart, you note that he has already undergone some testing in the ED, including a chemistry panel, complete blood cell count, noncontrast head CT scan, and ECG. The results of these tests are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	139 mEq/L (139 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.1 mEq/L (4.1 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	100 mEq/L (100 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)	18–24 mEq/L (18–24 mmol/L)
BUN	10 mg/dL (3.57 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.3 mg/dL (26.5 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Calcium	9.4 mg/dL (2.35 mmol/L)	9.2–10.5 mg/dL (2.30–2.63 mmol/L)
Magnesium	2.1 mg/dL (0.86 mmol/L)	1.6–2.4 mg/dL (0.66–0.99 mmol/L)
Phosphorus	4.4 mg/dL (1.42 mmol/L)	4.0–6.5 mg/dL (1.29–2.10 mmol/L)
Glucose	145 mg/dL (8.05 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
CBC		
WBC count	12,200/µL (12.2 × 10^9/L)	7,000–13,000/µL (7–13 × 10^9/L)
Hemoglobin	11.5 g/dL (115 g/L)	10.5–14 g/dL (105–140 g/L)
Platelet count	325 × 10^3/µL (325 × 10^9/L)	150–400 × 10^3/µL (150–400 × 10^9/L)
Other		
CT scan of the head without contrast	No acute intracranial abnormality	
ECG	Normal sinus rhythm	

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; CT, computed tomography; ECG, electrocardiogram; WBC, white blood cell.

You decide to order a urine toxicology screen. Because Ricky has been afebrile and you have a low suspicion for central nervous system (CNS) infection, you defer a blood culture and lumbar puncture. You also do not think that any metabolic or genetic testing is warranted at this time.

Urine toxicology screen results: positive for benzodiazepines but otherwise negative for drugs of abuse.

Arriving at a Diagnosis

Q: How do you develop an assessment for Ricky?

To think through Ricky's case, you decide to first ensure stability of his airway, breathing, and circulation. Then, you can interpret other key findings from his history, examination, and diagnostic testing and generate a list of findings to arrive at his diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Assessment of airway, breathing, and circulation: Ricky is somnolent, but his airway, breathing, and circulation are intact at the time of your evaluation. As evidenced by his sticky oral mucosa and decreased urination, he does appear to have mild dehydration related to recent poor oral intake.
   - History: Ricky is a typically developing 3-year-old boy with acute onset of generalized convulsive activity, described by his parents and EMS as "all over" shaking that lasted for approximately 5 minutes, which appears to be consistent with new-onset seizure. Ricky required benzodiazepine administration to abort the seizure. You attribute his somnolence on examination to both a postictal state and effects of the antiseizure medication (ASM).
   - Physical examination: Ricky's neurologic examination shows him to be somnolent but appropriately responsive, with symmetric movements and normal-appearing pupils. Additionally, there are no focal neurologic deficits, hyperreflexia, clonus, ataxia, or tremors.
   - Diagnostic evaluation
     - Laboratory tests: Ricky's blood work is all within normal limits, except for a slightly elevated blood glucose level, which you attribute to stress response related to his prolonged seizure activity. His urine toxicology screen is negative for drugs of abuse (other than the benzodiazepines that were required to abort his seizures), and there is no history that points to a specific drug ingestion that would prompt further testing of specific drug levels.
     - Imaging: Ricky's noncontrast head CT scan is normal, so intracranial hemorrhage is unlikely. It is also reassuring that there is no evidence of increased ventricle size to suggest an obstructive process that would lead to increased intracranial pressure.
     - Other studies: Ricky's ECG is normal, decreasing the likelihood of arrhythmia.
2. **Develop the list of findings.**

Q: What major findings have you identified for Ricky?

- Seizure activity lasting 5 minutes, requiring benzodiazepine administration
- Somnolence (attributed to postictal state and medication side effect)
- Poor oral intake with mild dehydration

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Ricky's presentation?

Although you are certain that Ricky had a seizure, the next step in his assessment is to clarify whether the seizure was provoked or unprovoked and, if possible, determine the underlying cause of his seizure. In reviewing Box 35.1, you have eliminated several possibilities of provoked seizures (eg, electrolyte disturbance, hypoglycemia, intracranial hemorrhage). You have a low suspicion for a CNS infection or tumor, metabolic/genetic etiology, or an underlying encephalopathy (acute or chronic). You also note that Ricky has been afebrile and has no prior history of a CNS insult. Because the etiology of his seizure cannot be determined at this point, you would best describe his seizure as unprovoked with unknown etiology.

Q: How are seizures further classified in children?

The International League Against Epilepsy classifies seizure type by clinical appearance at seizure onset: focal, generalized, or unknown (see Table 35.2). The seizure manifestations can then be subdivided into motor or non-motor.

- Focal-onset seizures originate in one hemisphere and may present with normal awareness or impaired awareness (even if brief). Awareness is usually determined based on the ability of the person having the seizure to later verify their awareness during the event.
  - The nomenclature for focal-onset seizures has recently changed. Focal aware seizures were previously referred to as *simple partial seizures*. Focal impaired awareness seizures were previously referred to as *complex partial seizures*.
  - Focal-onset seizures can evolve to cause bilateral tonic-clonic activity.

- Generalized onset seizures originate in both hemispheres and are associated with impaired awareness or loss of consciousness. Any motor manifestation of a generalized seizure is bilateral in nature from the onset. Nonmotor generalized seizures are called absence seizures, with typical absence seizures being most common among the types.
- Seizures may be temporarily classified as *unknown onset*, especially for instances in which the beginning of the seizure was not observed. Unknown onset seizures can frequently be reclassified into focal or generalized-onset after further evaluation.
- Seizures may also be referred to as *unclassified* when there is not yet enough information to categorize them.

Table 35.2. Classification of Seizure Types

	Focal onset	Generalized onset	Unknown onset
Motor	• Atonic • Automatisms • Clonic • Epileptic spasms • Hyperkinetic • Myoclonic • Tonic	• Atonic • Clonic • Epileptic spasms • Myoclonic • Myoclonic-atonic • Tonic • Tonic-clonic	• Epileptic spasms • Tonic-clonic
Nonmotor	• Autonomic • Behavior arrest • Cognitive • Emotional • Sensory	• Absence — Atypical — Eyelid myoclonia — Myoclonic — Typical	• Behavior arrest

Derived from Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017;58(4):531–542.

Q: How do you know if a child has epilepsy?

- Epilepsy is generally defined as 2 or more unprovoked seizures occurring at least 24 hours apart. A neurologist or epileptologist may also diagnose epilepsy when a patient's EEG or clinical picture is consistent with a known epilepsy syndrome or when they determine that a patient's risk of seizure recurrence is high.
- Examples of epilepsy syndromes include benign epilepsy with centrotemporal spikes (also referred to as Rolandic epilepsy), juvenile myoclonic epilepsy, West syndrome, Dravet syndrome, absence epilepsy, and Lennox-Gastaut syndrome, among others. The identification of an epilepsy syndrome is important because it can affect the need for further diagnostic evaluation, and it also affects treatment decisions.
- The etiology of epilepsy is generally classified within one (or more) of the following categories: genetic, metabolic, structural, infectious, immune, or unknown. The results of a patient's EEG, neuroimaging, and genetic testing can help with classification and identification of an underlying epilepsy syndrome.

Q: Does Ricky have epilepsy?

At this time, Ricky does not meet the definition for epilepsy based on his history or current diagnostic evaluation. However, this does not eliminate the possibility of an epilepsy diagnosis in the future, because approximately 50% of children with an unprovoked seizure will go on to have another unprovoked seizure within 2 years, although this number varies widely by study.

Q: Did Ricky present with SE? How would you categorize his seizures?

No, Ricky did not present with a seizure of greater than 5 minutes. From the description of the seizures, he appears to have experienced a generalized motor seizure with tonic-clonic activity.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with new-onset seizure?

- The patient has experienced a first-time seizure and has not returned to neurologic baseline.
- The patient is ill appearing or irritable.
- There is a need for further evaluation or treatment of an underlying cause, such as concern for CNS infection or autoimmune encephalitis, significant electrolyte abnormality or hypoglycemia, or evidence of an intracranial bleed or nonaccidental head trauma.
- The child is unable to maintain adequate oral intake.

You decide that Ricky requires hospitalization to ensure return to his neurologic baseline. Additionally, he has not yet demonstrated that he can maintain his hydration.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Ricky is a 3-year-old previously healthy and typically developing boy presenting with a new-onset generalized motor seizure that resolved after administration of midazolam. The most likely diagnosis is a first-time unprovoked seizure of unknown etiology. Ricky is experiencing continued somnolence and mild dehydration. He requires hospitalization for serial neurologic assessments and rehydration.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Although Ricky's seizure activity has ceased, you review the literature related to seizure recurrence and SE to guide you in writing his admission orders and to prepare for next steps should he have additional seizures.

1. **Treatment of SE:** SE is a neurologic emergency. Prolonged seizure activity can lead to respiratory and/or metabolic acidosis, hypoxemia, difficulties in regulating systemic blood pressures, hyperthermia, and rhabdomyolysis. In a minority of patients, these complications can lead to neurologic morbidity and even death.
   - Initial assessment of the patient's airway, breathing, and circulation should occur quickly while establishing IV access, administering supplemental oxygen, and securing an airway. ASM should be administered with the goal of seizure cessation within 5 to 10 minutes of the seizure's start or as soon as possible after presentation to medical care.
   - Abortive seizure therapies are divided into 4 categories: emergent (first-line), urgent (second-line), and third- and fourth-line drugs for refractory SE. Benzodiazepines (lorazepam or midazolam), preferably via the IV route, for up to 2 doses are recommended as first-line abortive seizure medications. Benzodiazepines are successful in stopping SE in less than 50% of children.
   - If seizure activity continues after 2 doses of a benzodiazepine, urgent administration of another medication such as levetiracetam, fosphenytoin/phenytoin, or valproic acid is indicated. Comparisons of levetiracetam, fosphenytoin, and valproic acid in stopping SE refractory to benzodiazepines have found no difference in their effectiveness, and they carry a similar risk of adverse effects.

2. **Initiation of maintenance seizure medications:** The decision to start a maintenance ASM should be made after considering the risks of both seizure recurrence and potential medication side effects. The financial implications of treatment with ASMs should also be considered.
   - The most common side effects of ASMs include somnolence, hypersensitivity reactions, changes in behavior, and systemic toxicity.
   - The patient's risk of seizure recurrence should be stratified, based on the following considerations:
     - The risk of seizure recurrence is higher in children with abnormal EEG and/or brain MRI.
     - For children who present with a first-time unprovoked seizure in SE, their recurrence risk is likely similar to those with a first brief seizure; however, if these children experience a seizure recurrence, it is more likely to be prolonged in nature.
   - If the EEG is normal and there are no other seizure risk factors, an ASM is typically deferred until a second unprovoked seizure occurs as the likelihood of epilepsy is then increased.
3. **Monitoring of somnolence/altered mental status:** In patients who present with new-onset seizure and persistent alteration in mental status, frequent reassessments are important to ensure return to baseline mental status. Additionally, use of continuous pulse oximetry or capnography can provide useful information about the child's cardiorespiratory status until there are clear signs of improvement in their mentation.
   - Clinicians must also be vigilant to promptly identify further seizure activity. Abrupt changes in vital signs could indicate subclinical SE.
   - Frequent reassessments will also alert the clinician to new findings that may alter the differential diagnosis or necessitate additional diagnostic testing or interventions.
   - There should be a low threshold for further testing with head imaging (if not already obtained), lumbar puncture, and/or continuous EEG monitoring if the patient does not show improvement in mental status over the next several hours or if there is further seizure activity.
4. **Mild dehydration:** Oral rehydration treatment is preferred; however, in the case of a patient with altered mental status, care must be taken to ensure the patient can safely swallow and protect their airway to avoid aspiration. Ricky has mild dehydration, as evidenced by his sticky oral mucosa and decreased urine output but otherwise normal skin turgor and capillary refill. He has demonstrated that he can effectively swallow by taking a few sips of juice in the ED, but he is too drowsy to maintain consistent intake.
5. **Further evaluation of first-time seizure:** As discussed in the diagnostic evaluation section, children with a first-time nonfebrile seizure should be evaluated by a neurologist and undergo a routine EEG. Additionally, an MRI of the brain should be considered in certain circumstances. Because Ricky has continued somnolence and is being admitted to the hospital, you plan to consult the neurology service. If he quickly returns to baseline, you suspect a nonurgent EEG can be performed in the outpatient setting and that an MRI of the brain will not be indicated.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment of SE:** In case Ricky has further seizures, you order lorazepam 0.1 mg/kg IV as needed for up to 2 doses for seizure lasting longer than 5 minutes, with the plan for second-line therapy to be levetiracetam IV should Ricky continue to have seizures.
- **Initiation of maintenance seizure medications:** You will discuss this further with the neurology service and make sure that Ricky's parents are involved in the discussion using shared decision-making; however, given normal neuroimaging and normal development, it is likely that ASM would be deferred until a second unprovoked seizure occurs.
- **Somnolence:** Neurologic assessments by nursing are ordered for every 4 hours. You also plan to reassess Ricky in approximately 1 hour to ensure he has no concerning examination findings and shows improvement in his mental status. Additionally, you order vital signs every 4 hours and continuous pulse oximetry monitoring.
- **Fluids and nutrition:** You order maintenance IV fluids. You also order clear liquids as tolerated and strict monitoring of intake and output.
- **First-time seizure evaluation:** You plan to consult the neurology team and perform further diagnostic evaluation if Ricky is not returning to his neurologic baseline or if a focal-onset seizure occurs.

Case Resolution

Later in the day, Ricky returns to his neurologic baseline without further seizures. He is tolerating a regular diet with adequate urine output after discontinuation of IV fluids. After discussion with both his parents and the neurology service regarding the risks and benefits of starting an ASM, Ricky's parents agree to defer initiation of any medications. They are aware that should Ricky have any subsequent seizure activity, then ASM would be warranted. Follow-up with Ricky's pediatrician and neurology clinic, including an outpatient EEG, is arranged prior to discharge. Ricky is prescribed rectal diazepam for emergency use at home.

Discharge Criteria

Q: How do you know when Ricky is ready to go home?

You can feel comfortable discharging your patient with new-onset seizure when the following criteria are met:

- The patient's mental status and neurologic examination are at baseline.
- If identified, the underlying cause of the seizure has been addressed.
- The patient is without further seizures during time observed in hospital and/or seizures have been controlled with ASM, if applicable.
- The patient is tolerating liquids by mouth with adequate urine output for age.
- Follow-up with the primary care physician and a neurologist has been arranged.
- The caregivers are comfortable with the care plan and have been educated on seizure precautions, ED return precautions, and appropriate use of home abortive seizure medications (eg, rectal diazepam) and/or maintenance ASMs, if applicable.

Anticipatory Guidance

Q: What instructions should you provide to Ricky's caregivers upon discharge?

- If Ricky has another seizure, the following steps and precautions should be taken:
  - Place him on his side to keep his secretions or vomit out of his airway.
  - Make sure the area around him does not have any sharp or hard objects.
  - Do not insert anything into his mouth, perform chest compressions, or restrain him in any way.
  - Pay attention to the time. If the seizure lasts 5 minutes or longer, use his abortive medicine as instructed and call 911.
- Return to the ED for altered mental status/confusion, persistent vomiting, lethargy, difficulty breathing, or new focal weakness.

Clinical Pearls

- A thorough history and the patient's age and categorization of seizure presentation are helpful in guiding an effective diagnostic evaluation of a first-time seizure.
- SE is a neurologic emergency. It is defined as continuous seizure activity lasting longer than 5 minutes or a series of epileptic seizures during which return to baseline mental status is not regained between ictal events within a 30-minute period.
- First-line drug treatment of SE is a benzodiazepine for up to 2 doses. If seizure activity continues, second-line medications such as fosphenytoin, levetiracetam, or valproic acid should be given.
- Neurology consultation or referral is indicated for any child presenting with new-onset seizures.

Documentation Tips

- Specify SE, if present.
- Document whether there is a known underlying epilepsy or the patient is experiencing new-onset seizures.
- Describe the underlying cause of the seizure (structural, metabolic, genetic, acquired, or unknown).
- Document the need for seizure precautions during admission and frequency of planned neurologic checks.

Suggested Reading

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CASE 36

Alberto, a 7-Year-Old Boy With Edema

CASE PRESENTATION

You have finished morning rounds when you are asked to see Alberto, a 7-year-old boy who has just arrived as a direct admission. Alberto's pediatrician requested admission because Alberto, who has allergic rhinitis, developed facial swelling in the context of taking amoxicillin-clavulanate for a presumed sinus infection. He had reassuring vital signs in the clinic and was in no distress, but he was noted to have weight gain from his most recent office visit and has new swelling of his ankles. Alberto was unable to provide a urine sample in the clinic, and his pediatrician has requested that you expedite his evaluation and management.

Patient History and Review of Systems

Q: What information should you collect from Alberto and his caregivers?

- History of present illness
  - Onset and duration of swelling, including any other edematous parts of the body
  - Exacerbating factors or times of worsening swelling (eg, upon awakening, after meals, in relation to taking amoxicillin-clavulanate)
  - Weight changes
  - Changes to bladder habits or urine appearance (eg, foamy urine)
  - Symptoms that resulted in the diagnosis of sinusitis
  - Other signs of recent illness, such as sore throat, fever, upper respiratory tract infection (URTI), cough, vomiting, or diarrhea
  - Associated symptoms, such as difficulty breathing, rashes, abdominal pain, joint pain, fatigue, or decreased energy
- Pertinent medical history, including underlying health status, home medications, vaccination status, and previous episodes of swelling
- Family history of kidney disease

CASE FOCUS

History and Review of Systems

From your conversation with Alberto and his parents, you learn that other than occasional allergic rhinitis, Alberto is healthy, active, and developing normally. His symptoms first began 8 days ago with a runny nose, sinus pressure, and nasal congestion. At that time, he visited his pediatrician and was prescribed amoxicillin-clavulanate for a suspected sinus infection.

Since starting the amoxicillin-clavulanate, Alberto's nasal congestion has improved, and his nasal drainage is no longer thick or green. Alberto's swelling was noticed around his eyes a few days ago and has been gradually worsening. They did not notice his ankle swelling until it was pointed out by his pediatrician. His parents also think his abdomen appears bigger, but they wonder if he may be constipated. Alberto cannot remember the last time he had a bowel movement. His parents have not noticed any fever, difficulty breathing, or rashes. They have noticed he seemed more fatigued the past few days. Alberto denies joint pain, abdominal pain, or any color changes of his urine. He reports he has only urinated once today despite drinking approximately 24 oz of liquid.

In addition to the current course of amoxicillin-clavulanate, Alberto takes cetirizine as needed for mild allergic rhinitis and has taken it once daily for the past 8 days. His parents do not recall any other illnesses over the past weeks other than his sinus infection. He has no other significant medical or surgical history, is up to date on his vaccinations, and he has never had swelling like this in the past. His parents deny any history of swelling or kidney disease on either side of the family.

Physical Examination

Q: What parts of the physical examination should you focus on for Alberto?

- Complete set of vital signs
- Current weight, with comparison to recent weight
- Head, eyes, ears, nose, and throat: periorbital edema, angioedema, oral ulcers, sinus tenderness, nares for evidence of drainage, evidence of photosensitivity, and pain or gaze limitation with extraocular movements
- Cardiac: any additional heart sounds
- Respiratory: tachypnea, respiratory distress, signs of pulmonary edema or pleural effusions
- Abdominal: signs of ascites, tenderness, masses, organomegaly, or flank pain
- Extremities: signs of peripheral edema (eg, pretibial, pedal)
- Genitourinary: signs of scrotal edema
- Skin: purpura or other rashes
- Visual inspection of urine sample

CASE FOCUS

Physical Examination

Alberto's vital signs on admission are within normal range, including a normal blood pressure of 97/58 mm Hg. His pediatrician sent records of his last 2 clinic visits, which show that he has gained approximately 2 kg over the last 8 days.

On examination, you find a well-developed child in no acute distress, with notable bilateral periorbital and facial edema. His eye examination is otherwise normal, with no photophobia, proptosis, or pain or limitation with eye movements. He has a normal oropharyngeal examination, no cervical lymphadenopathy, and there is no drainage noted from his nares. He has a normal cardiovascular examination without murmurs, rubs, or gallops. His lungs are clear to auscultation, with no signs of increased work of breathing. His abdomen is soft but with some fullness and mild tenderness to palpation diffusely. There is no appreciable organomegaly. He does not have any costovertebral angle tenderness to percussion. Mild flank edema is appreciated. He has mild scrotal edema with palpable Tanner I testes. On extremity examination, you note mild pretibial and pedal pitting edema and normal pulses in all extremities. You do not find any rashes or bruises on examination of Alberto's skin. He has not yet provided a urine specimen for visual inspection.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with swelling?

In developing your differential diagnosis for Alberto, you first review the pathophysiology of edema. This helps you group the possible diagnoses by their underlying mechanism. For Alberto, you are most concerned about the possibility of nephrotic syndrome but must also consider some types of glomerulonephritis (GN) or localized edema related to his URTI. The categorized differential diagnosis for a child with edema is shown in Table 36.1.

Table 36.1. Differential Diagnosis for a Child With Edema

Category	Causes
Decreased vascular oncotic pressure (hypoalbuminemia)	• Decreased albumin production: liver disease, sepsis • GI losses: protein-losing enteropathy • Protein malnutrition: kwashiorkor • Renal losses (nephrosis) — Drugs/toxins causing a secondary nephrotic syndrome — Genetic or metabolic: GSD, lipoprotein disorders, mitochondrial cytopathies, sickle cell disease, Alagille syndrome, α-1 antitrypsin deficiency, glutaric acidemia — GN[a]: IgA nephropathy, IgA vasculitis, Alport syndrome, postinfectious GN, lupus nephritis, ANCA-associated vasculitis with associated nephritis — Infections leading to a secondary nephrotic syndrome: HBV, HCV, HIV, malaria, syphilis, toxoplasmosis — Nephrotic syndrome[a]: idiopathic/minimal change disease, FSGS, membranous nephropathy, membranoproliferative GN, congenital nephrotic syndromes, variants of lupus nephritis, diabetic nephropathy — Oncogenic-related nephrotic syndromes: lymphoma, leukemia
Increased venous and capillary pressure	• Decreased arteriolar resistance (eg, from excessive body heat, insufficiency of sympathetic nervous system, or vasodilator drugs) • Increased venous hydrostatic pressure: venous obstruction or stasis (eg, extrinsic compression, venous thrombosis, liver cirrhosis impeding venous blood return, heart failure, immobilization) • Retention of sodium and water by the kidneys, leading to hypervolemia and increased hydrostatic pressure — Primary renal: AKD or CKD, ESRD, acute GN, nephrotic syndrome, mineralocorticoid excess — Secondary to decreased renal perfusion: heart failure, cardiomyopathy
Increased capillary permeability	Angioedema, anaphylaxis, sepsis, localized infection or inflammation,[a] or burns
Lymphedema	Failure of interstitial fluid to return to the central venous system related to abnormal development, dysfunction, or obstruction of the lymphatic system

Abbreviations: AKD, acute kidney disease; ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; GI, gastrointestinal; GN, glomerulonephritis; GSD, glycogen storage disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IgA, immunoglobulin A.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for pediatric patients who present with acute onset of edema and weight gain?

- Well-appearing patients presenting with generalized edema (anasarca) and weight gain should be evaluated for an underlying renal, cardiac, gastrointestinal, nutritional, or oncologic etiology. Severe malnutrition as the etiology is usually apparent based on the history, physical examination, and review of growth curves.

- Clinicians evaluating patients with anasarca and weight gain of unknown etiology should consider ordering the following tests:
  - Complete blood cell count to evaluate for anemia secondary to chronic kidney disease or low cell lines related to malignancies.
  - Serum chemistries to evaluate electrolytes, kidney function, and albumin, as all may be affected in renal disease. Additionally, liver enzymes may be abnormal for some liver diseases (eg, hepatitis, metabolic syndromes). If there is concern for liver synthetic dysfunction, serum coagulation studies should be obtained.
  - Urinalysis with microscopy to evaluate for protein, blood, or casts in the urine.
  - Chest radiograph to evaluate for pleural effusions, signs of heart failure, or malignancy.
- If a renal etiology is suggested by a low serum albumin level and proteinuria, the following tests should be obtained:
  - Lipid profile, because cholesterol and triglycerides are usually high in nephrotic syndrome.
  - Complement levels (C3 and/or C4), because these can be low in several glomerulonephropathies but are typically normal in nephrotic syndrome.
  - Urine sample, to calculate a spot protein to creatinine ratio.
- If a protein-losing enteropathy is suspected on the basis of hypoalbuminemia without proteinuria, a stool α-1 antitrypsin level should be obtained.

CASE FOCUS

Diagnostic Evaluation

You have low suspicion for malnutrition for Alberto, and therefore you decide to begin your evaluation with a complete blood cell count, serum chemistries, a urinalysis, and C3 and C4 levels. Additionally, you obtain a serum lipid panel, a spot urine protein to creatinine ratio, and a chest radiograph. The results of your evaluation are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	133 mEq/L (133 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	105 mEq/L (105 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	8 mEq/L (8 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	19 mg/dL (6.78 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.5 mg/dL (44.2 μmol/L)	0.3–0.6 mg/dL (26.5–53.0 μmol/L)
Glucose	95 mg/dL (5.27 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Albumin	1.8 g/dL (18 g/L)	3.6–5.6 g/dL (36–56 g/L)
Calcium	7.9 mg/dL (1.98 mmol/L)	9.2–10.5 mg/dL (2.30–2.63 mmol/L)
CBC		
WBC count	8,800/μL (8.8×10^9/L)	4,000–13,000/μL ($4–13 \times 10^9$/L)
Hemoglobin	14.8 g/dL (148 g/L)	11.5–14.5 g/dL (115–145 g/L)
Platelet count	210×10^3/μL (210×10^9/L)	$150–400 \times 10^3$/μL ($150–400 \times 10^9$/L)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Urinalysis with microscopy		
Glucose	Negative	Negative
Bilirubin	Negative	Negative
Ketones	Negative	Negative
Specific gravity	1.025	≤1.030
Protein	≥300 mg/dL (3.0 g/L)	Negative
Blood	Negative	Negative
Nitrite	Negative	Negative
Leukocyte esterase	Negative	Negative
Microscopy	No WBCs, RBCs, bacteria, or casts	Negative
Lipid panel		
Cholesterol	325 mg/dL (8.42 mmol/L)	<200 mg/dL (5.18 mmol/L)
Triglycerides	255 mg/dL (2.88 mmol/L)	<200 mg/dL (2.26 mmol/L)
HDL cholesterol	33 mg/dL (0.85 mmol/L)	27–67 mg/dL (0.70–1.74 mmol/L)
LDL cholesterol	290 mg/dL (7.51 mmol/L)	<130 mg/dL (3.37 mmol/L)
Complement studies		
C3 complement	132 mg/dL (1.32 g/L)	84–177 mg/dL (0.84–1.77 g/L)
C4 complement	37 mg/dL (0.37 g/L)	12–45 mg/dL (0.12–0.45 g/L)
Other		
Protein to creatinine ratio	8.2	<0.2
Imaging		
Chest radiograph	The heart and bones appear normal. No signs of increased pulmonary vascular markings. No focal consolidation, effusion, or pneumothorax.	

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RBC, red blood cell; WBC, white blood cell.

Arriving at a Diagnosis

Q: How do you develop an assessment for Alberto?

In developing an assessment, you first decide to interpret Alberto's history, physical examination, and diagnostic studies to develop a list of major findings that will help you narrow your differential diagnosis to the most likely diagnosis. Afterward, admission criteria can be generated for Alberto's suspected diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Alberto's history is significant for a recent sinusitis (either viral or bacterial) complicated by the development of edema and weight gain while taking amoxicillin-clavulanate.
   - Examination: Alberto's physical examination demonstrates a normal blood pressure and edema of his face and lower extremities. He also has suspected ascites, with fullness of his abdomen. His generalized edema (ie, anasarca) and recent 2 kg of weight gain are concerning for fluid overload.
   - Laboratory tests: There are several abnormalities in Alberto's laboratory test results. On his serum chemistries, his sodium level is slightly low (hyponatremia), his albumin level is low (hypoalbuminemia), and his calcium level is low (hypocalcemia). His hemoglobin level is slightly elevated (polycythemia), but other blood cell lines are normal. His urinalysis shows an elevated protein level (proteinuria) but without blood or signs of a urinary tract infection. On the lipid panel, his cholesterol and triglyceride levels are elevated (hyperlipidemia). Both complement levels are normal. A spot protein to creatinine ratio is significantly elevated at 8.2.
   - Imaging: Alberto's chest radiograph is overall normal, with no obvious abnormalities of lungs, heart, vasculature, mediastinum, bones, or diaphragm.
2. **Develop the list of findings.**

Q: What major findings you have identified for Alberto?

- Anasarca
- Hypoalbuminemia
- Proteinuria
- Hyperlipidemia
- Hyponatremia
- Hypocalcemia
- Recent sinusitis treated with antibiotics (improving)

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Alberto's presentation?

- Based on Alberto's history and examination, you are confident that you can rule out any complications directly related to his allergic rhinitis, sinus infection, and antibiotic use.
- With the significant proteinuria found on urinalysis, you are most suspicious of a renal etiology. GN is unlikely based on Alberto's normal blood pressure, complement levels, and creatinine level, as well as a lack of hematuria. With GN excluded, nephrotic syndrome is your leading diagnosis.

Q: What is nephrotic syndrome, and what are the different etiologies?

- Nephrotic syndrome is a renal disease characterized by increased permeability across the glomerular capillary walls. It is manifested by proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Hematuria and hypertension can be present in some patients.

- The vast majority of cases of nephrotic syndrome in pediatric patients are idiopathic, with most cases presumed to be from minimal change disease. Other causes of idiopathic nephrotic syndrome are focal segmental glomerulosclerosis (FSGS), membranous nephropathy, and membranoproliferative GN, among others. Idiopathic nephrotic syndrome is thought to be caused by immunologic insult against the cells lining the glomeruli.
- Secondary causes for nephrotic syndrome include certain infections (eg, HIV and hepatitis B and C), autoimmune disease such as systemic lupus erythematosus, and pharmacologic and oncologic causes.

Q: Does nephrotic syndrome explain all of Alberto's clinical findings?

Alberto demonstrates the classic features of nephrotic syndrome, including edema, proteinuria, hypoalbuminemia, and hyperlipidemia. His generalized edema is consistent with anasarca. His protein to creatinine ratio is 8.2, which is indicative of nephrotic-range proteinuria. The mild polycythemia may reflect a state of low intravascular volume despite being total-body fluid overloaded as evidenced by his acute weight gain. Alberto's hyponatremia is a result of the total-body fluid overload. His total calcium level is low because half of serum calcium binds to albumin, which is depleted. He has elevated cholesterol and triglycerides due to the urinary loss of key lipid transport proteins (including albumin), and a compensatory increase in triglyceride metabolism. His examination and laboratory test results are otherwise unremarkable; thus, secondary causes of nephrotic syndrome are less likely than idiopathic etiologies. With a relatively recent URTI/sinus illness, immunoglobulin A nephropathy and postinfectious GN should be considered; however, hematuria is generally seen with these illnesses and is not present in Alberto's case. The most common cause of idiopathic nephrotic syndrome in children his age is minimal change disease, with FSGS being the second most common.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with new-onset nephrotic syndrome?

- The patient has signs of significant fluid overload (eg, hypertension, hypoxemia, respiratory distress) requiring intensive medication management and monitoring.
- The patient has illness symptoms causing poor oral intake (eg, abdominal pain, distress from swelling, fatigue).
- The patient has acute or chronic kidney injury and/or electrolyte abnormalities.
- There are concerns for serious bacterial infection (eg, peritonitis).
- There are concerns for thromboses (deep vein thrombosis, pulmonary embolism).
- For patients with a new diagnosis of nephrotic syndrome, hospitalization for comprehensive patient and family education is sometimes required.

You determine that Alberto meets criteria for hospital admission based on significant anasarca and electrolyte abnormalities, which suggest the need for acute fluid management, diuresis, and close clinical monitoring while these issues are addressed.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Alberto is a 7-year-old overall healthy boy who presents with anasarca, hypoalbuminemia, hyperlipidemia, and proteinuria concerning for new-onset nephrotic syndrome. His laboratory test results also show mild hyponatremia from fluid overload. He requires hospitalization to improve his fluid status and to initiate treatment and management of his renal disease.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goal of therapy for nephrotic syndrome is to provide symptom management while initiating therapy to induce remission. Symptom management is usually achieved through use of diuretics, sodium restriction, and intravenous (IV) albumin infusions, if indicated.

1. **Acute management**
   - Fluid management: To address the patient's volume status, IV albumin with or without loop diuretics is commonly employed. This can be repeated once or twice daily as needed to improve symptoms related to volume overload. For Alberto, you decide to provide both an IV albumin infusion and a dose of IV furosemide.
   - Hypertension: Patients with nephrotic syndrome are at risk of hypertension related to volume overload. Their hypertension can be further compounded by acute kidney injury (AKI). Some patients may require antihypertensives and diuretics to control their blood pressure. Alberto's blood pressure is normal, so he does not require initiation of antihypertensives at this time.
   - Systemic steroids: Upon diagnosis of nephrotic syndrome, systemic steroids should be started. The exact dosing and course can vary slightly between institutions; however, recent consensus treatment recommendations are for prednisone to be given for 4 to 6 weeks (2 mg/kg to a maximum of 60 mg), followed by a tapering course for an additional 4 to 6 weeks (eg, 1.5 mg/kg [maximum of 50 mg] given every other day).
   - Dietary management
     - A low-sodium diet is important to prevent hypervolemia.
     - Many clinicians also employ daily fluid volume restrictions.
     - It is also important to ensure patients have adequate nutrition, which may require nutritional supplements.
2. **Monitoring**
   - Monitoring fluid balance and response to treatment: Daily or twice-daily weights should be ordered, along with recording all intake and output. Additionally, the patient's blood pressure should be monitored at least every 4 hours.
   - Serial laboratory testing: Hyponatremia is a common finding, resulting from a total body volume overload, but generally resolves as the patient's fluid status corrects. Intravascular volume depletion and diuresis commonly cause AKI, placing patients at risk of hyperkalemia. Although hypocalcemia is commonly found in patients with nephrotic syndrome, the ionized calcium level is usually normal and calcium correction is not required. To monitor for electrolyte disturbances, daily or twice-daily electrolyte, blood urea nitrogen, creatinine, and albumin levels should be ordered. Repeat testing of the urine albumin is generally not needed within the first week of steroid initiation because it can take over a week for the urinary protein losses to improve.
   - Monitoring for complications of nephrotic syndrome
     - Patients with nephrotic syndrome are in a hypercoagulable state for multiple reasons, including intravascular volume depletion, increased synthesis of prothrombotic factors, and urinary losses of antithrombotic proteins. Blood clots (eg, pulmonary embolism, deep vein thrombosis, cerebral venous sinus thrombosis, arterial thrombosis) occur in approximately 3% of childhood nephrotic syndrome patients.
     - With loss of immunoglobulins, patients are at increased susceptibility to encapsulated organisms such as *Streptococcus pneumoniae*. Infections to be vigilant for include spontaneous bacterial peritonitis (with ascites), pneumonia, bacteremia, sepsis, and cellulitis.

- Patients can develop abdominal pain, anorexia, and diarrhea secondary to bowel wall edema or hypoperfusion.
- Because the patient will be starting immunosuppression, physicians should ensure that all of the patient's vaccinations are up to date. Given the increased susceptibility to infections caused by *S pneumoniae*, pneumococcal immunization with the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent polysaccharide pneumococcal vaccine (PPSV23) are particularly important. Pneumococcal vaccines can be given during the steroid course.

3. **Specialist consultation and further diagnostic evaluation:** Depending on the availability of pediatric nephrologists at the institution, consultation with a nephrologist may assist in the management of fluid and electrolyte derangements and the treatment of hypertension when present. In some cases, a renal biopsy is also needed. Decisions about the need for a renal biopsy should be made in conjunction with a pediatric nephrologist.

Q: How do you know if your patient requires a kidney biopsy?

- For most children, especially those younger than adolescence, a biopsy will not be necessary during their initial presentation with nephrotic syndrome.
- Indications for renal biopsy are as follows:
  - The patient is older than 11 years.
  - There is persistent elevation of the patient's creatinine level.
  - Significant hematuria exists.
  - Hypocomplementemia is present.
  - There are findings indicative of another autoimmune disease process.
  - Infection with hepatitis B, hepatitis C, or tuberculosis is present.
  - The patient has hypertension.
  - The patient has not had an appropriate response to steroid therapy.

4. **Discharge and follow-up planning**
   - Continued outpatient screening for hypertension is recommended.
   - Frequent laboratory monitoring may be required, including urinalysis, home urine protein measurement (urine dipsticks), lipid profile, and serum glucose level (if chronic steroids are needed).
5. **Determining response to steroids**
   - Steroid response is an important prognostic factor. Because of this, monitoring of the patient's response to steroids is necessary to determine if further testing or treatment is required.
   - Steroid responsiveness is used to classify patients as steroid responsive, steroid dependent or frequently relapsing, or steroid resistant.
     - A steroid-responsive patient is expected to experience remission within 4 weeks of initiating steroids.
     - A steroid-dependent patient may initially respond to steroid treatment but relapse upon tapering of steroids. Even for steroid-responsive patients, when multiple relapses occur within a 6- to 12-month period, the patient is defined as frequently relapsing.
     - A steroid-resistant patient does not experience remission within 4 weeks of initiating steroid treatment. Steroid-resistant nephrotic syndrome is most commonly caused by FSGS.

- Remission is defined as any one of the following: a urine dipstick shows trace or negative albumin, proteinuria less than 4 mg/m^2/h, or a urinary protein to creatinine ratio less than 0.2 for 3 consecutive occasions.
- Although 85% to 90% of children will experience remission after an 8-week course of steroids, the majority of patients will experience relapses of their symptoms. These relapses commonly occur following minor infections.
- For patients who are steroid dependent or steroid resistant, there are multiple other pharmacologic agents that can be considered, including calcineurin inhibitors, alkylating agents, immunomodulators, and monoclonal antibodies. For these patients, clinicians should also consider obtaining a kidney biopsy, as outlined previously.

CASE FOCUS

Plan for Treatment and Monitoring

- **Consultation:** Given the availability of pediatric nephrologists at your institution, you plan to consult their team to assist with Alberto's fluid management.
- **Fluid overload treatment:** You plan to replete Alberto's intravascular volume and facilitate diuresis with an IV albumin infusion followed by furosemide. The number of infusions needed will be based upon Alberto's clinical response.
- **Steroid initiation:** You order a prednisone course to be started at 2 mg/kg once per day for 6 weeks and plan for a subsequent tapered course at 1.5 mg/kg every other day for an additional 6 weeks.
- **Monitoring:** You order serial examinations, strict monitoring of intake and output, vital signs every 4 hours, twice-daily weights, and daily serum electrolyte, blood urea nitrogen, creatinine, and albumin levels.
- **Diet:** You order a low-sodium diet and will add a fluid intake restriction if needed.
- **Education:** You begin educating Alberto's family about nephrotic syndrome and its complications.
- **Preventive medicine:** You ensure Alberto's vaccinations are current and will immunize him against PPSV23.

Case Resolution

Upon Alberto's admission, you are able to speak with a pediatric nephrologist by phone, and you start Alberto's diuresis and steroid course. Over the next 2 days, Alberto is treated with 3 rounds of IV albumin and furosemide, with marked improvement in his edema. Serial renal function panels do not show electrolyte derangements or an elevated creatinine level, indicating that there are no signs of AKI from the diuresis and fluid shifts. Alberto's albumin level improves to the lower end of normal on his day of discharge. He seems to do well with a lower-sodium diet and fluid restriction. No kidney biopsy is obtained, given that this is Alberto's first instance of nephrotic symptoms. He has scheduled follow-up in the nephrology clinic.

Discharge Criteria

Q: How do you know when Alberto is ready to go home?

You can feel comfortable discharging your patient with new-onset nephrotic syndrome when the following criteria are met:

- The patient has stable creatinine and electrolyte levels.
- The patient has improved volume status.
- The patient's vital signs are stable, including no uncontrolled hypertension.
- There is a clear steroid plan for the patient, typically an initial course of 4 to 6 weeks with a prolonged taper of 4 to 6 weeks thereafter.
- A clear follow-up plan with an outpatient provider, often a pediatric nephrologist, has been established.
- The family understands when to seek emergency care.

Anticipatory Guidance

Q: What instructions would you provide to Alberto's caregivers upon discharge?

- It is important that Alberto continue receiving his medications as prescribed, even if he is feeling better.
- Check Alberto's urine for albumin as recommended by his treating physician.
- Contact the pediatrician or pediatric nephrologist if Alberto is having any symptoms that would indicate worsening of nephrotic syndrome (eg, swelling, decreased urination, weight gain) or the development of a complication (eg, fever, difficult breathing, chest pain, abdominal pain, headache, or steroid side effects, such as mood change).

Clinical Pearls

- Nephrotic syndrome is renal disease a characterized by a combination of edema, proteinuria, hypoalbuminemia, and hyperlipidemia.
- Most cases of childhood nephrotic syndrome are idiopathic, with minimal change disease being the most common cause.
- Despite having significant edema, patients with idiopathic nephrotic syndrome are usually intravascularly depleted due to hypoalbuminemia.
- Treatment for idiopathic nephrotic syndrome is focused on symptom management and induction of remission. Symptom management usually includes diuretics, sodium restriction, and IV albumin, when needed. First-line induction therapy is systemic corticosteroids.
- Acute complications of nephrotic syndrome include thromboses and infections, among others.

Documentation Tips

- Document the presence of anasarca or signs of fluid overload on examination.
- Document when symptomatic hypoalbuminemia is present, and if there is a medical need for albumin infusions.
- Include the need for other IV medications, including diuretics or steroids, when appropriate.

Suggested Reading

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CASE 37

Reese, a 12-Year-Old Girl With Weight Loss

CASE PRESENTATION

You are covering the inpatient service when you are called by an adolescent medicine physician in your community regarding a 12-year-old girl named Reese. The physician is seeing Reese for the first time today after a referral for weight loss related to a suspected eating disorder. Reese's parents report that she has been severely restricting her diet for the past 2 months. In the adolescent medicine clinic today, Reese is found to have a low resting heart rate, orthostatic hypotension, and a 14-lb (6.4-kg) weight loss compared to her weight 2 months ago. You and the adolescent medicine physician decide to directly admit Reese to the pediatric unit.

Patient History and Review of Systems

Q: What information should you collect from Reese and her parents?

- History of present illness
  - Minimum and maximum weight in the past few years with a timeline of the weight loss
  - Goal weight according to the patient and any weight tracking, body image concerns, exercise frequency and duration, and use of pro-eating disorder websites
  - Diet restriction, 24-hour diet recall, binge eating, purging, caffeine and fluid intake
- Associated symptoms, specifically noting the following:
  - General: Sleep disturbances or feeling more fatigued than usual
  - Cardiovascular: Palpitations, chest pain, syncope, or dizziness
  - Respiratory: Shortness of breath or exercise intolerance
  - Gastrointestinal: Abdominal pain, fullness or bloating after eating, constipation, diarrhea, or rectal bleeding
  - Musculoskeletal: Muscle weakness or cramps
  - Hematologic: Easy bruising or pallor
  - Endocrine: Cold or heat intolerance, hair loss, or dry skin
- Medical and family history, noting any history of eating disorders, obesity, depression, anxiety, substance use disorder, inflammatory bowel disease (IBD), celiac disease
- Menstrual history: age at menarche, last menstrual period, frequency and duration of menses, and any changes in menstrual regularity
- Detailed HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment (refer to Section VII in the Appendix for an example of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

When Reese arrives at the pediatric unit, you learn by talking to her and her father that her weight was 90 lb (40.8 kg) (46th percentile) 2 months ago, which was her maximum lifetime weight. She has lost 10 lb (4.5 kg) since then, bringing her to her lowest recent weight of 80 lb (36.3 kg). When you ask Reese about her goal weight, she tells you that she would like to weigh less than 70 lb (31.8 kg). Reese's parents indicate that the onset of her symptoms was about 4 months ago, when she began watching cooking shows and searching for healthy food recipes online with her mother, who is also thin. For the past 2 months, Reese has been weighing her food and calculating calories to make sure she eats no more than about 1,000 kcal/day. She no longer eats her favorite ice cream, cookies, or milkshakes. She has started replacing some meals with sugar-free energy drinks. Reese weighs herself every day and tracks her weight in an app on her phone. Her parents reported these behaviors to Reese's pediatrician a few weeks ago. At that time, Reese was found to have lost 7 lb (3.2 kg). She has been seen by an outpatient psychologist and dietician for the past 2 weeks without any improvement. Today was Reese's first evaluation by a local adolescent medicine specialist.

You ask Reese to complete a diet recall for the last 24 hours, and she reports the following:

- Breakfast: none
- Snack: 1/2 banana with 1 tablespoon peanut butter
- Lunch: 3-oz piece of chicken with 1/2 cup vegetables
- Snack: none
- Dinner: 1 bagel with 1 tablespoon cream cheese
- Total fluid intake: 12 oz water

Reese denies binge eating, purging, or the use of laxatives or diuretics. She runs for 1 hour at school 3 times per week and walks for 1 hour every day on the home treadmill. When asked why she is restricting her diet, she states that she used to eat unhealthily and believes she was, and still is, "fat." Reese says that she has been feeling a little more tired than usual. She endorses dizziness upon standing but denies syncope. She also denies chest pain, palpitations, or shortness of breath. When she eats, she experiences abdominal pain with bloating. She has a bowel movement once per week. She endorses some pain when stooling but denies rectal bleeding. She complains of cold extremities and has noticed dry skin but no changes in her hair. She reports easy bruising on her extremities. Reese has not experienced any muscle weakness or cramping. She had her first period at the age of 10 years. Her menses are regular and last for 5 days, with her last menstrual period about 3 weeks ago. There is no family history of obesity, eating disorders, autoimmune diseases, or mental health concerns. You perform a detailed, private HEADSS assessment, which is significant for Reese feeling anxious and depressed if she eats "unhealthy" food. She has felt sad most days last month after eating foods she feels are unhealthy. For the past few months, she has no interest in hanging out with her friends, and she complains of low energy. She also endorses difficulty sleeping and trouble concentrating on her homework. She denies suicidal ideation.

Physical Examination

Q: What parts of the physical examination should you focus on for Reese?

- Complete set of vital signs, including weight (blinded to patient) and orthostatic blood pressure
- General appearance, including affect
- Head, eyes, ears, nose, and throat: presence of facial wasting, parotid enlargement, erosion of dental enamel, cavities, palatal petechiae, oral lesions or ulcers, thyromegaly, or thyroid nodules
- Cardiovascular: heart rhythm and rate, presence of murmur, peripheral perfusion
- Abdomen: quality and quantity of bowel sounds, tenderness, masses, appearance (eg, scaphoid, distended)
- Extremities: edema, decreased muscle mass, strength
- Integumentary: skin dryness, bruising, thin hair, hair loss, brittle nails, excoriations on the back of hands, lanugo

CASE FOCUS

Physical Examination

Reese's vital signs show a temperature of 36.6 °C (97.9 °F), a height of 59.8 in (152 cm), and a weight of 80 lb (36.3 kg), with a body mass index (BMI) of 15.7 (11th percentile). She has bradycardia with a pulse of 42 beats/min and a normal respiratory rate. Her heart rate rapidly increases when she stands up and is 72 beats/min after 3 minutes on her feet. Her blood pressures while lying and after 3 minutes of standing are 90/52 mm Hg and 78/42 mm Hg, respectively.

On examination, you note a thin girl who is anxiously tapping her feet. Reese makes minimal eye contact and has a restricted, dysphoric affect. She does not have facial wasting or parotid gland enlargement. Her oral mucosa is dry. Inspection of her mouth does not show any cavities, enamel erosion, or oral lesions. Her thyroid gland is normal. She is noted to be bradycardic without any murmurs, and her capillary refill time is 3 seconds. Her lung examination is unremarkable. Her abdomen is flat and nontender with hypoactive bowel sounds. You do not note any masses or organomegaly on abdominal palpation. On extremity examination, she has normal muscle mass and strength. Her hands and feet are cool to the touch. She does not have any peripheral edema and has normal hair without evidence of hair loss. You do not note lanugo. Her skin is dry but without bruising or other lesions.

Differential Diagnosis

Q: What is the differential diagnosis for a child or adolescent with weight loss and restrictive eating behaviors?

The differential diagnosis for a child or adolescent with weight loss and restrictive eating behaviors is shown in Table 37.1 and is divided into causes that seem more and less likely based on Reese's presentation.

Table 37.1. Differential Diagnosis for a Child or Adolescent With Weight Loss and Restrictive Eating Behaviors

Diagnoses of highest suspicion	• Anorexia nervosa[a] • Anxiety disorder • ARFID • Bulimia nervosa • Excessive exercise/energy imbalance • Hyperthyroidism • MDD • OCD
Other diagnoses to consider	• Adrenal insufficiency • Celiac disease • DM • Eosinophilic esophagitis • Gastroparesis • IBD • Infectious diarrhea • Intestinal malrotation • Malignancy • PUD • Pregnancy • Rheumatologic disease • Substance use disorder • Superior mesenteric artery syndrome

Abbreviations: ARFID, avoidant/restrictive food intake disorder; DM, diabetes mellitus; IBD, inflammatory bowel disease; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PUD, peptic ulcer disease.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with weight loss and restrictive eating behaviors?

Patients who present with weight loss in the setting of restrictive eating behaviors should be carefully evaluated for eating disorders while ruling out other diagnoses that may present similarly. Based on her history, physical examination, and outpatient evaluation, you are concerned that Reese has an eating disorder.

- The diagnosis of an eating disorder is based on clinical criteria, and a laboratory evaluation is not required for the diagnosis; however, patients with suspected eating disorders (especially those with features of malnutrition) should undergo a medical evaluation to assess possible complications of their malnutrition or purging behaviors. This evaluation may include the following studies:
  - Complete blood cell count (CBC): A CBC can help assess for anemia, leukopenia, or thrombocytopenia, all possible complications of eating disorders.
  - Serum electrolytes, including calcium, magnesium, and phosphorus levels, renal function, and liver enzymes: Electrolyte abnormalities are common in patients with eating disorders and can result from dehydration, malnutrition, vomiting, or laxative abuse.

- Urinalysis: Dilute urine on urinalysis may indicate water loading in patients who drink excess water in order to reduce hunger or misrepresent their weight.
- Electrocardiogram (ECG): Cardiac complications are most commonly associated with restrictive-type eating disorders and may be detected on ECG. Bradycardia and QT prolongation are the most common cardiac abnormalities in patients with anorexia nervosa. Cardiac dysrhythmias are due to malnutrition and electrolyte abnormalities. Heart rate and rhythm abnormalities improve with nutritional rehabilitation and electrolyte supplementation.
- Thyroid function studies: Thyroid abnormalities are commonly seen in patients with eating disorders as a response to starvation and can be detected with serum thyroid function studies. Individuals with anorexia nervosa often exhibit clinical features of hypothyroidism and biochemically have thyroid hormone abnormalities, such as normal to below-normal thyroid-stimulating hormone and notably low triiodothyronine levels. They also often have low to normal thyroxine (T_4) levels. These patients are generally not considered to be hypothyroid and show improvement in thyroid hormone profiles after nutritional rehabilitation.

- In addition to the previously listed workup, clinicians may also consider the following studies if there is concern for specific scenarios that may be associated with eating disorders, such as the following:
  - Low bone mineral density: Patients with high energy expenditures from intense exercise and inadequate caloric intake are at risk for developing low bone mineral density. This is commonly seen in athletes with disordered eating and is referred to as *relative energy deficiency in sport*. This merits evaluation by checking 25-hydroxy vitamin D, phosphorus, and alkaline phosphatase levels.
  - Hematologic abnormalities: Bone marrow function can be impacted as a result of nutritional deficiency from eating disorders. If patients have signs or symptom concerning for anemia (pallor, tachycardia, dizziness) and/or thrombocytopenia (petechia, bruising), or if CBC levels indicate these abnormalities, further workup may include iron studies, vitamin B_{12} level, prothrombin time/partial thromboplastin time, international normalized ratio, and peripheral blood smear.
- Although lower on the differential diagnosis, clinicians may also consider workup to rule out the following etiologies:
  - IBD or celiac disease: If patients are experiencing chronic diarrhea, abdominal pain, and bloating in addition to weight loss, physicians may consider obtaining a serum erythrocyte sedimentation rate and C-reactive protein level to evaluate for IBD, and a celiac panel (including tissue transglutaminase, and total immunoglobulin A levels) to evaluate for celiac disease.
  - Infectious diarrhea: If patients are experiencing diarrhea (either acute or chronic onset), it is important to rule out infectious diarrhea. Stool culture and stool microscopy for ova and parasites may be considered.
  - Pregnancy: Pregnancy should be considered in patients with weight loss, especially when the patient is also experiencing secondary amenorrhea. This can be seen in the first trimester, particularly if there is nausea associated with the pregnancy. This can be assessed with a urine pregnancy test.
  - Substance use: Weight loss can be associated with substance use. If there is concern for substance use on history from the patient or their caregivers, serum toxicology and/or urine drug screen should be considered.

CASE FOCUS

Diagnostic Evaluation

Upon Reese's admission, you obtain an ECG that shows sinus bradycardia with a heart rate of 49 beats/min but is otherwise normal.

You also obtain a CBC with differential, comprehensive metabolic panel, celiac disease panel, vitamin D level, and urine analysis. Reese's laboratory test results are as follows:

Laboratory test	Result	Reference range
CMP		
Sodium	140 mEq/L (140 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	105 mEq/L (105 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)	22–26 mEq/L (22–26 mmol/L)
BUN	22 mEq/L (7.85 mmol/L)	6–20 mEq/L (2.14–7.14 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)	0.5–0.9 mg/dL (44.2–79.6 µmol/L)
Glucose	76 mg/dL (4.22 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Calcium	9.2 mg/dL (2.30 mmol/L)	9.2–10.5 mg/dL (2.30–2.63 mmol/L)
Phosphorus	3.8 mg/dL (1.2 mmol/L)	3.3–5.4 mg/dL (1.1–1.7 mmol/L)
Albumin	4.2 g/dL (42 g/L)	3.6–5.2 g/dL (36–52 g/L)
Alkaline phosphatase	138 U/L (2.30 µkat/L)	100–320 U/L (1.67–5.34 µkat/L)
AST	30 U/L (0.50 µkat/L)	13–35 U/L (0.22–0.58 µkat/L)
ALT	29 U/L (0.48 µkat/L)	10–30 U/L (0.17–0.50 µkat/L)
Magnesium	2.7 mg/dL (1.11 mmol/L)	1.6–2.4 mg/dL (0.66–0.99 mmol/L)
CBC		
WBC count	3,900/µL (3.9×10^9/L)	4,000–10,500/µL ($4.0–10.5 \times 10^9$/L)
Hemoglobin	13.8 g/dL (138 g/L)	12.0–15.0 g/dL (120–150 g/L)
Hematocrit	40.4% (0.404)	35%–45% (0.35–0.45)
MCV	92 μm^3 (92 fL)	78–95 μm^3 (78–95 fL)
MCHC	34.2 g/dL (342 g/L)	32–36 g/dL (320–360 g/L)
RDW	14.9% (0.149)	11.4%–13.5% (0.114–0.135)
Platelet count	134 × 10^3/µL (134 × 10^9/L)	150–400 × 10^3/µL (150–400 × 10^9/L)
Thyroid function panel		
TSH	0.53 µIU/L	0.5–4.5 µIU/L
FT_4	0.83 ng/dL (10.68 pmol/L)	0.7–2 ng/dL (9.01–25.74 pmol/L)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CMP, comprehensive metabolic panel; FT_4, free thyroxine; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red blood cell distribution width; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Reese's urinalysis shows high specific gravity but is otherwise normal. Her celiac panel and vitamin D levels results are pending.

Arriving at a Diagnosis

Q: How do you develop an assessment for Reese?

To arrive at a diagnosis for Reese, you carefully interpret her history, vital signs, examination, and diagnostic testing. You next systematically assess her weight loss and finally create a list of findings and arrive at a diagnosis.

1. **Interpret key findings from the history and examination.**
   - History: Reese has a recent history of restricting her calorie intake while increasing her calorie expenditure through excessive exercise. As a result, she has had significant weight loss, with her BMI dropping from the 46th to the 11th percentile over a 2-month period. In addition, she has intense fear of weight gain. Reese is also experiencing postural dizziness, abdominal bloating after eating, constipation, cold intolerance, and dry skin. These symptoms are consistent with complications as result of restrictive nutrition and fluid intake. Furthermore, Reese endorses depressed mood, anxiety, decreased interest, difficulty falling asleep, difficulty concentrating, and low energy for at least a month. These findings increase your suspicion for an eating disorder as well as anxiety and depression.
   - Vital signs: Reese's heart rate and systolic blood pressure are below normal for her age. She also has orthostatic hypotension and significant orthostatic heart rate changes.
     - Orthostatic hypotension is defined as systolic blood pressure declining by more than 20 mm Hg or diastolic blood pressure declining by more than 10 mm Hg while standing compared to lying down.
     - Orthostatic heart rate is defined as heart rate increasing more than 20 beats/min while standing compared to lying down. Orthostatic heart rate changes that correlate with orthostatic hypotension may indicate hypovolemia.
   - Physical examination: Reese's examination is notable for her thin body and dehydration, as evidenced by her dry mucous membranes, dry skin, and tachycardia. Her hypoactive bowel sounds indicate slowing of bowel motility due to decreased food intake. Her affect and tapping feet are consistent with anxiety and depressed mood.
2. **Interpret key findings from the diagnostic studies:** Reese's CBC shows leukopenia and thrombocytopenia consistent with bone marrow dysfunction. Normal serum electrolyte and glucose levels indicate Reese's body has been compensating to balance electrolytes while receiving minimal nutrition. Her creatinine level is much higher than expected based on her low muscle mass, concerning for acute kidney injury secondary to dehydration. Her high urine specific gravity is consistent with severe dehydration. Her liver transaminase levels are within normal limits. Reese is found to have normal thyroid function given her normal thyrotropin and free T_4 levels.
3. **Assess weight loss.**
   - Assessment of a patient's weight loss and nutritional status involves several calculations and requires plotting the patient's parameters on growth curves.
     - Ideal body weight: Ideal body weight is defined as the weight that corresponds to a BMI of 50th percentile for the patient's sex and height. Using World Health Organization growth curves, Reese's ideal body weight is 91.5 lb (41.5 kg). Because she currently weighs 80 lb (36.3 kg), she is 87% of her ideal body weight on admission.
     - Weight loss percentage: Over the last 2 months, Reese has lost 10 lb (4.5 kg), which is 11% of her previous body weight (90 lb [40.8 kg]).
     - BMI *z* score: BMI *z* scores represent SDs from the mean BMI for the child's age and sex. Reese's BMI *z* score is −1.21, based on World Health Organization BMI-for-age graphs for girls aged 5 to 19 years old.
     - Malnutrition assessment: The degree of malnutrition is defined based on the patient's BMI *z* score or the percentage weight loss from their usual body weight. Reese's BMI *z* score is consistent with mild malnutrition, whereas her percent weight loss is concerning for severe malnutrition (Table 37.2).

Table 37.2. Malnutrition Degree Based on *Z* Score and/or Weight Loss

Malnutrition degree	BMI *z* score	Weight loss
Mild malnutrition	−1 to −1.9	5%–7.4% of usual body weight
Moderate malnutrition	−2 to −2.9	7.5%–9.9% of usual body weight
Severe malnutrition	≤−3	> 10% of usual body weight

Q: What are common laboratory abnormalities seen in patients with anorexia nervosa?

Although many patients with eating disorders have normal laboratory values, some may have abnormal laboratory findings. See Table 37.3 for common laboratory findings in patients with eating disorders.

Table 37.3. Laboratory Abnormalities Commonly Seen With Eating Disorders

Laboratory test	Potential abnormality	Causes
CBC	Low WBC count, hemoglobin, and platelet count	Bone marrow suppression secondary to malnutrition
Serum chemistries	Low sodium	Water loading, laxative use
	Low potassium, chloride, bicarbonate	Vomiting, laxative or diuretic use
	Low glucose, calcium, phosphate, magnesium	Poor nutrition, laxative use
	High BUN, creatinine	Dehydration
	Low prealbumin, high AST, high ALT	Starvation
Thyroid function	Low or normal TSH and FT_4	Euthyroid sick syndrome secondary to poor nutrition
Vitamin D	Low vitamin D	Poor nutrition
Iron studies	Low iron, low ferritin, high TIBC	Poor nutrition
Urine analysis	High specific gravity	Dehydration
	Low specific gravity	Decreased renal concentrating ability
	Presence of WBCs, protein, or blood	Renal insufficiency due to fluid restriction/vomiting

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; FT_4, free thyroxine; TIBC, total iron-binding capacity; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Q: What are the most common changes expected on ECG in a patient with anorexia nervosa?

- Cardiac functional changes secondary to malnourishment may cause sinus bradycardia (heart rate < 60 beats/min), prolonged PR interval, or heart block.
- Electrolyte abnormalities may cause prolonged QTc (> 450 msec) or arrhythmias.

4. Develop the list of findings.

Q: What major findings have you identified for Reese?

- Sinus bradycardia
- Orthostatic hypotension
- Weight loss of 11%, meeting criteria for severe malnutrition
- Restrictive nutrition intake
- Leukopenia
- Thrombocytopenia
- Depressed mood and symptoms of anxiety
- Dehydration
- Acute kidney injury

5. Revisit the differential diagnosis.

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Reese's presentation?

- Given Reese's history, physical examination findings, and diagnostic workup, you are most concerned for an eating disorder, specifically anorexia nervosa. Anorexia nervosa typically presents in early adolescence with restricted calorie intake, significant weight loss, fear of weight gain, and body image disturbance (see Box 37.1). Reese meets criteria for anorexia nervosa, restrictive type based on the following findings:
- She has decreased her calorie intake (1,000 kcal/d) and increased her calorie requirements.
- She has lost 11% of her usual weight over a 2-month period, meeting criteria for severe malnutrition.
- She has intense fear of gaining weight.
- She views her body as "fat" despite significant weight loss.
- She has been dieting and engaging in excessive exercise.
- Based on Reese's history and physical examination, you are able to rule out other eating disorders on your differential diagnosis.
  - Bulimia nervosa: Bulimia typically presents with recurrent binge-eating episodes and compensatory behavior, such as exercising or use of laxatives (Box 37.1). Reese does not meet criteria for bulimia nervosa because she denies binge eating.
  - Avoidant/restrictive food intake disorder (ARFID): ARFID typically presents with nutritional deficiency or weight loss as a result of an eating disturbance, such as apparent lack of interest in eating or food, avoidance based on the sensory characteristics of food, or concern about aversive consequences of eating (eg, pain, choking). Patients with ARFID do not have body image disturbances and do not engage in purging behavior. Given Reese's engagement in excessive exercising and an absence of eating disturbance, she does not meet criteria for ARFID.

- Symptoms of psychological disorders can contribute to the development of eating disorders, be exacerbated by an eating disorder, or both. Given Reese's history of depressed mood, it is important to explore the possibility of a diagnosis of major depressive disorder (MDD) in addition to anorexia nervosa.
  - To diagnose MDD, patients should be experiencing at least 5 MDD symptoms for most days over the previous 2 weeks. Additionally, these symptoms must represent a change from the patient's previous functioning, and at least 1 of the symptoms must include either depressed mood or a loss of interest. The symptoms to consider for the diagnosis of MDD include depressed mood, a diminished interest in hobbies, a decrease in appetite, difficulty sleeping, psychomotor agitation, fatigue, guilt, difficulty concentrating, and recurrent thoughts of death.
  - Because Reese has had a depressed mood, diminished interest in hobbies, difficulty sleeping, psychomotor agitation, fatigue, and difficulty concentrating on the majority of days for more than 2 weeks, she meets criteria for MDD. In this case, MDD is a secondary diagnosis due to Reese's restrictive eating behavior, excessive exercising, and body image disturbance.

Q: What other diagnoses have you eliminated?

Although you are confident in your diagnosis, you systematically think through some of the other etiologies on your differential diagnosis. These etiologies are unlikely, but given the potential morbidity and mortality with missing these diagnoses, you want to be certain to eliminate them for Reese.

- Malignancy: Malignancy may present with weight loss, easy bruising, leukopenia, and thrombocytopenia, as seen in Reese's case; however, her lack of fever, examination without findings of masses/organomegaly/adenopathy, the mild degrees of her thrombocytopenia and leukopenia, and her normal hemoglobin all argue against malignancy.
- Celiac disease: Celiac disease can present at any age with weight loss, abdominal bloating, and abdominal pain. Celiac disease classically manifests as loose, bulky stools from malabsorption, but it can also present with constipation. The results of Reese's celiac disease panel will potentially definitively rule out this diagnosis.
- Type 1 diabetes mellitus: Type 1 diabetes mellitus can present at any age with weight loss, but there are typically other symptoms present, such as polyuria, polydipsia, lethargy, and hyperglycemia. Reese does not have any of these additional findings.
- Hyperthyroidism/hypothyroidism: Thyroid abnormalities can present with symptoms similar to Reese's, but her normal thyroid function panel rules out this diagnosis.

Box 37.1. Diagnostic Features of Eating Disorders Commonly Seen in Children and Adolescents

Anorexia nervosa
• Restricted caloric intake relative to energy requirements, leading to significantly low body weight for age, sex, projected growth, and physical health
• Intense fear of gaining weight or engagement in behaviors that consistently interfere with weight gain, despite being at a significantly low weight
• Altered perception of body weight or body shape, self-perception/sense of self-worth excessively influenced by body weight or body shape, or a persistent lack of acknowledgment of the seriousness of the low body weight

Box 37.1. Diagnostic Features of Eating Disorders Commonly Seen in Children and Adolescents *(continued)*

Subtypes
• Restricting type: Weight loss is achieved primarily through dieting, fasting, and/or excessive exercise, with no repeated episodes of binge eating or purging in the previous 3 months
• Binge-eating/purging type: Repeated episodes of binge eating or purging (ie, self-induced vomiting or misuse of laxatives, diuretics, or enemas) have occurred in the previous 3 months
Bulimia nervosa
• Repeated episodes of binge eating followed by compensatory behaviors
• Binge eating is characterized by both of the following: — Episodes involve eating an amount of food within a distinct period of time (eg, 2 hours) that is significantly larger than most individuals would eat during a similar time frame under similar circumstances — Episodes are marked by the feeling that one cannot limit or control the overeating
• Inappropriate compensatory behaviors are repeatedly used to prevent weight gain, such as self-induced vomiting (purging); misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise
• The binge-eating and compensatory behaviors both occur at least once a week for 3 months, on average
• Self-perception/self-worth is excessively influenced by body weight and body shape
• The binge-eating and compensatory behaviors do not occur only during episodes of anorexia nervosa
Binge-eating disorder
• Repeated episodes of binge eating, with episodes occurring at least once a week for 3 months
• Binge eating is characterized by both of the following: — Eating an amount of food within a distinct period of time (eg, 2 hours) that is significantly larger than most individuals would eat during a similar time frame under similar circumstances — The feeling that one cannot limit or control the overeating during the episode
• The binge-eating episodes include 3 or more of the following: — Eating much more quickly than normal — Eating until uncomfortably full — Eating large amounts of food when not hungry — Eating alone due to embarrassment at the amount eaten — Feelings of guilt, disgust, depression, or anguish following the episode
• The binge eating is not associated with the use of inappropriate compensatory behavior, as in bulimia nervosa, and it does not occur only in the context of bulimia nervosa or anorexia nervosa

(continued)

Box 37.1. Diagnostic Features of Eating Disorders Commonly Seen in Children and Adolescents *(continued)*

ARFID
• A disrupted eating pattern (eg, seeming lack of interest in eating or food; avoidance based on the sensory qualities of food; concern about unpleasant consequences of eating) as evidenced by persistent failure to meet appropriate nutritional and/or energy needs associated with 1 (or more) of the following: — Significant weight loss or, in children, failure to achieve expected growth and/or weight gain — Marked nutritional deficiency — Reliance on enteral feeding or oral nutritional supplements — Significant interference with psychosocial functioning
• The disrupted eating pattern cannot be better explained by lack of available food or by an associated culturally sanctioned practice
• The disrupted eating pattern cannot be attributed to a coexisting medical condition or better explained by another mental illness or disorder
• If the disrupted eating pattern occurs in the context of another condition or disorder, the severity of the disrupted eating pattern exceeds that which is routinely associated with the condition or disorder
Examples of other specified feeding or eating disorders
• Atypical anorexia nervosa: All criteria for anorexia nervosa are met, but body weight is within or above the normal range despite significant weight loss
• Bulimia nervosa of low frequency and/or limited duration: All criteria for bulimia nervosa are met, but binge eating and related compensatory behaviors occur less than once a week and/or for less than 3 months, on average
• Binge-eating disorder of low frequency and/or limited duration: All criteria for binge-eating disorder are met, but binge eating occurs less than once a week and/or for less than 3 months, on average
• Purging disorder: Recurrent purging behavior, such as self-induced vomiting and/or the misuse of laxatives, diuretics, or other medications, occurs in the absence of binge eating with the intent to alter body weight or body shape

Abbreviation: ARFID, avoidant/restrictive food intake disorder.

Derived from Hornberger LL, Lane MA; American Academy of Pediatrics Committee on Adolescence. Identification and management of eating disorders in children and adolescents. *Pediatrics*. 2021;147(1):e2020040279.

6. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with anorexia nervosa?

- The patient's weight is less than or equal to 75% of ideal body weight.
- The patient's heart rate is below 50 beats/min while awake or below 45 beats/min while asleep.
- The patient's systolic blood pressure is less than 90 mm Hg.
- The patient has significant orthostatic vital sign changes upon standing. This may include an increase in pulse by more than 20 beats/min or a decrease in blood pressure of greater than 20 mm Hg systolic or greater than 10 mm Hg diastolic.
- The patient's body temperature is less than 35.6 °C (96 °F).
- Cardiac arrhythmia is present.
- The patient has electrolyte abnormalities.

- The patient is experiencing acute food refusal.
- Outpatient treatment attempts have failed to improve patient's symptoms.
- The patient is expressing suicidal ideation.

Based on Reese's bradycardia, orthostatic hypotension, and food refusal despite outpatient treatment, Reese meets hospitalization criteria for acute medical stabilization of her anorexia nervosa. It is important to note that in addition to acute medical stabilization, Reese will require treatment of her underlying eating disorder. Treatment of eating disorders requires a specialized and multidisciplinary team not available in many general pediatric inpatient settings.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Reese is a previously healthy 12-year-old girl presenting with severe malnutrition, weight loss, bradycardia, orthostatic hypotension, leukopenia, and thrombocytopenia secondary to anorexia nervosa, restrictive type. She requires hospitalization for nutritional rehabilitation and medical stabilization.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The goal of hospitalization for patients with eating disorders is medical stabilization, monitoring for complications while providing nutritional rehabilitation and adequate weight gain. Acute care hospitalization often does not provide the structured environment and multidisciplinary care and therapy to treat eating disorder behavior; therefore, patients require a plan to continue treatment after discharge.

1. **Nutritional rehabilitation:** Nutritional rehabilitation and weight restoration are principal components of treating anorexia nervosa. A dietitian should be consulted to help guide treatment for all patients admitted with eating disorders.
   - Diet: Recent evidence suggests that a high-calorie diet, with calorie intake starting at 1,500 to 2,400 kcal/d and advancing by 100 to 250 kcal/d, is associated with significant weight restoration and a shorter hospital stay without an increased risk of refeeding syndrome. A low-calorie diet is not recommended because it lengthens hospital stays and slows weight gain.
   - Supplement drinks: Patients with anorexia nervosa may be resistant to finishing meals. Supplement drinks can be used in conjunction with meals to provide goal calories.
   - Nasogastric feeds and total parenteral nutrition: These methods provide calories if patients refuse oral nutritional intake. A combination of nasogastric and meal-based nutritional rehabilitation results in faster weight gain and delayed relapse. Total parenteral nutrition is not commonly used for patients with eating disorders because of potential complications.
   - The nutritional rehabilitation plan for Reese should consist of a high-calorie diet, including supplement drinks as needed, and plan for nasogastric feeds if Reese refuses oral nutritional intake.
2. **Hydration:** Most patients with anorexia nervosa are dehydrated because of fluid restriction. Fluid intake goals need to be met every day for appropriate hydration. Oral rehydration is preferred compared to intravenous (IV) fluids and can be initiated at a maintenance rate. In patients like Reese who are severely dehydrated, it is recommended to avoid fluid boluses, and IV fluids must be run at half the maintenance rate for weight given the

risk of causing electrolyte derangement, including hyponatremia. Hyponatremia can be seen in several different situations related to eating disorders. Purging can cause hyponatremia due to loss of salt and water. Hyponatremia can also occur in severe restrictive eating disorders as a result of a decreased ability of the kidneys to excrete free water due to low nutritional intake. Without enough food, even a fairly normal amount of water intake can lead to hyponatremia due to water retention. Assuring adequate nutritional intake at the same time as resuming normal fluid intake can prevent this type of electrolyte disturbance. Caution should be used with IV fluids if a patient is severely dehydrated and refuses to take in nutrition.

3. **Monitoring vital signs:** Patients with eating disorders often present with abnormal vital signs secondary to malnourishment. Patients with malnourishment are also at risk for developing cardiac arrhythmias; therefore, patients should be monitored on telemetry. Temperature, orthostatic heart rate, and blood pressure should be measured every morning. Weight should be measured daily after the first morning void. This weight should be blinded from the patient and measured on the same scale while the patient is in a gown. Vital signs should be measured every 4 hours during hospitalization.
4. **Monitoring activity level:** Patients' activity levels should be limited during hospitalization due to the need for energy conservation. Activity should be even more strictly limited when the patient is experiencing unstable vital signs. Patients with anorexia nervosa who have unstable vital signs are advised to have strict bed rest. Patients are allowed to perform minimal daily activity after vital signs are stable. Given Reese's tachycardia and the orthostatic changes in her blood pressure and pulse, she should initially be advised to maintain strict bed rest.
5. **Medication**
   - To help address anemia and optimize bone health, a multivitamin containing vitamin D and iron should be started in all patients with eating disorders and continued through nutritional rehabilitation.
   - Given concern for refeeding hypophosphatemia, clinicians should consider phosphate supplementation and subsequently decrease or discontinue supplementation based on phosphorus levels.
   - Thiamine supplementation is recommended in severely malnourished patients to prevent Wernicke encephalopathy.
   - Abdominal bloating and constipation after eating are common in patients with eating disorders. Restrictive food intake results in slowed gut motility and decreased gastric accommodation leading to inadequate production of digestive enzymes. As nutrition improves, abdominal bloating and constipation should likewise improve. Until then, a stool softener may be used to treat constipation.
6. **Monitoring laboratory test results**
   - Clinicians should consider obtaining urinalysis on the first morning void each day. The urine specific gravity indicates the patient's degree of hydration and can monitor for "water loading" (drinking water to artificially increase the weight). Given Reese's severe dehydration at presentation, it is reasonable to obtain daily urinalysis.
   - Serum electrolyte, magnesium, and phosphorus levels should be monitored daily for refeeding syndrome for the first 7 days after the start of nutritional rehabilitation. If a patient has any abnormal electrolyte levels, laboratory test results should be monitored every 6 to 12 hours.
7. **Mental health:** The most common co-occurring conditions associated with eating disorders in adolescents are anxiety and depression. It is recommended that clinicians consult the psychiatry and psychology teams for therapy initiation, support during hospitalization, and potential medication initiation. Fluoxetine is approved to treat depression in adolescents with anorexia nervosa. Olanzapine is shown to improve weight gain and functional thinking processes in patients with anorexia nervosa. Given Reese's history of depressed mood, it is advisable to consult the behavioral health team early in the course of Reese's treatment.
8. **Discharge plan:** There are outpatient, partial inpatient, and inpatient programs available for eating disorder treatment. The most appropriate discharge plan will vary by patient and local resources. It is important to begin to explore the potential discharge options for Reese early in her hospitalization to ensure an appropriate transition when she is medical stable for discharge.

Q: What exactly is refeeding syndrome, and why is it a concern in care for patients with anorexia nervosa?

Refeeding syndrome is a constellation of complications that can result from nutritional rehabilitation in malnourished patients. Refeeding syndrome can result in life-threatening multiorgan failure and metabolic derangements secondary to inadequate adenosine triphosphate (ATP) within the first week of nutritional rehabilitation.

- Pathophysiology: During a starvation period, glycogen stores are depleted, and fat, protein, and muscle catabolism become the major source of energy for the body. When nutritional rehabilitation starts, increase in carbohydrates causes insulin release that results in profound electrolyte shifts. Furthermore, phosphorus in the form of ATP is required for glucose metabolism. Cellular uptake of phosphorus as a result of insulin secretion and ATP synthesis causes depletion of phosphorus stores, which is known as *refeeding hypophosphatemia*, the hallmark of refeeding syndrome. Other laboratory abnormalities include hyponatremia, hypomagnesemia, and hypoglycemia.
- Prevention and treatment: Risk factors for refeeding syndrome include a higher degree of malnutrition, rapid weight loss, abnormal electrolytes prior to nutritional rehabilitation, use of diuretics or laxatives, and alcohol use. Gradual increase in calories in the beginning of nutritional rehabilitation can prevent refeeding syndrome. Patients with refeeding syndrome require replenishing of serum electrolytes. Oral supplementation of electrolytes is recommended. Starting prophylactic phosphate supplementation is a common practice to prevent refeeding hypophosphatemia; however, there is no evidence to support the benefits of prophylactic phosphate supplementation.
- Complications: Patients with refeeding syndrome may develop cardiac failure, arrhythmias, hemolytic anemia, muscle weakness, seizure, delirium, or coma. This condition also can result in sudden death.

CASE FOCUS

Plan for Treatment and Monitoring

- **Nutritional rehabilitation:** You consult a dietitian and together decide to begin Reese's total daily intake at 1,500 kcal and then increase by 250 kcal/d. You plan to have Reese take nutritional supplement shakes if she is not finishing meals or not gaining weight appropriately.
- **Hydration:** You decide to give Reese a fluid goal of 66 oz/day, including supplement shakes.
- **Vital signs:** You plan to obtain Reese's weight in a gown after she urinates each morning, orthostatic blood pressure and heart rate every morning, and vital signs every 4 hours. You also start monitoring her with telemetry for severe bradycardia or arrhythmia.
- **Activity level:** You decide to limit Reese's activity to strict bed rest for the first 24 hours of her hospitalization.
- **Medication:** You do not start phosphate supplementation because Reese's phosphorus level is normal. Given Reese's constipation, you start 1 capful of polyethylene glycol 3350 per day.
- **Monitoring laboratory test results:** You plan to obtain magnesium and phosphorus levels and a basic metabolic panel daily during the first 7 days of Reese's hospitalization while reaching her daily calorie goal to monitor for refeeding syndrome. You obtain urinalysis of the first morning void to monitor her fluid intake and renal health daily.
- **Mental health:** You consult the behavioral health team to evaluate Reese and start therapy and a selective serotonin reuptake inhibitor for depression.

Case Resolution

During the first 48 hours of her hospitalization, Reese's vital signs stabilize. Based on your hospital's eating disorder guidelines, you discontinue bed rest and allow Reese to take a 10-minute shower, go for a wheelchair ride, and sit up in a chair. During her stay, she gains 200 g/d on average and is able to take all of her meals by mouth. Both her celiac panel and vitamin D levels return to normal. After 7 days, you are able to discontinue her daily laboratory tests because her electrolyte levels continue to be normal. Eight days after her admission, in consultation with the mental health team and based on Reese's progress, you discharge Reese to a partial hospitalization program in your area.

Discharge Criteria

Q: How do you know when Reese is ready to go home?

You can feel comfortable discharging your patient with anorexia nervosa when the following criteria are met:

- The patient has reached greater than 75% of their median body weight for age and sex.
- The patient has stable vital signs as demonstrated by
  - Heart rate above 50 beats/min while awake and above 45 beats/min while asleep.
  - Systolic blood pressure above 90 mm Hg *and* change in orthostatic systolic blood pressure less than 20 mm Hg and diastolic pressures less than 10 mm Hg.
- The patient has normal serum electrolyte levels.
- Any abnormalities seen initially on ECG have resolved.
- The patient has consistently completed all their meals.
- An appropriate outpatient plan including follow-up with an adolescent medicine physician, dietitian, and therapist has been arranged.
- If a patient has stable vital signs, normal serum electrolyte levels, and a normal ECG but has not yet reached greater than 75% of their median body weight for age and sex and/or is not consistently finishing meals, transfer to a partial hospitalization program or inpatient eating disorder center may be appropriate.

Anticipatory Guidance

Q: What instructions should you provide to Reese and her caregivers upon discharge?

- Follow the meal plans as instructed by your dietitian.
- Limit activity level to basic daily activity. Avoid exercising.
- Follow up as directed with the outpatient adolescent medicine physician, dietitian, and therapist.
- Return to care for symptoms of chest pain or palpitations, syncope or loss of consciousness, food refusal for at least 24 hours, or suicidal ideation.

Clinical Pearls

- Patients presenting with sudden and significant weight loss, excessive exercising, restrictive or purging behaviors, and body image disturbance require evaluation for eating disorders.
- Patients with eating disorders require hospitalization if they have signs of medical instability, including unstable vital signs, organ failure, or food refusal.
- Nutritional rehabilitation is the mainstay of eating disorder treatment.
- Refeeding syndrome is the most serious complication during the first week of nutritional rehabilitation and can include potentially lethal electrolyte derangements. Monitoring of serum electrolyte levels is necessary during this period.
- Eating disorders are often associated with depression and/or anxiety. Pharmacotherapy in conjunction with therapy is recommended for treatment and prevention of relapses.

Documentation Tips

- Document the degree of dehydration and/or malnutrition on presentation, including BMI.
- Include previous unsuccessful outpatient treatment and any social barriers to outpatient management.
- Document any specific electrolyte disturbances that are present while monitoring for refeeding syndrome.
- Document orthostatic vital signs.
- Document cardiac/ECG concerns, including the presence of hypotension, bradycardia, or arrhythmia, and any need for telemetry monitoring.

Suggested Readings

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CASE 38

Lily, a 6-Month-Old Girl With Fever and Lethargy

CASE PRESENTATION

Lily is a 6-month-old girl with no significant medical history who presented to her pediatrician's office this morning with fever and increased sleepiness. Her pediatrician was concerned by her lethargy, so he referred her to the emergency department (ED). In the ED, a diagnostic evaluation is initiated, including serum laboratory studies, blood cultures, lumbar puncture (LP), chest radiograph, and a urinalysis with urine culture. The results of the laboratory studies are pending, but the ED physician reports that the chest radiograph is unremarkable. Lily receives an intravenous (IV) fluid bolus of 20 mL/kg normal saline and is given empiric ceftriaxone and vancomycin. The ED physician calls you to evaluate Lily for admission to the inpatient unit. After speaking to the ED physician caring for Lily, you begin your patient evaluation.

Patient History and Review of Systems

Q: What information should you collect from Lily's caregivers?

- History of present illness
  - Onset, duration, and progression of symptoms
  - Fever history, including onset, height, and method of temperature measurement
  - Changes in alertness, including lethargy or somnolence
  - Recent illnesses
  - Signs of dehydration (eg, decreased urine output, sunken appearance of eyes, absence of tears)
  - Associated symptoms, including difficulty breathing, cough, nasal congestion, vomiting, diarrhea, changes in oral intake, areas of tenderness, weakness, irritability, poor muscle tone, high-pitched cry, seizures, or rash
- Medical history, including recurrent infections or conditions conferring immunodeficiency (eg, anatomic or functional asplenia, HIV, complement deficiency), craniofacial trauma, central nervous system (CNS) abnormalities or procedures
  - Birth history, including gestational age
  - Developmental history
  - Immunization status, particularly *Haemophilus influenzae* and *Streptococcus pneumoniae*
- Chronic or recent medication use, including antibiotics

- Exposure history, including the following:
  - Sick contacts and attendance to child care
  - Travel and activity history, including recent water-related activities, animal contact, mosquito bites, and the possibility of tick exposure

CASE FOCUS

History and Review of Systems

From your conversation with Lily's family, you learn that Lily has had increased fussiness and poor appetite since yesterday afternoon. Last night, she had a rectal temperature of 38.5 °C (101.3 °F) and was fussy through most of the night. This morning, Lily was difficult to rouse and had an episode of vomiting when her father tried to give her a bottle of human (breast) milk. Her family then brought her to her pediatrician's office, where her pediatrician recommended Lily's family bring her to the ED.

Lily has been stooling normally, although she has had fewer wet diapers than normal. When asking about recent illnesses, you learn she was seen at her pediatrician's office 5 days ago for runny nose, nasal congestion, and cough and was diagnosed with a viral upper respiratory illness. She was not prescribed any medications, and these symptoms improved, but she continues to have lingering nasal congestion. Lily's parents have not noticed any changes to her anterior fontanelle, but they do feel that her eyes appear sunken. They deny any recent head trauma. Lily's review of systems is otherwise negative.

You learn that Lily has been generally healthy, apart from her recent upper respiratory illness. She has received all age-appropriate immunizations, including her 6-month vaccines 2 weeks ago. She does not take any medications other than acetaminophen on occasion. Lily was born at 36 weeks gestational age but did not require a neonatal intensive care unit (ICU) stay. There were no other complications during the pregnancy or delivery. She has been breastfed exclusively, with the recent introduction of solid foods at 6 months. She attends local child care with a few other children, some of whom have recently had upper respiratory infections. Her family denies any travel, and Lily has not had any recent animal contact, mosquito bites, or any tick exposures.

Her parents note that Lily's weight at her 6-month health supervision visit 2 weeks ago was 7.2 kg (roughly 50th percentile for age) and that she was just under 7 kg at her visit today.

Physical Examination

Q: What parts of the physical examination should you like to focus on for Lily?

- Complete set of vital signs
- Weight, length, and head circumference
- Level of consciousness and ability to arouse normally
- Assessment of fontanelles
- Neck stiffness or signs of meningismus: In neonates and infants, neck stiffness is uncommon and signs of meningismus may include irritability, especially with movement of the child
- Head, eyes, ears, nose, and throat: oropharynx and tympanic membranes for signs of infection, appearance of eyes (sunken, icteric), presence or absence of tears with crying, mucous membranes (moist, sticky, or dry)

- Cardiac, respiratory, abdominal, and musculoskeletal examinations for any localizing signs
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Skin: presence and distribution of any rashes, including mottling of the skin or any other lesions
- Neurologic: lethargy, focal neurologic deficits, abnormalities in muscle tone, deep tendon reflexes, or cranial nerve examination

CASE FOCUS

Physical Examination

At the time of your evaluation, Lily has a rectal temperature of 38.7 °C (101.7 °F). Her heart rate was 160 beats/min upon arrival to the ED but has slightly improved to 150 beats/min after receiving a fluid bolus. Her blood pressure, respiratory rate, and oxygen saturation are within normal limits. Her weight in the ED is 6.95 kg (34th percentile), length is 65 cm (38th percentile), and head circumference is 41.9 cm (41st percentile).

When speaking to Lily's parents, you notice Lily appears to be sleeping. She is wrapped in a blanket and held by her father. As you start your examination, she is arousable with stimuli, cries, and then falls back to sleep. Her face while crying appears symmetric. Her anterior fontanelle is full, but her posterior fontanelle is closed. She has some audible nasal congestion, but no active nasal drainage is noted. You notice her lips are cracked, and her oral mucosa is dry. She gags appropriately with use of a tongue depressor to examine her oropharynx, and you do not appreciate any pharyngeal erythema or other lesions. Her tympanic membranes are normal in appearance, and her neck is supple. She is tachycardic on auscultation but with a regular heart rhythm and no murmur. She has mild transmitted airway noises upon auscultation of her lungs, with nonlabored respirations. Her abdomen is soft, nondistended, and nontender without appreciable hepatosplenomegaly. When you survey her skin, you appreciate some scattered truncal petechiae with no other skin lesions. Lily's capillary refill time is mildly prolonged at 3 to 4 seconds, and her hands and feet are cold to the touch. Her pupils are equally round and reactive to light, changing from 7 mm to 3 mm. Extraocular movements appear intact, and there is no setting sun sign. Her eyes are without icterus or conjunctival injection. On her fundoscopic examination, you do not appreciate any optic disc edema. You notice Lily has generalized, decreased muscle tone but withdraws all 4 extremities from noxious stimuli. No ankle clonus is noted, and she has an upgoing Babinski reflex. Her patellar and ankle reflexes are normal.

CASE FOCUS

Urgent Intervention

Given Lily's tachycardia and decreased peripheral perfusion, you order a 20 mL/kg bolus of lactated Ringer solution to be given immediately using the push-pull method. You continue to think through Lily's case as her nurse administers the bolus.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an ill-appearing infant or young child with fever, petechial rash, and lethargy?

This combination of symptoms is highly concerning and requires consideration of an extensive differential diagnosis. Table 38.1 demonstrates a differential diagnosis for these symptoms and has been separated into diagnoses that appear more or less likely for Lily.

Table 38.1. Differential Diagnosis for an Ill-Appearing Infant or Young Child With Fever, Petechial Rash, and Lethargy

Diagnoses of highest suspicion	• Encephalitis, including infectious or autoimmune • Meningitis,[a] including bacterial,[a] fungal, or viral/aseptic • Meningococcemia[a] • MIS-C related to SARS-CoV-2 • Septic shock, DIC, or purpura fulminans
Other diagnoses to consider	• Acute hemorrhagic edema of infancy • Autoimmune or autoinflammatory conditions (eg, systemic JIA, NOMID) • Cerebral venous thrombosis in the setting of an underlying systemic infection • Endocarditis • IgA vasculitis with CNS involvement • Intracranial abscesses, including parenchymal, subdural, or epidural • KD • Malignancy, including leukemia • Measles infection (severe, with encephalitis) • Nonaccidental trauma • Viral hemorrhagic fevers • Viral syndromes, including enteroviral infections • Zoonotic infections (eg, RMSF, *Ehrlichiosis*, West Nile virus, murine typhus, leptospirosis)

Abbreviations: CNS, central nervous system; DIC, disseminated intravascular coagulation; IgA, immunoglobulin A; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; NOMID, neonatal-onset multisystem inflammatory disease; RMSF; Rocky Mountain spotted fever.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with fever, petechial rash, and lethargy?

When there is a high clinical suspicion for a fulminant and potentially lethal underlying etiology, such as with Lily, clinicians should rapidly perform diagnostic testing as they are simultaneously developing and implementing an initial treatment plan. Diagnostic testing to consider includes the following:

- Two sets of blood cultures obtained from different sites. Obtaining 2 blood cultures, instead of 1 culture, increases the likelihood of detecting bacteria in the bloodstream.

- Complete blood cell count (CBC) with differential. The presence of leukocytosis or cytopenias may be helpful in ruling in or out various diagnoses. A peripheral smear can be useful to evaluate for evidence of hemolysis, circulating blasts, or signs of asplenia (ie, Howell-Jolly bodies).
- Serum chemistries, to evaluate electrolytes, renal function, glucose, and liver enzymes.
- Serum inflammatory markers, although imperfect, can be a useful part of a patient's evaluation.
  - C-reactive protein (CRP): A normal CRP level has some utility in its negative predictive value for a bacterial illness, although it is not particularly sensitive or specific. Serial CRP levels are commonly used to monitor response to treatment.
  - Procalcitonin: If low, serum procalcitonin has a high negative predictive value for bacterial infections, but when elevated, its positive predictive value is insufficient to reliably differentiate between viral and bacterial etiologies.
- When meningitis is suspected, an LP and cerebrospinal fluid (CSF) analysis is an essential part of the diagnostic evaluation.
  - CSF studies should include cell counts, glucose, protein, Gram stain, and bacterial culture. If available, polymerase chain reaction (PCR) or antigen testing can be useful in detecting certain bacterial or viral pathogens that can cause meningitis or encephalitis. Acid-fast bacilli stains and cultures should be ordered when there is suspicion of a mycobacterial infection. An opening pressure should be obtained when feasible.
  - Contraindications to immediate LP include certain neurologic abnormalities, including signs of increased intracranial pressure, suspected space-occupying mass lesions, spinal anomalies or tethered cord, and abnormal neurologic findings (eg, hemiparesis or abnormal posturing). Additional contraindications to immediate LP include cardiopulmonary compromise, coagulopathy, or the presence of a skin infection at the site of anticipated LP. Signs of increased intracranial pressure may include papilledema, abnormal pupil size and reactivity, seizure activity, persistent emesis, abnormal breathing patterns, or mental status changes.
  - Head imaging: If LP is contraindicated because of a patient's neurologic status, an urgent head computed tomography (CT) scan (or rapid-sequence magnetic resonance imaging) should be obtained to evaluate the risk of brain herniation. Other clinical situations that require imaging prior to LP may include but are not limited to known immunodeficiency and certain CNS conditions (eg, CSF shunt, hydrocephalus, recent CNS trauma, recent neurosurgical procedure).
- Venous or arterial blood gas, lactic acid level, and coagulation studies should be obtained when there is clinical concern for acute respiratory failure, septic shock, or disseminated intravascular coagulation (DIC). DIC is a condition that can develop in severely ill patients (eg, patients who have sepsis, trauma, malignancy, burns) and results in activation of the coagulation cascade. The consumption of clotting factors, platelets, and fibrin simultaneously causes both microvascular thrombosis, which can lead to multiorgan dysfunction, and an increased risk of bleeding. Although there are not formal diagnostic criteria in children, the diagnosis of DIC requires abnormalities in coagulation markers over serial measurements.
- For patients in whom there is concern for certain tick-borne or rickettsial infections, serum PCR and/or antibody testing should be obtained (depending on the suspected etiology); however, for most tick-borne or rickettsial illnesses, treatment should be initiated immediately while results are pending. Common laboratory findings in many tick-borne or rickettsial illnesses include hyponatremia, leukopenia, thrombocytopenia, and transaminitis. A rash is present in many, but not all, tick-borne infections. Additionally, abnormal CSF findings are common. Refer to the most recent edition of the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases* or the Centers for Disease Control and Prevention website for specific testing and treatment recommendations.
- Evaluation for multisystem inflammatory syndrome in children should be considered for febrile patients with recent exposure to SARS-CoV-2. Testing includes serum inflammatory markers, CBC, comprehensive metabolic panel, serum troponin, and SARS-CoV-2 nasal testing by PCR and serum antibody titers. Clinicians should refer to the Centers for Disease Control and Prevention website for further discussion of the diagnostic evaluation.

CASE FOCUS

Diagnostic Evaluation

You quickly review the diagnostic workup completed by the ED physician. The results of these tests are as follows:

Laboratory test	Result	Reference range
CBC		
WBC count	24,300/μL (24.3 × 10^9/L)	7,000–13,000/μL (7–13 × 10^9/L)
RBC count	4.7 × 10^6/μL (4.7 × 10^{12}/L)	3.8–4.7 × 10^6/μL (3.8–4.7 × 10^{12}/L)
Hemoglobin	11.8 g/dL (118 g/L)	10.5–14 g/dL (105–140 g/L)
Hematocrit	35% (0.35)	32%–42% (0.32–0.42)
Platelet count	242 × 10^3/μL (242 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	67% (0.67)	15%–50% (0.15–0.50)
Lymphocytes	32.6% (0.326)	13%–70% (0.13–0.70)
Monocytes	0.4% (0.004)	4%–9% (0.04–0.09)
Serum chemistries		
Sodium	143 mEq/L (143 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.3 mEq/L (4.3 mmol/L)	3.5–6.3 mEq/L (3.5–6.3 mmol/L)
Chloride	103 mEq/L (103 mmol/L)	97–106 mEq/L (97–106 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)	19–24 mEq/L (19–24 mmol/L)
BUN	22 mg/dL (7.9 mmol/L)	5–18 mg/dL (1.8–6.4 mmol/L)
Creatinine	0.6 mg/dL (53.0 μmol/L)	0.1–0.4 mg/dL (8.8–35.4 μmol/L)
Glucose	92 mg/dL (5.11 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Albumin	4.2 g/dL (42 g/L)	2.2–4.8 g/dL (22–48 g/L)
AST	13 U/L (0.22 μkat/L)	9–80 U/L (0.15–1.34 μkat/L)
ALT	21 U/L (0.35 μkat/L)	13–45 U/L (0.22–0.75 μkat/L)
Total bilirubin	0.5 mg/dL (8.55 μmol/L)	< 1.2 mg/dL (20.52 μmol/L)
Inflammatory markers		
CRP	7.1 mg/dL (71 mg/L)	< 1 mg/dL (< 10 mg/L)
Procalcitonin	2.1 ng/mL	< 0.5 ng/mL
CSF studies		
Glucose	39 mg/dL (2.16 mmol/L)	≥ 60% of serum
Protein	105 mg/dL	5–45 mg/dL
WBC count	1150/mm^3	0–5/mm^3
RBC count	7/mm^3	0/mm^3
Neutrophils	93%	None

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CRP, C-reactive protein; CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

CASE FOCUS

Diagnostic Evaluation *(continued)*

Lily's urinalysis is normal except for an increased specific gravity and moderate ketones, and a chest radiograph demonstrates no abnormalities. A nasal respiratory pathogen PCR and SARS-CoV-2 antibody titers are pending. Two peripheral blood cultures and a CSF bacterial culture and Gram stains are pending at the time of your evaluation. Because your hospital has access to a rapid meningitis/encephalitis PCR and antigen panel, you decide to add this testing to the CSF sample remaining in the laboratory.

Because Lily has petechiae on your examination, you also decide to obtain coagulation studies, the results of which are as follows:

Laboratory test	Result	Reference range
PT	11.4 s	9–13 s
INR	1.1	0.9–1.2
PTT	34 s	25–37 s
Fibrinogen	275 mg/dL (2.75 g/L)	200–400 mg/dL (2–4 g/L)
D-dimer	0.31 µg/mL (1.70 nmol/L)	< 0.50 µg/mL (< 2.74 nmol/L)

Abbreviations: INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Arriving at a Diagnosis

Q: How do you develop an assessment for Lily?

To formulate an assessment for Lily, you decide to first evaluate her airway, breathing, and circulation. You will then interpret her history, vital signs, examination findings, and diagnostic evaluation to develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology or etiologies.

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - Assessment of airway, breathing, and circulation: Your initial assessment of Lily reveals a patent airway and appropriate oxygenation without concern for impending respiratory failure. Lily has tachycardia with a normal blood pressure, but her cool hands and feet and prolonged capillary refill time point toward decreased peripheral perfusion. Lily does have some element of dehydration/hypovolemia related to her decreased oral intake (about 3.5% based on her recent weight loss, corresponding to mild to moderate dehydration); however, her constellation of findings is concerning for developing severe sepsis or septic shock.
   - History: The history you obtained from Lily's family is pertinent for fever, fussiness, and progressive change in alertness in the setting of a recent respiratory illness.
   - Physical examination: Her physical examination findings include somnolence/lethargy, a full anterior fontanelle, and petechiae. When combined with her history of fever, these findings are concerning for a CNS infection. Whereas in children, the classic triad of headache, photophobia, or nuchal rigidity/neck stiffness is a more common manifestation of CNS infection, infants will present with nonspecific findings of a CNS infection (eg, irritability, changes in mentation or activity level, poor feeding, poor muscle tone).

- Serum studies: Lily's CBC demonstrates leukocytosis. Her elevated blood urea nitrogen and creatinine levels are consistent with acute kidney injury (AKI), likely secondary to dehydration or renal hypoperfusion. Her serum glucose level is within normal limits but should be used in the interpretation of her CSF glucose level, as shown in Table 38.2. Lily also has elevated CRP and procalcitonin levels; although not definitive, these values add to your suspicion of a bacterial infection.
- CSF: Lily's CSF shows a low glucose level, elevated protein level, and pleocytosis (increased white blood cells [WBCs]) with neutrophilic predominance. Table 38.2 shows CSF findings in healthy children and in various etiologies of meningitis. In applying this table to Lily's CSF, you believe that Lily's CSF values are concerning for a bacterial process. Although not applicable to Lily, in the event of a "traumatic tap" (bloody CSF sample), interpretation of CSF cell counts is limited; however, many clinicians approximate the actual WBC count by subtracting 1 WBC from the CSF analysis count for every 500 to 1000 red blood cells, although this is not definitive.

Table 38.2. Cerebrospinal Fluid Values Based on Various Clinical Scenarios

Clinical scenario	Glucose (mg/dL)	Protein (mg/dL)	WBC/mm^3	WBC differential	Gram stain
Healthy neonate	30–120	30–150	<30	No PMNs	No organisms
Healthy infant or child	40–80	20–40	<10	No PMNs	No organisms
Bacterial meningitis	<50% of serum	>100	>1000	>85%–90% PMNs	Variable depending on bacteria
Enteroviral meningitis	>50% of serum	40–60	<1000	>50% PMNs early in the course of illness <50% PMNs later in the course of illness	No organisms
Fungal meningitis	<50% of serum	>100	<500	Lymphocytic/monocytic predominance	No organisms
Tuberculosis meningitis	<50% of serum	>100	<300	Lymphocytic predominance	No organisms

Abbreviations: CSF, cerebrospinal fluid; PMN, polymorphonuclear cell; WBC, white blood cell.

- Assessment for sepsis: Lily's leukocytosis, fever, and tachycardia in the setting of a suspected infection meet the definition of sepsis. Her poor perfusion is concerning for the development of severe sepsis or septic shock, although she does not meet these criteria at this time. Refer to Section IV of the Appendix for systemic inflammatory response syndrome/sepsis definitions and age-based criteria.

2. **Develop the list of findings.**

Q: What major findings have you identified for Lily?

- CSF with pleocytosis, low glucose level, and elevated protein level concerning for bacterial meningitis
- Sepsis with concern for developing severe sepsis or septic shock
- Mild to moderate dehydration
- Oliguria
- AKI

3. Revisit the differential diagnosis.

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Lily's presentation?

As previously stated, and in comparison with Table 38.2, interpretation of Lily's CSF cell counts seems consistent with meningitis, in particular bacterial meningitis. Rickettsial illness or multisystem inflammatory syndrome in children seem less likely based on the results of her CSF studies.

Q: Who is at risk of bacterial meningitis?

- Neonates and young infants are at the highest risk of bacterial meningitis, but bacterial meningitis can occur in all age groups. Other risk factors for bacterial meningitis include immunodeficiency (including functional or anatomic asplenia), immunosuppression, unimmunized status, child care attendance, dermal sinus tracts to the CNS, head trauma/CSF leak, recent neurosurgery or implanted surgical devices, bacterial infection of contiguous areas (eg, sinusitis, mastoiditis), recent upper respiratory tract infection, travel to an area endemic for meningococcus, or exposure to a person with meningococcal or *H influenzae* type b (Hib) meningitis.
- The incidence of bacterial meningitis in infants and children older than 2 months has decreased following introduction of the Hib and pneumococcal vaccines.

Q: How is bacterial meningitis diagnosed?

- The reference standard for the diagnosis of bacterial meningitis is the growth of a bacterial pathogen on CSF culture; however, many clinicians would also diagnose bacterial meningitis if the patient has a positive blood culture in the setting of CSF pleocytosis or if the patient has positive molecular testing (eg, PCR or latex agglutination) on the CSF.
- The diagnosis of bacterial meningitis in a patient who has been pretreated with antibiotics can be challenging, and consultation with infectious disease specialists may be warranted in some cases.

Q: While cultures are pending, is there a reliable way to discriminate between viral and bacterial meningitis on the basis of history and laboratory findings?

- For infants and children who have CSF pleocytosis, calculation of the bacterial meningitis score (BMS) can help predict the risk of bacterial meningitis. This scoring system should be excluded for the following individuals:
  - Infants younger than 60 days
  - Patients pretreated with antibiotics
  - Patients who are immunocompromised
  - Patients with recent neurosurgical procedures
  - Patients with a petechial/purpuric rash
- This scoring system includes the following components, which are then added to calculate the score (score range = 0 to 6):
  - Positive CSF Gram stain (2 points)
  - CSF absolute neutrophil count greater than or equal to 1,000 cells/mm^3 (1 point) (calculated by multiplying the total WBC count by the percentage of neutrophils and dividing by 100)
  - CSF protein greater than or equal to 80 mg/dL (1 point)
  - Serum absolute neutrophil count of greater than or equal to 10,000 cells/mm^3 (1 point)
  - History of seizure on or prior to presentation (1 point)
- When none of these features is present (a score of 0), the risk of bacterial meningitis is very low, at 0.1%. A score of 1 point correlates with a 10% risk of bacterial meningitis, and scores of 2 through 6 points correlate with an 87% chance of bacterial meningitis. A meta-analysis of validation studies utilizing this score demonstrated that the scoring system has a sensitivity of 99.3% and a positive likelihood ratio of 2.6. A score of 0 showed a negative likelihood ratio of 0.01.
- Because Lily has petechiae on examination, this scoring system should not be applied to her.

Q: What are common bacterial etiologies of meningitis in infants and children?

- The most common bacterial etiologies of meningitis vary by age, as demonstrated in Table 38.3.
- Given Lily's age and presentation, she appears to be most at risk of infections caused by *S pneumoniae* or *Neisseria meningitidis*. However, you will need to await her blood and CSF culture results and CSF PCR result to make a definitive diagnosis.

Table 38.3. Common Bacterial Pathogens Causing Meningitis in Infants and Children

Age	Bacterial pathogen
Younger than 1 month	*Escherichia coli* Group B streptococcus *Listeria monocytogenes* *Klebsiella* spp
1 month to 2 years	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* *E coli*
Older than 2 years	*N meningitidis* *S pneumoniae*

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with suspected meningitis?

- All infants and children with suspected bacterial meningitis require hospitalization for close monitoring, empiric IV antibiotics, and other supportive measures.
- Many infants and children with suspected bacterial meningitis require initial care in the pediatric intensive care unit (PICU). Indications for admission/transfer to the PICU include the following:
  - The patient requires frequency of monitoring, laboratory draws, or nursing interventions above what can safely be performed on an acute care unit.
  - The patient has hemodynamic instability, respiratory failure, severe electrolyte or coagulation abnormalities, coma, refractory seizure activity, or persistent signs of increased intracranial pressure.

At this time, you feel that Lily should be admitted to your intermediate care unit for close monitoring.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Lily is a 6-month-old girl with no known underlying medical concerns who is being admitted with suspected acute bacterial meningitis. Additionally, she has findings of sepsis, hypovolemia, and AKI. She requires inpatient admission to your intermediate care unit for IV antibiotic therapy and close monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Lily's symptoms, you review the literature to remind yourself about the treatment of acute bacterial meningitis in infants and children. You are aware that bacterial meningitis caries significant risk of morbidity and mortality and that aggressive early empiric treatment and intensive monitoring are important. You decide to divide treatment considerations into the following components:

1. **Antimicrobial therapy**
   - For patients with a BMS of 0, it may be reasonable to monitor their clinical course while cultures are pending without providing antibiotics.
   - When there is clinical suspicion for bacterial meningitis, empiric antimicrobial therapy should be initiated immediately following LP. If the LP needs to be delayed because of contraindications or to obtain head imaging, empiric antibiotic therapy should be initiated immediately, prior to the LP.
   - Because bacterial pathogens vary by age, likewise, empiric antibiotic therapy varies somewhat based on age, as shown in Table 38.4.

Table 38.4. Empiric Treatment Options Stratified by Age for Bacterial Meningitis in Infants and Children

Age	Empiric treatment options
Younger than 1 month	Ampicillin *plus* third- or fourth-generation cephalosporin, with or without acyclovir
1 month or older	Vancomycin *plus* third-generation cephalosporin

   - Once culture results are known, antibiotic therapy can be narrowed based on identification and susceptibilities of the pathogen. Examples of commonly used antibiotic therapy for bacterial meningitis are shown in Table 38.5.

Table 38.5. Antibiotic Treatment Options for Common Bacterial Meningitis Pathogens in Infants and Children

Pathogen	Standard antibiotics	Alternative antibiotics[a]	Typical duration
Group B streptococcus	(Penicillin *or* ampicillin) with or without gentamicin	Ceftriaxone *or* cefotaxime	14–21 days
Escherichia coli	(Cefotaxime *or* ceftriaxone) with or without gentamicin	Cefepime *or* meropenem	21 days
Listeria monocytogenes	(Penicillin *or* ampicillin) with or without gentamicin	Trimethoprim-sulfamethoxazole *or* meropenem	14–21 days
Streptococcus pneumoniae	Penicillin *or* ampicillin	Cefepime *or* meropenem	10–14 days
Neisseria meningitidis	Penicillin *or* ampicillin	Cefotaxime *or* ceftriaxone	5–7 days
Haemophilus influenzae	Ampicillin	Cefotaxime *or* ceftriaxone	7 days

[a] Alternatives are recommended only if the pathogen is revealed to be nonsusceptible to the recommended treatments.

- If CSF and blood cultures are negative, CSF analysis is consistent with a viral etiology, and the patient is stable and improving, empiric antibiotic therapy may be discontinued; however, if there remains suspicion for bacterial meningitis because of pleocytosis in the setting of pretreatment with antibiotics or a positive blood culture, clinicians should consider completing a treatment course for meningitis. An empiric treatment course for culture-negative meningitis in neonates younger than 1 month is 14 days of ampicillin and cefotaxime. For infants and children older than 1 month, 10 days of ceftriaxone is a reasonable treatment course.
- Because Lily is 6 months old, you feel that the combination of IV vancomycin and ceftriaxone will provide adequate empiric coverage while her cultures and CSF PCR result are pending.

2. **Steroids**
   - Although controversial, dexamethasone may be used as adjunctive therapy for patients 6 weeks or older in whom there is suspicion for bacterial meningitis. Use of dexamethasone may reduce the likelihood of hearing loss, particularly with meningitis secondary to *H influenzae*, but it would need to be given with or prior to the first antibiotic dose.
   - Given that Lily has already received her first doses of antibiotics, you do not think that steroids will be beneficial in her case.
3. **Monitoring for complications:** Close monitoring for complications is particularly important in the first few days of treatment.
   - Hemodynamic instability: Until a patient with acute bacterial meningitis has stabilized, frequent monitoring of vital signs and urine output is warranted to detect possible progression to septic shock.
   - Electrolyte abnormalities: Patients should undergo close monitoring of electrolytes (particularly sodium level to rule out syndrome of inappropriate antidiuretic hormone secretion [SIADH]) and fluid balance.
   - Neurologic complications: Patients should also undergo frequent neurologic checks to evaluate for signs of increased intracranial pressure or seizure activity. Seizures occur in up to 25% of patients with bacterial meningitis. In infants, increased intracranial pressure may be heralded by an increase in their frontal occipital circumference; therefore, this measurement should be obtained daily for patients younger than 18 months.
   - Hematologic abnormalities: For patients with hematologic abnormalities or suspected DIC, CBC and coagulopathy laboratory values should be monitored closely. Transfusions with packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate may be needed; however, specific transfusion thresholds vary by clinician or institutional protocol. In patients with sepsis who have worsening hematologic abnormalities, care in a pediatric intensive care setting should be considered.
   - During the first couple of days of Lily's hospitalization, you plan to monitor her neurologic status and laboratory tests frequently, with the frequency determined by her clinical course.
4. **Specialist consultation**
   - Consultation with an infectious disease specialist may be indicated, particularly for complicated courses of meningitis, including patients
     - With a lack of clinical improvement.
     - Whose infection is caused by uncommon pathogens.
     - Who have evidence of an intracranial abscess or empyema.
     - With antibiotic-resistant pathogens.
     - With a predisposing medical history.
     - With recent neurosurgical procedures or implanted surgical devices (eg, shunts, cochlear implants).
   - Neurology consultation may be beneficial for patients who develop seizures, especially for those with focal or refractory seizures or seizures that occur more than 48 hours into treatment.

- Neurosurgery consultation should be obtained for patients with severely increased intracranial pressure, development of hydrocephalus, or other abnormalities on intracranial imaging.
- At this time, you will hold off on any consultations while you monitor Lily's clinical course on empiric treatment.

5. **Supportive care**
   - Pain: Acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids may be needed to provide relief of pain or fever in patients with meningitis. Because Lily has AKI and is receiving a nephrotoxic medication (vancomycin), you will initially provide acetaminophen with plans to escalate to opioids if needed for irritability.
   - Hydration: Infants and children who are somnolent or lethargic should be made nil per os (nothing by mouth) until they have improvement in their mental status. In the meantime, IV fluids or nasogastric feeds should be used to ensure adequate hydration. If signs of SIADH develop, restriction of fluids may be required. Lily has evidence of mild to moderate dehydration but is now status-post a 20 mL/kg IV normal saline fluid bolus. If her perfusion is improved, you will start her on maintenance IV fluids without providing further fluid boluses. You choose to use isotonic fluids for maintenance of hydration to decrease her risk of hyponatremia.
   - Therapy: Many infants and children with bacterial meningitis experience neurologic sequelae from their infection. As they are recovering, many benefit from evaluation by physical, occupational, and speech therapists, depending on their degree of neurologic impairment.
6. **Venous access considerations:** Because of the risk of complications in the first days of hospitalization, patients with suspected bacterial meningitis should always have adequate venous access. This can be accomplished by maintaining 2 peripheral IV lines, but occasionally central venous access is required, especially in patients who require care in the ICU or those who need a prolonged course of IV antibiotics. For Lily, you will have an additional peripheral IV line placed.
7. **Further testing**
   - Repeat LP: Repeat LPs to ensure CSF sterilization are not routinely indicated except in the setting of resistant organisms, lack of clinical improvement or clinical worsening, and/or use of dexamethasone, which can mask clinical symptoms.
   - Persistent or recurrent fever: It is common that patients with bacterial meningitis will have fever for 4 to 6 days after initiation of appropriate antibiotic therapy. Persistent or recurrent fever after 8 days of therapy is an indication to evaluate for complications (eg, abscesses, empyema, pericarditis, ventriculitis, nosocomial sources of infection).
   - CT scan or MRI with contrast is indicated to assess for abscess formation in patients with meningitis secondary to *Citrobacter* species, *Serratia marcescens*, *Proteus mirabilis*, and *Cronobacter sakazakii*.
   - Patients with confirmed invasive meningococcal disease may benefit from complement deficiency evaluation with CH50 and AH50 testing; if a deficiency is identified, patients 2 months or older should undergo a meningococcal conjugate vaccination series, and patients 10 years or older should undergo the serogroup B meningococcal vaccination series.
   - Hearing screen: Patients with confirmed bacterial meningitis are at risk of hearing loss and should undergo hearing screening prior to or just after discharge. If the findings are abnormal, repeat testing should be completed. The patient should be referred to an audiologist if this repeat testing is also abnormal.
8. **Prophylactic therapy:** In cases of meningococcal or Hib meningitis, close contacts of the patient are at risk of infection and may require prophylactic antibiotic treatment. Refer to the most recent edition of the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases* for further information about antibiotic options and which patient contacts require prophylaxis.

CASE FOCUS

Plan for Treatment and Monitoring

- **Antibiotic therapy:** You plan to continue empiric vancomycin and ceftriaxone and follow up on Lily's CSF Gram stain, CSF PCR panel, and blood, urine, and CSF cultures.
- **Steroids:** No steroids are indicated for Lily.
- **Monitoring:** You place Lily on continuous cardiorespiratory monitoring, order vital signs and nursing evaluations to be obtained every 2 hours, and order strict monitoring of urine output. You order a repeat CBC, renal function, and electrolytes to be obtained in 4 hours. You also order daily head circumference measurements.
- **Consultation:** Based on Lily's clinical course, you decide that specialist consultation is not required currently but may be needed depending on the pathogen identified or complications that may arise.
- **Supportive care:** You place Lily on nil per os status with isotonic IV fluids for rehydration and maintenance of hydration. You order acetaminophen as needed for pain and discomfort.
- **Venous access:** You will order that a second peripheral IV line be placed. You anticipate Lily will require placement of a peripherally inserted central catheter (PICC) in the coming days.

Case Resolution

Lily's Gram stain returns with a few gram-positive cocci in pairs, and her CSF PCR panel is positive for *S pneumoniae*. Serial laboratory tests over the next 24 hours demonstrate a stable CBC, serum electrolytes, and renal function. During this time, her blood pressure remains normal. On hospital day 3, she is transferred from the intermediate care unit to the acute care unit. Her CSF and blood cultures grow *S pneumoniae* susceptible to penicillin, and thus her antibiotic therapy is narrowed to IV ampicillin and continued for a total duration of 14 days given via a PICC. Lily passes a hearing test, returns to her neurologic baseline, and has her PICC removed prior to discharge home.

Discharge Criteria

Q: How do you know when Lily is ready to go home?

You can feel comfortable discharging your patient with meningitis when the following criteria are met:

- The patient is clinically and neurologically stable.
- The patient is able to tolerate oral intake.
- The patient is afebrile for 24 to 48 hours.
- The patient has completed IV antibiotic treatment or has plans to receive IV antibiotics at home.

Anticipatory Guidance

Q: What instructions should you provide to Lily's caregivers upon discharge?

- Return to care for fever, vomiting, poor feeding, or any other concerns.
- The PICC insertion site should remain covered and dry for approximately 24 hours after PICC removal, after which the dressing can be removed and bathing can resume as usual. Return to care for any redness or swelling at the site.
- Infants and children with bacterial meningitis are at an increased risk of cognitive or developmental delay. Because of this, regular follow-up evaluations by Lily's primary care physician are important to determine whether specific testing is required. A referral to physical, occupational, or speech therapy may be needed if any developmental delays are noted. Additionally, an evaluation by a developmental specialist may be beneficial if cognitive disabilities are noted as Lily ages.

Clinical Pearls

- Infants and younger children with meningitis may present with nonspecific findings (eg, irritability, changes in mental status, poor feeding, poor muscle tone), whereas older children have the more classic manifestations of headache, photophobia, and nuchal rigidity.
- The diagnosis of meningitis is established based on CSF cell counts, glucose level, protein level, and culture.
- Empiric antibiotic therapy should be initiated immediately if LP is contraindicated or if obtaining a head CT is indicated prior to LP.
- Antibiotic therapy and its duration are dependent on the pathogen identified.

Documentation Tips

- Document the suspected or confirmed etiology of meningitis when possible (eg, bacterial, viral, fungal).
- Interpret abnormal CSF laboratory findings (eg, document *pleocytosis* instead of only listing the elevated CSF WBC count in the laboratory results).
- Document sepsis if present and additional workup and cultures performed.
- Document frequency of neurologic checks needed during the admission.

Suggested Reading

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CASE 39

Isla, a 15-Month-Old Girl With Fever and Rash

CASE PRESENTATION

You are the admitting physician when Isla, a previously healthy 15-month-old girl, presents to the emergency department (ED) with 7 days of fever, mild congestion, cough, and a new rash. Two days ago, Isla was seen by her pediatrician and diagnosed with a viral illness. Her mother brought her to the ED today because of the development of the rash. In the ED, Isla is noted to be pale, inconsolably irritable, and refusing oral intake. The ED physician obtains a chest radiograph, which is normal. Blood work, including culture, complete blood cell count (CBC) with differential, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and comprehensive metabolic panel (CMP), is ordered and is pending. Additionally, the ED physician obtains a respiratory panel by polymerase chain reaction (PCR) and a urinalysis (UA). Given Isla's ill appearance and the need for further monitoring and evaluation, the ED physician calls you to evaluate her for admission.

Patient History and Review of Systems

Q: What information should you collect from Isla's caregivers?

- History of present illness
  - Timeline and characteristics of presenting symptoms
  - Specific characteristics of fever, including its duration, height, frequency (eg, daily, intermittent), and pattern (eg, worse in the evening)
  - Specific characteristics of rash, including morphology, color, distribution, and pruritis or pain
- Associated symptoms, including ear tugging, red eyes, cracked lips, difficulty breathing, emesis, abdominal pain, diarrhea, loss of appetite, decreased urine output, fatigue, weakness, joint pain, and hand or foot swelling
- Medical history, including underlying health status, recent medications, and immunization status
- Allergies to medications, foods, or environmental exposures
- Exposure history, including recent travel; sick contacts, including attendance to child care or recent exposure to SARS-CoV-2; exposures to food, water, plants, insects, or animals that may predispose to foodborne illnesses or zoonotic infections

CASE FOCUS

History and Review of Systems

From your conversation with Isla's mother, you learn that Isla is a fully immunized, otherwise healthy child who is meeting all of her developmental milestones. Isla's mother tells you that Isla's fever started 7 days ago and reached a maximum temperature of 38.5 °C (101.3 °F). Her mother states that Isla's fevers have occurred daily, throughout the day with no clear pattern. Isla has been fussy with her fevers and has experienced some mild congestion and a nonproductive cough that preceded the onset of her fever by a day or two, but otherwise she has not had other symptoms. Isla's mother reports that the rash started yesterday, and although it concerns her, it does not seem to be causing Isla any discomfort. The rash started as red spots over Isla's chest that then spread to her face and the rest of her body. Overall, Isla has been drinking well but has not been eating as much as normal. Her urine output is slightly decreased from her baseline, but she continues to have 5 to 6 wet diapers each day.

Isla does attend child care, but her family is not aware of any sick contacts, and no one in the household has recently been ill. Isla and her family have not traveled recently, they do not have any pets, and they do not live in an area endemic for rickettsial diseases. Her mother has not noticed any mosquito bites. Isla has not ingested any contaminated food or water to her mother's knowledge. She does not take regular medications, but her mother has given her acetaminophen for her fever over the last week. She has no known allergies to environmental elements, medications, or foods.

Physical Examination

Q: What parts of the physical examination should you focus on for Isla?

- Complete set of vital signs
- General appearance (well, ill, or toxic), level of alertness, or distress
- Mucous membrane changes, including oral, genital, and conjunctival findings
- Cardiac: murmur or gallop
- Peripheral perfusion, including capillary refill time and quality of central and peripheral pulses
- Respiratory: work of breathing, presence of wheezing or crackles
- Abdomen: liver and spleen sizes
- Musculoskeletal: presence of warm or swollen joints, joint range of motion
- Presence of lymphadenopathy and characteristics (diffuse or localized)
- Stiff neck or other meningeal signs
- Skin: assessment of rash (see Section VI of the Appendix for details regarding characterization of rashes)

CASE FOCUS

Physical Examination

Isla's vitals show that she is febrile, with a temperature of 38.8 °C (101.8 °F), and has mild tachycardia with a heart rate of 140 beats/min. She is not tachypneic (respiratory rate: 18 breaths/min). She has an oxygen saturation of 99% on room air and a normal blood pressure for her age (96/52 mm Hg).

On examination, Isla is alert but fussy, pale, and ill appearing but nontoxic. She has pale conjunctiva, but her sclera are anicteric. She has mild nasal congestion, clear tympanic membranes, no oral lesions, a posterior pharynx without erythema, and moist mucous membranes. Her neck is supple with no meningismus. She has no cervical, axillary, or inguinal lymphadenopathy. On cardiovascular examination, she is tachycardic, but with a regular rhythm and no murmurs or gallops. Her central and peripheral pulses are normal. You note a capillary refill time of 1 to 2 seconds. On pulmonary examination, her lungs are clear to auscultation bilaterally with no signs of increased work of breathing. Her abdomen is soft, nontender, and nondistended. Her liver and spleen are palpated 3 cm and 2 cm below the costal margin, respectively. Her genitourinary examination is normal. She has no warm or swollen joints.

On examination of Isla's skin, you note nonblanching, erythematous macules consistent with petechiae generalized over her entire body, but most prevalent on her face and chest. There is no palm or sole involvement. No purpura, plaques, nodules, pustules, vesicles, or bullae are present. No enanthem or erythroderma is noted.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with fever and a petechial rash?

- With the information you have gathered thus far, you are concerned that Isla may have hemophagocytic lymphohistiocytosis (HLH). You decide to think through the infectious and noninfectious diagnoses that may present similarly, as shown in Table 39. 1.

Table 39.1. Differential Diagnosis for a Child With Fever and a Petechial Rash

Infectious causes	• Bacterial etiologies — Bacteremia (eg, *Staphylococcus*, *Pneumococcus*) — Infective endocarditis — Meningococcal disease — *Mycoplasma* — Rickettsial illnesses, including RMSF — TSS • Viral illnesses — Arboviruses, such as West Nile virus — Atypical measles — EBV or CMV — Enteroviral infections (specifically coxsackievirus and echovirus) — Influenza — Parvovirus B19 — SARS-CoV-2

(continued)

Table 39.1. Differential Diagnosis for a Child With Fever and a Petechial Rash *(continued)*

Noninfectious causes	• Hematologic or oncologic — ITP — Leukemia • Vasculitides and other inflammatory conditions — DRESS syndrome — HLH[a] — IgA vasculitis — KD — MIS-C — SLE — Systemic JIA, with or without macrophage-activation syndrome

Abbreviations: CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; IgA, immunoglobulin A; ITP, idiopathic thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; RMSF, Rocky Mountain spotted fever; SLE, systemic lupus erythematosus; TSS, toxic shock syndrome.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with fever and rash?

- Disorders that present with fever and rash range from benign and self-limited to rapidly progressive and life-threatening. The previously listed differential spans from infective processes to hematologic or malignant etiologies to vasculitides and other inflammatory conditions. Hence, it may be important to start with a broad workup in an ill-appearing child.
- Petechiae can be a presenting sign of thrombocytopenia, so it is vital to check a CBC. A CBC is also important to assess the white blood cell (WBC) count and differential, which may give clues to an infectious or malignant etiology.
- In an ill-appearing child with a fever, inflammatory markers and a blood culture should be considered. Moreover, for an ill-appearing child with both fever and petechiae, a blood culture and CBC should always be obtained, and coagulation studies and serum lactate levels should be strongly considered.
- Many of the previously listed differential diagnoses have systemic involvement, and thus it is reasonable to obtain a CMP to evaluate electrolytes and kidney and liver function. Clinicians should also consider a UA to assess for source of infection, evidence of kidney injury, or for the sterile pyuria that is often seen in Kawasaki disease (KD).
- Given the number of viral illnesses that present with fever and a rash, clinicians should also consider a respiratory panel by PCR, which also includes *Mycoplasma* and SARS-CoV-2. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) titers, serum enteroviral PCR, or parvovirus testing should also be considered.

Q: Some of the differential diagnoses require more extensive, specific tests. Given Isla's ill appearance, it is important to be prepared for the next steps in her workup. To assess these etiologies, what further diagnostic evaluation would you consider?

- A lumbar puncture (LP) with cerebrospinal fluid (CSF) indices and culture will evaluate for meningococcal meningitis, which would be a higher consideration if the patient demonstrated altered mental status, meningeal signs, a toxic appearance, or seizure activity.
- An echocardiogram would evaluate cardiac function, look for coronary artery aneurysms with KD, or assess for endocarditis.
- To test for Rocky Mountain spotted fever (RMSF), an indirect immunofluorescence assay for RMSF may be ordered.
- Physicians may consider obtaining a lactate dehydrogenase (LDH) level, uric acid level, peripheral smear, or a bone marrow biopsy to further evaluate for malignancy.
- The diagnostic testing for multisystem inflammatory syndrome in children (MIS-C) includes an evaluation for
  - Recent SARS-CoV-2 infection, as evidenced by a positive nasal PCR, serologies, or a known positive contact.
  - Multisystem organ involvement, which may be evidenced by clinical symptoms or abnormalities on echocardiogram, electrocardiogram, B-type natriuretic peptide, troponin, CBC with differential, or CMP.
  - Inflammatory markers, such as CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, cytokines, and interleukin (IL)-6.
- In addition to a broad workup to assess for multisystem organ involvement, physicians should consider ordering an antinuclear antibody panel to evaluate for systemic lupus erythematosus, especially in older children or teens with a family history of autoimmune conditions.
- To evaluate for HLH, it is vital to obtain a ferritin level, triglycerides, and D-dimer, which are often high, and a fibrinogen level, which is typically low.
- Macrophage-activation syndrome (MAS) occurs in children with underlying systemic rheumatologic disorders, most commonly systemic-onset juvenile idiopathic arthritis (JIA). A systemic disease flare has similar clinical features, sometimes making early MAS difficult to diagnosis. When MAS is being considered in a patient with known or suspected systemic JIA, the following laboratory evaluation should be obtained: CBC, CMP, ESR, D-dimer, ferritin level, fibrinogen level, and triglycerides. It is important to note that in systemic JIA, an elevated platelet count would be expected in addition to elevated fibrinogen levels; however, with MAS, these levels will likely be low. Therefore, in a patient with systemic JIA, a relatively normal fibrinogen level and platelet count or a precipitous drop in levels that were initially elevated should raise concern for MAS. Additionally, in MAS, there can be paradoxical drop in the ESR, which is normally elevated in systemic JIA, due to fibrinogen consumption. This can be another important diagnostic clue.
- If the patient had a medication exposure 2 to 8 weeks prior to disease onset, it would be important to assess for drug reaction with eosinophilia and systemic symptoms syndrome and order a CBC with differential, liver function tests, creatinine level, and a UA, with the consideration of testing for herpesvirus infections such as human herpesvirus 6.

CASE FOCUS

Diagnostic Evaluation

You review Isla's CBC with manual differential, CRP level, ESR, CMP, respiratory panel by PCR, and UA performed by the ED physician. The results are as follows:

Laboratory test	Result	Reference range
CBC		
WBC count	3,500/μL (3.5 × 10^9/L)	7,000–13,000/μL (7–13 × 10^9/L)
Hemoglobin	7.4 g/dL (74 g/L)	10.5–14 g/dL (105–140 g/L)
Hematocrit	19.2% (0.192)	32%–42% (0.32–0.42)
MCV	87 μm^3 (87 fL)	72–88 μm^3 (72–88 fL)
Platelet count	59 × 10^3/μL (59 × 10^9/L)	150–450 × 10^3/μL (150–450 × 10^9/L)
Bands	2% (0.02)	0–1% (0–0.01)
Neutrophils	18% (0.18)	23%–70% (0.23–0.70)
Lymphocytes	73% (0.73)	15%–67% (0.15–0.67)
Monocytes	5% (0.05)	4%–10% (0.04–0.10)
Eosinophils	0% (0)	0%–3% (0–0.03)
Variant lymphs	2% (0.02)	0% (0)
Unclassified cells	0% (0)	0% (0)
Inflammatory markers		
CRP	12 mg/dL (120 mg/L)	< 1 mg/dL (10 mg/L)
ESR	10 mm/h	0-10 mm/h
Serum chemistries		
Sodium	140 mEq/L (140 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.3 mEq/L (4.3 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	110 mEq/L (110 mmol/L)	97–107 mEq/L (97–107 mmol/L)
CO_2	21 mEq/L (21 mmol/L)	18–24 mEq/L (18–24 mmol/L)
Anion gap	9 mEq/L (9 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	10 mg/dL (3.57 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.4 mg/dL (35.4 μmol/L)	0.1–0.4 mg/dL (8.8–35.4 μmol/L)
Glucose	80 mg/dL (4.44 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Calcium	9.8 mg/dL (2.45 mmol/L)	9.2–10.5 mg/dL (2.30–2.63 mmol/L)
Protein, total	7.0 g/dL (70 g/L)	5.6–7.5 g/dL (56–75 g/L)
Albumin	3.2 g/dL (32 g/L)	3.6–5.2 g/dL (36–52 g/L)
Bilirubin, total	2.0 mg/dL (34.21 μmol/L)	<1.2 mg/dL (20.52 μmol/L)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Serum chemistries *(continued)*		
Alkaline phosphatase	190 U/L (3.17 µkat/L)	150–420 U/L (2.51–7.01 µkat/L)
AST	172 U/L (2.87 µkat/L)	9–80 U/L (0.15–1.34 µkat/L)
ALT	182 U/L (3.04 µkat/L)	5–45 U/L (0.08–0.75 µkat/L)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CO_2, carbon dioxide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; WBC, white blood cell.

- **UA: specific gravity 1.020, trace ketones, negative protein, trace blood with 5 red blood cells (RBCs) per high-power field**
- **Respiratory panel by PCR: negative for *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Bordetella parapertussis*, and the following viruses: respiratory syncytial virus, adenoviruses, influenza viruses, human rhinovirus/enteroviruses, human metapneumovirus, parainfluenza viruses, and coronaviruses (including SARS-CoV-2)**
- **Blood culture: pending**

After you review Isla's initial laboratory test results, you are concerned about the significant cytopenias and transaminitis within the context of Isla's fever, petechial rash, and hepatosplenomegaly. To help further elucidate her diagnosis, you decide to order further tests, including EBV and CMV titers; SARS-CoV-2 serologies; ferritin level, triglycerides, fibrinogen level, and D-dimer to evaluate for HLH; LDH level, uric acid level, and a peripheral smear to evaluate for malignancy; a fractionated bilirubin level, gamma-glutamyltransferase (GGT), and coagulation panel given her liver abnormalities; reticulocyte count to evaluate bone marrow response to anemia; and a type and screen for potential need of future transfusion.

These results are as follows:

Laboratory test	Result	Reference range
Ferritin	11,020 ng/mL (11,020 µg/L)	10–60 ng/mL (10–60 µg/L)
Triglycerides	140 mg/dL (1.58 mmol/L)	27–125 mg/dL (0.31–1.41 mmol/L)
Fibrinogen	120 mg/dL (1.2 g/L)	220–440 mg/dL (2.2–4.4 g/L)
D-dimer	1.7 µg/mL FEU (9.31 nmol/L FEU)	≤0.40 µg/mL FEU (≤2.19 nmol/L FEU)
LDH	450 U/L (7.52 µkat/L)	150–500 U/L (2.51–8.35 µkat/L)
Uric acid	2.3 mg/dL (0.14 mmol/L)	1.7–5.8 mg/dL (0.10–0.35 mmol/L)
GGT	35 U/L (0.58 µkat/L)	5–32 U/L (0.08–0.53 µkat/L)
Bilirubin, direct (conjugated)	1.2 mg/dL (20.52 µmol/L)	<0.2 mg/dL (<3.42 µmol/L)
PT	14.0 s	12.2–15.5 s
INR	1.0	0.8–1.2
PTT	30.5 s	26.5–35.5 s

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Result	Reference range
Reticulocyte count	5 × 10^3/μL (5 × 10^9/μL)	0.5–1.5 × 10^3/μL (0.5–1.5 × 10^9/μL)
EBV IgM, EBV IgG, EBNA	Undetectable	NA
CMV IgM, CMV IgG	Undetectable	NA

Abbreviations: CMV, cytomegalovirus; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; FEU, fibrinogen equivalent unit; GGT, gamma-glutamyltransferase; Ig, immunoglobulin; INR, international normalized ratio; LDH, lactate dehydrogenase; NA, not applicable; PT, prothrombin time; PTT, partial thromboplastin time.

- **A review of Isla's peripheral smear shows anemia with mild hypochromia, rouleaux, rare spherocytes, thrombocytopenia, mature WBCs, and the absence of blasts and schistocytes.**
- **SARS-CoV-2 serology: pending**

You defer ordering an RMSF immunofluorescence assay and an antinuclear antibody panel and do not perform an LP at this time. You decide to hold off on an echocardiogram unless Isla's blood culture is positive, she has evidence of worsening cardiac function (her heart rate does not respond to adequate fluid resuscitation and fever control, or she has changes in peripheral perfusion), or she develops further symptoms consistent with KD or MIS-C.

Arriving at a Diagnosis

Q: How do you develop an assessment for Isla?

To arrive at Isla's diagnosis, you will first assess her overall clinical status, and then interpret the key findings from her history, examination, and diagnostic studies. From this information, you will develop a list of findings and narrow your differential diagnosis to the most likely etiology (or etiologies).

1. **Assess Isla's overall clinical status:** When evaluating a patient's clinical status, one of the first considerations in all patients is whether they appear well, ill, or toxic. In this case, Isla is ill appearing with concern for developing systemic inflammatory response syndrome or sepsis based on her vital signs (fever, tachycardia) and laboratory findings (leukopenia). She also has multiple worrisome laboratory test results but is hemodynamically stable with a normal blood pressure and normal peripheral perfusion.

CASE FOCUS

Urgent Intervention

Because of Isla's ill appearance and your concern that she is developing systemic inflammatory response syndrome or sepsis, you order an intravenous (IV) normal saline bolus at 20 mL/kg and a dose of IV cefepime. While you are waiting for the nurse to gather these supplies, you continue with your assessment.

2. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Isla is a 15-month-old healthy girl who presents with fever for 7 days, mild congestion and cough, and a new-onset rash. She has not had any conjunctival injection or changes to her lips, hands, or feet, and despite poor food intake, her hydration status at home has been adequate.
   - Physical examination: Isla's vital signs show tachycardia and fever but are otherwise normal. Her examination shows that she is ill appearing with a disseminated petechial rash, which does not involve her palms or soles, and mild hepatosplenomegaly. She has no meningismus or any localizing infectious signs on examination. She has no lymphadenopathy, mucous membrane changes, joint findings, or changes to her hands and feet.
   - Diagnostic evaluation: Isla's laboratory results are notable for moderate neutropenia, normocytic anemia, and thrombocytopenia with appropriately elevated reticulocyte count. She has transaminitis with a direct hyperbilirubinemia and elevated GGT level but reassuring coagulation studies. She also has an elevated CRP level, significantly elevated ferritin level, slightly low fibrinogen level, and elevated D-dimer level.
     - The first laboratory findings to consider are Isla's cytopenias. An important classifier in evaluating cytopenias is to determine how many cell lines are affected and, if multiple lines are affected, the combination of the specific cell lines. Isla's laboratory values classify her as having pancytopenia. Isla's WBC count is slightly low (3,500/µL [3.5×10^9/L]), and when analyzing the differential, you calculate her absolute neutrophil count to be 700/µL (0.7×10^9/L), which qualifies as moderate neutropenia.
     - The second set of laboratory findings to consider are Isla's transaminitis, elevated GGT level, and direct hyperbilirubinemia. These laboratory abnormalities could be an indication of cell breakdown or of liver injury or failure; however, her coagulation panel (a measure of liver synthetic function) is normal, which is reassuring.
     - The third set of laboratory findings to consider is Isla's elevated CRP level and normal ESR. Inflammatory markers can be elevated in a variety of medical conditions. Because the CRP level is disproportionately elevated compared to the ESR, consideration of more acute inflammation might be warranted.
     - Finally, ferritin is an acute phase reactant, so in an acute illness or inflammatory condition, it is expected to be elevated. However, Isla's ferritin level is significantly more elevated than expected (11,020 ng/mL [11,020 µg/L]). Fibrinogen is also an acute phase reactant, and her slightly low fibrinogen level may be an indication that fibrinogen is being used up more quickly than the body can produce it, as occurs when the body is overactive in breaking down and clearing blood clots. Isla also has an elevated D-dimer level, which is a protein fragment produced by cross-linked fibrin degradation. Hence, there is evidence of increased fibrinolysis, which may indicate intravascular coagulation and thrombotic disease.

3. **Develop the list of findings.**

Q: What major findings have you identified for Isla?

- Fever for 7 days
- Mild congestion and cough
- Petechial rash
- Mild hepatosplenomegaly
- Pancytopenia (moderate neutropenia, normocytic anemia, thrombocytopenia)
- Transaminitis with direct hyperbilirubinemia and elevated GGT level
- Elevated CRP level
- Significantly elevated ferritin level, slightly low fibrinogen level, and elevated D-dimer level

4. Revisit the differential diagnosis.

Q: Reviewing your differential now, within the context of Isla's examination and laboratory findings, how does this change your list of likely diagnoses?

- Infectious conditions
  - Toxic shock syndrome is less likely, given the timeline of Isla's symptoms and the absence of an erythroderma or hypotension.
  - Viral illnesses often cause transient cytopenias, which is commonly referred to as *viral suppression*. There are multiple mechanisms by which viral infections can influence hematopoietic stem cell biology. However, given Isla's negative respiratory panel by PCR, negative EBV and CMV titers, and her other abnormal diagnostic results, a viral illness is less likely to explain her clinical picture. Considering Isla's length of fever and the presence of nasal congestion and cough, though, it is possible that a viral illness preceded or precipitated her current illness.
  - To eliminate bacteremia as the etiology of Isla's symptoms, you will need to wait for her blood culture results.
- Hematologic or oncologic process
  - Idiopathic thrombocytopenic purpura (ITP) is less likely, as patients with ITP are usually well appearing, with an isolated thrombocytopenia and bruising or petechiae as the predominant clinical finding.
  - Because of bone marrow suppression with leukemia, there is usually subsequent pancytopenia. Other laboratory findings that may be seen with leukemia are elevated LDH level, elevated alkaline phosphatase level, and hyperuricemia and/or hyperphosphatemia secondary to tumor lysis. Patients with leukemia also often present with fever and petechiae or bruising as well as hepatosplenomegaly and lymphadenopathy. Isla's peripheral smear shows no signs of blasts, making leukemia less likely, but a formal bone marrow biopsy would be needed to definitively rule it out.
- Vasculitides and other inflammatory conditions
  - Immunoglobulin A (IgA) vasculitis is unlikely due to the lack of joint or gastrointestinal involvement and the fact that patients with IgA vasculitis are usually more well appearing, afebrile or with low grade fevers, and have a normal platelet count.
  - Systemic lupus erythematosus would also be highly unlikely for a child of Isla's age but should be considered for older children and adolescents.
  - Drug reaction with eosinophilia and systemic symptoms syndrome is unlikely given the lack of corresponding medication exposure.
  - KD diagnosis requires 5 days of fever and 4 out of 5 clinical criteria (or 2 out of 5 *plus* supplemental laboratory criteria for incomplete/atypical KD). See Case 14 for full criteria. Other than rash, Isla does not exhibit any of the other signs of KD.
  - Systemic JIA with MAS is typically associated with a salmon-colored and evanescent (comes and goes in relation to fever) rash; however, the development of MAS is commonly associated with a more persistent rash, possibly petechial. Although many of Isla's laboratory values (eg, elevated ferritin level, thrombocytopenia, elevated aspartate aminotransferase level, low fibrinogen level) can be consistent with MAS, this diagnosis seems less likely given that she does not have a history suggestive of systemic JIA and has no evidence of arthritis on examination.
  - MIS-C related to SARS-CoV-2 should be considered in infants, children, and adolescents who present with symptoms and laboratory test results that include
    - Fever.
    - Laboratory evidence of inflammation, including but not limited to 1 or more of the following: an elevated CRP level, ESR, fibrinogen level, procalcitonin level, D-dimer level, ferritin level, LDH level, or IL-6 level; elevated neutrophils; reduced lymphocytes and low albumin level.

- Evidence of clinically severe illness requiring hospitalization with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurologic).
- No alternative plausible diagnoses.
- Positive for current or recent SARS-CoV-2 infection by reverse transcriptase-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.
- At this time, the diagnosis of MIS-C is possible if no alternative diagnosis is discovered and if Isla's SARS-CoV-2 serology is consistent with recent infection.

— HLH is an aggressive, life-threatening disease of excessive immune activation. It is a great mimicker of other diseases and usually presents with an ill-appearing patient with fever and multiorgan system involvement. HLH remains high on your differential diagnosis.

Q: What is HLH, and how is it diagnosed?

- The pathophysiology of HLH is thought to be secondary to a hyperinflammatory state with a dysregulation of the immune system or, more specifically, an absence of downregulation, which leads to tissue destruction. The typical barrier to treatment of HLH is a delay in diagnosis, given its rare, variable clinical presentation with lack of specific clinical and laboratory findings.
- HLH can be seen in patients of all ages and is often classified as being either primary (genetic) or secondary (sporadic). Primary HLH is typically seen between birth and 18 months of age, with the highest incidence in children younger than 3 months. Often patients with secondary HLH will present in the context of an infectious trigger that disrupts immune homeostasis. Primary HLH may present even in the absence of infection. HLH can occur either as a single episode or a relapsing illness and often occurs in patients with underlying immunodeficiencies or autoimmune disease.
- The HLH-2004 trial diagnostic criteria are used to help identify children with HLH. Patients must have homozygosity or compound heterozygosity for verified HLH-associated mutations (ie, *PRF1*, *UNC13D*) or gene defects of other immune regulatory genes (identified by whole exome sequencing or HLH gene panel) or have 5 of the following 8 findings:
  - Fever of at least 38.5 °C (101.3 °F)
  - Splenomegaly
  - Peripheral blood cytopenia, with at least 2 of the following: hemoglobin less than 9 g/dL (90 g/L) (for infants <4 weeks, hemoglobin <10 g/dL [100 g/L]); platelet count less than 100×10^3/μL (100×10^9/L); and an absolute neutrophil count less than 1,000/μL (1×10^9/L)
  - Hypertriglyceridemia (fasting triglycerides >265 mg/dL [2.99 mmol/L]) and/or hypofibrinogenemia (fibrinogen <150 mg/dL [1.50 g/L])
  - Hemophagocytosis in bone marrow, spleen, lymph node, or liver
  - Low or absent natural killer cell activity
  - Ferritin level greater than 500 ng/mL (500 μg/L)
  - Elevated soluble CD25 (α-chain of IL-2 receptor) 2 SDs above age-adjusted laboratory-specific norms
- Isla meets 5 out of the 8 criteria.
- Of note, a study of ferritin levels in pediatric patients found a value greater than 10,000 ng/mL (10,000 μg/L) to be 90% sensitive and 96% specific for HLH. It is also important to note that triglyceride levels often elevate later in the disease process and can be normal on initial evaluation. Other features include elevated transaminases and bilirubin, elevated LDH level, elevated D-dimer level, and abnormal CSF indices if there has been central nervous system cell infiltration.

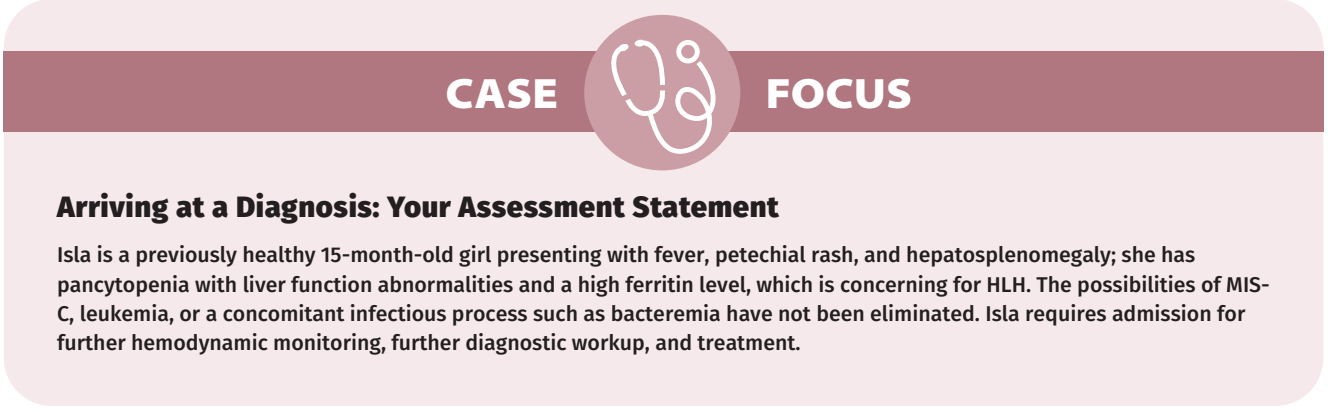
Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Isla's presentation?

You are concerned about the possibility of HLH and determine that leukemia and MIS-C both need to be definitively excluded.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with fever, cytopenias and concern for HLH or MIS-C?

Patients with fever, cytopenias, and concern for HLH or MIS-C require prompt admission for monitoring of their hemodynamic status and expedited diagnosis and treatment.



Arriving at a Diagnosis: Your Assessment Statement

Isla is a previously healthy 15-month-old girl presenting with fever, petechial rash, and hepatosplenomegaly; she has pancytopenia with liver function abnormalities and a high ferritin level, which is concerning for HLH. The possibilities of MIS-C, leukemia, or a concomitant infectious process such as bacteremia have not been eliminated. Isla requires admission for further hemodynamic monitoring, further diagnostic workup, and treatment.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

When there is concern for HLH, management should include fever control, packed RBC or platelet transfusions as needed, and empiric antibiotic coverage while awaiting all the laboratory and pathology results. Once the diagnosis of HLH is confirmed, specific therapeutic intervention may be initiated.

1. **Fever control:** Acetaminophen may be used as a first-line medication to help control fever in patients with suspected HLH; however, it is important to use acetaminophen sparingly and monitor liver function. Because of increased risk of bleeding with thrombocytopenia, ibuprofen should be avoided.
2. **Transfusions:** Packed RBC and platelet transfusions should be considered to help correct cytopenias. Blood products should be irradiated to reduce the risk of possible transfusion-associated graft-versus-host disease complication when there is a suspicion for leukemia or HLH.
3. **Antibiotics:** Bacterial infections remain on the list of possible diagnoses in ill-appearing patients, and therefore it is imperative to continue broad spectrum antibiotics. Additionally, because infections can trigger secondary HLH, it is important to treat the underlying condition when identified.
4. **HLH-specific treatment:** The HLH-94 protocol consists of 8 weeks of induction therapy with etoposide and dexamethasone, with intrathecal therapy for patients with central nervous system involvement. Etoposide is given twice weekly for the first 2 weeks, and once weekly for weeks 3 through 8. Dexamethasone is preferred because it can cross the blood-brain barrier. It can be given intravenously or orally and tapered over the 8-week induction. If no clinical improvement is evident by week 2 or 3 of therapy, salvage therapy should be considered. Salvage therapy may include anakinra, antithymocyte globulin, or alemtuzumab. Treatment failure could be demonstrated by a lack of clinical improvement and/or persistently elevated ferritin levels, D-dimer levels, or liver enzymes. Allogenic hematopoietic cell transplant is the treatment of choice for congenital HLH or when initial treatment has failed.
5. **Monitoring:** As previously mentioned, children with HLH can deteriorate rapidly, especially given the multiorgan system involvement characteristic of the condition, and thus it is important to closely monitor the patient. Monitoring is often performed initially in the intensive care or intermediate unit setting, where cardiac

monitoring and more frequent vital signs can be obtained. It is also critical to have objective data such as specific laboratory test results to monitor and trend during the patient's clinical course to help determine the effectiveness of therapy or potential for deterioration.

6. **Consultations:** It is crucial that physicians know when to suspect HLH, how to recognize it, and how to work closely with other specialists to comanage patients who have been or may be diagnosed with HLH. It is important to consult a hematologist-oncologist and work collaboratively to care for the patient. In some hospitals, a rheumatologist also helps comanage the patient. In younger children, a genetic consultation must be considered due to their higher risk of having primary HLH, especially given the implications for further management and family counseling.

CASE FOCUS

Plan for Treatment and Monitoring

- **Fever control:** Given Isla's thrombocytopenia and risk of bleeding, you decide not to use ibuprofen for fever control. You will use acetaminophen sparingly but will monitor closely for worsening liver function.
- **Transfusions:** Due to Isla's stable hemodynamic status and lack of active bleeding, you hold off on any packed RBC or platelet transfusion. You have a low threshold for giving these therapies, especially prior to any procedures.
- **Antibiotics:** You continue empiric IV cefepime until Isla's blood culture returns negative at 48 hours.
- **HLH-specific treatment:** You begin to review HLH protocol in anticipation of diagnosis confirmation.
- **Monitoring:** Currently, Isla is ill but hemodynamically stable. She is placed on cardiac monitoring with vital signs to be obtained every 4 hours. In addition to monitoring her clinical status, and barring any clinical changes, you closely follow her CBC, CMP, ferritin level, and D-dimer level.
- **Consultations:** You consult the hematology-oncology team to help guide management and further testing. The hematologist-oncologist recommends a bone marrow biopsy and aspirate as well as ordering further laboratory studies, including natural killer cell activity, soluble CD25, an immunologic profile, genetic studies, and an LP to determine whether there is CSF involvement.

Case Resolution

The following morning, Isla's SARS-CoV-2 serology returns as negative for recent infection and her blood culture remains negative. She undergoes a bone marrow aspirate and biopsy, the results of which show histiocytes with rounded contour and cytoplasmic projections and hemophagocytes with a single ingested mature RBC, nucleated RBC progenitor, and granulocyte. There are no increased blasts seen that would suggest leukemia. Based on these findings, Isla is definitively diagnosed with HLH. Isla is started on HLH induction therapy with etoposide and dexamethasone in accordance with the HLH-94 protocol. She is then transferred to the oncology service for continued inpatient treatment and monitoring.

Discharge Criteria

Q: How do you know when Isla is ready to go home?

Recovery from HLH tends to be prolonged. Discharge from the hospital can be considered when all of the following criteria have been met:

- Fever and other vital signs have normalized.
- Laboratory values confirm marked improvement, if not normalization.
- A careful outpatient plan, including medications (eg, a steroid taper) and close follow-up with primary care and subspeciality providers has been established.

Anticipatory Guidance

Q: What instructions should you provide to Isla's caregivers upon discharge?

- Specific signs and symptoms that should prompt medical attention include new fever, especially if persistent or high; reappearance or worsening of rash; poor oral intake; enlarged lymph nodes; excessive bleeding; weakness; or seizures.
- It is vital to maintain strict adherence to the medication regimen and outpatient follow-up appointment schedule.

Clinical Pearls

- Fever with a rash is a common pediatric presentation with a large differential. Important stratifiers must include whether the patient is well, ill, or toxic appearing and the type of rash.
- An important classifier in evaluating cytopenias and developing a differential is determining how many cell lines are affected, and if multiple, the combination of the specific cell lines.
- HLH is a great mimicker and can have a variable presentation, but it must be considered in ill-appearing patients with fever and multiorgan system involvement without an obvious cause.
- Although the majority of children with HLH have a severe clinical presentation with evidence of multiorgan involvement and rapid clinical deterioration, it is important to maintain an index of suspicion for HLH even in more well-appearing or nontoxic-appearing children with fever.
- Hemophagocytosis alone is neither pathognomonic of, nor required for, the diagnosis of HLH.

Documentation Tips

- Consider including a diagnosis of possible sepsis in the assessment, as the patient is ill appearing and being treated with antibiotics. With the diagnosis of HLH, sepsis may later be concluded as ruled out, but it is initially a valid potential diagnosis.
- For cytopenias, it is important to include in notes all the medical terminology for the sake of clinical validity, such as neutropenia, anemia, and thrombocytopenia.

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Rena, a 14-Year-Old Girl With Abdominal Pain and Vomiting

CASE PRESENTATION

Rena is a 14-year-old girl with no underlying medical diagnoses who presents to the emergency department (ED) for severe right lower quadrant (RLQ) abdominal pain and vomiting. In the ED, she has moderate relief of symptoms after a dose of morphine, ondansetron, and a normal saline bolus. The physician in the ED obtains an RLQ ultrasound that shows a well visualized, normal appendix. A pediatric surgeon is consulted and determines that Rena has a nonsurgical abdomen. The ED physician calls you with a request that you evaluate Rena for hospitalization to provide pain control, hydration, and further evaluation if needed.

Patient History and Review of Systems

Q: What information should you collect from Rena and her caregivers?

- History of present illness
  - Pain history: onset and progression, quality, location, severity, alleviating and aggravating factors, and radiation
  - Onset, duration, and frequency of vomiting, and appearance of vomitus
  - Fluid intake history and estimation of recent urine output
  - Presence of dysuria, urinary frequency, hematuria, and/or urgency
  - Other associated symptoms, such as fever, headache, sore throat, cough, difficulty breathing, constipation, diarrhea, polyuria/polydipsia, joint pain, or rash
- Medical history, including chronic medical conditions, history of similar episodes, and vaccination status
- Menstrual history, including any change in vaginal discharge from baseline
- Social history, including HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, specifically inquiring about sexual history and marijuana use (refer to Section VII in the Appendix for an example of a complete HEADSS assessment)
- Diet history, including recent dietary intake
- Exposure history, including recent sick contacts and travel
- Medication use, including over-the-counter medications, vitamins, and recent antibiotic use
- Family history of gallbladder disease or kidney stones

CASE FOCUS

History and Review of Systems

From your conversation with Rena and her family, you learn that approximately 4 hours ago, Rena was awakened by lower right-sided, colicky abdominal pain radiating to her groin. She characterizes her pain as an 8 in severity on a scale of 0 to 10 upon arrival to the ED and as a 5 after administration of morphine. She reports dysuria and increased urinary frequency but without urinary urgency. There is no change in her urine color. She has not tolerated any oral intake today, and she had 3 episodes of nonbloody, nonbilious emesis at home and 2 additional episodes in the ED, despite receiving ondansetron. She had 2 small voids in the ED. She has not recently had fever, headache, sore throat, cough, difficulty breathing, constipation, diarrhea, polyuria/polydipsia, joint pain, or rash.

This is the first time Rena has had these symptoms. She has no prior significant medical history. She consumes a regular well-balanced diet, has daily soft stools, and thinks she drinks about one 16-oz bottle of water per day.

She had menarche 2 years ago and has regular monthly menses, the last being approximately 2 weeks ago. During her confidential interview, she reports that she has never had sexual intercourse and does not use any substances containing tetrahydrocannabinol. She has not had any recent sick contacts or travel and does not take any medications at home. She has received all of her recommended vaccinations. Her mother had a kidney stone in the past that passed spontaneously, but otherwise her parents and siblings are healthy.

Physical Examination

Q: What parts of the physical examination should you focus on for Rena?

- Complete set of vital signs
- General appearance: ability to sit still and perception of discomfort/pain
- Mucous membranes: moist, sticky, or dry
- Oropharynx: presence of erythema, lesions, or exudates
- Peripheral perfusion: pulses, capillary refill, presence or absence of edema
- Abdomen: tenderness, rigidity, peritoneal signs (eg, pain with “heel tap” maneuver), distention, bowel sounds, guarding, masses
- Genitourinary: appearance of external genitalia, presence of discharge
- Musculoskeletal: peripheral edema, obvious deformities, costovertebral tenderness
- Skin: pallor, rashes, lesions, discoloration
- Visualization of urine, if available

CASE FOCUS

Physical Examination

Rena's vital signs show that she is afebrile and tachycardic, with a heart rate of 130 beats/min at rest. She is slightly tachypneic, with a respiratory rate of 24 breaths/min and has an oxygen saturation of 98% on room air. Her blood pressure is within normal limits for her sex, age, and height, at 110/75 mm Hg. Her weight is 55 kg, and her height is 162 cm, with a body mass index of 20.6 kg/m^2.

On examination, Rena appears uncomfortable, shifting positions frequently in her hospital bed. You notice that her oral mucosa is moist, and no pharyngeal erythema or exudates are present. On auscultation, you appreciate a regular cardiac rhythm with no murmurs. She is tachycardic but has normal peripheral perfusion and pulses. Her lungs are clear to auscultation without adventitious breath sounds or increased respiratory effort. Her abdomen is not distended, and her bowel sounds are normal. Her abdomen is soft and nondistended but is tender to palpation at the RLQ and suprapubic area. Psoas, obturator, and Rovsing signs are negative. She has no rebound tenderness, and her pain is not worsened with a "heel tap" maneuver. She flinches with pain when you percuss her right costovertebral angle. She has normal external genitalia and has no skin rashes or peripheral edema.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent girl with abdominal pain and vomiting?

There are many causes of abdominal pain and vomiting in adolescent girls; however, the etiologies can be narrowed based on a complete history and thorough physical examination. Table 40.1 demonstrates a differential diagnosis for these symptoms and has been separated into diagnoses that appear more or less likely for Rena.

Table 40.1. Differential Diagnosis for an Adolescent Girl With Abdominal Pain and Vomiting

Diagnoses of highest suspicion	• Acute infectious gastroenteritis • Appendicitis • Ectopic pregnancy (with or without rupture) • Mesenteric adenitis • Nephrolithiasis[a] • Ovarian/adnexal torsion[a] • PID • Ruptured or hemorrhagic ovarian cyst[a] • UTI, specifically pyelonephritis[a]

(continued)

Table 40.1. Differential Diagnosis for an Adolescent Girl With Abdominal Pain and Vomiting *(continued)*

Other diagnoses to consider	• Abdominal migraine • Abdominal trauma • Acute intermittent porphyria • Adrenal insufficiency • Biliary disease, specifically cholecystitis or cholelithiasis • Cannabinoid hyperemesis syndrome • Constipation • Cyclic vomiting syndrome • DKA • Functional abdominal pain • Gastritis or PUD • Hematocolpos • Hereditary angioedema • IBD • IgA vasculitis • Intestinal volvulus • Meckel diverticulitis • Pancreatitis • Peritonitis • Pneumonia • Small bowel obstruction • Streptococcal pharyngitis • TSS

Abbreviations: DKA, diabetic ketoacidosis; IBD, inflammatory bowel disease; IgA, immunoglobulin A; PID, pelvic inflammatory disease; PUD, peptic ulcer disease; TSS, toxic shock syndrome; UTI, urinary tract infection.

[a] Denotes the diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for an adolescent girl who presents with abdominal pain and vomiting?

- The diagnostic evaluation of patients with abdominal pain should be guided by the patient's history and physical examination because the differential diagnosis is very broad. The differential diagnosis should be narrowed based on the patient's age and the location of their pain (eg, right upper quadrant, epigastric, RLQ, periumbilical).
- The clinician must carefully consider etiologies that require urgent evaluation and treatment. Symptoms that may point toward a more emergent etiology may include severe or worsening pain, hematochezia, bilious vomiting, peritoneal signs, or the presence of sepsis, lethargy, or ill appearance.
- Based on Rena's history, examination, and workup in the ED, you are most suspicious of nephrolithiasis, pyelonephritis, acute gastroenteritis, appendicitis, mesenteric adenitis, or ovarian pathology as the cause of her symptoms. Additionally, ectopic pregnancy should remain a consideration. Refer to Table 40.2 for the clinical features and evaluation of these diagnoses.

Table 40.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Adolescent Girls With RLQ Pain

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Acute infectious gastroenteritis	Vomiting and diarrhea with or without abdominal pain and fever	Laboratory tests: None needed except in cases of anuria/severe dehydration; stool studies should be considered if bacterial or parasitic infection is suspected (see Case 1). Imaging: None
Appendicitis	Abdominal pain that migrates from periumbilical to RLQ; fever, vomiting, anorexia; presence of peritoneal signs (rebound, involuntary guarding, or positive "heel tap") is common.	Laboratory tests: CBC Imaging: RLQ US and/or CT scan of the abdomen with IV contrast
Ectopic pregnancy	Abdominal pain from distension of the fallopian tube Vaginal spotting or bleeding is common. Tubal rupture is associated with worsening pain and peritonitis; patients can develop hemorrhagic shock.	Laboratory tests: Urine or serum pregnancy test Imaging: If pregnancy test is positive, pelvic US (transvaginal preferred early in pregnancy) to evaluate for intrauterine or extrauterine pregnancy
Mesenteric adenitis	Acute onset of abdominal pain (RLQ most common), with or without fever and vomiting	Laboratory tests: None Imaging: Usually diagnosed based on findings on RLQ US or CT scan of the abdomen during evaluation for appendicitis
Nephrolithiasis	Acute onset flank, abdominal, or groin pain; vomiting is common; dysuria and gross hematuria may occasionally be present.	Laboratory tests: UA with microscopy; serum creatinine, electrolytes, and calcium; if confirmed, urinary solutes and stone analysis Imaging: Plain radiograph (least sensitive), RBUS, CT scan of the abdomen/pelvis without contrast (most sensitive) (refer to Table 40.3 for advantages and disadvantages of these imaging modalities)
Ovarian/adnexal torsion	Acute onset lower abdominal pain (constant or episodic) with nausea, vomiting, and peritonitis Torsion is most common in the setting of enlarged adnexa related to cysts or neoplasms.	Laboratory tests: None indicated Imaging: Pelvic US with Doppler Clinicians should maintain a low threshold for surgical consultation when ovarian or adnexal torsion is suspected, as imaging can be normal early in the course.
PID	Pelvic or suprapubic pain with or without fever, vomiting, or abnormal vaginal discharge; abnormal vaginal bleeding and dyspareunia may be present. Risk is highest in adolescents with a history of unprotected sexual intercourse.	Diagnosis is primarily based on clinical features (cervical motion, uterine, or adnexal tenderness). Refer to Case 17, Tables 17.2 and 17.3, for the recommended evaluation and diagnostic criteria.

(continued)

Table 40.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Adolescent Girls With RLQ Pain *(continued)*

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Pyelonephritis	Back or abdominal pain, fever, and vomiting, with or without concomitant dysuria, urinary urgency, or urinary frequency	Laboratory tests: UA with microscopy and urine culture; if there is concern for sepsis, consider CBC, electrolytes, renal and liver function, and blood culture. Imaging: Consider RBUS or CT scan of the abdomen (generally not necessary unless complicated pyelonephritis or complications suspected).
Ruptured or hemorrhage ovarian cyst	Acute onset of lower abdominal pain; mid-cycle follicle rupture (*mittelschmerz*) is similar but less severe.	Laboratory tests: CBC if hemorrhagic cyst suspected Imaging: Pelvic US with Doppler (pelvic free fluid may be the only abnormality noted once a cyst has ruptured)

Abbreviations: CBC, complete blood cell count; CT, computed tomography; IV, intravenous; PID; pelvic inflammatory disease; RBUS: renal bladder ultrasonography; RLQ, right lower quadrant; UA, urinalysis; US, ultrasonography.

Table 40.3. Comparison of Imaging Modalities Used to Detect Nephrolithiasis

	RBUS	CT scan
Advantages	• No radiation • Low cost • High positive predictive value if a stone is detected • Detects most types of stones that can be seen on CT scan • Can be performed at the bedside	• Higher sensitivity and specificity for diagnosis • Can detect smaller stones, total stone burden, ureteral stones, obstruction, and subtle hydronephrosis • Can better detect alternative diagnoses • Allows for better determination of stone composition by detecting density of stone in Hounsfield units
Disadvantages	• Low sensitivity (less likely to detect stones in children who have nephrolithiasis) • Does not work well for children with BMI >85th percentile • Does not detect very small stones or ureteral stones • Does not allow for determining stone composition	• Delivers significant radiation dose • More expensive • No difference from RBUS in types of stones that can be detected • Requires patient cooperation in the scanner

Abbreviations: BMI, body mass index; CT, computed tomography; RBUS, renal bladder ultrasonography.

CASE FOCUS

Diagnostic Evaluation

You review the workup completed in the ED, which included a complete blood cell count and basic metabolic panel in addition to the RLQ ultrasonography (US). You decide to also obtain a urinalysis with microscopy, urine culture, urine human chorionic gonadotropin test, and renal bladder ultrasonography (RBUS) (to avoid the radiation associated with computed tomography scan). You also consider obtaining pelvic US with Doppler to evaluate Rena's ovaries but decide to wait for the results of her urine studies and RBUS before proceeding with any additional diagnostic testing.

Rena's test results are as follows:

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	136 mEq/L (136 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	101 mEq/L (101 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	12 mEq/L (12 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	17 mg/dL (6.07 mmol/L)	6–20 mg/dL (2.14–7.14 mmol/L)
Creatinine	0.7 mg/dL (61.9 μmol/L)	0.5–0.9 mg/dL (44.2–79.6 μmol/L)
Glucose	83 mg/dL (4.61 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Calcium	9 mg/dL (2.25 mmol/L)	9.2–10.5 mg/dL (2.30–2.63 mmol/L)
CBC		
WBC count	9,000/μL (9×10^9/L)	4,000–10,500/μL ($4.0–10.5 \times 10^9$/L)
Hemoglobin	13 g/dL (130 g/L)	12–15 g/dL (120–150 g/L)
Hematocrit	41% (0.41)	35%–45% (0.35–0.45)
Platelet count	320×10^3/μL (320×10^9/L)	$150–400 \times 10^3$/μL ($150–400 \times 10^9$/L)
Urine studies		
Urine β-hCG	Negative	Negative
pH	7.5	4.5–8
Color	Yellow	Yellow
Specific gravity	1.15	1.005–1.030
WBC count	Occasional	Occasional
Blood	3+	Negative
RBC count	50–100/HPF	Negative
Leukocyte esterase	Negative	Negative
Nitrites	Negative	Negative
Protein	Trace	Negative

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory Test	Result	Reference Range
Urine studies *(continued)*		
Glucose	Negative	Negative
Casts	Negative	Negative
Crystals	Crystalluria	Negative
Culture	Pending	No growth
Imaging		
RLQ ultrasound	Normal appearing appendix	
RBUS	5-mm stone located in the right distal ureter with mild right-sided hydronephrosis	

Abbreviations: β-hCG, beta human chorionic gonadotropin; BUN, blood urea nitrogen; CBC, complete blood cell count; HPF, high-power field; RBC, red blood cell; RBUS, renal bladder ultrasound; RLQ, right lower quadrant; WBC, white blood cell.

Arriving at a Diagnosis

Q: How do you develop an assessment for Rena?

In thinking through Rena's case, you decide to first interpret her history, vital signs, examination findings, and diagnostic evaluation to develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology or etiologies. Afterward, admission criteria can be generated for your specific diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: On history, Rena has acute onset of abdominal pain, dysuria, and vomiting with the absence of fever, constipation, or diarrhea. Acute infectious gastroenteritis seems unlikely, given the severity of her pain and the lack of fever or diarrhea. Her report that she has no history of sexual intercourse decreases suspicion for pelvic inflammatory disease and pregnancy.
   - Physical examination: Rena's vital signs and examination show tachycardia, mild tachypnea, normal perfusion, moist mucosa, RLQ abdominal tenderness, a lack of peritoneal signs, and the presence of right-sided costovertebral angle tenderness. Her lack of peritoneal signs does not completely eliminate the possibility but decreases the likelihood of appendicitis, ovarian torsion, or other surgical emergencies. Her vital sign abnormalities are likely related to her pain.
   - Diagnostic evaluation: Her diagnostic evaluation shows microscopic hematuria without pyuria, a normal white blood cell count, a normal appearing appendix on US, a negative human chorionic gonadotropin test, and an RBUS that shows a 5-mm right-sided ureteral stone with mild hydronephrosis. These findings help to definitively establish Rena's diagnosis and eliminate pyelonephritis, appendicitis, and pregnancy-related complications as the cause of her symptoms.
   - After her fluid bolus in the ED, Rena has no overt clinical signs of significant dehydration other than her tachycardia and mild tachypnea, which are both likely partly explained by her pain. Her pain is somewhat improved after a dose of intravenous (IV) morphine.

2. **Develop the list of findings.**

Q: What major findings have you identified for Rena?

- Acute onset of abdominal pain and vomiting
- Tachycardia with mild tachypnea
- Costovertebral angle tenderness
- Microscopic hematuria
- A 5-mm right-sided ureteral stone with associated hydronephrosis

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Rena's presentation?

- Although nephrolithiasis can commonly be an incidental finding unrelated to the patient's symptoms, the location of Rena's stone within the ureter with concomitant hydronephrosis (which causes renal colic and vomiting) is consistent with nephrolithiasis as the etiology of Rena's symptoms.
  - Urinary tract stones are likely to cause obstruction and hydronephrosis (and therefore become symptomatic) as they pass through narrowed portions of the urinary tract, such as the ureteropelvic junction, the location where the ureters cross the common iliac vessels, and the ureterovesical junction.
  - Nephrolithiasis is frequently associated with gross or macroscopic hematuria, vomiting, and abdominal, groin, or flank pain. The pain is commonly intermittent, corresponding with periods of obstruction. It should be noted that nephrolithiasis can also cause other urinary symptoms (eg, urinary frequency, dysuria) even in the absence of an infection, particularly as the stone moves into the distal ureter.
- Risk factors for pediatric nephrolithiasis include a family history of nephrolithiasis, dehydration, certain dietary factors (in particular the ketogenic diet, excess animal protein consumption, and a high-sodium diet), urologic anomalies that predispose to urinary stasis, predisposing medical conditions (eg, inflammatory bowel disease, short gut syndrome, cystic fibrosis, and immobilization), and some medications or supplements (eg, vitamin D_3, vitamin C, calcium, furosemide, topiramate, ceftriaxone).
- The majority of urinary tract stones are composed of calcium oxalate or calcium phosphate, with cystine, struvite, and uric acid stones occurring less commonly. The risk of stone formation increases as concentrations of these constituents increase in the urine, which is why dehydration can precipitate stone formation. Determining the underlying etiology for a patient's stone formation can be useful to help develop strategies to decrease their risk of stone recurrence.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with renal or ureteral stones?

Many patients with nephrolithiasis can be managed on an outpatient basis. Hospitalization should be considered in the following situations:

- The patient has severe pain that is not controlled by oral medications.
- The patient has fever with concern for complicated pyelonephritis.
- The patient has intractable vomiting, electrolyte disturbances, or renal insufficiency requiring IV hydration and monitoring.
- Signs of obstruction necessitating further medical or surgical intervention are present.
- The patient has a history of a congenital abnormality (eg, a solitary kidney), increasing the risk of complications.

Because of Rena's persistent vomiting and inability to tolerate oral intake, she warrants hospitalization for further treatment and monitoring.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Rena is a 14-year-old previously healthy girl presenting with acute-onset RLQ abdominal pain, flank pain, and vomiting secondary to a 5-mm ureteral stone associated with mild hydronephrosis. She is hemodynamically stable at this time but requires hospitalization for intractable vomiting and pain control.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The initial focus of medical management of nephrolithiasis is to treat symptoms with supportive care and to determine the likelihood of spontaneous stone passage. If spontaneous passage is likely, clinicians can facilitate stone passage with use of medical-expulsive therapy. If spontaneous passage is unlikely or contraindicated, urologic procedures may be required. The underlying etiology of nephrolithiasis will also need to be determined to help with long-term management decisions. For Rena, you decide to divide her treatment considerations into the following components:

1. **Supportive care**
   - Pain control: Most patients with nephrolithiasis respond well to a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. An example would be scheduled IV ketorolac with oral oxycodone as needed for breakthrough pain, with a transition to oral NSAIDs once pain is improved. It is important to be cautious with NSAID use in patients with renal insufficiency so as to not exacerbate the renal injury. Therefore, urine output, blood pressure, and the patient's weight should be closely monitored while on IV ketorolac.
   - Hydration: In patients who have vomiting and dehydration, IV hydration should be used to help replenish intravascular volume and to promote passage of the ureteral stone. Typically, isotonic fluids are run at maintenance (or up to 2 times maintenance) rate until the patient can tolerate adequate oral intake without emesis. It is recommended that oral intake is increased significantly (eg, at least 2 L/day in older children) in the setting of nephrolithiasis.
   - Antiemetics: Ondansetron can be useful for management of the nausea and vomiting associated with renal colic.
2. **Antimicrobials:** Treatment with empiric antibiotics should be considered if the patient has pyuria, fever, ill appearance, or other indications that there is an associated urinary tract infection. Later, treatment should be tailored based on urine culture and sensitivities.
3. **Stone passage or removal**
   - The likelihood of spontaneous stone passage depends on the size and location of the stone. In approximately 50% of cases, small calculi (<10 mm in diameter) pass spontaneously or with the help of medical expulsive therapy, whereas larger calculi (>10 mm in diameter) are more likely to require further intervention. The narrowest segment of the ureter is the ureterovesical junction, a common site where stones might not pass spontaneously. Because Rena's stone is 5 mm in diameter, there is a reasonable chance that it will pass with IV hydration and without the need for urologic intervention.

- Medical expulsive therapy: In addition to hydration, clinicians can consider using medical expulsive therapy (eg, α-adrenergic blockers, such as tamsulosin) to facilitate the passage of small distal ureteral stones. For small stones (< 10 mm in diameter), medical expulsive therapy has been proven safe and effective in the pediatric population. Stone passage may take up to 4 to 6 weeks, although the patient will usually have resolution of the pain earlier. To ensure stone passage, visualization of the stone via straining of the urine or repeat imaging is often necessary.
- Surgical intervention
  - Urgent urologic intervention: Occasionally, urgent intervention to decompress the urinary system may be required. Urgent urologic intervention is generally only indicated in certain situations (eg, an obstructing stone with a concurrent urinary tract infection; complete ureteral obstruction with resultant acute kidney injury; severe, refractory pain). Urgent interventions usually involve placement of a stent to facilitate urinary drainage.
  - Nonurgent urologic intervention: For stones that have not passed after a reasonable trial of medical therapy (2–3 weeks), for stones that are unlikely to pass spontaneously (eg, staghorn calculi, stones > 10 mm in diameter), and for multiple asymptomatic stones within the kidney, there are several urologic procedures clinicians can consider for stone removal, with extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy being most common. Shock wave lithotripsy is usually considered first-line treatment for stones less than 20 mm in diameter.

4. Further testing

- If not previously obtained, a urine culture and metabolic laboratory evaluation is recommended for all patients with nephrolithiasis. The metabolic evaluation includes serum calcium, magnesium, phosphorus, blood urea nitrogen, and creatinine levels. Patients found to have hypercalcemia should undergo a diagnostic evaluation into the etiology (eg, parathyroid hormone and vitamin D levels). Likewise, abnormalities in other serum electrolytes should prompt an investigation into the underlying etiology.
- To prevent recurrent nephrolithiasis, it is important to first understand the underlying etiology. In the United States, metabolic abnormalities (ie, abnormalities in urinary solute concentrations) are the most common cause of nephrolithiasis.
  - Stone collection and analysis are important to determine the etiology and risk of recurrence. This should be attempted for every patient presenting with nephrolithiasis and can be achieved by straining the urine with each void. When a cystine or struvite stone is found, this stone analysis is diagnostic of the underlying etiology of stone formation (see Table 40.4).
  - It is also helpful to obtain a 24-hour urine collection for solute analysis, including urinary calcium, phosphorus, magnesium, citrate, uric acid, sodium, oxalate, and cystine. Hypercalciuria is the most common finding in pediatric patients with nephrolithiasis, whereas hypocitraturia is the second most common.
    - For patients less than 60 kg, hypercalciuria is defined as a urinary calcium excretion of greater than 4 mg/kg/day. For patients greater than 60 kg, the definition of hypercalciuria varies but can be reasonably set as a urinary calcium value greater than 200 mg/day.
    - A spot urine assessment to calculate the urine calcium to creatinine ratio can also be useful, particularly for children who are not toilet-trained. For infants 6 months and younger, a normal spot calcium to creatinine ratio is less than 0.8 (mg/mg). For ages 7 months to 18 months, a normal ratio is less than 0.6. For ages 19 months to 6 years, a normal ratio is less than 0.4. For children older than 6 years, a normal ratio is defined as less than 0.2.
    - Most children with hypercalciuria will have idiopathic hypercalciuria; however, clinicians should consider modifiable risk factors (eg, certain medications, ketogenic diet) or medical conditions (eg, Bartter syndrome, some types of renal tubular acidosis) that are associated with hypercalciuria.

5. **Stone prevention strategies**
   - Improved hydration is universally recommended for patients with nephrolithiasis to decrease stone-forming urinary solute concentrations. It is recommended that children drink at least their maintenance rate in fluids each day. Adolescents should consume at least 2 L of fluid daily.
   - Table 40.4 shows the different metabolic etiologies of pediatric nephrolithiasis with the associated strategies that can prevent recurrent stone formation. Generally, a dietary approach is taken prior to pharmacological treatment.

Table 40.4. Etiologies and Management of Renal and Ureteral Stones

	Etiology	Prevention strategies
Hypercalciuria	Familial idiopathic hypercalciuria, dehydration, vitamin D excess, endocrinopathies (hypothyroidism, hyperparathyroidism, adrenocortical excess), disorders of bone metabolism, malignancy, medications (diuretics, antiepileptics, steroids), among other causes	Low-sodium diet, avoidance of vitamin C and D supplements; consider the addition of potassium citrate supplementation and/or thiazide diuretics.
Hyperoxaluria	Disorders of malabsorption, pancreatic disease, excessive intake of oxalate-rich foods. Fatty acids in the intestinal lumen bind calcium, leaving more oxalate to be absorbed and subsequently to be excreted in urine.	Low-sodium diet, probiotics, treatment of fat malabsorption (if present), avoidance of oxalate-rich foods (spinach, rhubarb, nuts, tea, wheat bran, strawberries); consider the addition of potassium citrate, pyridoxine, phosphate, and magnesium supplements.
Hypocitraturia	Low citrate levels lead to disinhibition of calcium oxalate and calcium phosphate nucleation, promoting crystal growth and aggregation. Causes can include renal tubular acidosis, some medications (diuretics, topiramate), genetic disorders, and high-protein diet.	Increase fruit and vegetable intake, avoid excessive protein intake; consider bicarbonate supplementation.
Hyperuricosuria	Low urine pH and excessive purine load, because uric acid is an end product of purine metabolism	Limit purine-rich foods; consider potassium citrate or bicarbonate supplementation to lower urinary pH; allopurinol can be used to lower serum uric acid levels in patients with disorders of purine metabolism.
Cystinuria	Rare autosomal recessive genetic defect in renal and intestinal transport of cysteine, orthinine, arginine, and lysine	Limit dietary sodium intake, encourage abundant hydration and urine alkalization; consider adding thiol drugs (eg, tiopronin, D-penicillamine, captopril).
Struvite	Urease-producing bacteria (*Proteus* spp, *Pseudomonas* spp, *Klebsiella* spp, *Serratia* spp, *Citrobacter* spp, *Morganella* spp) that produce very alkaline urine and high ammonium concentrations	Prevent urinary tract infections by abundant hydration and appropriate bathroom hygiene; consider prophylactic antibiotics for recurrent urinary tract infections.

6. **Monitoring:** While patients with nephrolithiasis are hospitalized, they should be monitored with routine vital signs and pain assessments, measurement of their intake and output, and straining of their urine. If possible, a 24-hour urine collection should be obtained to analyze factors that are either in excess or reduced. If fever or signs of sepsis develop, initiation of empiric antibiotics and consultation with urology is indicated. Additionally, worsening pain may indicate worsening urinary tract obstruction and is an indication for repeat imaging of the urinary tract.
7. **Consultations:** Clinicians should consider referring to or consulting a pediatric nephrologist and a pediatric urologist to help with the management of pediatric patients with nephrolithiasis. Indications for consultation/referral include, but are not limited to, concurrent urinary tract infection, large stones (>10 mm in diameter), staghorn calculi, worsening symptoms, failure to pass the stone within the expected time frame (2–3 weeks), or recurrent nephrolithiasis.

CASE FOCUS

Plan for Treatment and Monitoring

- **Supportive care**
  - **Pain control: You order IV morphine and IV ketorolac and will titrate the doses and frequency as needed. You plan to transition to oral analgesics once Rena is tolerating oral intake.**
  - **Hydration: After an initial normal saline bolus, you begin isotonic IV fluids at the maintenance rate and encourage oral hydration as tolerated.**
  - **Antiemetics: Ondansetron will be available for use as needed to treat nausea and vomiting.**
- **Antimicrobials: None is indicated for Rena.**
- **Stone passage: You start medical expulsive therapy with tamsulosin to facilitate stone passage.**
- **Further testing: To collect Rena's stone, you order that her urine should be strained every void. Any stone collected will be sent to the laboratory for analysis. You will also order a 24-hour urine collection for solute analysis.**
- **Prevention: You will provide education to Rena and her family about the importance of improved hydration. Any dietary recommendations will be based on her stone analysis and urine metabolic studies.**
- **Monitoring: You order vital signs and pain assessments every 4 hours and strict monitoring of Rena's intake and output.**
- **Consultation: You consult a pediatric urologist for assistance with assessing the etiology of the stone and to establish care.**

Case Resolution

Rena does not pass her stone while she is admitted; however, her pain and vomiting improve significantly overnight, and she is able to transition to oral NSAIDs for pain management. Her urine solute analysis shows findings consistent with hypercalciuria, and her serum electrolyte levels, including her calcium level, are normal. Given her lack of other risk factors and her normal serum laboratory studies, her hypercalciuria is likely familial in nature and was compounded by her baseline poor fluid intake, both of which contributed to the formation of a stone.

Prior to discharge home, Rena is tolerating oral fluids without emesis, urinating well, and is drinking sufficient volumes to facilitate stone passage. Additionally, she has normalization of her vital signs, and her pain is well controlled on an oral regimen. At the time of discharge home, she is advised to continue straining her urine, drink 2 L of fluid daily, start a low-salt diet, and follow-up with her primary care pediatrician within a few days.

Discharge Criteria

Q: How do you know when Rena is ready to go home?

You can feel comfortable discharging your patient with nephrolithiasis when the following general criteria are met:

- The patient is tolerating oral fluids and urinating well.
- The patient is tolerating oral pain medication with adequate relief of symptoms.
- Vital signs are within normal limits for age, and the patient appears hemodynamically stable without signs of infection.
- The patient and caregivers have been educated regarding home stone collection, hydration, diet, and follow-up.
- Appropriate follow-up is arranged including 6-week follow-up for repeat imaging if no stone is retrieved, 6-month follow-up with the primary care pediatrician for review of dietary modifications and repeat 24-hour urine collection, and follow-up with a urologist/nephrologist as indicated based on hospital course and stone analysis.

Anticipatory Guidance

Q: What instructions should you provide to Rena and her caregivers upon discharge?

- Continue to drink plenty of fluids (approximately 2 L/day) to encourage passage of the stone and prevent recurrent stones.
- Follow the pain control plan and seek care if pain acutely changes or worsens.
- Continue to strain the urine and collect the stone for analysis.
- A 3-day food diary is recommended to evaluate dietary components and assess dietary modifications (specifically initiation of a low-sodium diet and increased fluid intake) at the follow-up visit.
- Rena will need a repeat 24-hour urine collection approximately 6 to 12 months after the dietary modifications are made to evaluate the success of these changes.
- Seek care for fever and/or chills, poor oral fluid tolerance, worsening pain despite oral pain medications, or new/worsening blood in the urine.

Clinical Pearls

- Pediatric nephrolithiasis has a variety of causes, the most common of which is idiopathic hypercalciuria.
- Serum and urine tests, including a 24-hour urine collection, can help determine the underlying etiology of nephrolithiasis.
- The mainstay of treatment of small stones that can pass through the ureter is adequate hydration, reduced salt intake, and pain relief.
- For larger stones or cases involving complex anatomical challenges, surgical intervention might be required.
- Appropriate follow-up with the primary care physician is essential to ensure resolution of the stone and to monitor dietary modifications to prevent recurrence.

Documentation Tips

- Document the presence of severe pain requiring continued IV pain medications.
- Document the presence of dehydration, oral intolerance, intractable vomiting, acute kidney injury, and need for ongoing IV hydration, when applicable.
- Document the presence of hydronephrosis, congenital renal malformation, solitary kidney with obstruction, or urinary tract infection, when appropriate.
- Mention whether there is anticipated need for surgical intervention for stone removal.

Suggested Readings

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Malik, a 2-Year-Old Boy With Pneumonia and Persistent Fever

CASE PRESENTATION

You are working an overnight shift when you are called to the bedside of Malik, a patient on the inpatient unit. Malik is a 2-year-old boy who has been hospitalized for 2 days while being treated for community-acquired pneumonia (CAP). Since his admission, he has been receiving intravenous (IV) fluids and empiric IV ampicillin, and he has been requiring between 0.5 and 1 L/min of supplemental oxygen via nasal cannula for mild hypoxemia. Malik's nurse reports that his parents have concerns about his lack of improvement despite treatment with antibiotics and wish to speak to a physician.

Patient History and Review of Systems

Q: What information should you collect from Malik's medical record, nurse, and caregivers?

- History of present illness
  - Observations by the nurse and specific parental concerns
  - Onset and duration of symptoms, including duration and height of fever
  - Changes in symptoms since admission and starting antibiotics
  - Quality of cough (eg, harsh, barking, dry, productive)
  - Recent illnesses or antibiotic use
  - Recent choking or aspiration events
  - Exposure history
    - Recent travel and sick contacts, including possible SARS-CoV-2 exposure
    - Risk factors for *Mycobacterium tuberculosis* (eg, travel to or contact with a person from an endemic area; contact with an adult who is homeless, in a correctional facility, or abuses illicit drugs or alcohol)
  - Associated symptoms, such as chest pain, back pain, abdominal pain, vomiting, diarrhea, poor urination, altered mental status, or symptoms of *M tuberculosis* (eg, weight loss, night sweats, hemoptysis)
- Medical history
  - Any underlying health conditions, especially cystic fibrosis, immunodeficiency/recurrent infections, chronic respiratory failure, or sickle cell disease
  - Previous respiratory infections, especially those requiring antibiotic therapy or hospitalization
  - Vaccination status, including annual influenza vaccination
- Dosing of current antibiotics

CASE FOCUS

History and Review of Systems

In speaking to Malik's nurse, you learn that this is her second night caring for him. Both nights, he has been restless and fussy during her visits to the room. She notes that last night his vital signs were notable for mild hypoxemia, which was easily managed with 0.5 L/min of supplemental oxygen by nasal cannula; however, tonight he is requiring 1 L/min of supplemental oxygen to maintain saturations greater than 90%. She also mentions that he has continued to have fevers and poor oral intake.

You read Malik's medical record and learn that he was previously healthy and has been ill for 7 days in total. His symptoms have included a wet cough, nasal congestion, poor oral intake, and daily fever, with a maximum temperature of 39.3 °C (102.7 °F) at home and 39.6 °C (103.3 °F) in the hospital. Over the course of his illness, he has become more fatigued and developed decreased urination and difficulty breathing. In the emergency department, Malik underwent blood tests and a chest radiograph. He was diagnosed with CAP, started on oxygen and IV fluids and antibiotics, and hospitalized for further care.

At the time of his admission, Malik's parents reported they had been giving him acetaminophen and ibuprofen at home for fever but denied any other recent medications or antibiotics. Malik attends child care part-time, has not traveled anywhere recently, and has not had any sick contacts. He was born full-term, had 1 previous ear infection at 9 months that required antibiotics, has had no recurrent respiratory infections or diagnoses, and is up to date on all vaccinations.

From his chart review, you can also see that Malik has continued to have frequent fevers and mild tachycardia. His highest fever was 39.6 °C (103.3 °F) this afternoon. His respiratory examination has been relatively unchanged since admission, with mild tachypnea and mild increased work of breathing, but his oxygen need has increased. He has been receiving IV fluids for poor oral intake. You verify that his ampicillin is appropriately dosed for CAP.

During your discussion with his family, you learn that Malik's parents do not think his breathing, malaise, fevers, or poor appetite has improved in the past 2 days. His parents say that he has continued to be fussy, but he has not expressed that he is in pain. They report that Malik's urination has improved since he began receiving IV fluids. You learn that he has no tuberculosis risk factors or known choking or aspiration events. His parents deny other symptoms on your review of systems.

Physical Examination

Q: What parts of the physical examination should you focus on for Malik?

- Complete set of vital signs
- Level of consciousness and ability to arouse normally
- Respiratory: respiratory rate; inspection of the chest, including chest expansion and work of breathing (eg, use of accessory muscles, nasal flaring, grunting); auscultation of anterior and posterior lung fields
- Cardiovascular: murmurs or gallops, peripheral perfusion (peripheral pulses and capillary refill time)
- Mucous membranes: dry, sticky, moist

CASE FOCUS

Physical Examination

Malik's temperature has decreased to 39.2 °C (102.6 °F) after a dose of acetaminophen, which was given an hour prior to your examination. He has tachycardia with a heart rate of 160 beats/min and tachypnea with a respiratory rate of 48 breaths/min. His oxygen saturation is 94% on 1 L/min nasal cannula. He has a normal recorded blood pressure.

On examination, Malik is awake, alert, and in mild respiratory distress. He is fussy but consolable by his mother. His mucous membranes are moist, and he has normal conjunctiva and no cervical lymphadenopathy. He has symmetric chest expansion bilaterally with mild subcostal retractions and abdominal breathing. He is not grunting. On auscultation, his breath sounds are diminished in the right lower lobe with fine crackles. Other than his noted tachycardia, his cardiac examination is benign. He has normal peripheral pulses and a capillary refill time of less than 2 seconds. His abdomen is soft and nondistended with mild tenderness in the right upper quadrant. His neurologic examination is otherwise nonfocal.

Differential Diagnosis

Q: In a child with CAP, what are possible explanations for failed first-line antibiotic therapy?

Failed antibiotic therapy is defined as clinical worsening on therapy or no signs of clinical improvement within 48 to 72 hours of starting antibiotic therapy. Possible causes of failure of antibiotic therapy in children with CAP are shown in Table 41.1.

Table 41.1. Differential Diagnosis for Failure of Antibiotic Therapy in a Child With Community-Acquired Pneumonia

Diagnoses of highest suspicion	• Parapneumonic pleural effusion[a] • Resistant/different organism
Other diagnoses to consider	• Bronchopleural fistula • Foreign body aspiration • Lung abscess • Necrotizing pneumonia • New infection (eg, viral, urinary tract) • Noninfectious inflammatory process, such as seen with pneumonitis • Pneumothorax

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is warranted for a child in whom treatment of CAP has failed?

Further evaluation for the previously listed differential diagnoses should be performed in children who are not responding as expected to appropriate therapy, especially if they have increasing oxygen requirements or worsening respiratory distress.

- Imaging studies
  - The first step in evaluation of these patients is to obtain a 2-view chest radiograph, preferably upright and non-portable for best quality.
  - Chest ultrasonography (US) or chest computed tomography (CT) may be needed when there is suspicion for certain complications (eg, pulmonary effusion, empyema). In general, US is preferred over CT as the initial imaging modality to avoid radiation, determine presence or absence of pleural effusion, and characterize the effusion further (including size, complexity, specific location, and depth); however, a CT scan with contrast may be needed in certain situations to better characterize parenchymal abnormalities (eg, absent perfusion, necrosis, abscess) and evaluate for lymphadenopathy.
- Serum studies
  - Complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) can be helpful in evaluating the patient's response to therapy, although these tests are not particularly useful for differentiating viral from bacterial infections.
  - The serum procalcitonin level has been studied in adults as a way of differentiating between bacterial and viral causes of CAP. There is some evidence it may be beneficial during the initial diagnosis in pediatric CAP, but its use in assessing response to antibiotic therapy has not been well studied.
- Infectious testing
  - Although blood cultures are usually not indicated in the initial evaluation of CAP, blood culture results, when positive, may be useful in determining the etiology of a complicated pneumonia and may therefore impact decisions about antibiotic therapy.
  - Respiratory pathogen panel by polymerase chain reaction (PCR) should be considered if the results would change management, such as with detection of influenza or *Mycoplasma pneumoniae*.
  - Sputum culture may be helpful in older children or adolescents who are able to produce a reliable sample.
  - In certain situations (eg, when specific risk factors are present), a clinician may also consider testing for less common organisms, such as *M tuberculosis*, *Histoplasma capsulatum*, *Blastomyces* spp, *Coccidioides* spp, and *Legionella pneumophila*.

CASE FOCUS

Diagnostic Evaluation

Given Malik's worsening respiratory status, you decide to obtain a repeat CBC, ESR, CRP level, blood culture, and chest radiograph.

The results of Malik's laboratory testing compared to his prior laboratory test results are as follows:

Laboratory test	Results on admission	Current results (48 h later)	Reference range
WBC count	18,300/μL (18.3 × 10^9/L)	21,700/μL (21.7 × 10^9/L)	7,000–13,000/μL (7–13 × 10^9/L)
Neutrophils	65% (0.65)	81% (0.81)	23%–70% (0.23–0.70)
Lymphocytes	27% (0.27)	12% (0.12)	15%–67% (0.15–0.67)
Monocytes	6% (0.06)	7% (0.07)	4%–10% (0.04–0.10)
Hemoglobin	9.7 g/dL (97 g/L)	8.8 g/dL (88 g/L)	10.5–14 g/dL (105–140 g/L)
Platelet count	590 × 10^3/μL (590 × 10^9/L)	696 × 10^3/μL (696 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
ESR	86 mm/h	120 mm/h	0–10 mm/h
CRP	11.2 mg/dL (112 mg/L)	23.7 mg/dL (237 mg/L)	<1 mg/dL (<10 mg/L)

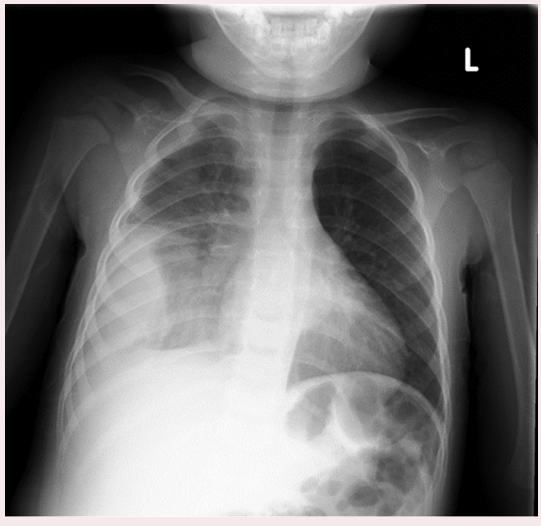
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

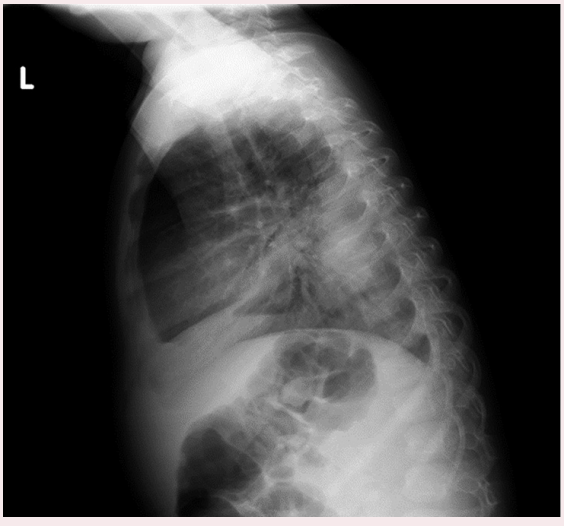
CASE FOCUS

Diagnostic Evaluation *(continued)*

Respiratory pathogen panel by PCR has been ordered and collected, but these results are pending.

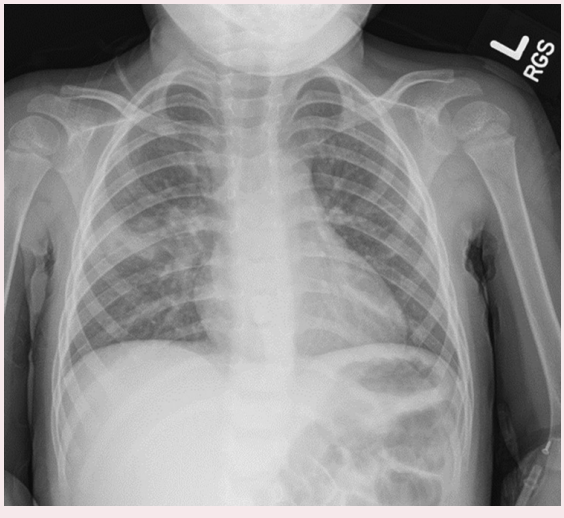
Current chest radiograph[a]:

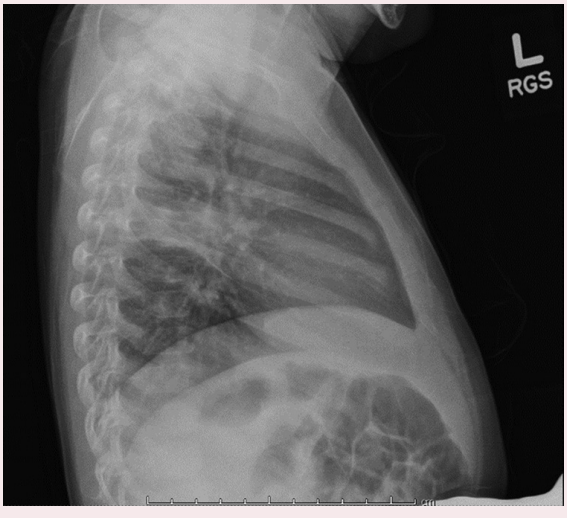




Current chest radiograph impression: There is complete opacification of the right lower lobe with a right-sided pleural fluid collection, which may be loculated given the appearance. There is no pneumothorax. Normal cardiac silhouette. No bony abnormalities.

Initial chest radiograph[a]:





Initial chest radiograph impression: There is opacification in the right lower lobe suggesting consolidation. There is no pneumothorax. Normal cardiac size and bones.

Based on concern for effusion on repeat chest radiograph, you decide to order right-sided chest ultrasonography for better characterization of the effusion.

Chest ultrasound impression: There is a moderately sized, loculated pleural fluid collection inferolaterally in the right chest.

[a] Refer to Section III of the Appendix for a primer on chest radiograph interpretation.

Arriving at a Diagnosis

Q: How do you develop an assessment for Malik?

In Malik's case, his repeat chest radiograph and ultrasound are diagnostic for complicated pneumonia with a pleural fluid collection concerning for empyema, but you decide to fully think through his history, examination, laboratory tests, and imaging to generate a list of findings that can then help you develop your treatment plan.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Malik is exhibiting clinical signs of worsening illness (increased fevers and oxygen requirement) despite more than 48 hours of appropriate empiric antibiotic therapy for CAP.
   - Laboratory test results
     - Malik's most recent CBC with differential shows leukocytosis that is increased from admission, a worsening anemia (as evidenced by the decrease in his hemoglobin level), and worsening thrombocytosis. Thrombocytosis can be interpreted as an acute phase reactant in the setting of an acute illness. Malik's decreasing hemoglobin level is likely multifactorial, caused by dilution from IV fluids, blood loss from phlebotomies, and decreased red blood cell production in the setting of an inflammatory state.
     - His ESR and CRP level have also increased significantly from admission. Although it is expected that Malik's ESR may be higher than on admission, a doubling of his CRP level is consistent with worsening infection.
   - Imaging
     - Chest radiograph: On Malik's most recent chest radiograph, increasing opacification is seen in the right lateral lower lobe, with new costophrenic angle blunting concerning for a parapneumonic pleural effusion or empyema.
     - Lung US results: There is a moderately sized loculated pleural fluid collection inferolaterally in the right chest. Based on the loculated nature of the effusion on US, the pleural effusion is complex.
   - Assessment for sepsis: Malik's laboratory test results and vital signs are consistent with the diagnosis of sepsis based on his leukocytosis, tachycardia, and tachypnea. He has no evidence of severe sepsis or septic shock. Refer to Section IV in the Appendix for the age-based systemic inflammatory response syndrome and sepsis criteria.
2. **Develop the list of findings.**

Q: What major findings you have identified for Malik?

- Respiratory distress
- Hypoxemia
- Anemia
- Thrombocytosis
- Right lower lobe pneumonia
- Failure of appropriate empiric antibiotic therapy
- Complex parapneumonic pleural effusion
- Sepsis (leukocytosis, tachypnea, tachycardia)

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Malik's presentation?

Although you still do not know the underlying causative organism, based on Malik's diagnostic evaluation, he has a complicated pneumonia with evidence of a complex parapneumonic pleural effusion that has failed first-line empiric antibiotic therapy. *Complicated pneumonia* is defined as pneumonia that is accompanied by parapneumonic effusions, empyema, necrotizing changes, multilobar disease, abscesses or cavities, pneumothorax, or bronchopleural fistula.

- *Parapneumonic effusions* are fluid collections in the pleural cavity that result from pleural inflammation. Radiologists describe effusions on US as simple or complex. Early in the course of illness, effusions are small, largely exudative, and free-flowing ("simple"). Over time, fibrin deposition over pleurae causes the effusions to become fibropurulent with septations or loculations ("complex"). Complex fluid collections contain debris, septations/loculations, and/or echogenic, solid appearing material.
- An *empyema* is an effusion that is loculated or septated with presence of grossly purulent fluid and/or bacteria.
- *Necrotizing pneumonia* is a severe form of lung disease associated with formation of cavitation within the lung parenchyma. Necrosis and tissue liquefaction are usually diagnosed by the presence of multiple gas-filled spaces within a pulmonary consolidation on chest radiograph or obvious liquefaction on CT scan with contrast. Areas of necrosis lack normal contrast perfusion and may contain cavities/abscesses.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with complicated pneumonia?

Although Malik is already hospitalized, his presentation and diagnosis prompt you to consider admission criteria for patients with complicated pneumonia. Hospitalization is warranted for all children with complicated pneumonia to expedite the clinical evaluation, consult with surgical specialists, provide IV antibiotic therapy, and provide close clinical monitoring.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Malik is a 2-year-old otherwise healthy boy who was initially admitted for hypoxemia and respiratory distress due to CAP of the right lower lobe. He has been treated with an appropriately selected and dosed parenteral antibiotic therapy. He is showing signs of persistent fever and worsening respiratory status, likely due to new development of a parapneumonic pleural effusion in the right chest. Therefore, he continues to require hospitalization for ongoing monitoring, oxygen supplementation, antibiotic therapy, and surgical management for treatment of his parapneumonic pleural effusion.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

The primary aspects of Malik's acute care will be to determine the need for surgical intervention and initiate broad-spectrum antibiotics. You decide to divide your treatment plan into the following components:

1. **Consultations**
   - For patients with moderate or large parapneumonic effusions, loculated effusions, or concern for empyema, the pediatric surgery team should be consulted to help assess options for management. Many times, chest tube placement and drainage of the effusion are required.
   - Other consultants in the patient's care may include the pediatric interventional radiologist for chest tube placement; the pediatric infectious disease team (who can help guide diagnostic testing, antibiotic selection and duration, transition to oral therapy, and provide appropriate follow-up); and the pediatric pulmonology team (for cases of recurrent pneumonias, need for diagnostic bronchoscopy, or concern for foreign body aspiration)
   - At your institution, it is common for the interventional radiologist to perform ultrasound-guided chest tube placement, so you will consult both the surgeon and the radiologist so they can discuss the best option for Malik.

2. **Drainage of effusion:** Drainage of parapneumonic effusions should be strongly considered in any patient with a large effusion or in patients with a moderate effusion who are not improving or in whom the effusion is affecting their respiratory status.
   - There are 2 modalities used to drain parapneumonic pleural effusions: chest tube placement (with or without fibrinolytics) or video-assisted thoracoscopic surgery (VATS). The decision between methods should be made in discussion with consultants.
   - In the past decade, there has been a trend toward initial treatment of pediatric empyema with chest tube placement and fibrinolysis instead of VATS. Currently, the literature shows similar outcomes between these 2 procedures in terms of length of hospital stay; however, chest tube placement has the advantage of being less invasive in comparison to VATS. Unfortunately, failure rates for initial chest tube placement with fibrinolysis seem to be greater than that of initial VATS, despite similar hospital outcomes.
3. **Antimicrobials:** Initial antibiotic treatment of parapneumonic effusions should be given parenterally. Before decisions can be made about antimicrobial agents, it is important to first review the most common causative organisms of CAP in children.

Q: What are the most common infectious etiologies of CAP?

In children, the causes of CAP differ by age, with viral etiologies predominating in infants and young children and bacterial etiologies predominating in school-aged children and adolescents. There are many different organisms that can cause CAP, and some are shown in Box 41.1. The most common bacterial causes of CAP in school-aged children are *Streptococcus pneumoniae* and *M pneumoniae*; however, in complicated pneumonia, *Staphylococcus aureus*, group A streptococcus, and anaerobes are seen at an increased frequency.

- Because of the serious nature of complicated pneumonia, it is important to start treatment with broad-spectrum antibiotics directed against both *S pneumoniae* and *S aureus*, the 2 most common organisms for this type of infection.
- In general, the initial empiric therapy for any complicated pneumonia should be a third-generation cephalosporin (eg, ceftriaxone, cefotaxime) and an antibiotic directed against methicillin-resistant *S aureus* infection (eg, vancomycin, clindamycin); however, the antibiotic regimen may vary somewhat based on individual patient characteristics and antibiotic resistance patterns for the geographic region.
- When possible, antibiotic therapy can later be narrowed, based on the patient's response to treatment and cultures (or other diagnostic testing) from the pleural fluid.
- The timing of the transition from parenteral therapy to oral therapy is not well established. In many cases, discussions with the local infectious disease team can be helpful in guiding these decisions. Despite the lack of clear guidelines, it is reasonable to transition to oral therapy once the patient has demonstrated significant improvement, such as resolution of any hypoxemia, improvement in serum inflammatory markers, resolution of fever (when possible), and after removal of any chest tubes.

Box 41.1. Selected Infectious Causes of Community-Acquired Pneumonia in Infants, Children, and Adolescents

Bacterial	Viral	Fungal
Chlamydophila pneumoniae *Coxiella* *Haemophilus influenzae* *Legionella pneumophila* *Mycoplasma pneumoniae* *Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes*	Adenovirus Coronavirus serotypes Human metapneumovirus Influenza Respiratory syncytial virus Rhinovirus	*Blastomyces* *Coccidioides* *Cryptococcus* *Histoplasmosis*

- The total duration of therapy usually ranges from 2 to 4 weeks, depending on the severity of the patient's infection and based on their response to therapy.
- For treatment of specific pathogens, refer to the most recent edition of the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases*.

4. **Diet**
   - In preparation for likely surgical intervention requiring anesthesia, the patient should be made nil per os (nothing by mouth) so that the procedure is not delayed.
   - Postoperatively, the patient should resume an unrestricted regular diet as tolerated.
5. **Supportive care**
   - Acetaminophen and/or nonsteroidal anti-inflammatory drugs can be used safely in the setting of complicated pneumonia.
   - Postoperatively, the patient may have pain unrelieved by first-line analgesics and may require opiates or ketorolac. Patients may also require scheduled analgesics for the duration of time the chest tube is in place.
   - Although institutional protocols differ on the exact goal saturation, you plan to provide oxygen supplementation as needed to maintain an oxygen saturation of at least 90%.
6. **Further laboratory/diagnostic testing**
   - Pleural fluid testing: When the pleural fluid is drained with surgical intervention, the studies that should be ordered include pleural fluid cell count with differential and pleural fluid Gram stain and culture. The pleural fluid should be held in the laboratory for PCR and antigen testing if available at your institution.
   - Serial chest radiographs: Serial chest radiographs should be obtained to monitor for chest tube complications (if placed), signs of worsening effusion, or other changes in the patient's pneumonia.
   - Serial laboratory studies: Most patients with complex pneumonia should have laboratory assessments every few

CASE FOCUS

Plan for Treatment and Monitoring

- **Consultations:** To assist in Malik's management, you consult pediatric surgery, interventional radiology, and the infectious disease specialist to help with further testing and treatment decisions.
- **Drainage of effusion:** After conversations among your consultants and the patient's family, the interventional radiology team plans to proceed with chest tube placement and fibrinolysis as the procedure is less invasive than VATS and will likely have a similar outcome. The surgery team will continue to follow and assist with any chest tube management.
- **Antimicrobials:** You discontinue IV ampicillin and start IV ceftriaxone and IV clindamycin. You will consider escalation to IV vancomycin if Malik is toxic appearing or if there is concern for clindamycin-resistant *S aureus*.
- **Monitoring:** You order strict monitoring of intake and output, including chest tube output (once in place), continuous pulse oximetry, and vital signs every 4 hours (including heart rate, blood pressure, and temperature).
- **Diet:** In preparation for anesthesia and surgical intervention, you order nothing by mouth, with IV fluids at his maintenance rate. After surgical intervention, Malik will be allowed to eat an unrestricted diet.
- **Supportive care:** You order acetaminophen or ibuprofen as needed for pain or fever. After his chest tube placement, you will reassess Malik's pain and escalate treatment as needed. You plan to continue supplemental oxygen as needed to maintain oxygen saturations of at least 90%.
- **Further laboratory/diagnostic testing:** You order pleural fluid studies: cell count and differential, pleural fluid Gram stain and culture, and PCR and antigen testing of pleural fluid. The surgery team plans to obtain a repeat chest radiograph postoperatively and requests a repeat radiograph tomorrow morning. You also order a CRP level, serum chemistries, and CBC to monitor liver enzymes, renal function, blood counts, and response to therapy.

Case Resolution

Malik successfully undergoes chest tube placement with pigtail catheter by interventional radiology and has fibrinolytics instilled daily for 3 days to assist with chest tube drainage. His pleural fluid and other infectious testing demonstrate the following results:

Laboratory test	Result	Reference range
Pleural fluid analysis		
Appearance	Purulent	Straw colored
WBC count	159,500/μL (159.5 × 10^9/L)	< 10,000/μL (10 × 10^9/L)
Segmented neutrophils	92% (0.92)	NA
Lymphocytes	3% (0.03)	NA
Monocytes	5% (0.05)	NA
Gram stain	Moderate WBC, no organisms	None to few WBC, no organisms
Culture	No growth for 5 days	Negative
Pleural fluid PCR for *Streptococcus pneumoniae* and *Staphylococcus aureus*	Negative	Negative
Additional studies		
Blood culture	No growth for 5 days	Negative
Respiratory pathogen panel by PCR (collected from nasopharynx)[a]	Negative	Negative

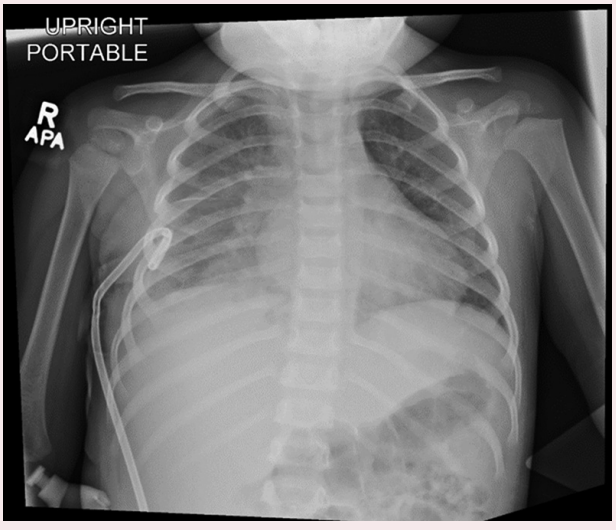
Abbreviations: NA, not applicable; PCR, polymerase chain reaction; WBC, white blood cell.

[a] Respiratory pathogen panel by PCR tests for influenza, respiratory syncytial virus, parainfluenza serotypes, adenovirus, human metapneumovirus, coronavirus serotypes, *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.

Because Malik's pleural fluid is grossly purulent with a white blood cell count greater than 50,000/μL (50 × 10^9/L), it is consistent with an empyema. His empyema responds well to fibrinolytics, with a total of 750 mL output in the 3 days after chest tube placement and clearing on subsequent chest radiographs. As his chest tube output decreases, it is removed at bedside by the surgery team 4 days after placement.

Case Resolution *(continued)*

Malik's chest radiograph prior to removal of his pigtail catheter:



It is common that organisms do not grow on pleural fluid culture, especially when antibiotics are initiated prior to drainage procedures; however, for Malik, you are also not able to identify the causative organism even after limited PCR testing. Once Malik is afebrile, off oxygen, tolerating good oral intake, and has a downtrending CRP level, he will be discharged home on oral amoxicillin-clavulanate with plans for close outpatient monitoring by his pediatrician and the infectious diseases physician. You anticipate Malik will receive a total of 3 to 4 weeks of antibiotic therapy if he continues to recover as expected.

days, including CRP, electrolyte panels and renal function, and CBC. Periodically, liver enzymes should also be assessed as these can be affected by β-lactam therapy. It is not uncommon for patients with severe pneumonia to also develop anemia related to inflammation and repeat phlebotomy. Transfusion with packed red blood cells can sometimes be required. Hyponatremia can also be seen related to syndrome of inappropriate antidiuretic hormone secretion. Prolonged β-lactam antibiotic therapy can be associated with leukopenia, eosinophilia, and transaminitis.

Discharge Criteria

Q: How do you know when Malik is ready to go home?

You can feel comfortable discharging your patient with complicated pneumonia when the following criteria are met:

- The patient is tolerating oral intake, including the ability to tolerate oral medications.

- No oxygen supplementation is required for approximately 12 to 24 hours.
- The patient has been afebrile for 24 hours.
- Tachypnea and tachycardia have resolved (stable vital signs) prior to discharge.
- Pain is controlled with oral medications.

Anticipatory Guidance

Q: What instructions should you provide to Malik's caregivers upon discharge?

- It is important for Malik to complete the total duration of oral antibiotics at home as prescribed.
- Malik's cough should slowly improve over the course of treatment. Complete resolution, however, may take up to 4 weeks or longer.
- Return to care for any signs of respiratory distress such as new fever, tachypnea, abdominal breathing, retractions, cyanosis, decreased oral intake with concern for dehydration, or inability to tolerate oral medications.

Clinical Pearls

- Complicated pneumonia describes a spectrum of lung disease (eg, parapneumonic effusion, empyema, necrotizing pneumonia) that should be considered in all children with an initial diagnosis of CAP who are not responding appropriately to therapy.
- When there is concern for a complicated pneumonia, initial diagnostic evaluation should include laboratory testing with CBC, blood culture, ESR, CRP level, and a 2-view chest radiograph.
- Evidence of a moderate-sized or greater pleural effusion on chest radiograph should be followed up with chest US for better characterization of the effusion.
- Pediatric surgery, interventional radiology, and pediatric infectious disease specialists may be helpful with decisions about surgical management and antibiotic therapy.
- Empiric antibiotic therapy for a complicated pneumonia should include an IV third-generation cephalosporin and clindamycin or vancomycin when there is concern for methicillin-resistant *S aureus* infection. Vancomycin may be preferred if the patient is toxic appearing.
- There are 2 modalities for draining a pleural effusion: chest tube placement (with or without fibrinolytics) or VATS, which is considered more invasive but tends to have a lower risk of treatment failure. Decisions about which modality to use should be made in conjunction with a pediatric surgeon and interventional radiologist whenever possible.

Documentation Tips

- Document if antibiotics were given prior to admission and whether outpatient management failed.
- When indicated, document the presence of acute respiratory failure with hypoxemia or hypercapnia, including the results of blood gases, if available.
- Document sepsis, if present.

- Include associated medical complexity or comorbid medical conditions (eg, chronic lung disease, technology dependence, immunosuppression).
- Document when there is complicated pneumonia or empyema and the need for chest tube placement.
- Discuss the need for continuous versus intermittent respiratory monitoring.

Suggested Readings

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CASE 42

Flora, an 8-Year-Old Girl With Worsening Epigastric Pain and Emesis

CASE PRESENTATION

Overnight while you are cross-covering patients, a nurse calls you with concerns about Flora, a patient whose abdominal pain is worsening, and requests that you evaluate her. You review your patient list and see that Flora is an 8-year-old girl who was admitted from the emergency department (ED) earlier that day with 2 days of abdominal pain and emesis. The admitting team noted signs of dehydration and mild abdominal tenderness and diagnosed her with suspected viral gastroenteritis. She was started on maintenance intravenous (IV) fluids, as well as ondansetron and acetaminophen as needed.

Patient History and Review of Systems

Q: What information should you collect from Flora, her nurse, caregivers, and medical record?

- History of present illness
  - Observations and concerns expressed by her nurse
  - Presenting symptoms, duration of symptoms, and changes in symptoms since hospitalization
  - Descriptors of abdominal pain: timing, quality, location and radiation, intensity and severity, alleviating and aggravating factors
  - Vomiting history, including onset, aggravating and alleviating factors, number of episodes per day, and quality of emesis (presence of blood or bile), with an estimate of volumes
  - Timing and description of last bowel movement, including character (eg, presence of blood in stool), and presence or absence of flatus
  - Signs of dehydration, including an estimation of recent urine output, sunken appearance to the eyes, malaise, and absence of tears
  - Exposure history, including recent dietary intake (raw or undercooked foods), possible toxic ingestions, sick contacts, travel, and activity history
  - Recent traumatic injuries or illnesses
  - Associated symptoms, such as fever, headache, sore throat, cough, chest pain, shortness of breath, diarrhea, back pain, altered mental status, rash, polyuria/polydipsia, weight loss, or urinary symptoms

- Medical history, including underlying health status, immunization status, surgical history, and history of similar episodes
- Recent medications or supplements
- Family history of *Helicobacter pylori* infection, pancreatitis, or gallstones

CASE FOCUS

History and Review of Systems

Upon review of Flora's medical record and after discussions with Flora, her nurse, and her parents, you learn that Flora has had 2 days of nausea; nonbloody, nonbilious vomiting; and progressively worsening continuous abdominal pain that she currently rates as 7 on a scale of 10. Her pain is worse when she eats and is most severe in the epigastric area and her back. Flora says that her pain is slightly improved when leaning forward. The pain and nausea have left her largely unable to tolerate anything by mouth.

Yesterday, she was evaluated by her pediatrician who prescribed ondansetron for suspected acute gastroenteritis. Despite ondansetron and acetaminophen at home, Flora continued to have abdominal pain and intermittent vomiting or retching. Last night, Flora was unable to sleep well because of the pain. Today, Flora has had poor urine output, increasing fatigue, worsening pain, and approximately 10 episodes of nonbloody, nonbilious emesis, which prompted her family to bring her to the ED.

In the ED, Flora's pain and emesis were temporarily relieved with IV morphine and IV ondansetron but have since returned. She has received a dose of acetaminophen since admission; however, Flora's nurse has noticed that she seems very uncomfortable and restless, more so than he expects of a patient with viral gastroenteritis.

Flora's review of systems is negative for diarrhea, bloody stool, fever, cough, respiratory symptoms, dysuria, or polyuria/polydipsia. Flora reports her last bowel movement was 2 days ago and was "normal." She has continued to pass flatus. Although the frequency of Flora's urine output at home is unknown, her mother says her only void since admission was a small volume and looked dark yellow despite Flora having received IV fluids for a few hours.

Flora's family is not aware of any sick contacts and denies prior similar episodes, recent travel, trauma, recent medications, antibiotics, animal exposures, ingestions, or changes in her diet. She has never had surgery or been hospitalized. She does attend school, has been developing normally, and is appropriately immunized according to the Centers for Disease Control and Prevention schedule. Flora was adopted as an infant, and her parents are unaware of any relevant family history. No one in the household has had *H pylori* infection, pancreatitis, or gallstones.

Flora's family remarks that they are very concerned about her worsening abdominal pain. She normally weighs 65 lb (29.5 kg) and her parents estimate that she has lost 4–5 lb (1.8–2.3 kg) since her illness began.

Physical Examination

Q: What parts of the physical examination should you focus on for Flora?

- Complete set of vital signs
- Current weight, with comparison to a recent outpatient weight (if known)
- General appearance: toxic appearance, distress, fatigue, decreased mentation
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Level of consciousness and ability to arouse normally
- Appearance of eyes (sunken, icteric), presence or absence of tears with crying
- Mucous membranes (moist, tacky or sticky, or dry)
- Abdomen: assessment for distension, quantity and quality of bowel sounds, location of tenderness, guarding, peritoneal signs (including rigidity or rebound), palpation of masses or organomegaly

- Skin: turgor, rashes, presence of periumbilical ecchymosis (Cullen sign), flank ecchymosis (Grey Turner Sign), bruising, abrasions, purpura, lesions, xanthomas, hyperpigmentation, jaundice
- Respiratory: auscultation, observation for depth of respirations and difficulty breathing
- Costovertebral angle tenderness
- Neurologic: signs of central nervous system dysfunction (eg, depressed mental status, focal neurologic deficits)
- Visual examination of emesis, if possible

CASE FOCUS

Physical Examination

Flora's vital signs reveal she has been afebrile, tachycardic (resting heart rate: 130–150 beats/min), and tachypneic (respiratory rate: 30–40 breaths/min). She has had normal blood pressures for age and normal oxygen saturations. Her weight upon arrival to the inpatient unit earlier was 61.3 lb (27.8 kg). Her weight at a recent clinic visit was 65.3 lb (29.6 kg), indicating an approximate weight loss of 6%.

On examination, Flora appears uncomfortable and anxious but is able to communicate appropriately with you. During the examination, she endorses persistent pain and nausea and has an episode of nonbloody, nonbilious, emesis of small volume. Her eyes appear sunken but are anicteric. Her mucous membranes are tacky, and her lips are dry. She is tachycardic without a murmur, and her peripheral pulses are normal. Her capillary refill time is prolonged (4 seconds), and her hands and feet are slightly cool. Her lungs are clear to auscultation with quick, shallow breaths. Her abdomen is mildly distended, and she has slightly decreased frequency of bowel sounds. With palpation, her abdomen is diffusely tender, but soft, with increased tenderness over the epigastrium. She does exhibit voluntary guarding, but you do not appreciate any peritoneal signs. No masses or organomegaly are palpated. There is no appreciable flank or costovertebral angle tenderness. The remainder of Flora's examination is normal, including a nonfocal neurologic examination.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a child with persistent abdominal pain and emesis?

There are many causes of abdominal pain and emesis in children; however, the etiologies can be narrowed based on a complete history and thorough physical examination. Table 42.1 demonstrates a differential diagnosis for these symptoms and has been separated into diagnoses that appear more or less likely for Flora.

Table 42.1. Differential Diagnosis for a Child With Abdominal Pain and Vomiting

Diagnoses of highest suspicion	• Acute infectious gastroenteritis (viral, bacterial, parasitic)[a] • Appendicitis (retroileal or retrocolic) • DKA • Ingestions or toxic exposures • Malrotation with or without volvulus • Pancreatitis[a] • PUD[a] • Small bowel obstruction • UTI or pyelonephritis

(continued)

Table 42.1. Differential Diagnosis for a Child With Abdominal Pain and Vomiting *(continued)*

Other diagnoses to consider	• Abdominal migraine • Adrenal insufficiency • Allergic reaction, including a delayed hypersensitivity reaction (eg, FPIES) • Cholecystitis, choledocholithiasis, cholangitis • Constipation • Cyclic vomiting syndrome • Hepatitis • Hypercalcemia • IBD • IgA vasculitis • Inborn errors of metabolism • Intussusception • Mesenteric adenitis • Ovarian (or testicular) torsion • Peritonitis or visceral perforation • Pneumonia • Postinfectious ileus • Urolithiasis

Abbreviations: DKA, diabetic ketoacidosis; FPIES, food protein–induced enterocolitis syndrome; IBD, inflammatory bowel disease; IgA, immunoglobulin A; PUD, peptic ulcer disease; UTI, urinary tract infection.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with acute-onset abdominal pain, vomiting, and dehydration?

- Clinicians seeing children presenting with these symptoms should prioritize evaluating for possible surgical emergencies (eg, acute abdomen, bowel obstruction, ovarian/testicular torsion). Common diagnostic studies for patients in whom there is concern for an acute surgical emergency may include serum electrolytes and inflammatory markers, ultrasonography (US), radiography, or computed tomography (CT). In young children, the most common cause of an acute abdomen is intussusception, whereas in older children, the most common cause is appendicitis. For Flora, her history and examination are less concerning for an acute abdomen at this time.
- Once an acute abdomen is ruled out, further diagnostic testing should be based on the patient's history and examination. Depending on the diagnoses of highest suspicion, tests that may be indicated include
  - Blood glucose level, to evaluate for hypoglycemia (in the setting of poor oral intake) or hyperglycemia (if there is a suspicion for diabetic ketoacidosis [DKA]).
  - Serum chemistries (including calcium and phosphorus, blood urea nitrogen [BUN], and creatinine levels), if there is concern for electrolyte derangements related to prolonged vomiting or significant dehydration.
  - Lipase and amylase levels, to evaluate for pancreatitis.
  - Urinalysis (UA; with culture when infection is suspected), to evaluate for urinary tract infection (UTI), urolithiasis, or DKA.
  - Complete blood cell count and inflammatory markers (eg, C-reactive protein), to assess for evidence of infection and inflammatory response.
  - Liver enzymes, bilirubin, and right upper quadrant US, if there is concern for gallstones, hepatic inflammation, or cholecystitis.
  - Upper endoscopy, if there is concern for peptic ulcer disease.

CASE FOCUS

Diagnostic Evaluation

You notice that Flora did not have any diagnostic testing when she was admitted earlier in the day. Based on her worsening symptoms, you decide to start your evaluation with laboratory testing. You would like to evaluate for pancreatitis, UTI, and DKA. You are also concerned about electrolyte abnormalities and acute kidney injury (AKI) given her hydration status. The results of these tests are as follows:

Laboratory test	Results	Reference range
Serum chemistries		
Sodium	143 mEq/L (143 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.7 mEq/L (3.7 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	111 mEq/L (111 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	17 mEq/L (17 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	15 mEq/L (15 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	21 mg/dL (7.50 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)	0.3–0.6 mg/dL (26.5–53.0 µmol/L)
BUN to creatinine ratio	26	10–20
Glucose	72 mg/dL (4 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
AST	34 U/L (0.57 µkat/L)	13–35 U/L (0.22–0.58 µkat/L)
ALT	29 U/L (0.48 µkat/L)	10–35 U/L (0.17–0.58 µkat/L)
Bilirubin, total	0.2 mg/dL (3.42 µmol/L)	<1.2 mg/dL (20.52 µmol/L)
Calcium	10 mg/dL (2.50 mmol/L)	9.2–10.5 mg/dL (2.30–2.63 mmol/L)
Pancreatic enzymes		
Amylase	200 U/L (3.34 µkat/L)	25–101 U/L (0.42–1.69 µkat/L)
Lipase	1,091 U/L (18.22 µkat/L)	4–39 U/L (0.07–0.65 µkat/L)
CBC		
WBC count	7,100/µL (7.1 × 10^9/L)	4,000–13,000/µL (4–13 × 10^9/L)
Hemoglobin	12.4 g/dL (124 g/L)	11.5–14.5 g/dL (115–145 g/L)
Platelet count	445 × 10^3/µL (445 × 10^9/L)	150–400 × 10^3/µL (150–400 × 10^9/L)
Other		
Triglycerides	89 mg/dL (1.01 mmol/L)	<130 mg/dL (1.47 mmol/L)
CRP	8.3 mg/dL (83 mg/L)	<1 mg/dL (10 mg/L)
Urinalysis	Specific gravity ≥1.030, positive for ketones but negative for glucose, leukocyte esterase, blood, or nitrites	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; CRP, C-reactive protein; WBC, white blood cell.

Arriving at a Diagnosis

Q: How do you develop an assessment for Flora?

In thinking through her case, you decide to first interpret Flora's history, vital signs, examination findings, and diagnostic evaluation and then assess her hydration status. This will help you develop a list of findings in order to narrow your differential diagnosis to the most likely etiology or etiologies.

1. **Interpret key findings from the history, vital signs, examination, and diagnostic evaluation.**
   - History: Flora is an 8-year-old otherwise healthy girl who presents with acute onset of moderate to severe abdominal pain, vomiting, and oral intolerance. Her symptoms were unrelieved with outpatient ondansetron and acetaminophen. She had temporary relief with IV morphine and ondansetron in the ED, but the use of IV fluids, acetaminophen, and ibuprofen since admission has failed to improve her symptoms. Her pain radiates to her back and is improved by leaning forward.
   - Physical examination: Her examination reveals abdominal tenderness that is worse in the epigastrium. She does not have any signs concerning for an acute surgical abdomen. She has multiple signs of dehydration (eg, sunken eyes, tacky mucosa, prolonged capillary refill time). She has experienced weight loss of approximately 6%, which suggests moderate dehydration.
   - Laboratory tests: An elevated serum lipase level points toward pancreatic inflammation. Flora's UA and serum chemistries are consistent with dehydration as indicated by the elevated specific gravity on UA, elevated BUN level, and elevated creatinine level for age (concerning for possible AKI) with a slight metabolic acidosis with an elevated anion gap. Her normal serum glucose level rules out DKA, and her UA results help to rule out UTI and urolithiasis.
2. **Develop the list of findings.**

Q: What major findings have you identified for Flora?

- Acute onset of abdominal pain and vomiting
- Mild anion gap metabolic acidosis
- Possible AKI
- Moderate dehydration
- Elevated serum amylase and lipase levels

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Flora's presentation?

Based on her clinical presentation and elevated serum amylase and lipase, you determine that Flora has acute pancreatitis.

Q: How is a diagnosis of acute pancreatitis made?

Acute pancreatitis is defined as inflammation of the pancreas, characterized by at least 2 of the following 3 criteria:

- Acute abdominal pain (for nonverbal children, consider other potential symptoms of pancreatitis, such as vomiting or fussiness).
- Pancreatic enzymes (amylase and/or lipase) elevated to at least 3 times the upper limit of normal.
  - Lipase: Serum lipase begins to increase between 4 to 8 hours after the onset of symptoms and typically peaks after 24 hours. Lipase can stay elevated for 7 to 14 days, therefore, it is helpful in diagnosing pancreatitis when patients present more than 24 hours after symptom onset. Lipase is more sensitive and specific than amylase, making it a useful laboratory marker of acute pancreatitis.
  - Amylase: Serum amylase levels rise faster than lipase levels in acute pancreatitis and often can normalize by 24 hours after the onset of symptoms. This timing limits the usefulness of serum amylase in patients with a delayed presentation. Serum amylase may be elevated on the basis of nonpancreatic pathology more frequently than lipase (eg, in renal injury).

- Radiologic evidence of pancreatic inflammation (pancreatic edema, fat stranding, or peripancreatic fluid collection or necrosis).
  - Radiographic studies are not necessary for the diagnosis of acute pancreatitis, but they can help to evaluate the etiology.
  - For patients with suspected *complicated pancreatitis* (defined as acute pancreatitis with complications such as cyst formation, necrosis, or fistulas), imaging should always be obtained. Imaging modalities are debated in the literature, but the general consensus in pediatrics supports transabdominal US if biliary pancreatitis is suspected and contrast-enhanced CT for patients with severe presentation or a deteriorating condition. Magnetic resonance cholangiopancreatography is useful in detecting distal pancreaticobiliary abnormalities.

Note: Additional classifications of pancreatitis exist (eg, acute recurrent pancreatitis, chronic pancreatitis) but are not discussed in this chapter.

Flora has the classic clinical signs of pancreatitis, including abdominal pain and vomiting, and amylase and lipase levels more than 3 times normal.

Q: How do you assess the severity of Flora's acute pancreatitis?

- Severe acute pancreatitis is characterized by severe acinar cell injury–mediated local inflammation with progression to systemic inflammatory response syndrome (SIRS). This is accompanied by multiple organ injury, which may lead to significant morbidity and mortality.
- The severity of the patient's disease does not correlate with the level of elevation of lipase or amylase. Markers of severe disease include the presence of uremia, hyperglycemia, hypoxemia, leukocytosis, and anemia.
- Consistent with adult literature, pediatric studies have suggested that an elevated BUN level can be a marker for severe acute pancreatitis. Obtaining a BUN level on presentation can also be a useful marker for assessing the underlying physiologic state of the patient, including the degree of intravascular volume depletion and prerenal azotemia. A persistent elevation or rise in BUN during hospitalization may reflect either a failure of volume resuscitation (ie, continued or worsening intravascular volume depletion) or deterioration of renal function.
- Flora's laboratory test results demonstrate elevated BUN and creatinine levels, and she has resting tachycardia and tachypnea, which could relate to pain, intravascular volume depletion, or SIRS. She does not currently demonstrate hyperglycemia, leukocytosis, anemia, or hypoxemia, making severe acute pancreatitis less likely. Because these findings can change over time, the severity of Flora's pancreatitis should be reassessed until clear improvement is demonstrated.

Q: How do you determine the underlying etiology of Flora's pancreatitis?

Causes of acute pancreatitis in children include the following:

- Idiopathic (the most common etiology in children)
- Medication or drug related: antiseizure medications, chemotherapy, immunomodulators, total parenteral nutrition (TPN)
- Infection (eg, mumps, *Mycoplasma*)
- Obstructive or anatomic: cholelithiasis, biliary tract cysts, Caroli disease, pancreatic duct stricture, pancreatic divisum, abdominal masses, postoperative complication
- Autoimmune or systemic disease: chronic kidney disease, DKA, Kawasaki disease, immunoglobulin A vasculitis, inflammatory bowel disease, systemic lupus erythematosus
- Genetic
  - α_1-antitrypsin deficiency, hypercalcemia, propionic acidemia, cystic fibrosis, familial hypertriglyceridemia
  - Mutations in the following genes are associated with an increased risk of pancreatitis: *PRSS1*, *SPINK1*, chymotrypsin-C, *CFTR*
- Toxin or exposure-related: alcohol, smoking, scorpion stings, spider bites
- Mechanical or traumatic: motor vehicle collision, bicycle handlebar injuries, abuse
- Nutritional etiologies (eg, severe malnutrition, as seen in eating disorders)
- Metabolic, including hypertriglyceridemia and hypercalcemia

In reviewing these causes of acute pancreatitis, you recall that Flora's family denied recent travel, illness, trauma, medications, insect bites or stings, or ingestions. Flora's family also denied symptoms of or risk factors for biliary pancreatitis. Additionally, Flora is fully immunized, has been developing appropriately, and her laboratory assessment is not consistent with DKA or hypertriglyceridemia. Given that this is Flora's first episode of pancreatitis and she has no history of associated diseases or exposures, idiopathic pancreatitis seems most likely.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a child with suspected pancreatitis?

Flora is already hospitalized, but you consider what would be reasonable admission criteria for a child with suspected pancreatitis:

- There is concern that a child will not be able to tolerate adequate oral intake.
- There is concern that pain or nausea will not be sufficiently managed at home.
- There is evidence of severe acute pancreatitis or concern for complications (eg, necrosis, pseudocyst formation).
- The patient's family is not comfortable with home management, return precautions, or the follow-up plan.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Flora is an 8-year-old otherwise healthy girl who presents with acute onset of epigastric abdominal pain, intractable vomiting, moderate dehydration, AKI, and an elevated anion gap metabolic acidosis. She has significantly elevated pancreatic enzymes consistent with a diagnosis of acute pancreatitis, which is likely idiopathic in nature. She requires continued hospitalization for fluid resuscitation, close clinical monitoring, and symptom management.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Most pediatric patients with acute pancreatitis have a mild course; however, patients with acute pancreatitis should receive aggressive fluid resuscitation and pain control. Cardiac, renal, and pulmonary complications of pancreatitis often present within the first 48 hours of illness; thus, patients require close clinical monitoring. The management and monitoring of acute pancreatitis can be divided into the following considerations:

1. **Pain control:** Pediatric studies are limited, but the mainstays of pharmacologic therapy to treat pancreatitis-associated pain are acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids.
   - If pain is uncontrolled with oral options, IV analgesia should be considered.
   - In small children or patients otherwise unable to verbalize or otherwise indicate their pain severity, monitoring for pain behaviors (eg, fussiness, inconsolability, grimace, restlessness) is especially important.
   - Given the severity of Flora's pain despite acetaminophen and her continued emesis, you will initiate IV analgesics.
2. **Fluid resuscitation and maintenance of hydration:** Patients with acute pancreatitis are at risk of intravascular volume depletion related to emesis, poor oral intake, and third-spacing of fluid into the abdomen. Because of this, timely fluid administration corrects hypovolemia and can prevent circulatory collapse and end-organ damage.

- In children with acute pancreatitis, fluid resuscitation should begin with 10 to 20 mL/kg IV boluses of crystalloids. Recent retrospective data suggests the use of lactated Ringer solution is associated with a shorter length of stay when compared to normal saline for fluid resuscitation and maintenance.
- For the first 24 to 48 hours, continued volume replacement should be provided at 1.5 to 2 times the maintenance IV fluid rate with normal saline or lactated Ringer solution plus 5% dextrose. The rate of IV fluid administration should be adjusted based on the patient's overall volume status and urine output (normally 1–4 mL/kg/h).
- Patients should be monitored closely for signs of third-space fluid sequestration (eg, peripheral, peritoneal, pleural).
- IV fluids should be discontinued once the patient has clinically improved and is able to maintain adequate hydration enterally.
- Because of Flora's dehydration and elevated BUN and creatinine levels, you will provide fluid resuscitation with an IV bolus of isotonic crystalloid and increase her IV fluid rate to 2 times maintenance for the next 24 hours. You will monitor her urine output and clinical examination closely to ensure her intravascular volume is adequate repleted.

3. **Nutrition:** Historically, patients with acute pancreatitis have been made nil per os (nothing by mouth) and placed on strict bowel rest to prevent stimulation of pancreatic exocrine secretions. Newer literature supports early enteral feeding initiation in mild pancreatitis, in the absence of contraindications.
   - Initiate early advancement to oral/enteral nutrition as tolerated. Early initiation of oral/enteral feedings may decrease both length of stay and the risk of end-organ dysfunction.
   - Nasogastric or nasojejunal feeds may be initiated if a patient is improving but is unable to tolerate oral feeding.
   - TPN should be reserved for children in whom enteral nutrition cannot be safely introduced within 5 to 7 days. TPN is considered a last resort given the need for placement of a central line.
   - Although there is a lack of strong evidence regarding the optimum diet following an episode of acute pancreatitis, general consensus supports initiation of a regular diet in mild cases.
   - Flora can resume a regular diet without fat restriction as her pain, nausea, and emesis improve.
4. **Further diagnostic testing**
   - Laboratory tests: All patients with acute pancreatitis should undergo baseline testing of serum electrolytes, renal function, and blood counts. A hepatic function panel and triglyceride and serum calcium levels should be obtained to investigate potential etiologies. Additionally, patients with recurrent pancreatitis or a relevant family history should undergo testing for genetic etiologies.
   - Imaging: Although pancreatic imaging is not required for the diagnosis of acute pancreatitis in children, it can be helpful in certain situations.
     - Pancreatic imaging is indicated when signs or symptoms of potential complications arise (eg, clinical deterioration or fever, worsening pain, uremia, SIRS, leukocytosis, respiratory distress). CT scan of the abdomen with IV contrast is the best imaging modality to evaluate for pancreatic infected necrosis or pseudocyst formation but is ideally performed more than 96 hours after the onset of symptoms.
     - If biliary pancreatitis or structural defects are suspected, transabdominal US should be obtained, with magnetic resonance cholangiopancreatography being reserved for cases in which visualization of the biliary and pancreatic ductal systems is required.
   - At this time, Flora appears to have a case of uncomplicated acute pancreatitis and will not require diagnostic imaging.
5. **Laboratory and clinical monitoring:** Close clinical monitoring of admitted patients with acute pancreatitis can provide indicators of developing complications, including fluid collections, necrosis, abdominal compartment syndrome, SIRS, and organ dysfunction or failure, which would necessitate transfer to the intensive care unit.

Recovery is primarily monitored clinically for uncomplicated acute pancreatitis. There is no indication to trend amylase and lipase levels in uncomplicated acute pancreatitis, and normalization of pancreatic enzymes is not necessary prior to resuming enteral feedings.

- Vital signs should be obtained at least every 4 hours during the first 48 hours of admission and during periods of aggressive hydration.
- Serum electrolytes and renal function should be monitored in the first 48 hours and corrected as appropriate, but there is no consensus recommendation regarding laboratory testing frequency.
- For Flora, you decide to monitor electrolytes and renal function every 12 hours for the first 24 hours of hospitalization to ensure she is responding to your interventions. Laboratory tests may then be reduced to daily frequency.

6. **Prophylactic adjuncts:** Routine use of prophylactic medications (eg, antibiotics, antioxidants, probiotics, protease inhibitors) is not recommended in acute uncomplicated pancreatitis in pediatrics. Of note, prospective pediatric studies are lacking in acute pancreatitis. Many current recommendations are obtained from retrospective pediatric studies and adult literature.
7. **Indications for specialist consultation**
   - Gastroenterology: Recurrent, chronic pancreatitis; pancreatic insufficiency or complications; anticipated need for endoscopic retrograde cholangiopancreatography
   - Pain/anesthesia: Persistent or difficult-to-control pain, patients with complicated or complex pain syndromes
   - Genetics: Recurrent and/or hereditary pancreatitis, hypertriglyceridemia
   - Surgery: Early consultation for any patient who develops a complication (eg, pancreatic pseudocyst, abscess, necrotizing pancreatitis)

CASE FOCUS

Plan for Treatment and Monitoring

- **Pain control:** Because Flora has not responded to as-needed acetaminophen alone, you decide to add IV morphine every 4 hours as needed to her pain management regimen. You will consider the addition of IV ketorolac once she receives appropriate fluid resuscitation and her creatinine has normalized.
- **Fluid resuscitation and maintenance of hydration**
  - Flora demonstrates signs consistent with moderate dehydration and intravascular volume depletion, so you decide to provide a lactated Ringer solution bolus of 20 mL/kg and then start IV fluids with lactated Ringer solution in 5% dextrose at a rate of 2 times maintenance based on her weight (ie, 140 mL/h). You will monitor Flora's urine output closely.
  - You plan to wean Flora's IV fluid rate as her clinical examination, symptoms, and oral intake improve.
- **Nutrition:** Because Flora is in the first 24 hours of her hospitalization, you elect to order a clear diet with plans to advance her diet to a regular diet as tolerated over the course of the hospitalization.
- **Further diagnostic testing:** No additional diagnostic testing is required at this time because Flora seems to have an acute presentation of idiopathic pancreatitis, you are intervening within the first 2 to 3 days of symptom onset, and you do not suspect a complication.
- **Clinical monitoring:** You order vital signs and nursing examinations every 4 hours, serial abdominal assessments and close monitoring of urine output and volume status.
- **Laboratory monitoring:** You order serum chemistries and renal function every 12 hours for the first 24 hours to ensure interventions are effective. You plan to space these tests then to every 24 hours while Flora is hospitalized as long as she continues to improve.

Case Resolution

Over the next 3 days, Flora receives fluid resuscitation and continues on IV pain medication until her enteral tolerance and pain improves. Her vital signs are closely monitored every 4 hours, and her tachycardia resolves. Her urine output returns to normal at 2 mL/kg/h. Her chemistries and renal function are trended every 12 hours for the first 24 hours and then spaced to daily, with noted resolution of metabolic acidosis and AKI. As her pain and nausea improve, she is weaned from IV fluids, and pain medications are transitioned to oral acetaminophen and ibuprofen to use as needed. Her course is uncomplicated, and she does not require further imaging or interventions. Flora and her family are provided education about pancreatitis and given strict return precautions. Follow-up plans are established with her pediatrician for 2 days after discharge.

Discharge Criteria

Q: How do you know when Flora is ready to go home?

You can feel comfortable discharging your patient with acute uncomplicated pancreatitis when the following criteria are met:

- The patient is able to tolerate diet and liquids at volumes sufficient to maintain hydration.
- Symptoms, including pain and nausea, can be managed by oral medications.
- Any electrolyte or acid-base abnormalities are corrected.
- Close follow-up is available or established.

Anticipatory Guidance

Q: What instructions should you provide Flora's caregivers upon discharge?

- Close follow-up in 2 to 3 days with Flora's primary care provider is needed to help identify potential complications or recurrence.
- Encourage fluids at frequent intervals to maintain adequate hydration.
- A nutritious diet is recommended.
- Over-the-counter medications, including acetaminophen and nonsteroidal anti-inflammatory drugs, can be used for pain control as needed.
- Signs of recurrence may include worsening abdominal pain, persistent vomiting, refusal of oral intake, dehydration (as evidenced by decreased urine output or weight loss), lethargy, and fevers.
- If there are any signs of recurrence or other concerns, return to the hospital for evaluation.

Clinical Pearls

- Serum lipase is a more sensitive biomarker than serum amylase for acute pancreatitis in children.
- Pancreatic enzyme levels and severity of disease do not necessarily correlate, and elevated pancreatic enzymes may not be present in all cases of acute pancreatitis. Additionally, pancreatic enzyme levels do not need to be trended once the diagnosis is made.
- Aggressive IV rehydration is recommended upon diagnosing acute pancreatitis, ideally with lactated Ringer solution.
- Unless in the case of extenuating circumstances, strict nil per os status and absolute bowel rest is not routinely indicated in cases of acute pancreatitis. If tolerated, early initiation of enteral feeds in the first 48 to 72 hours (oral vs nasogastric) has been shown to reduce length of stay and complications.
- In cases of mild acute pancreatitis, a regular diet is recommended.
- Complications, including necrosis or pseudocyst, are present in up to 10% of patients with pancreatitis; therefore, close clinical monitoring and outpatient follow-up is imperative.

Documentation Tips

- Document the presence of irritability, abdominal distension, epigastric abdominal pain, fever, or vomiting.
- Include abnormal amylase and lipase values, indicating the degree of elevation above normal.
- Include interpretation of imaging and whether it is consistent with pancreatitis.
- Document the need for supplemental IV fluids and the importance of monitoring volume status.
- Document the need for serial monitoring of electrolytes or renal function.
- Document whether imaging is indicated.

Suggested Reading

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CASE 43

Scott, a 3-Year-Old Boy With Bloody Diarrhea and Decreased Urination

CASE PRESENTATION

Scott is a 3-year-old boy with no significant medical history who is being admitted from the pediatric emergency department (ED) after presenting with 5 days of diarrhea. His parents are worried because his stools now contain blood, and they have noticed fewer wet diapers over the last 24 hours. In the ED, Scott received 2 fluid boluses totaling 40 mL/kg of normal saline (0.9%), he was started on intravenous (IV) fluids at his maintenance rate, and his stool was confirmed to be heme-positive by fecal occult blood testing. Laboratory tests were also performed and are pending. You arrive at Scott's bedside to admit him to your unit and learn more about his history and symptoms.

Patient History and Review of Systems

Q: What information should you collect from Scott's caregivers?

- History of present illness
  - Onset, duration, and progression of symptoms
  - Number of episodes of diarrhea, with an estimate of diarrheal volumes and description of stool
  - Presence of nausea and/or any episodes of vomiting; color of vomitus, if applicable
  - Signs of dehydration: estimation of recent urine output, sunken appearance to the eyes, malaise, lethargy, irritability, absence of tears
  - Possible exposures: recent dietary intake, including unpasteurized juice or dairy products or undercooked meats, seafood, or eggs; travel and activity history, including recent water-related activities and animal contact; sick contacts, including attendance to child care
  - Associated symptoms, such as fever, headache, abdominal or back pain, change in mentation, rash, or urinary symptoms
- Medical history, including underlying health status and immunization status (specifically rotavirus vaccine status)
- Medications, including recent use of antibiotics and over-the-counter medications

CASE FOCUS

History and Review of Systems

From your conversation with Scott's parents, you learn that Scott has been sick for 5 days. His symptoms started with multiple episodes of watery diarrhea, which have become darker in color. His parents estimate he was initially having between 8 and 10 watery stools each day, but the episodes of diarrhea are now becoming less frequent and contain bright red blood. Scott has not had any vomiting or nausea. He is having abdominal pain, frequently pointing to his stomach, saying "my tummy hurts," and occasionally crying from the pain. His parents are unable to correlate his pain to his bowel movements. Over the last day, he has had very few wet diapers outside of those with his bloody stool, and he has become progressively more listless and tired appearing. Scott was eating his regular diet before his illness started, and his family denies any concerning dietary exposures. He has continued to drink well throughout his illness, although his intake of food is decreased. Last week, Scott and his family went to a pumpkin patch in a nearby town, which also had a petting zoo, where he played for several hours. He has not had any known sick contacts, although a family friend who went to the same petting zoo said that their child developed diarrhea yesterday. Scott's family has been treating his abdominal pain with acetaminophen and ibuprofen. His parents have noticed that he feels warm to the touch today, but they have not taken his temperature. They deny that he has complained of headache, and they have not noticed any rash. His review of systems is otherwise negative. Scott has no chronic medical conditions, does not take any regular medications, and is up to date on his immunizations.

Physical Examination

Q: What parts of the physical examination should you focus on for Scott?

- Complete set of vital signs
- Height and weight, with comparison to most recent weight (if available)
- Level of consciousness and ability to arouse normally
- Appearance of eyes (sunken, icterus)
- Presence or absence of tears with crying
- Mucous membranes (moist, sticky, or dry)
- Peripheral perfusion: capillary refill time, color and temperature of extremities, quality of peripheral pulses
- Abdomen: tenderness, guarding, masses, quantity and quality of bowel sounds
- Respiratory: auscultation and depth of respirations
- External anal examination to evaluate for fissures and hemorrhoids
- Costovertebral angle tenderness
- Skin: turgor, presence of rashes (including petechiae and purpura), bleeding from IV site
- Assessment for edema, including the extremities, abdomen, back, and genitourinary area
- Neurologic: lethargy, cranial nerve palsies, other focal neurologic deficits
- Visual examination of the stool

CASE FOCUS

Physical Examination

Scott's weight upon arrival to the ED is noted to be 15.1 kg (66th percentile for age), and his height is 95 cm (50th percentile for age). His parents are unsure of a recent weight. His most recent vital signs demonstrate that he is febrile with a temperature of 38.5 °C (101.3 °F) and tachycardic (heart rate: 155 beats/min) with tachypnea (respiratory rate: 40 breaths/min). Scott's blood pressure is elevated for height and age (122/89 mm Hg), despite the fact that he was calm when his blood pressure was measured. His oxygen saturation is normal.

On examination, Scott appears flushed, appropriately responsive to your examination but crying for his mother. As he cries, his eyes glisten with tears, and there is no scleral icterus. He appears to have mild periorbital edema, and his oral mucosa is moist. Mild conjunctival pallor is noted. His cardiac and respiratory examinations are significant for tachycardia, tachypnea, and a few faint scattered crackles but are otherwise normal. His peripheral pulses are normal, his capillary refill time is less than 2 seconds, and his extremities are warm to the touch. As you examine his extremities, his mother remarks that his feet look "puffier" than normal, and you note there is mild pitting edema of his ankles. His bowel sounds are hyperactive, and his abdomen seems tender because he cries and pushes you away when you palpate it; however, there are no obvious masses, organomegaly, or peritoneal signs. You do not notice any rashes. His neurologic examination is nonfocal. Visualized stool shows dark brown, watery stool in Scott's diaper. Red blood is noted to be mixed into his stool. He voided a small amount of dark urine after his second saline bolus.

Differential Diagnosis

Q: Scott appears to be having symptoms involving multiple organ systems. Thinking broadly, what is the differential diagnosis for some of his symptomatology?

In complex cases such as Scott's, it can be useful to consider the differential diagnosis for the most prominent symptoms the patient is experiencing. For Scott, you think that his bloody diarrhea, decreased urination (oliguria), and hypervolemia (as evidenced by hypertension, pulmonary rales, and peripheral edema) will be useful for developing a differential diagnosis. The differential for bloody stool in children is explored in Table 34.1 (Case 34). From this table, you are most concerned about an infectious colitis. The differential diagnoses for oliguria and hypervolemia are shown in Box 43.1. The etiologies you are most concerned about for Scott are the possibility of decreased oncotic pressure or intrinsic renal pathology.

Box 43.1. Differential Diagnosis for a Child With Oliguria and Hypervolemia

Causes of oliguria	Causes of hypervolemia
• Prerenal etiologies — Decreased effective circulating volume (eg, GI losses, renal losses, hemorrhage) — Decreased oncotic pressure[a] (eg, nephrotic syndrome, malnutrition, protein-losing enteropathy) — Increased resistance to flow (renal artery stenosis) — Loss of vascular tone (sepsis, anaphylaxis) • Intrinsic renal etiologies[a]: glomerular, tubular, interstitial, or vascular injury (eg, acute tubular necrosis, glomerulonephritis, nephrotoxin exposure, interstitial nephritis, thrombotic microangiopathy [including TTP and HUS]) • Postrenal etiologies: obstruction (eg, urinary retention, ureteropelvic junction obstruction, renal calculi)	• Acute or chronic renal failure[a] • Capillary leak from severe inflammation, sepsis, etc • Cardiac dysfunction • Decreased oncotic pressure[a] • Iatrogenic from excessive fluid administration • Liver failure

Abbreviations: GI, gastrointestinal; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

[a] Diagnoses that seem most likely based on your patient's presentation

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with bloody diarrhea, oliguria, and hypervolemia?

- Given the broad differential diagnosis for these symptoms, clinicians should conduct testing for the etiologies of highest suspicion based on the patient's history and examination. Abdominal ultrasonography, upper gastrointestinal (GI) series, or computed tomography of the abdomen may be needed if there is concern for intussusception, midgut volvulus, or another acute intra-abdominal etiology.
- When there is concern for oliguria and hypervolemia, serum electrolytes, blood urea nitrogen, creatinine, and albumin levels, and a urinalysis (UA) should be obtained. It is also reasonable to obtain a CBC and liver function panel to evaluate for evidence of other organ system involvement. If glomerulonephritis is suspected because of the presence of hematuria, oliguria, and hypervolemia, clinicians should also obtain a C3 and C4. Refer to Case 30 for the diagnostic evaluation of suspected glomerulonephritis.
- When there is concern for anemia or a thrombotic microangiopathy (including thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]), a complete blood cell count (CBC) with differential, peripheral smear, and reticulocyte count should be obtained. When a hemolytic anemia is suspected based on these findings, obtaining a lactate dehydrogenase level and direct antiglobulin testing are warranted.
  - It should be noted that TTP is rare in children; however, when there is concern for TTP, ADAMTS-13 activity can be tested, as it is low in both the inherited and acquired forms of TTP. If ADAMTS-13 activity is low, anti-ADAMTS-13 autoantibodies should be obtained to evaluate for acquired TTP.
  - Patients with suspected HUS should have stool testing for evidence of Shiga toxin–producing *Escherichia coli* (STEC) as outlined in the following section. Additionally, for patients with suspected HUS and a negative stool testing, serologic testing for antibodies against some STEC serotypes can be performed. When other causes of HUS are suspected, further testing should be directed by subspecialist consultation.
- When evaluating a patient with bloody diarrhea, it may be prudent to test a stool sample to confirm the presence of blood. If the stool sample is positive for blood, the bleeding should then be classified as upper GI tract bleeding, which usually presents as hematemesis or melena, or lower GI tract bleeding, which usually presents as hematochezia.

— For suspected infectious etiologies of lower GI tract bleeding, stool should be sent for the following tests:

- Stool culture[a]: Testing for STEC, *Yersinia enterocolitica*, *Salmonella* spp, *Shigella* spp, and *Campylobacter* spp.
- Stool testing for the presence of Shiga toxins or genes that encode Shiga toxins. A rectal swab for Shiga toxins can be collected if there is a delay in obtaining a stool sample.
- *Clostridioides difficile* testing[a]: *C difficile* testing may vary by institutional protocol but should include some combination of glutamate dehydrogenase testing, nucleic-acid amplification testing, and toxin testing. *C difficile* infection is unlikely in infants and children younger than 2 years of age, but should be considered in that population when there is a lack of an alternative explanation for their symptoms.
- Microscopy[a] or direct fluorescent antibody testing to evaluate for ova and parasites.
- Viral testing of the stool (most often done by polymerase chain reaction) should be considered for patients who are immunocompromised.

[a] Of note, at many institutions, obtaining a stool pathogen panel by polymerase chain reaction may be more timely and cost-effective than performing these tests separately.

CASE FOCUS

Diagnostic Evaluation

As you review Scott's chart, you note that the ED physician ordered a CBC with differential and peripheral smear as well as a renal function panel, UA, and electrocardiogram. The results are as follows:

Laboratory test	Results	Reference range
Serum chemistries		
Sodium	137 mEq/L (137 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	107 mEq/L (107 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	15 mEq/L (15 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	50 mg/dL (17.85 mmol/L)	6–20 mg/dL (2.14–7.14 mmol/L)
Creatinine	2.2 mg/dL (194.5 µmol/L)	0.2–0.4 mg/dL (17.7–35.4 µmol/L)
Glucose	85 mg/dL (4.72 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Albumin	3.1 g/dL (31 g/L)	3.6–5.2 g/dL (36–52 g/L)
CBC with peripheral smear		
WBC count	19,300/µL (19.3×10^9/L)	4,000–13,000/µL ($4–13 \times 10^9$/L)
RBC count	2.5×10^6/µL (2.5×10^{12}/L)	$4.0–5.1 \times 10^6$/µL ($4.0–5.1 \times 10^{12}$/L)
Hemoglobin	7 g/dL (70 g/L)	11.5–14.5 g/dL (115–145 g/L)
Hematocrit	19.5% (0.195)	33%–43% (0.33–0.43)
MCV	80.5 μm^3 (80.5 fL)	76–90 μm^3 (76–90 fL)
MCH	28 pg/cell	26–31 pg/cell
MCHC	35 g/dL (350 g/L)	32.4–35 g/dL (324–350 g/L)
RDW	15% (0.15)	11.3%–13.5% (0.113–0.135)
Platelet count	58×10^3/µL (58×10^9/L)	$150–400 \times 10^3$/µL ($150–400 \times 10^9$/L)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Results	Reference range
CBC with peripheral smear *(continued)*		
MPV	12.5 fL	6.4–9.5 fL
Neutrophils	45% (0.45)	54%–62% (0.54–0.62)
Lymphocytes	50% (0.50)	25%–33% (0.25–0.33)
Monocytes	5% (0.05)	3%–7% (0.03–0.07)
Eosinophils	0% (0)	1%–3% (0.01–0.03)
Basophils	0% (0)	0%–0.75% (0–0.0075)
Blasts	0% (0)	0% (0)
Anisocytosis	Slight	
Poikilocytosis	Slight	
RBC morphology	Abnormal	
Polychromasia	Slight	
Elliptocyte	Slight	
Schistocyte	Moderate	
Tear drop	Slight	
Urinalysis		
pH	6	4.5–8
Specific gravity	1.030	1.005–1.025
Glucose	Negative	Negative
Protein	1+	Negative
Bilirubin	1+	Negative
Urobilinogen	Negative	Negative
Blood	Moderate	Negative
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocytes	Negative	Negative
Clarity	Turbid	Clear
Color	Dark Yellow	Yellow
RBC (microscopy)	5–10/HPF	Occasional
Other		
ECG	Sinus tachycardia	NA

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; ECG, electrocardiogram; HPF, high-power field; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; NA, not applicable; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell.

Given Scott's history and these test results, you decide to order the following stool studies: *C difficile* testing and stool culture, microscopy for ova and parasites, and testing for Shiga toxin. You also add an order for a reticulocyte count to his CBC and find that his reticulocyte count is elevated. With concern for hemolysis, you order a direct antiglobulin test, which is negative.

Arriving at a Diagnosis

Q: How do you develop an assessment for Scott?

In developing your assessment, you must carefully consider Scott's clinical presentation, history, and the laboratory studies that are available to you. You also begin addressing aspects of Scott's clinical status that require immediate attention.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History, vital signs, and physical examination
     - The notable findings from Scott's history and examination include the presence of fever, diarrhea (now with blood), abdominal pain, pallor, fluid overload (edema, hypertension, pulmonary crackles), and decreased urination.
       - Although dehydration may have initially contributed to Scott's oliguria, it should not have caused his peripheral edema or hypertension with fluid resuscitation. Scott's parents have been giving him nonsteroidal anti-inflammatory drugs (NSAIDs) for his pain, which can contribute to renal injury in the setting of dehydration, but you are not sure that explains all of his findings.
       - Scott's peripheral edema could also be caused by hypoalbuminemia (eg, nephrotic syndrome, protein-losing enteropathy) or cardiac dysfunction; however, his examination and diagnostic evaluation do not yield any other findings consistent with these etiologies.
     - On examination, he is also noted to have tachycardia, which could be caused by sepsis, pain, anxiety, anemia, or the presence of fever. Likewise, you suspect Scott's tachypnea is due to his fever and fluid overload. Although his individual symptoms can be explained by a number of etiologies, the combination of oliguria, edema, and hypertension suggests that the unifying diagnosis is likely related to renal dysfunction.
     - Other key aspects of Scott's history are a recent visit to a petting zoo and a second sick contact with the same exposure. This, along with his fever, alerts you to the possibility of an infectious etiology for his illness.
   - Diagnostic findings
     - The results of Scott's serum chemistries demonstrate findings of acute kidney injury (AKI) as suggested by the markedly elevated creatinine and blood urea nitrogen levels. Additionally, Scott has a mild metabolic acidosis with an elevated anion gap, which may be at least partly related to the elevated urea in the blood (see Box 1.1 in Case 1 for causes of metabolic acidosis).
     - Scott's UA shows mild proteinuria and microscopic hematuria consistent with renal disease. Additionally, moderate blood with only 5 to 10 red blood cells per high-power field suggests hemoglobinuria.
     - Scott's CBC and peripheral smear offer several clues toward the correct diagnosis as well.
       - His hemoglobin and hematocrit levels are low, consistent with anemia. An elevated reticulocyte count is consistent with acute blood loss or hemolysis as the etiology for his anemia, and the presence of schistocytes (ie, fragmented red blood cells) is consistent with a microangiopathic hemolytic anemia. His thrombocytopenia combined with an increased mean platelet volume suggests a consumptive thrombocytopenia.
       - Both a high reticulocyte count and high mean platelet volume decrease the likelihood that his CBC findings are caused by bone marrow failure. The combination of a microangiopathic hemolytic anemia and thrombocytopenia is suggestive of 1 of 3 diagnoses: disseminated intravascular coagulation (DIC), TTP, or HUS.
   - Assessment for sepsis: Scott's fever, tachycardia, and leukocytosis in the setting of a suspected infection are consistent with the diagnosis of sepsis. Additionally, the presence of his laboratory abnormalities (ie, thrombocytopenia and AKI) suggests severe sepsis. There are no current findings of septic shock (refer to Section IV of the Appendix for a discussion of sepsis, severe sepsis, and septic shock).

2. **Develop the list of findings.**

Q: What major findings have you identified for Scott?

- Bloody diarrhea with abdominal pain and fever
- Oliguria with AKI
- Mild proteinuria and hematuria
- Elevated anion gap metabolic acidosis
- Fluid overload (as evidenced by hypertension, bilateral pulmonary crackles, and new-onset peripheral edema)
- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Severe sepsis

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Scott's presentation?

- The list of findings for Scott includes AKI, microangiopathic hemolytic anemia, and thrombocytopenia. In the setting of a recent diarrheal illness, these findings constitute the classic triad of HUS.
- Although a combination of dehydration from acute gastroenteritis and NSAID use can cause AKI related to acute tubular necrosis, this should not result in anemia and thrombocytopenia. DIC can have similar laboratory findings to HUS, but patients with DIC are very ill appearing and should not have hypertension. If there is a need to further evaluate for the presence of DIC, serum coagulation studies are needed. TTP can also cause similar laboratory findings as HUS but is uncommon in children and does not fit Scott's clinical history.

Q: What is HUS?

- HUS is one of the thrombotic microangiopathic syndromes, which includes TTP, and can be further delineated into primary (atypical) HUS and secondary HUS.
  - Primary HUS is thought to relate to genetic or acquired dysregulation of the complement alternative pathway. Secondary HUS occurs secondary to a disease or treatment, including an infection.
  - Most HUS in children is secondary, with the vast majority being caused by an intestinal infection with STEC. STEC serotype 0157 is most commonly implicated, although others can be causative. Invasive *Streptococcus pneumoniae* infections are the second most common cause of secondary HUS. In the United States, intestinal infections caused by *Shigella* spp are unlikely to cause HUS.
- Children can be exposed to STEC through exposure to an infected person or contaminated water or food, including undercooked beef and unpasteurized juices. Additionally, many cattle and farm animals shed STEC in their stool. Outbreaks have been associated with petting zoos.
- The clinical findings in HUS are precipitated by damage to the endothelial cells in the microvasculature of the kidneys and other organs. In STEC-HUS, this damage is caused by the direct effects of Shiga toxin. This endothelial damage leads to thrombus formation resulting in renal dysfunction, consumptive thrombocytopenia, and fragmentation hemolysis, the hallmarks of the disease.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with suspected HUS?

HUS can rapidly progress to renal failure, and patients with this condition may require transfusions or dialysis. Patients with this suspected diagnosis should be hospitalized to closely monitor for developing hemodynamic instability or evidence of worsening renal function, anemia, and thrombocytopenia.

Based on Scott's suspected diagnosis and signs of hypervolemia, anemia, and AKI, you decide that he requires hospitalization for urgent treatment and close monitoring.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Scott is an otherwise healthy 3-year-old boy who presents with diarrhea, oliguria, peripheral edema, hypertension, AKI, thrombocytopenia, and microangiopathic hemolytic anemia suggestive of HUS caused by STEC, which he may have acquired at the petting zoo. His peripheral edema and hypertension are likely reflective of fluid overload after receiving IV fluids in the ED. Given his risk of worsening renal insufficiency, anemia, or thrombocytopenia, he should be hospitalized for ongoing supportive care and close monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Treatment of HUS is largely supportive, focused on managing renal insufficiency, hemolysis, thrombocytopenia, and infection as well as monitoring for complications. In thinking through Scott's plan for treatment and monitoring, you decide to divide his treatment considerations into the following components:

1. **Expert consultation:** Consultation with a pediatric nephrologist is usually warranted except in mild cases. Consultation with a pediatric hematologist is also important, especially when the diagnosis is uncertain or when questions about blood or platelet transfusions arise. Depending on the patient's clinical course and complications, consultation with an infectious disease specialist, pediatric surgeon, or gastroenterologist may be needed. Upon Scott's admission, you contact a pediatric nephrologist for consultation.
2. **Fluid management and hypertension**
   - Closely monitoring the fluid status of patients with HUS is an important part of their care. Indicators of their fluid status include their intake and output, blood pressure, physical examination findings, and changes in weight. Because accurate measurement of urinary output can be helpful, some patients may require a Foley catheter.
   - There is evidence that fluid administration prior to or early in the course of STEC HUS reduces the rates of central nervous system involvement and the need for dialysis; however, for patients who are already demonstrating signs of intravascular volume overload, further administration of fluids can be detrimental.
   - To manage fluid overload and hypertension, clinicians should consider administering furosemide, and if this is not sufficient, an antihypertensive (eg, clonidine, calcium channel blocker).
   - For patients with hypertension, their hypertension may become so severe that they can develop hypertensive emergency or even posterior reversible encephalopathy syndrome, requiring emergent treatment and an escalation in care.
   - In discussion with the pediatric nephrologist, clinicians must also consider when dialysis is warranted. Possible scenarios for dialysis include oliguria or anuria, severe azotemia, worsening electrolyte abnormalities, and the need for an improved fluid balance to allow nutritional support.
3. **Correction and monitoring of electrolyte abnormalities:** Patients with HUS should be monitored closely for electrolyte abnormalities such as hyperkalemia, worsening uremia, and hyponatremia, with the frequency of laboratory testing being determined by the severity of their renal insufficiency. For Scott, he will initially require frequent laboratory monitoring given his creatinine level of 2.2 mg/dL (194.5 µmol/L), mild acidosis, and risk of hyperkalemia.

4. **Correction and monitoring of anemia and thrombocytopenia:** Because of ongoing hemolysis, it is not uncommon for patients with HUS to require blood transfusions. When hypervolemia is present and a blood transfusion is required, clinicians should consider use of furosemide and monitor patients closely throughout the transfusion to ensure there are no signs of congestive heart failure or worsening respiratory status. Occasionally, dialysis may be needed to remove excess fluid after transfusion. Platelet transfusion can be avoided in the absence of severe thrombocytopenia or bleeding. Patients with significant hemolysis and the need for transfusions should undergo serial monitoring of their CBC. For Scott, you plan to provide a blood transfusion and monitor his CBC at least twice daily.
5. **Anti-infectives:** The role of antibiotic use in STEC-HUS is controversial; however, most experts recommend avoiding antibiotics given concerns for cell lysis and increased Shiga toxin release. For HUS related to *S pneumoniae*, early antibiotic therapy is an important part of treatment. For Scott, the suspected etiology of his HUS is STEC, so it is prudent to avoid antibiotics at this time.
6. **Monitoring:** As previously discussed, you plan to monitor Scott's fluid status by keeping track of his intake and output, vital signs, and weights.
   - Although renal dysfunction and hematologic abnormalities are the most common manifestations of HUS, patients with HUS are also at risk of diffuse thrombotic events and multiorgan dysfunction, including seizures, stroke, hypertensive encephalopathy, bowel necrosis or perforation, pancreatitis, and myocardial dysfunction or ischemia. Many patients hospitalized with HUS require hemodialysis. Although most patients with STEC-HUS eventually recover without sequelae, mortality rates are up to 5% and long-term sequelae such as chronic kidney disease or hypertension may be evident in up to 30% of survivors.
   - The monitoring plan for patients with HUS should include observation for any evidence of complications of HUS and should involve frequent vital sign monitoring, repeated examinations, and frequent neurologic checks. When electrolyte disturbances are present, telemetry or bedside cardiac monitoring should be considered. Serial laboratory assessments should be performed as previously discussed, with the frequency dictated by the severity of the patient's condition.
   - For severe hypertension, anuria, significant fluid overload, or dangerous electrolyte abnormalities unresponsive to medical management, initiation of hemodialysis or transfer to a higher level of care may be needed.
7. **Additional therapeutic options:** Treatment of primary (atypical) HUS includes eculizumab, a monoclonal antibody targeting the complement activation pathway. Studies evaluating its use in secondary HUS have mixed results and further studies are ongoing. Therapeutic plasma exchange appears to have limited utility in STEC-HUS.
8. **Diet:** Nutrition is an important component of care for ill patients, but the added fluid volume can be complicated in patients with oliguria or anuria. In the setting of significant renal pathology, a "renal diet," which is low in sodium, potassium, phosphorus, and protein, may be needed. Additionally, a daily fluid limit (ie, fluid restriction) may be required to prevent fluid overload. Working closely with a registered dietician and a pediatric nephrologist can help optimize the patient's diet. For Scott, you will initiate a renal diet and consult a registered dietician upon admission.
9. **Antipyretics and analgesics:** For patients with HUS, acetaminophen can be used as needed for pain or fever; however, NSAIDs (and other nephrotoxic medications) should be avoided. In the setting of renal insufficiency and because of their antimotility properties, opioids should only be used with caution. For Scott, you will order acetaminophen on admission.
10. **Public health:** Although there is some variation in reporting procedures among states, all STEC cases should be reported to the local department of public health. This is especially important in Scott's case as his disease may be related to exposure at the petting zoo, which could lead to other infected individuals.

CASE FOCUS

Plan for Treatment and Monitoring

- **Expert consultation:** Upon Scott's admission, you contact the on-call pediatric nephrologist for further guidance.
- **Fluid management and hypertension:** Because of Scott's fluid overload and hypertension after receiving 40 mL/kg of fluid in the ED, you administer a dose of IV furosemide. You will monitor Scott's intake and output closely and maintain a low threshold for placement of a Foley catheter to accurately monitor his urine output.
- **Correction and monitoring of electrolyte abnormalities:** Based on Scott's initial laboratory test results showing a markedly elevated creatinine level and hemolysis, you are concerned about his risk of worsening renal insufficiency and electrolyte abnormalities. You plan to obtain repeat serum laboratory studies in 2 to 4 hours to monitor his electrolytes and renal function.
- **Correction and monitoring of anemia and thrombocytopenia:** Scott appears fluid-overloaded, so blood transfusions should be used judiciously; however, you determine that ongoing hemolysis in the presence of a hemoglobin of 7 g/dL (70 g/L) requires a packed red blood cell (pRBC) transfusion. To avoid worsening of his fluid status, you will monitor him closely throughout his transfusion and administer a dose of furosemide prior to and following the transfusion. You order a type and cross and a 10 mL/kg pRBC transfusion to be started after his dose of furosemide. You will obtain a repeat CBC after Scott's transfusion.
- **Anti-infectives:** You will need to follow-up on Scott's stool studies but do not anticipate starting any anti-infectives.
- **Monitoring:** Your order vital signs every 4 hours, strict monitoring of intake and output, frequent neurologic checks, and telemetry monitoring to assess for developing complications of HUS.
- **Diet:** You allow a renal diet as tolerated and consult a registered dietician. You anticipate a fluid restriction will be required if his urinary output and volume overload do not improve.
- **Antipyretics and analgesics:** You order acetaminophen as needed for pain and fever.
- **Public health:** You call the local public health department to report Scott's case and possible exposure to *E coli* 0157 at the petting zoo.

Case Resolution

Over the next 12 hours, Scott's fluid overload and hypertension worsen despite use of furosemide. Scott requires ongoing pRBC transfusions to ensure his hemoglobin is maintained at a safe level, and he is started on hemodialysis to remove excess fluid, allow initiation of nutritional support, and maintain safe blood pressures. His stool studies confirm the presence of Shiga toxin and STEC. Despite the need for dialysis, Scott remains clinically stable, without the need for ventilatory support or the development of extrarenal complications. Dialysis is stopped after a week, and Scott is discharged home within 14 days of his admission, without the need for any medications to control his blood pressure and with a creatinine level that is near his baseline. After discharge, he will continue to be followed by the nephrologist as an outpatient.

The local health department investigates based on your report and finds 10 more cases of STEC in individuals who visited the petting zoo over a 2-week period, including Scott's friend who had begun to develop similar symptoms. Fortunately, no other cases progress to HUS.

Discharge Criteria

Q: How do you know when Scott is ready to go home?

You can feel comfortable discharging your patient with HUS when the following criteria are met:

- Renal function has returned to baseline or has stabilized.
- Microangiopathic hemolytic anemia has resolved, and the platelet count is improving.
- Hypertension is well controlled.
- Caregivers are educated about blood pressure monitoring, medication administration, and any dietary changes that may need to be followed after discharge.
- The patient is maintaining adequate oral intake.
- Follow-up with general pediatrician and any subspecialist, such as nephrologist, is ensured.

Anticipatory Guidance

Q: What instructions should you provide to Scott's caregivers upon discharge?

- Monitor the amount and color of stools to ensure continued resolution of the disease.
- Avoid use of NSAIDs, such as ibuprofen, until Scott has been cleared for their use by his nephrologist.
- Monitor Scott's urine output closely.
- Follow a low-salt diet during recovery.
- Return to care for fever, altered mental status, lethargy, inability to tolerate oral fluids, decreased urination, new blood in the stool, worsening abdominal pain, pallor, severe headache, or any new concerns.

Clinical Pearls

- The most common cause of acute renal failure in children is HUS.
- HUS is generally classified into 2 types: primary (atypical) or secondary.
- In the United States, most cases of HUS are secondary HUS, caused by STEC.
- The possible manifestations of HUS are numerous, but the classic triad includes renal insufficiency, microangiopathic hemolytic anemia, and thrombocytopenia.
- Antibiotics are generally not recommended for STEC-HUS because there is concern that there will be increased toxin release, further exacerbating the disease.
- Care for HUS is generally supportive, with management of fluid status, blood pressure, electrolyte abnormalities, and anemia being key components.

Documentation Tips

- Document the presence of AKI, oliguria, anemia, and thrombocytopenia.
- Mention the results of stool cultures, if ordered.
- Document the need for IV fluid hydration for stool losses.

Suggested Reading

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CASE 44

Lucy, a 16-Year-Old Girl With Altered Mental Status

CASE PRESENTATION

Lucy is a 16-year-old girl who is being seen in the emergency department (ED) for confusion and vomiting. In the ED, her noncontrast computed tomography (CT) scan of the head is negative for intracranial hemorrhage, the result of a finger-stick blood glucose test is normal, and she is given an intravenous (IV) fluid bolus of normal saline (0.9%) at 20 mL/kg and a dose of IV ondansetron. Multiple serum and urine studies are collected and are pending. The ED physician reports that Lucy has a Glasgow Coma Scale score of 13. Because of Lucy's altered mental status, the ED physician calls you to discuss hospitalization for close monitoring and further diagnostic evaluation, if needed. After speaking to the physician caring for her in the ED, you begin your evaluation.

Patient History and Review of Systems

Q: What information should you collect from Lucy's caregivers?

- History of present illness
  - Detailed timeline of symptoms, including whether symptoms had a sudden onset or whether there was a slow progression over time, surrounding events, and total duration of symptoms
  - Description of her confusion
  - Characterization of emesis, including frequency, presence of blood, and color of vomitus
  - Recent changes in behavior or sleep patterns
  - Recent history of head trauma
  - Possible exposures, including sick contacts, toxic or hazardous chemicals in the house or garage, and prescription or over-the-counter medications in the household (including vitamins, herbs, or supplements)
  - Associated symptoms, such as fever, headache, cough, diarrhea, abdominal pain, loss of consciousness, seizures, rash, or urinary symptoms
- Medical history, including any history of similar symptoms and immunization status
- Social history, including a detailed HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment (if possible), including recent stressors, use of intoxicants, or suicidal ideation (refer to Section VII of the Appendix for an example of a complete HEADSS assessment)
- Family history of migraines, liver disease, mental illness, or psychosis

CASE FOCUS

History and Review of Systems

Lucy is not able to answer many questions, so the history is obtained from her mother. In speaking with her mother, you learn that Lucy was found in her bedroom approximately 30 minutes before presentation to the ED pacing around her room, appearing agitated and confused. Lucy was not coherent and was not able to tell her mother what caused her symptoms. She was in her usual state of health just 4 hours prior, during breakfast. Lucy had 2 episodes of nonbloody, nonbilious emesis on the way to the ED. Her mother denies any known head trauma, headache, fever, cough, abdominal pain, diarrhea, or recent illnesses. Lucy has not had any loss of consciousness or seizures of which her mother is aware.

Lucy was diagnosed with depression 2 months ago for which she has been receiving counseling and taking escitalopram. Her mother supervises Lucy when she takes her escitalopram and does not think there are any pills missing. Lucy is otherwise healthy and is fully immunized. There are several over-the-counter medications at home, including multiple vitamins, allergy medications, and analgesics but no other prescription medications. Her mother does not know if Lucy has access to illicit drugs. Her mother tells you that Lucy's father has left work to return home and perform a search for missing medications or any illicit substances. Lucy's family history is significant for depression in her mother and suicide completion in an uncle. Because of her altered mental status, a HEADSS assessment could not be performed.

Physical Examination

Q: What parts of the physical examination should you focus on for Lucy?

- Complete set of vital signs
- Level of consciousness and ability to arouse normally
- Head: signs of closed head injury
- Eyes: pupil size and reactivity, fundoscopic examination for papilledema
- Mucous membranes (moist, sticky, dry)
- Cardiovascular: auscultation for heart rate, rhythm, and the presence of any murmurs; peripheral perfusion
- Respiratory: respiratory pattern and ability to maintain airway
- Abdomen: tenderness, guarding, masses, organomegaly, quantity and quality of bowel sounds
- Skin: rashes or signs of injury
- Neurologic: signs of central nervous system (CNS) dysfunction or increased intracranial pressure (eg, depressed level of consciousness, Cushing triad, papilledema, cranial nerve palsies, focal neurologic deficits)

CASE FOCUS

Physical Examination

Lucy's vital signs are significant for a temperature of 38.1 °C (100.6 °F). She is tachycardic (heart rate: 120 beats/min when calm) and hypertensive (blood pressure: 142/90 mm Hg). She has a normal respiratory rate and oxygen saturation. Her weight is 60 kg.

On examination, Lucy is awake and restless in bed. She is unable to answer most of your questions and does not consistently follow commands. You notice that she appears flushed. She has no signs of head injury. Her pupils are 7 mm bilaterally and are reactive to light, but she is unable to sit still to allow fundoscopic examination. No scleral icterus or conjunctival injection is noted. Her mucous membranes are dry. She has a normal range of motion of her neck and a normal respiratory examination with a regular respiratory pattern and an ability to maintain her airway. She is tachycardic but has no murmurs, rubs, or gallops. Her peripheral pulses are normal, and her capillary refill time is 2 seconds. Her abdominal examination reveals hypoactive bowel sounds and mild tenderness to palpation diffusely. Her abdomen is soft, however, and is nondistended without rebound tenderness or guarding. No organomegaly or intra-abdominal masses are noted. Her skin feels warm to the touch, but other than her facial flushing, she has no other rashes. She has well-healed linear scars on her left forearm. A peripheral IV line is inserted into her right antecubital fossa. She has no joint swelling or tenderness. She is oriented to person but not to place or time. She also appears to have audiovisual hallucinations, as she is noted to be talking to one of her friends who is not present. Her face appears symmetric, her reflexes are normal throughout, and she has symmetric use of her extremities without any apparent deficits. She does not have any rigidity, tremors, or clonus.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for a patient with altered mental status?

There are many causes of altered mental status; however, the etiologies can be narrowed based on a complete history and thorough physical examination. Table 44.1 demonstrates a differential diagnosis for altered mental status and has been separated into the diagnoses that appear more or less likely for Lucy.

Table 44.1. Differential Diagnosis for an Adolescent With Altered Mental Status

Diagnoses of highest suspicion	• CNS infection (meningitis, encephalitis, cerebellitis) • CNS inflammation (eg, ADEM, anti-NMDA receptor encephalitis, anti-MOG-associated encephalomyelitis) • Confusional migraine • Psychiatric disorders (eg, mania, psychosis) • Toxic ingestion, intoxication,[a] or overdose[a]
Other diagnoses to consider	• Carbon monoxide poisoning • Concussion/head trauma • CNS vasculitis • CVA (including ischemia or hemorrhage) • DKA • Electrolyte abnormalities • Hypertensive encephalopathy • Hypoglycemia • Increased intracranial pressure • Intracranial mass • Metabolic or hepatic encephalopathy, including acute intermittent porphyria • PANS • Preeclampsia • PRES • Seizure (postictal state or nonconvulsive status) • Severe sepsis or septic shock • Thyrotoxicosis • Uremia • Wilson disease

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CVA, cerebrovascular accident; DKA, diabetic ketoacidosis; MOG, myelin oligodendrocyte glycoprotein; NMDA, N-methyl-D-aspartate; PANS, pediatric acute-onset neuropsychiatric syndrome; PRES, posterior reversible encephalopathy syndrome.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for patients who present with acute onset of altered mental status and vomiting?

- As illustrated by the differential diagnosis in Table 44.1, altered mental status can be the presenting symptom for a broad range of conditions. Most often, a thorough history and physical examination can help narrow the differential prior to initiating a diagnostic workup. If clinicians are unable to obtain an adequate history from the patient, collateral data should be sought from parents/caregivers, other family members, or friends.
- Clinicians should be particularly mindful to consider (and exclude, if necessary) etiologies that would require urgent evaluation and treatment, including but not limited to intracranial bleeding, intracranial infections, severe sepsis, hypoglycemia, electrolyte abnormalities, ingestions, and diabetic ketoacidosis.
- Depending on the scenario, the diagnostic evaluation for patients with altered mental status may require serum electrolyte studies and blood glucose level, head imaging, cerebrospinal fluid studies, toxicology studies, thyroid studies, liver enzyme levels, serum ammonia level, electrocardiogram (ECG), venous or arterial blood gas levels, lactate level, pregnancy testing, methemoglobin level, and/or electroencephalogram.

- In Lucy's case, the history provided by her mother and features from her physical examination are concerning for a toxic ingestion. Because of this, you plan to focus your initial diagnostic evaluation on identifying the causative substance(s) and evaluating for systemic effects. Although a broad evaluation is usually warranted initially, specifics from each patient's case can be used to help guide further testing.
  - Initial diagnostic testing should include obtaining a bedside blood glucose level, comprehensive metabolic panel, complete blood cell count, and ECG. Additionally, patients should have an IV line inserted and be placed on continuous cardiorespiratory monitoring.
  - If the patient is biologically female, clinicians should also obtain a pregnancy test.
  - Because coingestions may occur, it is important to obtain urine toxicology to detect drugs of abuse and serum levels for acetaminophen, salicylates, tricyclics, and ethanol. Because routine drug screening on serum and urine samples can miss many common intoxicants (including oxycodone and fentanyl), further targeted or extended testing may be needed in certain situations. These extended tests generally employ use of chromatography or mass spectrometry; however, results may not be available for several days. When these extended tests are being considered, it may be important to consult with a toxicologist and your hospital's laboratory department.
  - Poison Control Centers and toxicologists may help assist in assessing potential toxicities and severity of exposures. Additionally, they may recommend certain additional diagnostic studies as part of the patient's evaluation; therefore, they should be contacted as soon as possible once the patient is stabilized. A regional Poison Control Center is available 24 hours a day at 800/222–1222.

CASE FOCUS

Diagnostic Evaluation

The results from Lucy's evaluation in the ED have returned and are as follows:

Laboratory test	Results	Reference range
Serum chemistries		
Sodium	136 mEq/L (136 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	108 mEq/L (108 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	8 mEq/L (8 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	18 mg/dL (6.43 mmol/L)	6–20 mg/dL (2.14–7.14 mmol/L)
Creatinine	0.69 mg/dL (61.0 µmol/L)	0.5–0.9 mg/dL (44.2–79.6 µmol/L)
Glucose	92 mg/dL (5.11 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
ALT	34 U/L (0.57 µkat/L)	5–35 U/L (0.08–0.58 µkat/L)
AST	33 U/L (0.55 µkat/L)	5–35 U/L (0.08–0.58 µkat/L)
Alkaline phosphatase	69 U/L (1.15 µkat/L)	30–120 U/L (0.50–2.0 µkat/L)
GGT	7 U/L (0.12 µkat/L)	5–24 U/L (0.08–0.40 µkat/L)
Total bilirubin	0.9 mg/dL (15.39 µmol/L)	<1.5 mg/dL (25.66 µmol/L)
Lipase	28 U/L (0.47 µkat/L)	4–39 U/L (0.07–0.65 µkat/L)
CK	56 U/L (0.94 µkat/L)	24–140 U/L (0.40–2.34 µkat/L)

(continued)

CASE FOCUS

Diagnostic Evaluation *(continued)*

Laboratory test	Results	Reference range
Toxicology tests		
Ethanol	<3 mg/dL (0.65 mmol/L)	0–10 mg/dL (0–2.17 mmol/L)
Salicylate	<3 mg/dL	0–20 mg/dL
Acetaminophen	180 µg/mL (1,190.5 µmol/L)	10–30 µg/mL (66.1–198.4 µmol/L)
Tricyclic	Negative	Negative
Urine drug screen	Negative for benzodiazepine, amphetamines, barbiturates, cocaine metabolites, MDMA, opiates, PCP, cannabinoids	Negative
Urine studies		
Urine hCG	Negative	Negative
Urinalysis	Negative for glucose, ketones, protein, leukocyte esterase, nitrite	Negative
Electrocardiogram		
ECG	Sinus tachycardia, with a rate of 118 beats/min; QTc: 453 ms (370–450 ms); QRS: 120 ms (80–100 ms)	
Imaging		
CT scan of the head without contrast	No acute intracranial abnormality	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CT, computed tomography; ECG, electrocardiogram; GGT, γ-glutamyltransferase; hCG, human chorionic gonadotropin; MDMA, 3,4-methylenedioxymethamphetamine; PCP, phencyclidine.

Because a high serum acetaminophen level was found, you decide to obtain baseline serum coagulation studies (prothrombin time, international normalized ratio [INR], and activated partial thromboplastin time). The results of these studies are normal.

Arriving at a Diagnosis

Q: How do you develop an assessment for Lucy?

In thinking through her case, you decide to conduct an initial assessment of Lucy's stability, summarize the findings from her history, vital signs, physical examination, and diagnostic evaluation to generate a list of findings and narrow your differential diagnoses to the most likely etiology.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Assessment of Lucy's airway, breathing, and circulation: The first step in your assessment of a patient with a suspected toxic ingestion is to ensure stabilization of their airway, breathing, and circulation. For Lucy, her airway, breathing, and circulation are intact at the time of her admission.

- History: Lucy has a history of depression and takes escitalopram. She presents with acute onset of vomiting, confusion, and agitation and was known to be in her usual state of health 4 hours prior. She has no history of head trauma, preceding symptoms, or fever, which decreases your suspicion of a traumatic brain injury or an infectious or inflammatory CNS process. Multiple medications are kept in the home.
- Vital signs and physical examination: Lucy's vital signs are significant for an elevated temperature, tachycardia, and hypertension. Her significant examination findings include restlessness, the inability to reliably answer questions or follow commands, flushed skin, mydriasis with normal reactivity, dry mouth, forearm scarring, hallucinations, and hypoactive bowel sounds. She does not have any meningismus, hyperreflexia, clonus, rigidity, or tremors, and her neurologic examination appears otherwise nonfocal. You suspect that her abnormal vital signs and physical examination findings represent a toxidrome from her ingestion.
- Diagnostic evaluation: Lucy's glucose and electrolytes are normal, ruling out multiple etiologies, including hypoglycemia and diabetic ketoacidosis. Her toxicology screening shows an elevated acetaminophen level but no detectable amounts of salicylates, tricyclics, ethanol, benzodiazepines, amphetamines, barbiturates, cocaine metabolites, 3,4-methylenedioxymethamphetamine, opiates, phencyclidine, or cannabinoids. Although there are many ingested substances that cannot be eliminated based on this limited testing, you can be certain that acetaminophen was involved in Lucy's ingestion. Her transaminases and liver synthetic function (coagulation studies) are normal. Her ECG shows a prolonged QRS and mildly prolonged QTc interval, both of which can be nonspecific findings but are important to monitor. Her CT scan of the head detected no intracranial abnormalities, ruling out intracranial hemorrhage and decreasing your suspicion of increased intracranial pressure.

2. Develop the list of findings.

Q: What major findings have you identified for Lucy?

- Acute-onset encephalopathy (altered mental status), as evidenced by confusion, agitation, and hallucinations
- History of depression and evidence of self-injury (cutting)
- Hyperthermia, hypertension, tachycardia, flushed skin, mydriasis, and dry mouth
- Elevated acetaminophen level
- ECG changes (QRS widening and QTc prolongation)

3. Revisit the differential diagnosis.

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Lucy's presentation?

- In reviewing your differential diagnosis, you think you can quickly eliminate many of the possibilities based on Lucy's history, examination, and initial diagnostic evaluation. Although psychiatric causes remain a concern, Lucy's history is more consistent with an overdose.
- When considering an overdose, the patient's history and physical examination can be helpful to identify signs of a specific toxidrome. For Lucy, her examination findings and laboratory test abnormalities can only be explained by an overdose with acetaminophen *and* another medication or medications with serotonergic, sympathomimetic, or anticholinergic effects. Although the possibility of an overdose of a sympathomimetic or her escitalopram cannot be eliminated completely, Lucy's urine is negative for cocaine, phencyclidine, and amphetamines, and she does not demonstrate any hyperreflexia, clonus, tremors, or elevated creatine kinase, making you most suspicious of an anticholinergic medication such as diphenhydramine. See Table 44.2 for a comparison of common toxidromes.

Q: What are some features of antihistamine toxicity?

An overdose of first-generation antihistamines (eg, diphenhydramine) presents with an anticholinergic toxidrome. As noted in Table 44.2, a common mnemonic used to remember the effects of an anticholinergic toxidrome is "mad as a hatter, hot as a hare, blind as a bat, red as a beet, dry as a bone." For diphenhydramine, severe toxicity is seen at doses of 10 to 15 mg/kg or more than 1 g.

Table 44.2. Common Toxidromes

	Sympathomimetic	Opioids	Anticholinergic	Cholinergic	Serotonergic
Examples	Cocaine, amphetamines, pseudoephedrine	Heroin, morphine, codeine, fentanyl, methadone	Antihistamines, TCAs, atypical antipsychotics	Organophosphates, nerve agents, physostigmine	SSRIs, MAOIs, meperidine, dextromethorphan
Characteristics or mnemonic	Mimics the fight-or-flight response	Decreased mentation and decreased respiratory rate	"Mad as a hatter, hot as a hare, blind as a bat, red as a beet, dry as a bone"	SLUDGE: **S**alivation, **L**acrimation, **U**rination, **D**efecation, **G**I upset, **E**mesis	Autonomic and neuromuscular hyperactivity
Key clinical findings					
Temperature	Hyperthermia	Hypothermia	Hyperthermia	–	Hyperthermia
Pulse	Tachycardia	Bradycardia	Tachycardia	Bradycardia	Tachycardia
Blood	Hypertension	Hypotension	Hypertension	–	Hypertension
Respiratory rate	Tachypnea	Bradypnea, apnea	–	Dyspnea	Tachypnea
Skin	Diaphoresis	–	Dry	Diaphoresis	Diaphoresis
Neurologic	Agitation, seizures, hyperreflexia	Sedation, coma, CNS depression	Agitation, seizures	–	Agitation, confusion, hyperreflexia,
Pupillary findings	Mydriasis	Miosis	Mydriasis	Miosis	Mydriasis
GI	–	Constipation	Constipation	Emesis, diarrhea	Increased bowel sounds
Genitourinary	Urinary retention	–	Urinary retention	Enuresis	–
Other	Tremors, hyperalert, paranoia	–	Hallucinations	–	Rigidity, increased CK, tremors, trismus

Abbreviations: CK, creatine kinase; CNS, central nervous system; GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Adapted with permission from Gershel JC, Rauch DA, eds. *Caring for the Hospitalized Child: A Handbook on Inpatient Pediatrics*. American Academy of Pediatrics; 2013:317–325.

- Central symptoms ("mad as a hatter"): agitation, hallucinations, confusion, sedation, coma, seizures
- Peripheral symptoms: hypertension, tachycardia, hyperthermia ("hot as a hare"), mydriasis ("blind as a bat"), dry skin ("dry as a bone"), cutaneous flushing ("red as a beet"), urinary retention
- ECG findings: sinus tachycardia, prolongation of QRS and QTc intervals (due to sodium channel blockade)

Q: What are symptoms of acute acetaminophen toxicity, and how does it develop over time?

Acetaminophen is metabolized by the liver to create a toxic metabolite called *N-acetyl-p-benzoquinone imine*. Glutathione helps in the detoxification of N-acetyl-p-benzoquinone imine. When glutathione stores are depleted, toxic metabolites result in hepatocellular injury. Stages of acetaminophen toxicity and associated symptoms are as follows:

- Stage 1 (0–24 hours): nausea, malaise, vomiting, abdominal discomfort, pallor, diaphoresis, or asymptomatic
- Stage 2 (24–72 hours): right upper quadrant pain, hepatomegaly, liver injury develops (aspartate aminotransferase, alanine aminotransferase [ALT], and bilirubin levels begin to rise), coagulation studies (prothrombin time, INR) may be abnormal
- Stage 3 (72–96 hours): anorexia, nausea, vomiting, malaise, peak hepatotoxicity, encephalopathy (possible), metabolic acidosis, renal failure, coagulopathy, pancreatitis, hypoglycemia, coma, cardiomyopathy
- Stage 4 (>96 hours): recovery or progression to multiorgan failure and death

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with acetaminophen and anticholinergic overdose with suspected suicidal intent?

- Acetaminophen toxicity: Patients who require N-acetylcysteine (NAC) treatment should be admitted (see discussion on NAC treatment in the Developing a Plan for Treatment and Monitoring section).
- Diphenhydramine (anticholinergic) toxicity: Patients with significant persistent CNS toxicity (hallucinations, somnolence, delirium, coma), or persistent tachycardia should be admitted for observation.
- Suspected suicidal intent: Patients with a suicide attempt or active suicidal ideation generally require admission to an inpatient psychiatric facility following medical stabilization.

Lucy requires hospitalization for treatment of her ingestion, close monitoring of her clinical status and laboratory values, and psychiatric care for suspected suicidal intent.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Lucy is a 16-year-old girl with a history of depression who has been taking escitalopram and who presents with acute onset of altered mental status, an elevated serum level of acetaminophen, and clinical features most consistent with an anticholinergic toxidrome. The intentionality of her ingestion is unknown at this time. She requires admission for medical management of her ingestion, close monitoring for complications of her ingestion, and psychiatric stabilization.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Lucy's symptoms, you review the literature to remind yourself about the treatment of acetaminophen and anticholinergic toxicities in infants, children, and adolescents. You decide to divide your treatment considerations into the following components:

1. **Initial stabilization**
   - Supportive care, including noninvasive ventilation or intubation, may be needed for patients who cannot maintain adequate oxygenation and ventilation.
   - If a patient is hypotensive, resuscitation with crystalloid fluids (eg, normal saline, lactated Ringer solution, Plasma-Lyte) is indicated.
   - Naloxone should be given to patients in whom there is suspicion of respiratory depression related to an opioid ingestion.
   - Because Lucy's airway, breathing, and circulation are intact, no urgent intervention for these aspects of her status is required. Given that her QRS is widened and her QTc is borderline prolonged, you plan to initiate telemetry and obtain a repeat ECG in 4 hours.
2. **Consultation with experts:** As mentioned previously, with any intentional or unintentional ingestion, it is important to seek help from the local Poison Control Center. They can provide valuable insight into managing patients who present with toxic ingestions. For complicated cases, medical toxicologists can be consulted as well.
3. **Use of activated charcoal:** Activated charcoal is a gastrointestinal (GI) decontamination method used to inhibit absorption of drugs after an ingestion. There are some ingestions for which use of activated charcoal is contraindicated, such as heavy metals, corrosives, alcohols, and essential oils.
   - If a patient has impaired consciousness or does not have a secure airway, activated charcoal should not be administered.
   - Activated charcoal must be given early, as it is usually most effective when given within 1 to 2 hours of ingestion. For this reason, it is most often administered in the ED. In Lucy's case, she presented after this time window; therefore, she was not given activated charcoal.
4. **Treatment of acetaminophen overdose**

Q: How do you determine the need for therapy for acetaminophen overdose?

- The lesser of 150 mg/kg or 7.5 g of acetaminophen over a 24-hour period is considered to be a toxic ingestion.
- To assess the risk of severe hepatotoxicity from an acute overdose, a serum acetaminophen concentration should be obtained 4 hours after the ingestion or as soon as possible thereafter. Based on this serum concentration level, patients can be risk stratified using the Rumack-Matthew Nomogram (see Figure 44.1).
- The antidote to acetaminophen overdose is NAC. The goal is to initiate treatment within 8 hours of the ingestion or as soon as possible if the time of the ingestion is unknown. It is rare for patients with acetaminophen overdose to require liver transplantation when NAC is initiated within 8 to 10 hours of the ingestion.
  - Indications for immediate NAC treatment are as follows:
    - The acetaminophen level drawn at 4 or more hours after the acetaminophen ingestion is above the treatment line on the Rumack-Matthew Nomogram.
    - There is an inability to measure a serum acetaminophen concentration quickly.
    - The ingested amount is known to be greater than 200 mg/kg or 10 g.
    - The patient presents more than 8 hours after the ingestion.
    - The time of ingestion is unknown.
    - There is any clinical evidence of toxicity.

- Be aware that when acetaminophen is coingested with medications that decrease GI motility (anticholinergics and opioids), absorption and time to peak might be delayed, making use of the nomogram challenging.
- Decisions regarding treatment of chronic or repeated supratherapeutic doses should be made in conjunction with Poison Control; however, general indications include any detectable acetaminophen level or any elevation in ALT.

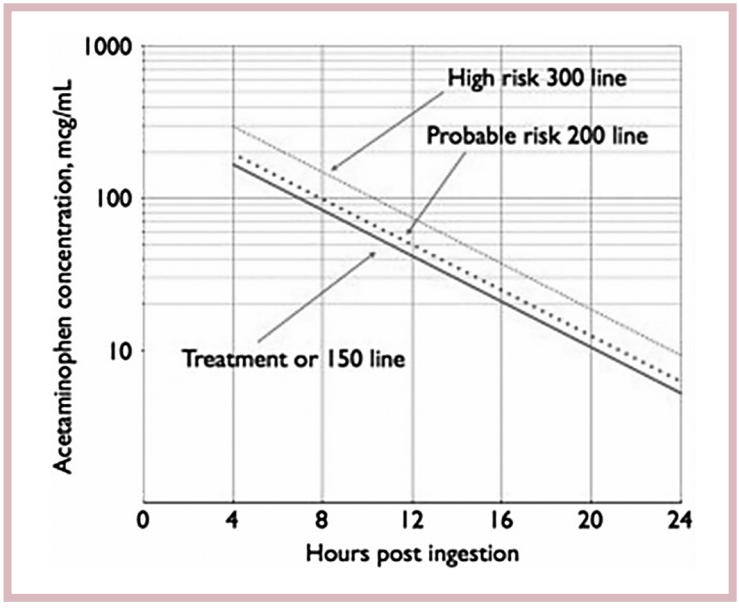

Figure 44.1. Rumack-Matthew nomogram.

Reprinted with permission from Nadler A, Fein DM. Acetaminophen poisoning. *Pediatr Rev*. 2018;39(6):316–318.

Q: What are the dosing options for NAC, and what additional monitoring is required?

- NAC comes in 2 formulations, as follows:
  - Oral: 140 mg/kg loading dose, followed by 70 mg/kg every 4 hours for 72 hours (for a total of 18 doses). The oral form is unpalatable, and patients have difficulty tolerating this regimen.
  - IV (3-bag protocol): 150 mg/kg over 60 minutes, followed by 12.5 mg/kg/h for 4 hours, followed by 6.25 mg/kg/h for 16 hours (for a total of 21 hours of IV infusion). Nonimmunoglobulin E–mediated anaphylactoid reactions can occur with IV administration of NAC. Most reactions are self-limited and are improved by slowing the infusion rate; however, occasionally treatment with antihistamines, albuterol, or epinephrine is needed.
- Repeat liver function tests, coagulation studies, and an acetaminophen level should be obtained 2 hours before the end of the third bag of IV NAC or at the end of the 72-hour oral protocol. Poison Control can assist with decisions about the continuation or discontinuation of NAC based on these laboratory values.
  - In general, if the acetaminophen level is greater than or equal to 10 µg/mL (66.1 µmol/L), or if aspartate aminotransferase or ALT is elevated, IV NAC should be repeated at a dose of 6.25 mg/kg/h given over 16 hours. Poison Control can help guide decisions about continuation of the oral treatment protocol if needed.
  - If needed, NAC at a dose of 6.25 mg/kg/h given over 16 hours can be repeated multiple times until the acetaminophen level has improved, ALT is downtrending, and INR is less than 2.
- Patients should be monitored for clinical signs of liver failure, including but not limited to jaundice, abdominal pain, bleeding, dark urine, and encephalopathy.

5. **Treatment of an anticholinergic overdose**

Q: What is the treatment and monitoring required for an anticholinergic toxicity?

- The primary treatment of anticholinergic toxicity is supportive care.
- Pharmacologic treatment options are as follows:
  - Agitation and seizures due to anticholinergic toxicity can be treated with benzodiazepines.
  - Sodium bicarbonate can be used to treat a widened QRS interval, but the decision should be made in conjunction with the Poison Control Center or a toxicologist.
  - Physostigmine is a cholinesterase inhibitor that can be considered for severe anticholinergic symptoms. It should only be administered after discussion with a toxicologist, and the patient must have a normal QRS interval and not have coingested other sodium-channel blocking agents.
- Monitoring for other effects should be conducted as follows:
  - Patients with anticholinergic toxicity are at risk for arrhythmias and should be placed on continuous cardiac monitoring. Worsening tachycardia might point toward increasing toxicity.
  - Frequent vital signs and neurologic assessments should be obtained, and seizure precautions should be taken. Increasing hyperthermia may indicate increasing toxicity.
  - Monitor for urinary retention by tracking urine output. Urinary retention might contribute to agitation. Insertion of a urinary catheter may be required.
  - Perform serial abdominal examinations to assess for intestinal ileus. Upright and lateral decubitus abdominal radiograph can assist with this diagnosis, when needed.
- Other considerations: Patients with altered mental status from anticholinergics are at risk of unintentionally harming themselves or others. Appropriate safety precautions must be taken, including having a bedside sitter when needed.

6. **Mental health**

- Suicide and suicide attempts are potential complications of depression that have significant morbidity and mortality. Suicide is the second leading cause of death in adolescent patients, making depression an important chronic illness to address during hospitalization. Therefore, it is imperative to thoroughly and thoughtfully evaluate and address the underlying depression and precipitating events that may have contributed to the presentation of a suicide attempt.
- It is important to assess risk factors to better understand why the patient may have intended to harm themselves. A thorough HEADSS assessment can help in this process.
  - It is vital to perform a confidential HEADSS assessment with all adolescents. In this case, special effort should be made to ask about stressors, bullying, abuse, violence, human trafficking, substance use, and other adverse experiences that may have contributed to the overdose. Based on this assessment, further evaluation and intervention might be warranted.
- Psychiatry evaluation: Once the patient has returned to their neurologic baseline, a psychiatric evaluation is helpful to determine the patient's intent, psychiatric comorbidities, and disposition.
- Safety: To ensure the patient has a decreased likelihood of self-harm or suicide attempt while hospitalized, they should be under constant visual observation. This is usually accomplished by having a psychiatric sitter who is physically present at the patient's bedside until the time of discharge or until they are found to no longer be at risk.
  - Before discharge home, a safety plan needs to be made. This plan may include identification of the following: signs of a developing crisis, useful coping strategies, people or places that can provide distraction from suicidal thoughts, people the patient can trust to ask for help (ie, family or friends), professionals/hotlines to call in a crisis, and a plan for restricting access to lethal means at home.

- Although you need to perform a HEADSS assessment for Lucy when she is lucid, you decide it will be beneficial to have a social worker meet with the family to identify any other family stressors and discuss strategies to create a safe environment in the home.

7. **Additional considerations for care**
   - Hydration and diet: Clinicians should consider starting maintenance IV fluids in patients whose altered mental status prevents them from taking in adequate fluids by mouth. A patient who is alert and able to manage their airway can be given a regular diet unless severe liver injury, vomiting, or an ileus were to develop.
   - Clinicians should be cautious of using antipsychotic medications or antiemetics, including ondansetron or promethazine, as they can also cause QT prolongation. Promethazine can also have effects that are similar to anticholinergic syndrome, including urinary retention, blurry vision, and constipation.
   - Obtaining corroborating information: In Lucy's case, you plan to obtain further information to help identify what substance(s) she has ingested. If her father is not able to make any discoveries at home, friends should be contacted to see what information they can offer about possible substance use. Additionally, an extended serum toxicology panel via mass spectroscopy can be obtained if needed.

CASE FOCUS

Plan for Treatment and Monitoring

- **Airway, breathing, and circulation:** You order telemetry monitoring for Lucy and a repeat ECG to be obtained in 4 hours.
- **Consultation with Poison Control:** You plan to contact Poison Control about Lucy's case to seek their advice on her care and monitoring.
- **Activated charcoal:** Lucy is likely outside the window for activated charcoal administration; therefore, you do not plan to administer activated charcoal.
- **NAC treatment of acetaminophen overdose:** You initiate 3-bag IV NAC protocol and monitor Lucy for anaphylactoid reactions. You order repeat laboratory tests (liver enzymes, acetaminophen level, and coagulation studies) prior to the end of the 21-hour NAC protocol.
- **Supportive care for anticholinergic overdose:** You order IV lorazepam as needed for agitation and seizures, frequent neurologic assessments, and measurements of urine output to ensure there is no urinary retention.
- **Mental health:** You order a HEADSS assessment to take place when Lucy is lucid. You also request social work and psychiatry consults and a bedside sitter.
- **Hydration and diet:** You order maintenance IV fluids until Lucy is tolerating oral intake.
- **Parent follow-up:** You will follow up with Lucy's father regarding medications or other substances found at home.

Case Resolution

At the time of Lucy's hospital admission, you learn that her father found an empty bottle of acetaminophen-diphenhydramine in her room. The bottle originally contained 30 capsules, and each capsule has 500 mg of acetaminophen and 25 mg of diphenhydramine. This discovery is consistent with your suspected diagnosis. The number of pills remaining in her bottle of escitalopram is as expected based on her daily dosing.

Lucy is able to complete the NAC protocol over 21 hours without any complications. At that time, her repeat laboratory tests show that her transaminases are normal, her INR is 1.1, and her acetaminophen level is less than 2 ug/mL (13.2 µmol/L). After admission, Lucy does not have any further vomiting or abdominal pain, and she is able to maintain oral hydration.

During the first 24 hours of her hospital stay, Lucy's mental status slowly returns to baseline. You perform a HEADSS examination when she is coherent, and she confirms the ingestion was a suicide attempt. The following day, the child psychiatry team evaluates Lucy and recommends inpatient psychiatric treatment. Lucy is transferred to an inpatient psychiatric facility that day for acute treatment and stabilization of her mental health.

Discharge Criteria

Q: How do you know when Lucy has been medically cleared for transition to an inpatient mental health facility?

You can feel comfortable medically clearing your patient with an intentional ingestion when the following criteria are met:

- Medical therapy has been completed and an appropriate period of monitoring has taken place.
- The patient is back to their baseline mental status, has normal vital signs, is tolerating an oral diet, and all laboratory and ECG abnormalities have normalized.

Anticipatory Guidance

Q: What instructions should you provide to Lucy's caregivers upon discharge from the medical unit?

- Ensure that all medications, supplements, and weapons are securely stored.
- Close follow up with the mental health team is very important. To address all factors that precipitated this event, participation of the entire family is commonly needed.
- Once Lucy is home, she should return to care if she has altered mental status, is unable to tolerate oral fluids, has severe abdominal pain, is unable to void on her own, or is having suicidal or homicidal thoughts.

Clinical Pearls

- Altered mental status can have many causes, but in all age groups, the possibility of a toxic ingestion needs to be thoroughly evaluated.

- The acetaminophen toxicity nomogram is used for acute ingestion and excludes chronic use and extended-release products.
- When coingested with medications that decrease GI motility (anticholinergics and opioids), absorption and time to peak might be delayed.
- A mnemonic used to remember anticholinergic syndrome is "mad as hatter, hot as a hare, blind as a bat, red as a beet, dry as a bone."
- A serum acetaminophen level should be obtained at least 4 hours after ingestion. Levels obtained sooner do not reflect peak concentration and cannot be used to guide therapy.
- NAC is the treatment of acute acetaminophen toxicity.
- The treatment of anticholinergic syndrome is usually supportive.
- Suicide is the second leading cause of death in individuals between the ages of 10 and 24; therefore, it is imperative that pediatric hospitalists evaluate and begin to address underlying etiologies of this presentation.

Documentation Tips

- Document contact with the Poison Control Center.
- Clarify side effects of ingested medication, both observed and potential.
- Discuss the type and frequency of monitoring needed during hospitalization.
- Document treatments of ingestion.

Suggested Readings

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CASE 45

Sam, a 10-Month-Old Boy With Hypoglycemia

CASE PRESENTATION

Sam, a 10-month-old boy who was born full term, presents to the emergency department (ED) with vomiting, diarrhea, and lethargy. During the ED evaluation, he is found to have a point-of-care (POC) glucose level of 37 mg/dL (2.05 mmol/L). He is unable to tolerate oral intake; therefore, he is given an intravenous (IV) bolus of dextrose 10% in water totaling 5 mL/kg. A repeat POC blood glucose level is obtained, which is 82 mg/dL (4.55 mmol/L). Sam is then placed on maintenance IV fluids of 5% dextrose in normal saline. Afterward, he is still sleepy and shows no interest in drinking but is becoming more responsive. Because he is young and is still showing no interest in drinking fluids, the ED physician calls you to evaluate him for admission.

Patient History and Review of Systems

Q: What information should you collect from Sam's caregivers?

- History of present illness
  - Course of illness and events leading up to presentation
  - Intake and output for the last day, including the timing of hypoglycemia in relation to his most recent intake
  - Exposures: possible substance ingestion, including alcohol, medications kept in the home, or unsecured medications brought into the home by visitors
  - Additional symptoms, such as fever, cough, congestion, mental status changes, tremulousness, syncope, seizure activity, or recent trauma
- Medical history
  - Any episodes of hypoglycemia, including in the perinatal period, or episodes of symptoms suspicious for hypoglycemia (eg, irritability, sweating, tremulousness/jitteriness, fatigue/lethargy, seizure)
  - Chronic medical conditions, growth and developmental history, and regular medications
  - Newborn screen results
- Family history of hypoglycemia, unexplained infant deaths, or metabolic disorders
- Social history, including living situation, child care, and sick contacts

CASE FOCUS

History and Review of Systems

From your conversation with his parents, you discover that Sam has no chronic medical conditions and was born full term after an uncomplicated pregnancy and delivery. He did not have episodes of low blood sugar after birth, did not require a stay in the neonatal intensive care unit, and his newborn screen was normal. For the past 2 days, he has had decreased appetite and 4 to 5 episodes of nonbloody, nonbilious emesis per day. Since last evening, he has had 3 episodes of nonbloody diarrhea. He took less than half of his normal formula volume yesterday, and since waking up this morning, he has only had 2 fl oz of formula (19 kcal/fl oz, prepared correctly), which he vomited back up. His last wet diaper was over 12 hours ago. His mother decided to bring him to the ED because he was lethargic after his afternoon nap. She describes that Sam was becoming progressively more tired throughout the morning, which is the opposite of his usual active, smiling self. His mother denies any recent fever, sick contacts, trauma, medication or substance ingestions, or previous episodes of hypoglycemia. His mother has type 1 diabetes, for which she uses insulin. Her insulin is stored in a cabinet that the children in the home cannot access. The family also keeps over-the-counter medications such as acetaminophen and ibuprofen in a locked medication box. They deny any current visitors to the home. As a child, Sam's maternal uncle had a condition in which he had to eat frequently to avoid low blood glucose. Sam lives with his mother, father, and a school-aged sibling. He just started attending child care. He has been growing and developing normally since birth. He crawls, pulls himself up to stand, responds to his name, and frequently babbles.

Physical Examination

Q: What parts of the physical examination should you focus on for Sam?

- Complete set of vital signs
- Review of growth curves, if available
- Mental status, specifically whether it has improved with dextrose or remains altered despite correction of hypoglycemia
- Hydration status: tear production, mucous membranes (moist, tacky, or dry), anterior fontanelle (size and degree of fullness, if still physiologically open)
- Abdomen: tenderness, masses, hepatomegaly, splenomegaly
- Dysmorphic features: cleft lip/palate, midline defects, hemihypertrophy, macroglossia
- Genitals: micropenis, ambiguous genitalia
- Neurologic: developmental status, nystagmus, vision (grossly), muscle tone, strength
- Skin: hyperpigmentation, cafe au lait macules, jaundice

CASE FOCUS

Physical Examination

Sam's vital signs demonstrate that he is afebrile but has mild tachycardia. His respiratory rate, blood pressure, and oxygen saturation are normal. His growth curves show that his weight has been tracking along the 50th percentile since birth. His length and head circumference are tracking along the 60th percentile.

On examination, Sam is asleep in his mother's arms and wakes to tactile stimuli. His anterior fontanelle is small but feels slightly sunken. His eyes are anicteric. His lips and oral mucosa are dry, and he is not producing tears when he cries. He has normal facies and no cleft palate or macroglossia. He has a normal cardiac and respiratory examination. His peripheral pulses are normal, but his capillary refill time is slightly prolonged at 3 seconds. His abdomen is soft, nontender, and without masses. There is no hepatosplenomegaly appreciated. His bilateral testes are descended, and he has normal genital size and appearance for age. His neurologic examination is grossly normal, demonstrating appropriate strength as he pushes you away. He is able to sit in his mother's lap unsupported. He visually tracks and reaches for toys. You do not appreciate any dysmorphic features, hyperpigmentation, hemihypertrophy, or skin lesions.

Differential Diagnosis

Q: What is the differential diagnosis for an infant or child with hypoglycemia?

The differential diagnosis for hypoglycemia in an infant or child is broad and contains many rare diseases and disorders. First, it is important for clinicians to understand the pathophysiology of glucose homeostasis. Under normal conditions, the body must take in enough glucose through meals, absorb the glucose from the intestinal tract into the bloodstream, release the correct amount of insulin, move glucose into cells, and store glucose as glycogen. In starvation states or hypoglycemia, multiple hormones and metabolic pathways are needed to suppress insulin secretion, convert stored energy into fuel, and increase serum glucose levels. This process results in the conversion of glycogen to glucose, triglycerides to free fatty acids and glycerol, and protein into amino acids that can be used in gluconeogenesis. Free fatty acids are then converted into ketones, which can be used as an energy source for the brain. Defects in any of these processes can lead to an energy imbalance and hypoglycemia.

The differential diagnosis for hypoglycemia in infants and children can be divided into categories as shown in Table 45.1. From this list, you are most concerned about ketotic hypoglycemia but also need to consider exogenous insulin administration and metabolic disorders, such as a fatty acid oxidation defect.

Table 45.1. Differential Diagnosis of Hypoglycemia in Infants and Children

Idiopathic	Ketotic hypoglycemia[a] (sometimes referred to as idiopathic ketotic hypoglycemia)
Hormonal imbalance/endocrine	• Congenital hyperinsulinism • Dumping syndrome • Exogenous insulin[a] • Hyperthyroidism • Hypopituitarism, including growth hormone deficiency, hypothyroidism, and adrenal insufficiency • Insulinoma • Syndromic hyperinsulinism (eg, Beckwith-Wiedemann) • Withdrawal of exogenous steroids
Metabolic	• Fatty acid oxidation defects[a] • Fructose-1,6-diphosphatase deficiency • Galactosemia • Glycogen storage diseases • Mitochondrial respiratory chain defects • Organic acidemias
Toxic ingestions/overdoses	• β-blockers • Ethanol • Salicylates • Sulfonylureas
Decreased glucose production	• Liver disease • Reye syndrome
Increased glucose requirements	• Perinatal stress • Severe infections (eg, sepsis) • Severe burns
Neonatal transition	• Maternal diabetes • Premature/SGA neonate • Transitional neonatal hypoglycemia

Abbreviation: SGA, small for gestational age.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for an infant or child who presents with hypoglycemia?

- Diagnostic testing may not be necessary if the cause of hypoglycemia is obvious, such as when associated with a known β-blocker ingestion, insulin overdose, sepsis, a severe burn, or when hypoglycemia occurs during the first 2 days after birth.
- If the cause of the patient's hypoglycemia is not obvious, a critical sample should be obtained. A critical sample includes an array of tests on the patient's blood and urine and should be collected at the time of hypoglycemia (ie, when the serum glucose level is < 50 mg/dL [2.78 mmol/L]) and prior to treatment. Interpretation of the results from the critical sample can help determine the underlying etiology of the hypoglycemia episode, but treatment of hypoglycemia should not wait for the results of these tests. Instead, treatment should be performed concurrent with or immediately following the blood collection. Refer to Box 45.1 for recommended serum tests. When not enough blood is collected, tests should be prioritized based on their diagnostic utility. It is reasonable to wait for the collection of urine specimens until after stabilizing the patient. Certain clinical scenarios or patient examination features may change which laboratory tests are prioritized.
- When the diagnostic evaluation was not completed during the period of hypoglycemia, a period of diagnostic fasting should be considered. Diagnostic fasting should be performed in consultation with a pediatric endocrinologist or metabolic specialist and should occur in the hospital setting, where serial measurement of the patient's blood glucose and β-hydroxybutyrate can be performed, a critical sample can be obtained, and appropriate treatment can be rapidly administered. Additionally, patients with suspected hyperinsulinism can undergo a glucagon stimulation test at the time of their hypoglycemia.
- Persistent or recurrent hypoglycemia are indications that further investigation is warranted.

Box 45.1. Recommended Evaluation for Infants and Children With Hypoglycemia, in Priority Order

Highest priority tests	Medium priority tests	Lowest priority tests[a]	Other tests to consider
Serum electrolyte panel[b] (for bicarbonate level, anion gap calculation, and to confirm serum glucose) β-hydroxybutyrate[b] Lactate[b,c] Free fatty acids[b,c] Urine ketones[d]	Insulin level[b] C-peptide[b] Cortisol[b] GH[b] Ammonia[c]	Free carnitine Acylcarnitine profile Serum amino acids Pyruvate	Urine organic acids[d] Serum toxicology screen for ethanol and salicylates (when suspected based on history, examination, or laboratory test results) Stimulation tests: corticotropin or GH MRI of the pituitary gland

Abbreviations: GH, growth hormone; MRI, magnetic resonance imaging.

[a] Laboratory tests that have improved diagnostic accuracy if performed on the critical sample.

[b] Testing that is only accurate when performed on a critical sample.

[c] Laboratory tests for which samples must be placed on ice at time of draw.

[d] Laboratory tests that should be performed on the first urine specimen obtain after the hypoglycemic event.

Derived from Tabarrok M, Smith J, Cossey M, et al. Hypoglycemia guideline. Dell Children's Medical Center, Evidence-Based Outcomes Center. 2015. Accessed March 4, 2022. https://www.dellchildrens.net/wp-content/uploads/sites/60/2019/08/DCMC-Hypoglycemia-Guideline.pdf

CASE FOCUS

Diagnostic Evaluation

You confirm that the ED physician ordered laboratory tests while placing Sam's IV line, prior to administering dextrose 10% in water. The results of these tests are as follows:

Laboratory test	Result	Reference range
Sodium	140 mEq/L (140 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.6 mEq/L (3.6 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	105 mEq/L (105 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)	18–24 mEq/L (18–24 mmol/L)
Anion gap	20 mEq/L (20 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	24 mg/dL (8.57 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.5 mg/dL (44.2 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	35 mg/dL (1.94 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
β-hydroxybutyric acid	4.3 mmol/L	0.02–0.27 mmol/L
Lactate	0.8 mmol/L	0.5–2 mmol/L
Ammonia	15 µmol/L	11–35 µmol/L
Cortisol	23 µg/dL (634.5 nmol/L)	5–25 µg/dL (137.9–689.7 nmol/L)
C-peptide	0.8 ng/mL (0.26 nmol/L)	0.4–2.2 ng/mL (0.13–0.73 nmol/L) (fasting)
Repeat POC glucose (after IV dextrose bolus)	82 mg/dL (4.55 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)

Abbreviations: BUN, blood urea nitrogen; IV, intravenous; POC, point-of-care.

Pending tests: Insulin, free fatty acids, growth hormone (GH). Urine ketones were not collected.

Based on these results and Sam's euglycemia at the time of your evaluation, you defer any other testing.

Arriving at a Diagnosis

Q: How do you develop an assessment for Sam?

Your first concern is Sam's overall acute stability. Because his blood glucose level is currently normal, you initially focus on determining his hydration status. Afterward, you can consider whether he has risk factors for developing recurrent hypoglycemia.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - Assessment of hydration status: With his decreased energy level, sunken fontanelle, dry lips, mild tachycardia, and 3-second capillary refill in the setting of gastrointestinal (GI) losses, Sam continues to experience a mild to moderate degree of dehydration (which you estimate as approximately 5% dehydration).

- History: Sam developed lethargy, dehydration, and hypoglycemia in the setting of 2 days of vomiting, diarrhea, and poor oral intake. He has had normal growth and development. Sam does have an uncle with a history concerning for a metabolic disorder. Sam's normal newborn screen makes fatty acid oxidation defects or other inborn errors of metabolism less likely. As with most children, he is at risk of ingesting medications or other substances that can lead to hypoglycemia, though his mobility is limited, and his mother thinks an ingestion is unlikely. In this case, medical child abuse should be considered because there is insulin at home and exogenous insulin administration could lead to hypoglycemia; however, this seems less likely given that his presentation is associated with dehydration, prolonged fasting, vomiting, and diarrhea.
- Examination: Other than findings consistent with dehydration, Sam's physical examination is normal. The absence of hepatomegaly or other dysmorphic features on examination argues against a glycogen storage disorder or a genetic syndrome such as Beckwith-Wiedemann. With Sam's normal genitalia, growth, and development, endocrine disorders such as adrenal insufficiency or GH deficiency are unlikely as well. His history and examination show that he is not in a state of excessive glucose consumption, as he does not have severe burns and is not septic.
- Diagnostic evaluation: See Figure 45.1 for an algorithm that demonstrates how a patient's critical sample values can help narrow the diagnostic possibilities.

Q: How do you interpret Sam's diagnostic testing?

- Sam's serum laboratory studies confirm hypoglycemia (serum glucose: 35 mg/dL [1.94 mmol/L]), show a low bicarbonate level (metabolic acidosis) with an elevated anion gap, and demonstrate signs of dehydration with elevated blood urea nitrogen and creatinine levels (consistent with acute kidney injury [AKI]). His elevated β-hydroxybutyrate level indicates a state of ketosis. It is likely that both the loss of bicarbonate in his stool and the production of ketones from fasting are contributing to his metabolic acidosis.
- Because Sam was hypoglycemic with a serum glucose of 35 mg/dL (1.94 mmol/L) at the time of this laboratory test, this was an appropriate critical sample.
- His critical sample results show that his β-hydroxybutyric acid level is elevated, indicating he is in a state of ketosis. Ketone production is a normal reaction to starvation state. Patients with fatty acid oxidation defects cannot appropriately convert fat stores for ketones, leading to low ketone levels while fasting. The presence of significant ketosis and acidosis decreases the likelihood that Sam has a fatty acid oxidation disorder.
- Sam's lactate and cortisol levels are both within a normal range, helping to eliminate some metabolic and endocrinologic etiologies.
- Given his somnolence, it is important to note that his ammonia level is normal. A normal ammonia level also argues against a fatty acid oxidation defect or an organic acidemia.
- His C-peptide level is appropriate for someone in a fasting state. His normal C-peptide level rules out exogenous insulin administration, which is especially important given that his mother has a history of type 1 diabetes mellitus and has regular access to insulin.

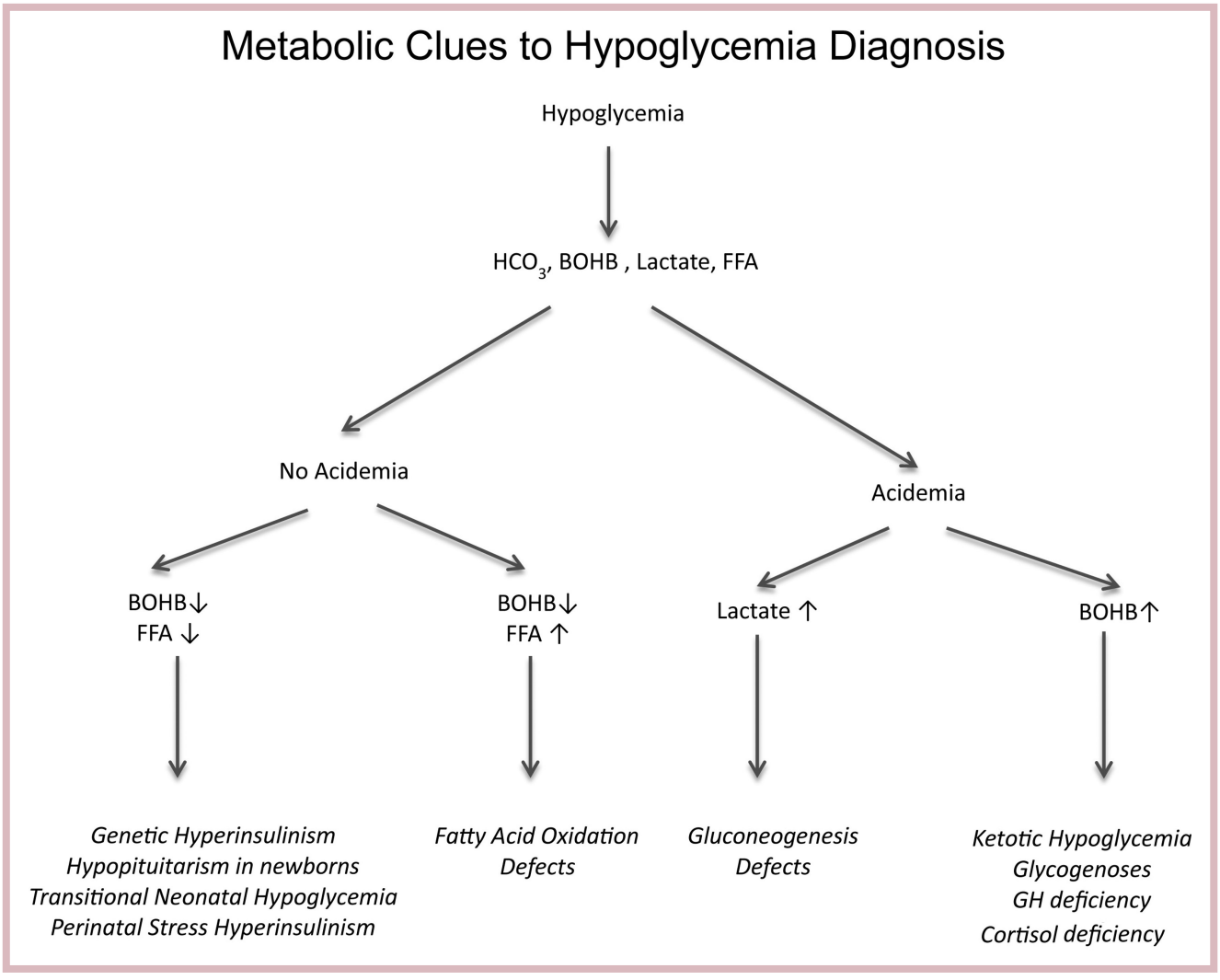

Figure 45.1. Metabolic clues to hypoglycemia diagnosis.

Abbreviations: BOHB, β-hydroxybutyrate; FFA, free fatty acids; GH, growth hormone; HCO_3, bicarbonate.

Reprinted with permission from Thornton PS, Stanley CA, De Leon DD, et al; Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr.* 2015;167(2):238–245.

2. Develop the list of findings.

Q: What major findings have you identified for Sam?

- Mild to moderate dehydration
- Hypoglycemia
- Ketosis
- Acute-onset vomiting and diarrhea
- Metabolic acidosis (with a high anion gap)
- AKI

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Sam's presentation?

- Considering the differential diagnosis, idiopathic ketotic hypoglycemia is the leading etiology of Sam's hypoglycemia. Idiopathic ketotic hypoglycemia is a diagnosis of exclusion but is commonly seen in younger children (usually ages 1–6 years). Children in this age range have a high demand for glucose as a primary energy source because their brain/body mass ratio is high, and their brain heavily depends on glucose for energy. Idiopathic ketotic hypoglycemia manifests in otherwise healthy children during fasting periods or intercurrent illnesses. It is thought that children prone to idiopathic ketotic hypoglycemia have increased basal metabolic rates, and possibly lower rates of endogenous glucose production, when compared to older children and adults.
- This diagnosis seems to fit well with Sam's current presentation. He appears to have an acute illness, likely gastroenteritis (with vomiting and diarrhea) with poor oral intake leading to dehydration and a fasting state. He is otherwise healthy, growing and developing normally, and lacks dysmorphic features or other obvious abnormalities on examination. His laboratory test results and physical examination findings are not consistent with most metabolic or endocrine derangements. As idiopathic ketotic hypoglycemia is a diagnosis of exclusion, you decide to continue to revisit your differential diagnosis as you gather more clinical data and monitor Sam's condition.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with hypoglycemia?

- The child requires further support and monitoring to avoid additional hypoglycemic events.
- The child has intractable vomiting, refuses oral rehydration solution (ORS), or is not able to consume sufficient fluid volumes to keep up with ongoing losses and to maintain serum glucose levels.
- Significant electrolyte abnormalities are present.
- The child has an unusual amount of drowsiness or irritability.
- Uncertainty about the diagnosis or illness severity exists, especially in an infant or young child.

You decide that Sam meets the criteria for hospital admission based on his current state of dehydration and significant hypoglycemia with continuing GI losses.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Sam is a 10-month-old otherwise healthy boy presenting with lethargy secondary to idiopathic ketotic hypoglycemia and mild to moderate dehydration. Additionally, he has a mild AKI and elevated anion gap metabolic acidosis. In the setting of vomiting, diarrhea, and poor intake, these findings likely relate to acute gastroenteritis leading to poor oral intake and subsequent ketotic hypoglycemia. His significant hypoglycemia, dehydration, lethargy, young age, and decreased oral intake warrant inpatient admission.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

To prevent brain injury, the primary focus for the management of hypoglycemia is to quickly reestablish and then maintain euglycemia. For Sam, his dehydration will need to be addressed as well.

1. **Management of acute gastroenteritis, rehydration, and maintenance of hydration:** Many patients with mild to moderate dehydration can undergo rehydration orally or via nasogastric tube; however, IV fluids may be needed for patients with lethargy, persistent nausea or vomiting, or significant abdominal pain. Additionally, a patient's hydration should be maintained by providing their hourly fluid requirements in accordance with the Holliday-Segar method. To maintain a patient's hydration, it is also important to keep up with their ongoing fluid losses; therefore, replacement fluids should be provided for each episode of emesis and diarrhea. For more information about treatment of dehydration and the maintenance of hydration, refer to Case 1.
2. **Correction of hypoglycemia**
   - For a patient with mild symptomatic hypoglycemia who is tolerating oral intake, providers can have the patient drink 4 fl oz of apple juice, or another juice with high fructose content, to increase blood glucose. The patient's blood glucose level should then be rechecked every 15 minutes until there is resolution of the hypoglycemia. Afterward, having the child eat foods high in complex carbohydrates, such as whole wheat crackers, can help to ensure they are able to maintain their serum glucose levels.
   - In cases of severe, symptomatic hypoglycemia or for patients who are unable to tolerate oral intake, the patient should be given an IV dextrose bolus to quickly raise the blood glucose level and resolve hypoglycemia (goal dextrose infusion: approximately 0.2–0.5 g/kg per dose). Refer to Table 45.2 for simple dextrose dosing options.
     - Once the dextrose bolus is given, the patient should be reevaluated clinically for symptom resolution, and the blood glucose level should be checked.
     - The dextrose percentage (concentration) to be administered depends on the type of venous access in place.
       - Peripheral lines (ie, IV): up to D12.5 (12.5% dextrose) for continuous infusions and D25 (25% dextrose) for bolus rescue doses can be provided via peripheral IV line. Because of the high osmolarity of D25 and its risk as a vesicant when extravasation occurs, it should be infused slowly at no more than 2–3 mL/min.
       - Central lines (ie, peripherally inserted central catheter, port, Broviac): It is safe to administer up to D30 (30% dextrose) for continuous infusions or D50 (50% dextrose) for bolus rescue doses via central venous access.

Table 45.2. Amount of IV Dextrose Bolus to Administer Based on Dextrose Concentration

Dextrose concentration	Amount
D10	2–5 mL/kg per dose
D25	1–2 mL/kg per dose
D50	1 mL/kg per dose

   - For patients with hyperinsulinism or insulin overdose, glucagon can be used to acutely increase the blood glucose. In an emergency, glucagon can be administered intramuscularly.

3. **Maintenance and monitoring of euglycemia:** Once the hypoglycemia has been corrected, prevention of recurrent hypoglycemia needs to be ensured. For patients who are tolerating oral intake, a diet rich in complex carbohydrates can often be used to ensure maintenance of euglycemia. When patients are unable to tolerate carbohydrates reliably by mouth or if their hypoglycemia persists or recurs despite this, a continuous infusion of IV dextrose can be provided instead.
   - To determine normal hourly glucose requirements for infants and children (and thus how much dextrose to add to a patient's IV fluids), it can be beneficial to calculate the glucose infusion rate (GIR).
     - The GIR is the rate (mg/kg/min) at which glucose needs to be delivered to ensure euglycemia.
     - There are 2 different methods of calculating GIR, based on the age-related goals provided in Table 45.3:
       - GIR = ([% dextrose in IV fluid] × [hourly rate of infusion]) / (6 × [weight in kg])
       - GIR = ([rate of infusion in mL/kg/day] × [% dextrose]) / 144

Table 45.3. GIR Goals by Age

Patient age	GIR goal
Neonates and young infants	4–6 mg/kg/min
Older infants and children	3–5 mg/kg/min

Abbreviation: GIR, glucose infusion rate.

   - The POC serum glucose level should be checked frequently (eg, every 15 min) until euglycemia (>70 mg/dL [3.89 mmol/L]) is achieved. Afterward, POC checks can be spaced based on clinical status, anywhere from 30 minutes to 4 hours apart. Glucose checks usually can be discontinued if glucose levels are stable over several readings, but checks may need to be restarted if the patient's clinical status worsens or when transitioning from IV dextrose infusions to oral intake.
   - Persistent hypoglycemia despite an appropriate GIR could be an indication that the patient has an underlying metabolic disorder or hyperinsulinism, as these patients often have a higher GIR requirement. For these patients, consultation with a pediatric endocrinologist or metabolic specialist is warranted.
4. **Other treatment or supportive measures:** When an underlying cause of the patient's hypoglycemia has been identified, treatment or other supportive care should be initiated.
5. **Patient and family education:** Patients and families should be educated about the signs and symptoms of hypoglycemia. Additionally, some patients may benefit from having a glucometer and/or serum ketone meter at home.

CASE FOCUS

Plan for Treatment and Monitoring

- **Rehydration therapy:** Sam requires further rehydration based on his vital signs and physical examination findings. You estimate that he is approximately 5% dehydrated on your evaluation, which represents approximately 480 mL of water loss with this illness. You order an IV normal saline bolus of 20 mL/kg (approximately 200 mL) to be given over 2 hours. You plan to reassess Sam's hydration status and his ability to continue his rehydration therapy by mouth after this bolus is complete.
- **Maintenance fluid and dextrose-infusion therapy:** Based on the Holliday-Segar method[a] and using a suspected preillness weight of 9.7 kg, you calculate that Sam's maintenance fluid requirements are 40 mL/h. Using the GIR calculations, you determine that a dextrose percentage of 5% should be sufficient to ensure he maintains euglycemia (using a minimum GIR of 3 mg/kg/min for his age). Because of this, you order 5% dextrose in normal saline at 40 mL/h, with the addition of 20 mEq/L potassium chloride once he voids.
- **Hypoglycemia monitoring:** As Sam is already euglycemic and appearing much more active, you plan to obtain POC blood glucose levels every 4 hours for the next 8 hours and will check his level again when he transitions from IV fluids back to a regular diet.
- **Antiemetics:** You order oral ondansetron as needed to treat nausea and vomiting.
- **Monitoring:** You order monitoring of intake and output, vital signs every 4 hours, and daily weights; repeat electrolytes, blood urea nitrogen, and creatinine levels can be obtained later in the day if needed based on Sam's clinical status.
- **Diet:** You allow Sam to resume oral intake on demand as desired. Use of an ORS (eg, Pedialyte) is encouraged.
- **Education:** You plan to educate Sam's family about the symptoms of hypoglycemia, the importance of avoiding prolonged periods of fasting, and how to use a glucometer at home.

[a] See Case 1 and Table A.4 in the Appendix for more information on the Holliday-Segar method.

Case Resolution

During the initial monitoring period of Sam's admission, 2 consecutive POC glucoses are noted to be 85 mg/dL (4.72 mmol/L) and 98 mg/dL (5.44 mmol/L), after which time the POC checks are stopped. Sam remains on IV fluids overnight with some marginal oral intake of around 6 fl oz before falling asleep. He has no further episodes of emesis and has one loose, but more formed, stool. In the morning, he tolerates 4 fl oz of formula without issue. His IV fluids are discontinued, and a repeat POC glucose level 2 hours later is 88 mg/dL (4.88 mmol/L). Because he continues to show interest in feeding, he is discharged home. When the pending test results come back, his insulin, free fatty acids, and GH serum levels are all within normal limits for a child in a fasting state.

Discharge Criteria

Q: How do you know when Sam is ready to go home?

You can feel comfortable discharging your patient with hypoglycemia and dehydration when the following criteria are met:

- The patient is able to maintain a blood glucose level above 70 mg/dL (3.89 mmol/L) for more than 2 hours without the need for IV dextrose.
- The patient is tolerating sufficient oral fluids to keep up with GI losses.
- The patient is tolerating complex carbohydrates.
- Adequate follow-up is ensured.

Anticipatory Guidance

Q: What instructions should you provide to Sam's caregivers upon discharge?

- Sam's episode of hypoglycemia was likely related to poor oral intake during his illness.
- During future illnesses, to avoid dehydration and hypoglycemia, give fluids containing glucose, such as ORS (eg, Pedialyte). It is important to encourage small amounts of fluid frequently.
- Return to care for lethargy, decreased urine output (no urination for ≥ 8–12 hours), difficulty breathing, or for any other concerns.

Clinical Pearls

- Clinical signs of hypoglycemia include jitteriness, irritability, lethargy, altered mental status, and, in severe cases, coma or seizures.
- A critical sample collected during the period of hypoglycemia, and before treatment, is helpful to elicit the cause of hypoglycemia. Serum electrolytes, β-hydroxybutyrate, urinary ketones, and lactate levels are readily accessible and should be the tests of highest priority.
- Idiopathic ketotic hypoglycemia is one of the most common causes of hypoglycemia in young children; however, it is a diagnosis of exclusion once more serious etiologies have been eliminated.
- The goal of therapy for hypoglycemia is to quickly correct the blood glucose level and ensure patients are able to maintain euglycemia.

Documentation Tips

- Document whether there is persistent altered mental status following treatment of hypoglycemia.
- Mention whether there is presence of recurrent hypoglycemia.
- Document frequency of blood glucose checks and neurologic checks during admission, and the need for IV fluids containing dextrose.

Suggested Reading

Thornton PS, Stanley CA, De Leon DD, et al; Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr*. 2015;167(2):238–245 PMID: 25957977 https://doi.org/10.1016/j.jpeds.2015.03.057

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Makayla, a 16-Year-Old Girl With Fever and Blurry Vision

CASE PRESENTATION

Makayla is a 16-year-old girl who presents to the emergency department (ED) with fever and blurry vision. Upon presentation, she is febrile and ill appearing with concerning neurologic changes, including gait instability, difficulty starting her urine stream, and difficulty swallowing, leading the ED physician to obtain a computed tomography (CT) scan of the head, comprehensive metabolic panel, complete blood cell count, C-reactive protein (CRP) level, and a blood culture. Makayla's head CT scan and all of her laboratory tests are within normal limits, and the ED physician orders a normal saline bolus and a dose of ibuprofen. The ED physician is concerned about Makayla's constellation of symptoms and feels that she needs further infectious and neurologic workup, and he calls you to evaluate Makayla for admission.

Patient History and Review of Systems

Q: What information should you collect from Makayla and her caregivers?

- History of present illness
  - Duration, timing, and intensity of fever
  - Detailed history of vision changes: duration, timing, presence of blurry or double vision, and any other abnormalities (eg, visual field defects, complete loss of vision, loss of color vision)
  - Eye redness, discharge, pain, or difficulty with eye movements
- Detailed history of other presenting neurologic symptoms (gait changes, difficulty starting urine stream, difficulty swallowing) and any other neurologic changes, such as headache, photophobia, or phonophobia; changes in mentation, changes in respiration, facial asymmetry, extremity weakness, numbness or tingling, neuropathic pain, difficulty with walking or coordination
  - Recent head or neck trauma, surgeries, or procedures
  - Recent illness or infectious exposures
- Associated symptoms, especially dental pain, facial pain or swelling, ear pain, sore throat, nasal congestion, or neck pain or stiffness
- Medical history, medication use, and immunization status, including seasonal influenza vaccination

- Family history of neurologic or autoimmune disorders
- Complete HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, including illicit substance use and any recent stressors (refer to Section VII in the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

When you arrive at the ED, you meet Makayla and her parents. Makayla explains that she has experienced 8 days of fever with a maximum temperature of 38.3 °C (100.9 °F). She is taking regular doses of ibuprofen and acetaminophen, which temporarily reduce her fever. She describes 2 days of worsening, persistent bilateral blurry vision, which she differentiates from double vision. She denies other vision changes (eg, blind spots, color blindness). She has bilateral pain with eye movements, particularly when looking to the right, which persists despite pain medication. She denies eye redness or discharge. Over the past day, she has become increasingly unsteady when walking and states that her legs feel weak. Makayla has also noticed some numbness of her legs bilaterally. She describes trouble starting her urine stream and notes that she last urinated yesterday. She reports several episodes of nonbloody, nonbilious vomiting over the past 2 days. She also has had increasing difficulty swallowing solid foods. Her parents state that her mentation is at baseline.

A detailed review of systems is positive for several days of generalized myalgias and rigors. She denies headache, rhinorrhea, facial asymmetry, nasal congestion, facial pain or swelling, dental pain, ear pain, sore throat, and neck pain or stiffness. She denies any head or neck trauma. She has not experienced any recent illnesses or exposures. Other than acetaminophen and ibuprofen, she denies use of any medications and denies use of illicit drugs. Prior to this illness she was well, without chronic medical conditions, and has never had surgery. Makayla's family history is significant for a paternal grandmother with rheumatoid arthritis. Her mother states that Makayla is fully immunized but has not yet received her seasonal influenza vaccine.

You ask Makayla's parents to step out of the room in order to conduct a complete HEADSS assessment. Aside from feeling some anxiety about what might be causing her current symptoms, Makayla reports that she does not have any significant stressors. She feels safe at home and enjoys school. Makayla denies any illicit substance use.

Physical Examination

Q: What parts of the physical examination should you focus on for Makayla?

- Complete set of vital signs
- Level of consciousness and mental status
- Head, ears, nose, and throat: evidence of trauma to the head or face, sinus tenderness, bulging tympanic membranes, oral ulcers or lesions, mucous membranes (moist, sticky, or dry), dental caries or signs of dental abscess; enlargement, asymmetry, erythema, or exudates of the tonsils
- Neck: swelling, tenderness, stiffness, Kernig and Brudzinski signs
- Eyes: conjunctival injection, pupillary response or asymmetry, papilledema, visual acuity, visual fields
- Respiratory: tachypnea or bradypnea, increased difficulty breathing or shallow respirations, breathlessness or difficulty completing sentences, diminished breath sounds
- Neurologic
  - Cranial nerves, including extraocular eye movements and facial symmetry
  - Strength, muscle tone, and involuntary movements
  - Signs of cerebellar dysfunction (eg, dysmetria, intention tremor, ataxia, dysdiadochokinesia)
  - Upper and lower limb reflexes, including evaluation for clonus and Babinski sign
  - Gait
  - Rectal tone and saddle anesthesia

CASE FOCUS

Physical Examination

Upon arrival in the ED, you note that Makayla is lying in bed and appears anxious but is awake, alert, and appears nontoxic. Her vital signs show that she is febrile, with a temperature of 38.2 °C (100.8 °F), and she has tachycardia, with a heart rate of 120 beats/min. Her respiratory rate is 15 breaths/min, and her blood pressure is 120/85 mm Hg, both of which are normal for her age.

Her eye examination reveals strabismus with deviation of the right eye inward and bilateral lateral nystagmus. She does not have any conjunctival injection. Fundoscopic examination shows edema of the optic discs bilaterally. There is no evidence of uveitis or retinal changes. She has an afferent defect of bilateral pupils. She has bilaterally intact extraocular movements with pain in all directions. The use of a Snellen chart reveals her visual acuity is 20/200 bilaterally. She does not have diplopia, and her visual fields are intact.

Makayla's face is symmetric, and her tongue is midline when protruding. Her gross motor examination reveals her bilateral lower extremity strength to be a 3 on a scale of 0 to 5. Her upper extremity strength is a 5 on a scale of 0 to 5 bilaterally. Makayla has normal muscle tone, and you do not note any involuntary movements. She has paresthesia and numbness in her bilateral lower extremities and partially in her inner thigh, perineum, and buttock. She has decreased rectal tone. Her lower extremity reflexes are +3 (very brisk) bilaterally. She demonstrates bilateral positive Babinski reflexes and clonus. Her upper extremity reflexes are normal. She has no pronator drift and has normal rapid alternating movements. She has an unsteady gait and requires assistance when walking.

Her head and neck examinations are overall unremarkable without evidence of trauma. She does not have neck pain or stiffness. Her Kernig and Brudzinski signs are negative. Her abdomen demonstrates a suprapubic palpable firm mass, but there is no tenderness, guarding, or rebound tenderness. Her cardiac and pulmonary examinations are normal.

Differential Diagnosis

Q: What is the differential diagnosis for an adolescent with visual defects, lower extremity weakness, and hyperreflexia associated with fever and vomiting?

The differential diagnosis for an adolescent with these symptoms is shown in Table 46.1 and is divided into causes that seem more and less likely based on Makayla's presentation.

Table 46.1. Differential Diagnosis for an Adolescent With Visual Defects, Lower Extremity Weakness and Hyperreflexia Associated With Fever and Vomiting

Diagnoses of highest suspicion	• CNS inflammatory disorders — ADEM — AFM — MOG antibody-associated encephalomyelitis — MS — NMOSD[a] — Optic neuritis — TM
Other diagnoses to consider	• Infectious etiologies — Bacterial CNS infection (meningitis, encephalitis, abscess), including less common pathogens (eg, *Bartonella henselae*, *Borrelia burgdorferi*, *Treponema pallidum*, *Mycoplasma pneumoniae*) — Bacterial sinusitis and/or orbital cellulitis with intracranial extension — Viral meningoencephalitis (eg, adenovirus, EBV, enterovirus, HIV, HSV, human polyomavirus 2, influenza, measles, rabies, VZV, West Nile virus) • Neoplastic etiologies — Paraneoplastic disorder (limbic encephalitis) — Primary CNS tumor (lymphoma, glioma, astrocytoma) • Nutritional deficiency (eg, vitamin B_{12}) • Other CNS inflammatory disorders — Anti-NMDA receptor encephalitis — Disorders of the peripheral nervous system (eg, Guillain-Barré syndrome with Miller Fisher syndrome variant) — Hashimoto encephalopathy — Primary CNS vasculitis — Seronegative autoimmune encephalitis — Systemic inflammatory disorders (eg, sarcoidosis, Sjögren syndrome, SLE, juvenile dermatomyositis) • Other etiologies — FNSD (also known as *conversion disorder*) — Ischemic stroke (cerebral or spinal cord) — Substance use or withdrawal

Abbreviations: ADEM, acute demyelinating encephalomyelitis; AFM, acute flaccid myelitis; CNS, central nervous system; EBV, Epstein-Barr virus; FNSD, functional neurological symptom disorder; HSV, herpes simplex virus; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMDA, N-methyl-d-aspartate; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus; TM, transverse myelitis; VZV, varicella-zoster virus.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for an adolescent presenting with visual defects, lower extremity weakness, and hyperreflexia associated with fever and vomiting?

- Considering the differential diagnoses, the following should be included in an initial evaluation of patients presenting with the previously mentioned symptoms:
  - CT scan of the head without contrast: In children and adolescents with acute neurologic changes, a head CT scan is typically the first imaging modality obtained because it is rapid and widely available. Additionally, a head CT scan should be performed prior to lumbar puncture (LP) if there are any signs of increased intracranial pressure (eg, focal neurologic deficits, altered mental status, papilledema).
  - LP: An LP should be performed to assess opening pressure and obtain cerebrospinal fluid (CSF) for testing.
    - CSF should undergo the typical evaluation, including cell counts, protein level, glucose level, Gram stain, and bacterial culture.
    - If there is suspicion of malignancy, CSF cytology should be considered.
    - If CSF studies are indicative of infection, clinicians can consider a meningitis/encephalitis CSF polymerase chain reaction (PCR) panel.
    - In cases of autoimmune or inflammatory central nervous system (CNS) disease, CSF studies are typically nonspecific but may include pleocytosis and elevated protein. Additionally, when there is concern for autoimmune encephalitis, CSF and serum antibody titers against extracellular CNS antigens should be measured (eg, N-methyl-d-aspartate [NMDA] receptor, myelin oligodendrocyte glycoprotein [MOG], glutamic acid decarboxylase 65).
    - Oligoclonal bands are a class of immunoglobulins that can be found in the serum and CSF. Oligoclonal bands present in CSF and not in serum can have high sensitivity but poor specificity, particularly for multiple sclerosis (MS). They are most commonly associated with MS (present in 40%–90% of cases) but can occur in cases of acute demyelinating encephalomyelitis (ADEM) or anti-NMDA receptor encephalitis. The presence of oligoclonal bands in CSF is considered nonspecific, as oligoclonal bands are also associated with infections, autoimmune diseases, malignancies, lymphoproliferative disorders, and other inflammatory conditions of the CSF.
  - Magnetic resonance imaging (MRI) of the brain: MRI of the brain with and without gadolinium contrast is the single most helpful tool in diagnosing CNS autoimmune and inflammatory conditions and excluding less likely diagnoses such as stroke and tumor. Depending on the clinical presentation, the addition of MRI of the spine may be necessary to evaluate for neuromyelitis optica spectrum disorder (NMOSD), MS, transverse myelitis (TM), spinal cord infarction, and acute flaccid myelitis (AFM).
- Additional diagnostic evaluation to consider includes the following:
  - Complete blood cell count: Neutrophilic leukocytosis with left shift can be indicative of an acute bacterial infection. Inflammatory conditions and malignancies can also present with an elevated white blood cell count.
  - Acute phase reactants: Erythrocyte sedimentation rate (ESR) and CRP, though nonspecific, may be elevated in the presence of a serious bacterial infection, inflammatory disease, or tissue injury.
  - Electroencephalogram (EEG): When seizures or encephalopathy are suspected based on history or physical examination, abnormalities found on EEG can support these diagnoses.
  - Urine drug screen: This screen is helpful for patients presenting with acute neurologic changes of unclear etiology.
  - Basic metabolic panel: This panel should be considered to evaluate serum electrolytes, renal function, and glucose level.
  - Creatine kinase (CK): A serum CK level should be considered for any patient presenting with myalgias and weakness. If CK is elevated, it may indicate the presence of a myositis, but the underlying etiology would need further exploration.

CASE FOCUS

Diagnostic Evaluation

After you complete Makayla's history and examination, you review the results of her laboratory evaluation from the ED, which are as follows:

Laboratory test	Results	Normal range
CBC		
WBC count	6,500/μL (6.5 × 10^9/L)	4,000–10,500/μL (4.0–10.5 × 10^9/L)
Hemoglobin	14.2 g/dL (142 g/L)	12.0–15.0 g/dL (120–150 g/L)
Hematocrit	46.4% (0.464)	35%–45% (0.35–0.45)
Platelet count	272 × 10^3/μL (272 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
BMP		
Sodium	136 mEq/L (136 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4.3 mEq/L (4.3 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	100 mEq/L (100 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)	22–26 mEq/L (22–26 mmol/L)
Anion gap	12 mEq/L (12 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	13 mg/dL (4.64 mmol/L)	6–20 mEq/L (2.14–7.14 mmol/L)
Creatinine	0.8 mg/dL (70.7 μmol/L)	0.5–0.9 mg/dL (44.2–79.6 μmol/L)
Glucose	102 mg/dL (5.66 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
Other studies		
CK	60 U/L (1.0 μkat/L)	24–140 U/L (0.4–2.3 μkat/L)
ESR	46 mm/h	0–10 mm/h
CRP	13 mg/L (130 mg/L)	< 1 mg/dL (10 mg/L)

Abbreviations: BMP, basic metabolic panel; BUN, blood urea nitrogen; CBC, complete blood cell count; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Additionally, you decide to order a urine drug screen. Makayla is unable to urinate spontaneously for the urine drug screen. You suspect that the suprapubic mass noted during your physical examination is her distended bladder. You decide to perform a bladder catheterization to relieve her bladder distention and collect a urine specimen. The bladder catheterization results in 600 mL of yellow urine and resolution of the suprapubic mass.

Makayla's urine drug screen is negative.[a]

Based on your differential diagnosis, you decide to perform an LP. You send the CSF for cell counts, protein, glucose, Gram stain, and bacterial culture. Additionally, you order a meningitis/encephalitis PCR panel and oligoclonal bands. The results of this evaluation are as follows:

CSF studies		
Laboratory test	**Results**	**Normal range**
Clarity/color	clear/colorless	clear/colorless
WBC count	92 cells/mm^3	≤5 cells/mm^3
WBC differential	90% lymphocytes 10% monocytes	40%–80% lymphocytes 15%–45% monocytes
RBC count	3 cells/mm^3	0 cells/mm^3
Protein	253 mg/dL	20–45 mg/dL

CASE FOCUS

Diagnostic Evaluation *(continued)*

CSF studies *(continued)*		
Laboratory test	**Results**	**Normal range**
Glucose	52 mg/dL	>50 mg/dL
Gram stain	Moderate WBC, no organisms	
Opening pressure	14 cm H_2O	<28 cm H_2O
Oligoclonal bands	Negative	Negative
Meningitis/encephalitis panel[b]	Not detected	Not detected

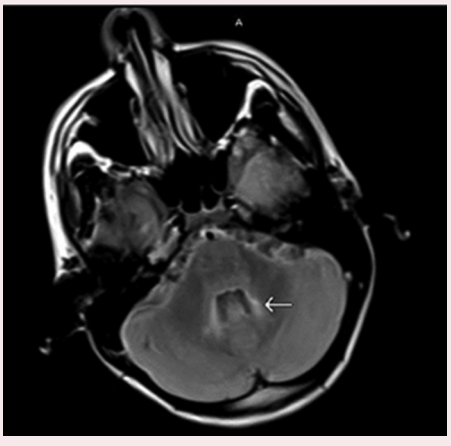
Abbreviations: CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

[a] Urine drug screen includes tetrahydrocannabinol (cannabinoids), cocaine, opiates, oxycodone, phencyclidine, amphetamines, 3,4-methylenedioxymethamphetamine (ecstasy), barbiturates, benzodiazepines, methadone, and propoxyphene.

[b] Meningitis/encephalitis PCR panel includes *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, group B streptococcus, *Streptococcus pneumoniae*, cytomegalovirus, enteroviruses, herpes simplex virus (HSV)–1, HSV-2, HSV-6, human parechovirus, varicella-zoster virus, *Cryptococcus neoformans*, and *Cryptococcus gattii*.

You also obtain an MRI of the orbits, brain, and spine. The results of Makayla's MRI are as follows:

MRI of the brain and complete spine: multiple abnormalities, including patchy T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities in the cerebellar white matter, area postrema of the dorsal medulla, and lower pons. Also present is bilateral optic nerve enhancement and increased T2 signal of periependymal surfaces of the fourth ventricle (see image), third ventricle, and aqueduct. T2 intensities of the central cord span 4 vertebral segments. There is contrast enhancement in T1 images of the spinal cord lesion and the nerve root enhancement of the cauda equina.



Axial MRI of the brain shows FLAIR bright signal along the margins of the fourth ventricle (arrow). On FLAIR sequences (and T2, not shown), gray matter containing high water content is a brighter signal than adjacent white matter, and CSF, which is normally dark. This allows detection of lesions in the brain parenchyma and periventricular regions.

Radiologist interpretation: MRI findings of bilateral acute optic neuritis, acute TM, and abnormal signal in the area postrema are consistent with neuromyelitis optica and correlate with the clinical presentation of area postrema syndrome.

Arriving at a Diagnosis

Q: How do you develop an assessment for Makayla?

To determine Makayla's diagnosis, you first review the key findings of her history, physical examination, and diagnostic studies.

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Makayla is a healthy 16-year-old girl presenting with 8 days of fever (maximum temperature: 38.3 °C [100.9 °F]); several days of myalgias and rigors; 2 days of blurry vision, nonbloody nonbilious vomiting, and eye pain with movement; and 1 day of difficulty walking, decreased urination, and difficulty voiding. She also reports some difficulty swallowing solid foods. The acute onset of her symptoms makes a neoplastic process less likely.
   - Physical examination: Makayla's examination shows that she is febrile and tachycardic with a bilateral afferent pupillary defect, pain with extraocular eye movements, decreased visual acuity (20/200), and papilledema. Her lower extremity examination is significant for bilateral lower extremity weakness, paresthesia, and hyperreflexia. Additionally, she has decreased rectal tone and evidence of urinary retention, which was relieved by placement of a urinary catheter. The distribution of her neurological symptoms is consistent with a CNS disorder and is unlikely to be the result of a peripheral nervous system disorder.
   - Diagnostic evaluation: Makayla's head CT scan is normal, and the results of her serum laboratory tests are normal other than elevated inflammatory markers. Her CSF evaluation demonstrates pleocytosis and elevated protein in the CSF, negative oligoclonal bands, and a negative meningitis/encephalitis PCR. Her CSF findings are more consistent with an inflammatory disorder than infectious meningitis. Her MRI findings show optic neuritis, abnormal area postrema, and acute TM.
2. **Develop the list of findings.**

Q: What major findings have you identified for Makayla?

- Findings of acute TM, acute optic neuritis, and abnormal area postrema on MRI
- Nausea and vomiting
- CSF lymphocytic pleocytosis with elevated CSF protein
- Dysphagia
- Fever

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Makayla's presentation?

In Makayla's case, the CSF findings of pleocytosis and elevated protein, MRI findings of hyperintense lesions, and the negative infectious workup raise concern for neurologic inflammatory diseases such as MS, NMOSD, ADEM, MOG, and NMDA encephalitis. More specifically, her constellation of MRI findings (abnormal area postrema signal, acute TM, optic neuritis, periependymal hyperintensity) are very specific for NMOSD. Although optic neuritis can be seen in a variety of neurologic disorders, longitudinally extensive TM (inflammation extending ≥3 vertebral segments) is classically found in NMOSD.

Q: What is NMOSD, and what are the associated diagnostic criteria?

- NMOSD is a relapsing autoimmune astrocytopathic disorder resulting in demyelination and axonal damage that commonly targets optic nerves and the spinal cord.
- The most recent revised diagnostic criteria require the presence of 1 core clinical characteristic if antibody positive or 2 core characteristics if antibody negative. Aquaporin (AQP)-4 immunoglobulin G (IgG) antibodies are present in 70% of NMOSD patients. The core clinical characteristics include
  - Optic neuritis.

- Acute myelitis.
- Area postrema syndrome.
- Acute brainstem syndrome.
- Symptomatic narcolepsy.
- Acute diencephalic clinical syndrome.
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions.

Based on these criteria, you can diagnose Makayla without AQP4 IgG antibody results because she displays 4 of the 7 core characteristics of NMOSD.

Q: Is MS still a possibility for Makayla? What about anti-NMDA-receptor encephalitis, ADEM, AFM, or MOG antibody-associated encephalomyelitis?

- MS: MS is a relapsing demyelinating disease that targets white matter, followed by axonal and neuronal loss. It is primarily a clinical diagnosis and can be excluded in this case for several reasons. Simultaneous bilateral optic neuritis is less common in MS compared to NMOSD, as is a longitudinally extensive spinal cord lesion. MRI findings typical of MS include Dawson fingers, which are ovoid lesions oriented perpendicular to the ventricle margins and corpus callosum. Lesions are also found juxtacortical, infratentorial, and in the cervical spinal cord. Additionally, oligoclonal bands are more common in MS, found in 40% to 90% of pediatric patients.
- Anti-NMDA receptor encephalitis: Anti-NMDA receptor encephalitis is a monophasic autoimmune disease that is typically associated with a prodromal upper respiratory infection followed by psychiatric symptoms, insomnia, memory defects, and seizures. It can progress into catatonia, mutism, dystonia, arrhythmias, and autonomic instability. It can also be associated with ovarian teratomas and herpes simplex virus encephalitis. Makayla's lack of psychiatric symptoms or seizures at onset would be atypical of anti-NMDA encephalitis, making this diagnosis unlikely.
- ADEM: ADEM is a monophasic immune-mediated demyelination disorder that is associated with a viral or vaccine trigger. Patients can present similar to Makayla. Common signs and symptoms of ADEM include fever, headache, emesis, and neurological signs, including optic neuritis, spinal cord symptoms, and hemiparesis. Patients can also have meningismus, seizures, pyramidal signs, ataxia, and/or mutism. MRI findings show patchy poorly marginated hyperintense lesions in the perivenous and subependymal area, commonly in the cortical-subcortical border. Makayla's MRI finding are not consistent with this diagnosis.
- AFM: AFM is a neurotropic illness affecting lower motor neurons and cranial nerves. This condition is typically preceded by an upper respiratory infection or gastrointestinal symptoms and presents with progressive flaccid weakness in the affected spinal cord region. On MRI, there is typically only enhancement of the gray matter (specifically the anterior horn cells) of the spinal cord. AFM is not associated with optic neuritis, which helps exclude this diagnosis in Makayla.
- MOG antibody-associated encephalomyelitis: MOG antibody-associated encephalomyelitis is a demyelinating disease that may present similarly to NMOSD with optic neuritis and TM. Unlike NMOSD, MOG antibody-associated encephalomyelitis may resemble ADEM, with findings of encephalopathy, behavioral changes, and seizures along with an increased risk of cerebellar and brainstem involvement. Because of the similarities between NMOSD and MOG antibody-associated encephalomyelitis, providers should check for MOG antibodies when either condition is possible.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with a CNS inflammatory condition, such as NMOSD?

All patients with acute and potentially reversible neurologic manifestations from active CNS lesions require hospitalization to expedite treatment in an effort to reduce both their morbidity and mortality.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Makayla is a 16-year-old girl presenting with fever, blurry vision, pain with extraocular movements, bilateral lower extremity weakness, dysphagia, and urinary retention, with MRI findings diagnostic for bilateral optic neuritis, area postrema abnormal signal, and TM. These findings are consistent with NMOSD. Admission is indicated for initiation of immunomodulatory medications and management of potential complications.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Patients who are in an acute flare-up with active CNS lesions will require short-term aggressive intravenous (IV) treatment with immunomodulatory medications to decrease the ongoing insult and help reduce morbidity and mortality. They will also need initiation of long-term oral or IV immunomodulatory medications in chronic or relapsing diseases. Additionally, patients usually require evaluation and treatment by a multidisciplinary team.

1. **Consultations**
   - Neurology consult: Involving a pediatric neurologist is important for patients presenting with focal neurologic findings and initial workup indicative of serious CNS disease.
   - Ophthalmology consult: Any patient with unexplained visual symptoms should have an evaluation by an ophthalmologist. A thorough ophthalmology examination should be performed to identify changes in visual acuity, visual field deficits, and retinal or optic nerve changes.
2. **Further confirmatory or diagnostic testing**
   - AQP4 antibody: AQP4 antibodies are often found in the serum and CSF of patients with NMOSD. AQP4 antibodies are very specific for NMOSD and helpful when ruling out other possible diagnoses.
   - When confirming the diagnosis of NMOSD, providers must exclude other conditions associated with neurologic syndromes that mimic NMOSD. These conditions include the following:
     - MOG antibody-associated encephalomyelitis: CSF and serum should be tested for the presence of MOG antibodies to help rule out the diagnosis of MOG antibody-associated encephalomyelitis.
     - Sarcoidosis: Evaluation for sarcoidosis may reveal mediastinal adenopathy on chest radiograph, and elevated serum angiotensin-converting enzyme or IL-2 receptor levels.
     - Paraneoplastic syndrome: Evaluation for paraneoplastic syndrome includes testing for paraneoplastic/autoimmune encephalitis antibodies in serum and CSF.
     - Chronic infectious diseases: Certain chronic infectious diseases, such as HIV, syphilis, and tuberculosis may also mimic NMOSD. Therefore, further testing aimed at ruling out these diagnoses should be obtained.

3. **Immunomodulating agents:** Under the direction of a neurologist, the treatment approach for CNS inflammatory and demyelinating conditions involves the use of acute and long-term immunomodulating agents. These immunomodulating agents include steroids, antimetabolites, alkylating agents, calcineurin inhibitors, monoclonal antibodies, and IV immunoglobulin.
   - High-dose (or "pulse-dose") corticosteroid therapy is the first-line treatment of acute inflammation in NMOSD and other autoimmune and inflammatory conditions. IV therapy with methylprednisolone is used for the acute phase followed by an oral steroid taper.
   - Antimetabolites interfere with essential metabolic routes in immune cells and prevent proliferation or cause apoptosis.
   - Alkylating agents, such as cyclophosphamide, cause breakage of DNA strands and cell death.
   - Calcineurin inhibitors, such as tacrolimus and cyclosporine, work by inhibiting interleukin (IL)-2 availability and expression blocking T-cell activation.
   - Monoclonal antibodies bind immune cells and proteins in a variety of ways to prevent cell proliferation, promote cell death, and suppress immune system function.
   - IV immunoglobulin is a pooled group of antibodies collected from human plasma. It downregulates antibody production by B-cells and interferes with B-cell proliferation and activation.
   - Apheresis has also been used to deplete the autoimmune antibodies and modulate the immune response.
   - Certain disease-modifying drugs used for MS have been shown to worsen NMOSD symptoms, including interferon-β, natalizumab, fingolimod, alemtuzumab, and dimethyl fumarate.
   - For Makayla, it is appropriate to discuss all of these options with a neurologist prior to initiating immunomodulating agents.
4. **Monitoring:** Patients with active CNS lesions should be monitored closely for any progression of symptoms and for signs of response to therapy. The team should repeat Makayla's neurologic examination daily to direct further treatment. If her examination is not improving on first-line therapy, then the neurology team may recommend additional treatment. Additionally, she will need to be monitored for medication side effects.
5. **Rehabilitation:** Once patients are starting to show recovery from acute inflammation and are medically stable, it is important to involve physical therapy, occupational therapy, and speech therapy, working alongside a physical medicine and rehabilitation physician and a psychiatrist.
6. **Supportive care**
   - Fluids and nutrition: Because of the complex sensorimotor processes involved in swallowing, dysphagia and poor oral intake are often seen in patients with neurologic disorders, including CNS inflammatory disease. Patients with dysphagia are at risk of dehydration, malnutrition, and aspiration. Prompt evaluation by a speech therapist and a dietician will help prevent and manage these complications. Patients may require further workup, such as a video swallow study. They may also require nasogastric feedings to help prevent aspiration until dysphagia improves. As Makayla is experiencing dysphagia, consulting a speech therapist and a dietician is appropriate early in her management.
   - Urinary retention/incontinence: Urinary incontinence or retention may occur when there is insult to the CNS. Makayla presented with cauda equina syndrome, which disrupts the parasympathetic signals to the urethral and pelvic floor. Patients with urinary retention require close monitoring of urine output and monitoring for urinary retention with postvoid residual bladder scans. Of note, the presence of incontinence does not rule out urinary retention, and patients with incontinence should still be evaluated with bladder scans. A urologist or physiatrist is typically helpful in managing urinary retention in the presence of CNS disease and should be consulted early for all patients experiencing these symptoms, including Makayla.

- Constipation: In any CNS insult, there can be slowing of bowel movements and decreased sensation or control of the rectal sphincter, which can lead to constipation or fecal incontinence. Even though Makayla is not currently experiencing constipation, she is at risk for developing constipation and should be started on a bowel regimen with laxatives, stool softeners, and/or prokinetic medications.
- Pain: Up to 86% of patients with NMOSD experience neuropathic or spastic pain. Antiseizure medications (eg, carbamazepine, gabapentin) are considered first-line therapy, followed by antidepressants (eg, amitriptyline). Antispasmodics (eg, baclofen) and analgesics (eg, tramadol, opiates) are other options. Makayla is not currently experiencing pain; however, an appropriate pain regimen should be promptly initiated in the event she begins to experience pain.
- Mental health: Patients with NMOSD are at risk of developing fatigue, cognitive deficits, and psychological conditions (eg, depression). Patients may lose their ability to independently complete activities of daily living, contributing to fatigue and depression. Cognitive difficulties may be caused by primary brain involvement and/or underlying depression, fatigue, or medications. Patients may also develop sleep disturbances related to urinary retention/incontinence and spastic pain. The mental health team should be consulted in Makayla's case to help proactively address these aspects of her care.

CASE FOCUS

Plan for Treatment and Monitoring

- **Consultations:** You consult the neurology service to help direct further diagnostic testing and treatment options for Makayla. The neurology team will participate in daily family-centered rounds and adjust recommendations as Makayla's case progresses. You also plan to consult ophthalmology to help closely monitor Makayla's visual symptoms.
- **Immunomodulating agents:** Under the recommendation of the neurology team, you initiate treatment pulse (high-dose) methylprednisolone for 5 days. You will plan for apheresis if you do not see significant improvement.
- **Monitoring:** To monitor Makayla's progress, you plan to perform daily neurologic examinations. You will closely follow her vital signs and perform a daily review of symptoms to detect any side effects from treatment. Additionally, the team plans to repeat an MRI of her brain and spine and obtain an ESR and CRP level after completion of treatment.
- **Rehabilitation:** You consult the physical medicine and rehabilitation team, including physical therapy, occupational therapy, and speech therapy. The physical medicine and rehabilitation team will help direct long-term care by determining whether Makayla will need inpatient or outpatient rehabilitation services.
- **Supportive care**
  - Fluids and nutrition: You start Makayla on nasogastric feeds and consult a dietician to follow her nutritional status over the long term.
  - Urinary retention/incontinence: You order intermittent bladder catheterization as needed for urinary retention and consult the urology team to follow Makayla's neurogenic bladder management.
  - Constipation: Makayla's condition puts her at risk for constipation; therefore, you preemptively start polyethylene glycol.
  - Pain: You plan to start gabapentin as needed if Makayla develops neuropathic pain.
  - Mental health: You consult psychiatry and psychology to help Makayla cope with her diagnosis.

Case Resolution

Makayla is started on long-term immunosuppressive therapy with rituximab after completing 5 days of high-dose steroids and apheresis, which she requires because her symptoms did not improve with steroids alone. Following her treatment, a repeat MRI, ESR, and CRP level show improvement in her acute inflammation. Her visual acuity and dysphagia also improve significantly with only mild residual deficits; however, she continues to have weakness in her lower extremities. She has regular visits with physical therapy and occupational therapy during her hospitalization and is eventually transferred to the inpatient rehabilitation service.

While in the rehabilitation unit, Makayla continues to have urinary retention and requires intermittent self-catheterization. The child psychiatrist diagnoses Makayla with an adjustment disorder with a depressed mood as a result of her NMOSD diagnosis. Her adjustment disorder and depressed mood are successfully treated with frequent psychotherapy sessions.

After a week, the previously ordered CSF and serum AQP4 antibody tests return positive. The serum MOG antibody test is negative. Makayla meets the diagnostic criteria for anti-AQP4 antibody-positive NMOSD based on her typical MRI findings of longitudinally extensive acute TM spanning at least 3 vertebral segments, optic neuritis, periependymal inflammation, and area postrema syndrome.

Discharge Criteria

Q: How do you know when Makayla is ready to go home?

You can feel comfortable discharging your patient with NMOSD when the following criteria are met:

- The patient has completed daily IV therapies and/or apheresis targeting acute inflammation.
- The patient's neurologic examinations are improving.
- A long-term rehabilitation plan has been established.
- A plan for maintaining adequate nutrition and hydration has been established.
- The patient is demonstrating adequate control of urinary retention.
- A long-term plan for mental health care has been established.

Anticipatory Guidance

Q: What guidance should you provide to Makayla and her caregivers upon discharge?

- There is an 86% chance that patients with NMOSD will relapse. This average timing of relapse occurs of around 14 months to the diagnosis. Therefore, Makayla should follow up closely with a neurologist.
- The recovery of neurological deficits can take years, and some patients may experience permanent deficits. For the best chance of recovery, Makayla should participate in ongoing physical therapy, occupational therapy, and rehabilitation services.
- Makayla will need follow up with urology and/or physiatry to manage ongoing urinary retention and potential complications (eg, urinary tract infections). Because Makayla is requiring intermittent catheterization, she is at risk for urinary tract infections and should promptly seek medical care if she develops fever, abdominal pain, or dysuria.
- Damage to the neurologic function of bowel and rectal/pelvic floor muscles may result in constipation. Dietary changes and adequate hydration may be adequate to treat constipation. However, if constipation persists, there may be permanent damage to the neurologic function of the bowel or rectal/pelvic floor muscles. If this occurs, a more aggressive bowel regimen should be considered to avoid chronic constipation and stool impaction.

Clinical Pearls

- Fever with acute neurologic changes has a broad differential including infectious, autoimmune, inflammatory, and other etiologies. Key symptoms such as nausea, vomiting, vision changes, findings on neurologic examination, mental status, and meningismus can narrow the differential.
- Symptoms of pain with extraocular movements and blurry vision should be evaluated for optic neuritis with an ophthalmic examination and orbital imaging.
- It is important to initiate immunomodulating therapy quickly in cases of acute CNS inflammation to stop ongoing neuronal damage and preserve visual and motor function.
- Patients with NMOSD will need a multidisciplinary approach to address multiple sequalae in the long term, including visual deficits, motor deficits, neuropathic and spastic pain, spastic paralysis, urinary incontinence/retention, constipation, depression, fatigue, and nutrition.

Documentation Tips

- Document when there is the presence of aphasia or ataxia; blindness, diplopia, or vision change; dysarthria or dysphagia; or paresis or paralysis.
- Document whether there are mental status or respiratory examination changes.
- Document the frequency of neurologic examinations needed during the admission.
- Include whether CNS imaging is planned within 24 hours of admission.

Suggested Readings

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Olive, a 4-Month-Old Girl With Lethargy and Hyponatremia

CASE PRESENTATION

Olive, a 4-month-old girl, presents to the emergency department (ED) with lethargy. Since being diagnosed with respiratory syncytial virus (RSV) bronchiolitis by her pediatrician 2 days ago, her parents report that Olive has been more listless, and they brought her into the ED today when she became difficult to arouse.

Upon arrival to the ED, Olive is noted to be lethargic and tachypneic, and she is uninterested in drinking. The ED physician orders several laboratory tests, including serum electrolytes. Olive's laboratory test results are notable for a serum sodium level of 126 mEq/L (126 mmol/L). The ED physician calls you to discuss Olive's case and requests that you consider her for admission.

Patient History and Review of Systems

Q: What information should you collect from Olive's caregivers?

- History of present illness
  - Timeline of illness, including onset of any fever, cough, and difficulty breathing
  - Further description and timeline of changes in mental status and alertness
  - Changes in urine output, including the number and volume of wet diapers
  - History of head injury or exposure to potentially toxic substances
  - Sick contacts, including child care attendance
- Detailed feeding history
  - Composition of feeds (human [breast] milk, formula, or both)
  - If breastfed, duration and frequency of nursing sessions
  - If formula fed, how formula is mixed; baseline volumes and frequency of feedings
  - Recent deviations from normal feeding pattern/volumes
  - Additional intake (eg, solid foods, water, juices, herbal teas)
- Associated symptoms, such as vomiting, diarrhea, polyuria, polydipsia, abnormal movements, or seizures
- Medical history, including relevant birth history, growth, development, and immunization history
- Medications, including supplements
- Social history, including screening for food insecurity

CASE FOCUS

History and Review of Systems

After meeting Olive and her parents, you learn that Olive is a full-term infant girl with no chronic medical conditions. Her respiratory illness started 4 days ago, primarily with cough and nasal congestion, and her symptoms have been worsening since that time. Her parents took her to her pediatrician 2 days ago, where she was diagnosed with RSV bronchiolitis. Her parents are concerned about increasing "sleepiness" since her diagnosis, and they tell you they brought Olive to the ED today because she was difficult to arouse and was not waking up to feed. Her parents also describe worsening cough, retractions, and tachypnea at home since her last visit to her pediatrician.

Olive has had decreased urine output for the past 2 days. At baseline, she has 8 to 9 wet diapers per day, though she has had only 1 wet diaper today and 4 wet diapers in the past 48 hours. Olive has had 1 day of decreased oral intake. Normally, she takes 4 to 5 fl oz of standard infant formula 5 times per day; today, she has barely taken 1 fl oz total. Her parents tell you they use one scoop of formula per 2 fl oz of water and have not given Olive any water, teas, or juices.

On the morning of presentation, Olive had 1 episode of nonbloody, nonbilious emesis, but her parents deny fevers, diarrhea, abnormal movements, or seizures. She attends child care, where several other children have been sick recently with upper respiratory infection symptoms. Her parents state that Olive is growing well, and her growth has been tracking along the 10th percentile since birth. She is meeting all of her developmental milestones and is up to date on her immunizations. She has not taken any recent medications. They deny any possibility of an accidental toxic ingestion or head injury. Olive lives at home with her parents, and food insecurity screening is negative.

Physical Examination

Q: What parts of the physical examination should you focus on for Olive?

- Complete set of vital signs
- Overall appearance: level of consciousness (ability to arouse, responsiveness)
- Evaluation of volume status: assessment of fontanelle, mucous membranes, presence or absence of tears, capillary refill
- Weight, with comparison to recent values
- Extremities: perfusion, pulses, edema
- Respiratory: auscultation for quality of breath sounds and any adventitious sounds, assessment of work of breathing, including retractions (suprasternal, intercostal, subcostal), nasal flaring, grunting, head-bobbing, prolonged exhalation
- Abdomen: distention, masses, organomegaly
- Skin: rashes, bruising, any other lesions
- Neurologic: abnormal movements, pupillary response, muscle tone, primitive reflexes (palmar and plantar grasp), spinal reflexes

CASE FOCUS

Physical Examination

Olive's vital signs show that she is afebrile (temperature: 37.4 °C [99.3 °F]) and tachypneic (respiratory rate: 45 breaths/min). She has a normal oxygen saturation (93% on room air), heart rate (130 beats/min), and blood pressure (85/45 mm Hg). Her weight is 5.5 kg, which is the same weight recorded at her pediatrician's office 2 days earlier.

On examination, you note that Olive appears sleepy and is difficult to arouse. Her mucous membranes are moist, and she has normal skin turgor. Her anterior fontanelle is soft and flat. On her respiratory examination, she coughs intermittently, and you notice clear rhinorrhea. Olive has mild increased work of breathing with mild subcostal and suprasternal retractions and intermittent nasal flaring. You hear breath sounds bilaterally, with diffuse expiratory wheezes, and crackles. There are no areas of diminished breath sounds. Her cardiovascular examination is normal.

Her skin examination shows no rashes, bruises, or other lesions. She has good peripheral pulses, and her capillary refill time is 2 seconds. She does not have any peripheral edema. Her abdomen is soft and nondistended without organomegaly or palpable masses.

On her neurologic examination, Olive appears lethargic, and she withdraws to noxious stimuli. Both pupils measure 3 mm in diameter and constrict equally and bilaterally with light exposure. She has mild truncal and axial hypotonia. You note intact palmar and plantar grasp reflexes, with normal bilateral biceps, patellar, and Achilles reflexes. You do not see any abnormal movements.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an infant with hyponatremia?

The differential diagnosis for an infant with hyponatremia is shown in Table 47.1.

Table 47.1. Differential Diagnosis for an Infant With Hyponatremia

Hypertonic hyponatremia		• Hyperglycemia • IVIG therapy • Mannitol therapy
Isotonic hyponatremia (also called *pseudohyponatremia*)		• Hyperlipidemia • Hyperproteinemia
Hypotonic hyponatremia	Hypovolemia	• Diuretic induced (thiazide, loop diuretics) • Extrarenal losses (burns, pancreatitis) • Hyponatremic dehydration (eg, in gastroenteritis) • Mineralocorticoid deficiency • Salt-losing nephropathy
	Euvolemia	• Formula dilution • Glucocorticoid deficiency • Hypothyroidism • Hypotonic IV fluid administration • Primary polydipsia • SIADH[a] • Other water intoxication (eg, tap water enemas)
	Hypervolemia	• Heart failure • Liver cirrhosis • Nephrotic syndrome • Protein-losing enteropathy • Renal failure (acute or chronic)

Abbreviations: IV, intravenous; IVIG, intravenous immunoglobulin; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

[a] Diagnosis that seems most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for a patient presenting with hyponatremia in addition to RSV, tachypnea, and inability to arouse normally?

- In the inpatient setting, hyponatremia is one of the most commonly encountered electrolyte abnormalities, affecting up to 3% of hospitalized children. As evidenced by the broad aforementioned differential, hyponatremia is a common finding for multiple conditions.
- It is always critical to consider diagnoses that require more urgent evaluation and treatment, such as adrenal insufficiency; however, with a thorough history and physical examination, many of these etiologies can be placed lower on the differential, and the diagnostic evaluation can be tailored to the suspected etiology.

- Further laboratory evaluation of hyponatremia should include serum osmolality (SOsm), urine osmolality (UOsm), and urine sodium (UNa). Ideally, UOsm and UNa should be obtained at the same time as serum electrolytes and SOsm, allowing all laboratory tests to reflect the same physiologic mechanisms, thus helping determine the etiology of the patient's hyponatremia.
- If the history and physical examination raise concerns for other etiologies of hyponatremia (eg, hypothyroidism, congenital adrenal hyperplasia), additional laboratory studies may be warranted.
  - Newborn screening programs have been able to identify most infants with congenital hypothyroidism; however, for infants presenting with hypotonia, prolonged jaundice, constipation, an umbilical hernia, or a large open fontanelle, measurement of thyroid-stimulating hormone is appropriate to rule out congenital hypothyroidism.
  - Infants with congenital adrenal hyperplasia typically present with hyponatremia, hyperkalemia, and hypotensive shock with a salt-wasting crisis at 2 to 3 weeks after birth due to lack of mineralocorticoid activity. Adrenocorticotropic hormone and plasma cortisol can be obtained to assess for adrenal insufficiency in these cases.
  - Inborn errors of metabolism should be suspected in an infant with failure to thrive and multiorgan involvement (seizures, hepatomegaly, hypotonia). In these cases, it is appropriate to start by obtaining a full electrolyte panel to assess for acidosis and hypoglycemia in addition to an ammonia level.

CASE FOCUS

Diagnostic Evaluation

The ED physician collected serum electrolytes and a urine sample. You begin by reviewing these results and then decide to obtain SOsm, urine sodium, UOsm, and serum cortisol levels to complete your initial workup.

Laboratory test	Result	Reference range
Serum chemistries		
Sodium	126 mEq/L (126 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)	3.5–5.8 mEq/L (3.5–5.8 mmol/L)
Chloride	99 mEq/L (99 mmol/L)	97–108 mEq/L (97–108 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)	19–24 mEq/L (19–24 mmol/L)
Anion gap	7 mEq/L (7 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	5 mg/dL (1.79 mmol/L)	5–18 mg/dL (1.79–6.43 mmol/L)
Creatinine	0.35 mg/dL (30.9 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	89 mg/dL (4.94 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)
SOsm	259 mOsm/kg	275–295 mOsm/kg
Cortisol	8 µg/dL (220.7 nmol/L)	2–25 µg/dL (55.2–689.7 nmol/L)
Urine studies		
UOsm	412 mOsm/kg	50–1,200 mOsm/kg
UNa	46 mEq/L	10–25 mEq/L

Abbreviations: BUN, blood urea nitrogen; SOsm, serum osmolality; UNa, urine sodium; UOsm, urine osmolality.

Additionally, the ED physician obtained a chest radiograph, the findings of which are consistent with viral bronchiolitis, and a venous blood gas, which is normal.

Arriving at a Diagnosis

Q: How do you develop an assessment for Olive?

To arrive at her diagnosis, you first review Olive's history, physical examination, and diagnostic evaluation to develop a list of findings that aids in narrowing your differential diagnosis to the most likely etiology. Afterward, admission criteria can be generated for your specific diagnosis.

1. **Interpret key findings from the history, physical examination, and diagnostic evaluation.**
   - History: Olive has a known respiratory viral infection with acute onset of lethargy, poor feeding, and oliguria.
   - Physical examination: Olive's examination is notable for signs of altered mental status, respiratory distress, and pulmonary findings consistent with her known diagnosis of RSV bronchiolitis. Her flat anterior fontanelle, moist mucous membranes, normal skin turgor, and absence of peripheral edema are consistent with euvolemia. Her stable weight since her recent pediatrician visit further supports this assessment.
   - Diagnostic studies: Olive's serum and urine studies are remarkable for a low SOsm, hyponatremia, and a UNa of 46 mEq/L. Given her hyponatremia and low SOsm, with appropriate homeostasis you would also expect her UOsm to be low. Her UOsm of 412 mOsm/kg is inappropriately high, which indicates that she is not diuresing.
     - The next step in interpreting your diagnostic findings is to assess the severity of Olive's hyponatremia. Severity of hyponatremia is determined by the serum sodium level and symptomatology.
       - Mild hyponatremia: Serum sodium level of 130 to 134 mEq/L (130–134 mmol/L)
       - Moderate hyponatremia: Serum sodium level of 125 to 129 mEq/L (125–129 mmol/L)
       - Severe hyponatremia: Serum sodium level below 125 mEq/L (125 mmol/L)
       - Hyponatremic encephalopathy: Most patients with hyponatremia are asymptomatic, with their low plasma sodium level being an incidental finding. Symptomatic patients tend to have symptoms that are vague (eg, headache, nausea, emesis). Patients with moderate to severe hyponatremia (especially those with a rapid decrease in sodium concentration) are at risk for developing hyponatremic encephalopathy, which is a consequence of cerebral edema. Hyponatremic encephalopathy can manifest as altered mental status, disorientation, seizure, coma, respiratory arrest, or even death.
     - Olive's serum sodium level of 126 mEq/L (126 mmol/L) is considered moderate hyponatremia. With her degree of lethargy, she also qualifies as having hyponatremic encephalopathy.
2. **Develop the list of findings.**

Q: What major findings have you identified for Olive?

- Moderate hyponatremia
- Hyponatremic encephalopathy
- Low SOsm
- High UNa and UOsm
- Oliguria
- Respiratory distress
- RSV bronchiolitis

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Olive's presentation?

Olive's history, physical examination, and diagnostic findings lead you to think the etiology of her hyponatremia is syndrome of inappropriate antidiuretic hormone secretion (SIADH), which she likely developed as a complication of RSV bronchiolitis. It is important, however, to systematically think through the pathophysiology of hyponatremia to confirm your suspicion.

Q: What is the pathophysiology of hyponatremia?

- Hyponatremia develops when there is a higher amount of total body water relative to total body sodium, which can happen by a number of processes.
- To evaluate a patient with hyponatremia, it is first important to understand how the body regulates SOsm and intravascular volume. This occurs primarily through 2 mechanisms: antidiuretic hormone (ADH) and thirst.
  - When osmoreceptors sense a rise in SOsm, this increases ADH secretion and thirst, thereby returning the sodium concentration to normal by both increased renal water retention and increased water consumption.
  - When osmoreceptors sense a decreasing osmolality, this halts ADH secretion, leading to normalization of the plasma sodium concentration.
  - Additionally, when baroreceptors sense volume depletion and/or hypotension, this stimulates a combination of thirst and ADH secretion. Volume depletion takes precedence over osmolality, stimulating ADH secretion even in the setting of hyponatremia (such as seen in hypovolemic hyponatremia).
- In many cases, the patient's history can pinpoint the etiology of their hyponatremia; nevertheless, having an organized system for approaching patients with hyponatremia is helpful. For Olive, you suspect SIADH related to her pulmonary disease is the most likely cause of her hyponatremia, but you decide to systematically interpret her laboratory findings further to be certain. Figure 47.1 provides a useful algorithm that can assist in narrowing the differential diagnosis for a patient with hyponatremia. Of note, cerebral salt wasting can cause hyponatremia in patients with traumatic brain injury, meningitis, or recent neurosurgical interventions. Because its pathophysiology is poorly understood, it is not discussed further here.

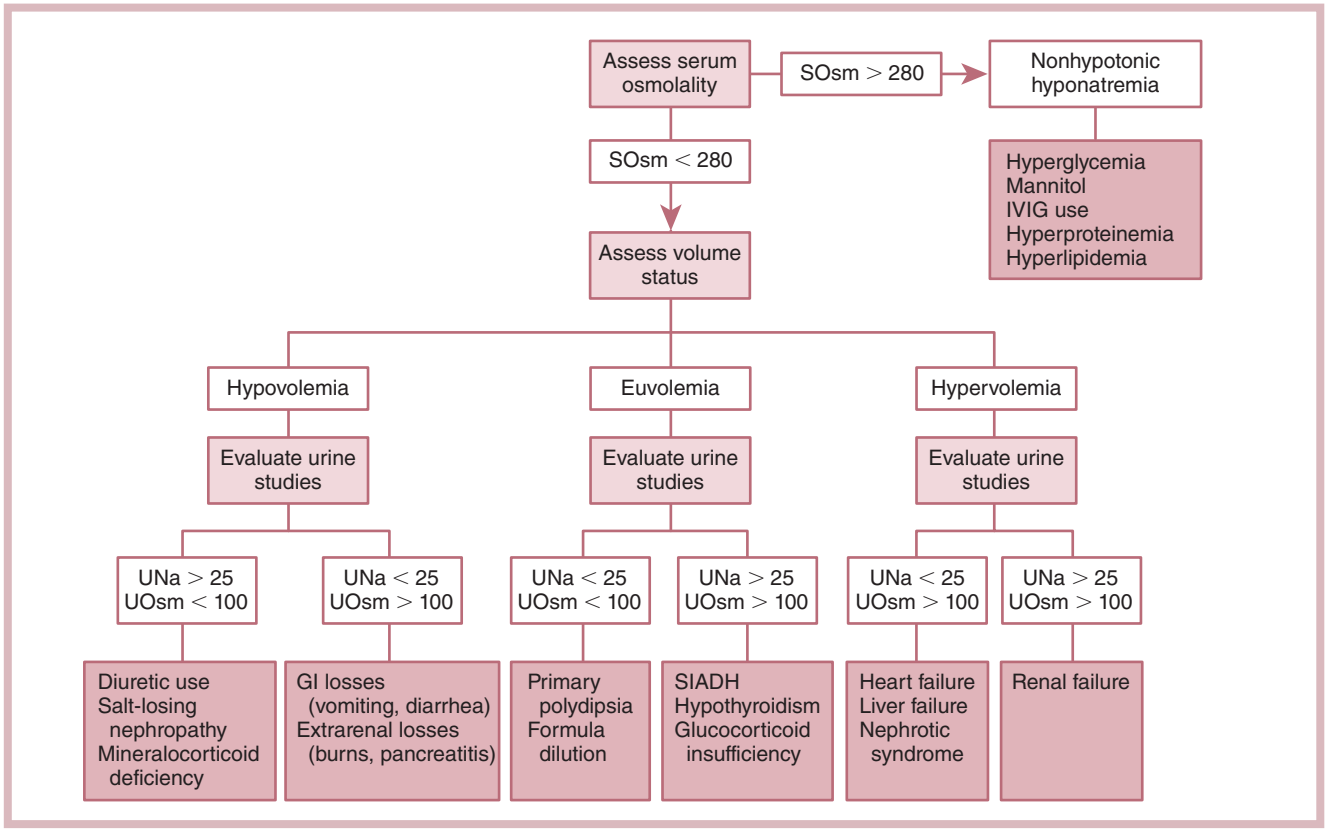

Figure 47.1. Approach to determining the etiology of hyponatremia in pediatric patients.

Abbreviations: GI, gastrointestinal; IVIG, intravenous immunoglobulin; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SOsm, serum osmolality; UNa, urine sodium; UOsm, urine osmolality.

- Stepwise use of the algorithm in Figure 47.1 will help you confirm or refute Olive's suspected diagnosis.
  - Determining Olive's serum tonicity
    - Normal SOsm ranges from 280 to 285 mOsm/kg and is considered isotonic. SOsm below this range is considered hypotonic, while SOsm above this range is considered hypertonic. Of note, there are slight differences in osmolality, tonicity, and osmolarity, defined as follows:
      - Osmolality is a measure of solute concentration per unit mass of solvent (mOsm/kg).
      - Tonicity is a measure of an osmotic gradient in reference to 2 solutions across a membrane (eg, extracellular fluid in reference to intracellular fluid).
      - Osmolarity is a measure of solute concentration per unit volume of solvent (mOsm/L). Because the volume of a solution can change (especially with changes in temperature), osmolarity is rarely used or measured in practice.
    - Sodium molecules make up a large portion of SOsm and are the primary determinant of extracellular osmolality; therefore, hyponatremia is most commonly a hypotonic condition with the exception of the following uncommon scenarios:
      - Although rare, clinicians should consider hypertonic hyponatremia in situations where the patient has hyperglycemia, mannitol use, or intravenous (IV) immunoglobulin use (which is often suspended in mannitol), as these can all increase SOsm.
      - Isotonic hyponatremia (sometimes called *pseudohyponatremia*) can occur in the setting of hyperproteinemia or hyperlipidemia because of laboratory artifact.
    - It is important to compare the patient's measured SOsm to your calculated SOsm, as large discrepancies in these numbers, known as an *osmolar gap*, may change the differential.
    - You determine that Olive's euvolemic hyponatremia is hypotonic based on the following interpretation of her serum studies:
      - $\text{SOsm} = 2\,[\text{Na}^+] + \frac{[\text{blood urea nitrogen}]}{2.8} + \frac{[\text{glucose}]}{18}$
      - $\text{Olive's calculated SOsm} = 2\,[126] + \frac{5}{2.8} + \frac{89}{18} = 258\ \text{mOsm/kg}$
    - Olive's measured SOsm is 259 mOsm/kg, which is consistent with your calculation.
  - Determining Olive's volume status: On examination, Olive appears euvolemic, which makes diagnoses characterized by fluid loss (gastroenteritis, burns, pancreatitis, diuretic use, salt-losing mineralocorticoid deficiency) unlikely, as these diagnoses would present with hypovolemia. Her euvolemia also reduces suspicion for heart failure, liver cirrhosis, nephrotic syndrome, or renal failure, which are characterized by water retention and hypervolemia.
  - Incorporating findings from her urine studies: When considering her urine studies, you note that Olive has an inappropriately high UNa (>25 mEq/L) and UOsm (>100 mOsm/kg) given her hypotonic hyponatremia. You narrow your differential to SIADH, hypothyroidism, or a glucocorticoid insufficiency. As previously discussed, Olive's history and physical examination do not support a diagnosis of hypothyroidism or glucocorticoid insufficiency. All of these factors support your presumptive diagnosis of SIADH.

Q: What are the different etiologies of SIADH?

- Many conditions cause SIADH, including the following:
  - Pulmonary disease: bronchiolitis, pneumonia, asthma, tuberculosis
  - Central nervous system (CNS) disease: CNS infection, hydrocephalus, neoplasm, trauma, hemorrhage
  - Medication use, especially carbamazepine, oxcarbazepine, vincristine, cyclophosphamide, tricyclic antidepressants, narcotics, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, desmopressin, ciprofloxacin, and amiodarone
  - Other etiologies: nausea, pain, postoperative state, some malignancies, certain systemic infections (eg, Rocky Mountain spotted fever), and 3,4-methylenedioxymethamphetamine (ecstasy)
- Of these, it seems that Olive's SIADH is related to her RSV bronchiolitis.

Q: What does it mean to say ADH release is "inappropriate"?

- To determine whether ADH activity is appropriate or inappropriate, it is important to understand its physiology. ADH is stored in the posterior pituitary gland. When released, ADH binds to the V2 receptors in the collecting tubule of the nephron, which signals for increased aquaporin incorporation into the membrane, stimulating water reabsorption from the lumen of the collecting duct into the renal interstitium.
- Two mechanisms that trigger appropriate release of ADH are
  - Increased SOsm, as sensed by osmoreceptors, which primarily exist in the hypothalamus.
  - Decreased effective blood volume or blood pressure, as sensed by baroreceptors in the carotid sinus, aortic arch, cardiac atria, and pulmonary venous system.
- As Olive has hypotonic serum and a normal blood pressure and circulating blood volume, the release of ADH is inappropriate, meaning that ADH is being released without an osmotic stimulus increasing plasma volume. As a result of increased plasma volume, renin is suppressed and natriuretic peptide release is increased. Renin suppression causes aldosterone suppression, and increased atrial natriuretic peptide causes an increase in UNa excretion.

Q: How do you determine if Olive's hyponatremia is acute or chronic?

- Based on the progression of her symptoms, Olive's hyponatremia likely developed over the course of 1 to 2 days; therefore, it is an acute hyponatremia.
- Chronic hyponatremia is less likely to be symptomatic and is generally defined as being present for more than 48 hours, during which time cerebral cell adaptation has taken place.
- Long-standing hyponatremia is uncommon in infants and children, except for children taking predisposing medications or with certain pulmonary, renal, or neurologic conditions.

4. Consider admission criteria.

Q: What are reasonable admission criteria for a patient with hyponatremia from SIADH?

Although hyponatremia is a common finding in hospitalized infants and children, it is less commonly the cause for admission. The mainstay in its treatment is correction of the underlying etiology. If a patient has mild, asymptomatic hyponatremia and the offending etiology can be safely treated or removed in the ambulatory setting, then outpatient treatment after parental education may be appropriate. However, infants and children with moderate to severe hyponatremia or those with hyponatremic encephalopathy are at risk for acute decompensation and should be hospitalized for stabilization and treatment. Admission is indicated for hyponatremia from SIADH in the following scenarios:

- There is concern for hyponatremic encephalopathy.
- Moderate to severe hyponatremia exists, requiring correction.
- An underlying cause of SIADH is present that requires admission for treatment.

Olive has moderate, symptomatic hyponatremia, based on her serum sodium level of 126 mEq/L (126 mmol/L) and her history of lethargy. Considering the aforementioned criteria, you decide to admit Olive for management of

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Olive is a 4-month-old girl with known RSV bronchiolitis who presents with lethargy and is found to have acute onset of moderate hyponatremia with concern for hyponatremic encephalopathy secondary to bronchiolitis-induced SIADH. She requires admission for treatment and careful monitoring.

her acute symptomatic hyponatremia, which you suspect is due to RSV bronchiolitis-induced SIADH.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Olive's symptoms, you review the literature to remind yourself about the treatment of hyponatremic encephalopathy and SIADH in children. You decide to further divide treatment considerations into the following components:

1. **Treatment of the underlying cause:** The definitive treatment of SIADH is discontinuation of or treatment of the underlying etiology. For Olive, bronchiolitis is the most likely etiology. Because bronchiolitis is a self-limited condition, it should be treated with supportive care as usual.
2. **Rapid intervention:** Select cases of hyponatremic encephalopathy may require rapid intervention. Although osmotic demyelination can occur if hyponatremia is corrected too quickly, this exceedingly rare consequence should not preclude treatment for hyponatremic encephalopathy, which itself carries the risk of neurologic consequences if left untreated.
   - Patients presenting with hyponatremic encephalopathy should be urgently treated with hypertonic saline (3%) at a dose of 2 mL/kg (maximum dose: 100 mL). This can be repeated until the patient's neurologic status is improved. This treatment should result in an increase of serum sodium by 3 to 5 mEq/L (3–5 mmol/L). Although many patients with mild mental status changes do not require expeditious therapies, because Olive has symptoms consistent with hyponatremic encephalopathy, it is appropriate to initiate immediate treatment.
   - Although rare in children, some cases of osmotic demyelination are irreversible and can result in devastating brain injury. Patients with profound hyponatremia (serum sodium level < 120 mEq/L [120 mmol/L]) are at increased risk of this. Symptoms of osmotic demyelination may not develop until days after sodium correction and can include dysarthria, dysphagia, disorientation, seizures, coma, paralysis, and death.
3. **Gradual correction of sodium levels:** After initial urgent correction or in cases when urgent intervention is not indicated, the clinician must determine the most appropriate method for gradually correcting the hyponatremia.
   - For asymptomatic hyponatremia related to SIADH, first-line treatment is fluid restriction. Although there are no guidelines outlining the amount of fluid restriction required, restriction to 60% of the total daily fluid needs is a reasonable starting point. Further restriction may be necessary in patients whose sodium levels do not respond to this level of restriction. For Olive, it is reasonable to impose an oral intake restriction at 60% of her daily maintenance fluid rate and adjust based on her sodium levels.
   - Less commonly used therapies include furosemide with sodium supplementation, ADH receptor antagonists (eg, vaptans, which inhibit free water reabsorption), or urea supplementation (which promotes osmotic diuresis).

For Olive, you will only utilize this approach, with the aid of subspecialists, if fluid restriction proves to be ineffective.

4. **Monitoring electrolytes:** Sodium levels should be closely monitored in all patients admitted with hyponatremia from SIADH.
   - For acute and chronic SIADH, clinicians should continue to monitor sodium levels every 2 to 4 hours to avoid overcorrection.
   - For acute hyponatremia related to SIADH, sodium correction should be limited to 10 to 12 mEq/L (10–12 mmol/L) during the first 24 hours to avoid the development of osmotic demyelination.
   - For chronic hyponatremia related to SIADH, the correction should be more gradual to avoid CNS complications, with a goal correction of less than 6 to 8 mEq/L (6–8 mmol/L) over 24 hours.
   - Because Olive has acute hyponatremia related to SIADH, you plan to check her sodium level every 2 hours initially, with a goal of correcting her sodium no faster than 10 to 12 mEq/L (10–12 mmol/L) during the first 24 hours.
5. **Monitoring output:** While controlling intake with fluid restriction, it is important to continue to track urine output closely to monitor for fluid retention. Appropriate urine output is considered to be at least 1 mL/kg/h.
6. Consultations
   - Pediatric intensive care unit: For patients requiring more frequent laboratory monitoring than allotted on the acute care floor or more frequent neurologic checks than possible because of staffing ratios, a pediatric intensive care unit consult and possible transfer may be warranted.

CASE FOCUS

Plan for Treatment and Monitoring

- **Treatment of the underlying cause:** You anticipate that Olive's SIADH will improve as her RSV bronchiolitis resolves, and you will provide supportive care for her bronchiolitis as needed (eg, suctioning, supplemental oxygen for hypoxemia).
- **Rapid intervention:** Because you are concerned for hyponatremic encephalopathy, you initiate treatment with a 2 mL/kg bolus of hypertonic saline (3% sodium chloride) infused through a peripheral IV. You plan to repeat these infusions as needed until Olive's encephalopathy improves. In addition to obtaining vital signs every 4 hours with oxygen saturations, you plan to assess Olive's neurologic status at least every 4 hours.
- **Continued management:** After resolution of Olive's hyponatremic encephalopathy, you plan to slowly correct her serum sodium level to the normal range through oral fluid restriction. You calculate Olive's daily fluid need based on her weight (5.5 kg) to be 22 mL/h, or 528 mL over 24 hours. You plan to restrict Olive's oral fluid intake to 60% of this amount, allowing her to drink up to 10.5 fl oz of formula per day.
- **Monitoring electrolytes:** After her hypertonic saline bolus(es), you will evaluate Olive's serum sodium levels every 2 hours to ensure that levels are not rising too rapidly. Once her lethargy improves and you transition to fluid restriction, you will check Olive's sodium level every 4 hours to ensure an appropriate rate of correction of less than 5 mEq/L (5 mmol/L) over the next 12 hours, with a plan to liberalize her fluid intake if she is correcting too quickly.
- **Monitoring output:** You will monitor Olive's urine output every 4 hours by saving her diapers and weighing them to estimate her hourly rate.
- **Consultations:** Olive is currently hemodynamically stable. You plan to consult your institution's subspecialists (eg, pediatric endocrinology, pediatric nephrology) after giving Olive an initial hypertonic saline bolus. You are able to closely monitor her on the acute care unit with frequent vital sign and neurologic checks, but you will consider discussion with a pediatric critical care specialist if Olive's hyponatremia or mental status worsen.

Case Resolution

Olive's encephalopathy resolves after 1 hypertonic saline bolus, and her hyponatremia slowly improves with fluid restriction over the next 3 days. As her RSV bronchiolitis improves, her fluids are liberalized without any recurrence of her hyponatremia. Subsequently, she is tolerating her regular home diet and is noted to have appropriate urine output. No further concerns for neurologic compromise emerge, and her parents report that she is back to her neurologic baseline. Given her improvement, you decide that it is safe to discharge Olive home. You advise her parents that Olive should see her pediatrician for follow-up in 2 to 3 days.

- Endocrinology or nephrology: Clinicians should consider subspecialty consultation for cases of severe hyponatremia or hypotonic encephalopathy.

Discharge Criteria

Q: How do you know when Olive is ready to go home?

You can feel comfortable discharging your patient with SIADH when the following criteria are met:

- Normalization and maintenance of plasma sodium levels on oral fluids has been achieved.
- The patient has returned to baseline neurologic status without other concerns for acute neurologic changes.
- Follow-up with the patient's pediatrician within 2 to 3 days has been ensured.

Anticipatory Guidance

Q: What instructions should you provide to Olive's caregivers upon discharge?

- Monitor Olive's neurologic status and return to care if she becomes confused, lethargic, or has acute changes from her baseline activity level.
- Because Olive's SIADH is secondary to bronchiolitis, resolution of her bronchiolitis should also cause resolution of her SIADH. Fluid restriction is not required at home, and Olive should return to her normal feeding routine. Return to care is recommended if she has fewer than 4 wet diapers in 24 hours.

Clinical Pearls

- Assessment of SOsm, total body fluid volume status, UNa, and UOsm are essential in determining the diagnosis for patients with hyponatremia.
- Acute, symptomatic hyponatremia with neurologic changes should be treated quickly to avoid severe morbidity and mortality.
- SIADH is best treated with fluid restriction and treatment of the underlying cause.

Documentation Tips

- Interpret abnormal electrolyte laboratory findings (eg, document "hyponatremia" instead of only listing the laboratory results).
- Document symptoms associated with any electrolyte disturbances and also the measures required to correct electrolyte abnormalities.
- Discuss the type and frequency of monitoring needed during the hospitalization.
- Document the suspected etiology of hyponatremia and/or evaluation required.

Suggested Readings

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CASE 48

Aria, a 16-Year-Old Girl With Headache and Confusion

CASE PRESENTATION

A 16-year-old previously healthy girl, Aria, presents to the emergency department (ED) with headache and confusion. While in triage, Aria has 2 episodes of emesis and several staring episodes. While being transported to a room, she has 20 seconds of convulsive movements that self-resolve, after which she is confused, sleepy, and does not recognize her parents. The ED physician obtains initial laboratory studies including a complete blood cell count (CBC) with differential, comprehensive metabolic panel, C-reactive protein (CRP) level, procalcitonin level, coagulation studies, urinalysis, urine drug screen, and pregnancy test. All of these studies are unremarkable. A blood culture is pending. A computed tomography (CT) scan of the head is performed, and the preliminary read is negative for any acute intracranial pathology. The ED physician gives Aria a dose each of acetaminophen and ondansetron, and due to concern for seizures, the physician also gives her a loading dose of levetiracetam. She also starts Aria on a continuous electroencephalogram (EEG). In the intervening 2 hours, Aria has not returned to her baseline neurologic status. The ED physician calls you to request admission for further evaluation and monitoring.

Patient History and Review of Systems

Q: What information should you collect from Aria and her caregivers?

- History of present illness
  - Headache history, including duration, quality, and timing
  - Description of confusion, including onset, progression over time, and noted behavioral changes
  - Description of convulsive movements, including origination in the body, whether both sides of the body were involved, presence of eye deviation, level of consciousness during the episode, and mental status after the episode
  - Recent illness, especially respiratory or diarrheal illnesses
  - Exposure history, including recent travel, insect bites (especially ticks and mosquitoes), contact with cats or kittens, close exposure to wild animals, or animal bites
  - Recent trauma, especially to the head or neck
- Associated symptoms, including fever, fatigue, neck pain/stiffness, vision changes, nausea, vomiting, muscle aches, weakness, tingling/numbness in extremities, difficulty with ambulation or speech, rash, or recent unexplained weight loss

- Medical history, including vaccinations, surgeries, history of similar episodes or seizures, congenital or rheumatic heart disease, chronic illnesses (eg, lupus), or immunocompromised status
- Medications, including over-the-counter, prescribed, and those of family members or present in the home
- Family history, especially of seizures or other chronic illnesses (eg, lupus, immunocompromised status)
- HEADSS (Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression) assessment, including sexual activity, history of sexually transmitted infections, substance use, and psychosocial stressors (refer to Section VII of the Appendix for components of a complete HEADSS assessment)

CASE FOCUS

History and Review of Systems

Upon meeting Aria and her parents in the ED, you learn that her headaches began 4 days ago. Aria has some difficulty with word finding, making it difficult for her to describe her headaches in detail, but she describes her headaches as frontal and associated with fatigue and photophobia. Her headaches improved with acetaminophen but were severe enough that she needed to lie down in a dark room after school each day. Her mother reports that, while at school today, Aria sent her text messages that did not make any sense. Soon afterward, Aria's teacher called to report that Aria "was saying weird things and can't seem to remember some words." Aria's mother immediately picked up Aria from school and brought her to the ED. In the car ride to the ED, Aria seemed sleepy, somewhat confused, and needed assistance putting on her seat belt.

Aria does not remember what happened at school or when she first arrived at the ED. Her mother reports that in the ED, Aria had sudden onset of abnormal movements, which has never happened before. Descriptions from Aria's mother and the ED staff indicate that the movements consisted of right arm and leg jerking, during which Aria seemed to be unconscious. Aria's mother is unsure if Aria had eye deviation during this episode. The episode lasted 20 seconds and then stopped without intervention. Afterward, Aria was confused and sleepy for 2 hours. Now, she recognizes her parents and, per their report, seems subdued and a little frightened but is otherwise herself.

Prior to her headaches starting 4 days ago, Aria was healthy without any known medical conditions. She has not had recent fevers, illnesses, weight loss, rash, or exposure to sick contacts. She has not complained of nausea, vomiting, fatigue, neck pain or stiffness, muscle aches, weakness, sensory changes, difficulty walking, or visual changes. She is fully vaccinated but has not had any recent vaccinations. The family denies any recent travel, insect/tick bites, or interaction with wild or domesticated animals. Her family history is negative for a chronic illness, seizure disorders, or immunodeficiencies. Aria has no history of recent trauma.

You ask Aria's parents to leave the room briefly so that you may complete a HEADSS assessment, and you learn that Aria does well in school, lives in a safe and loving home, and has not been sexually active or tried drugs or alcohol. Aria denies any new or unusual stressors.

Physical Examination

Q: What parts of the physical examination should you focus on for Aria?

- Complete set of vital signs
- Head: signs of trauma
- Eyes: visual field testing and fundoscopic examination for papilledema
- Appearance of mucous membranes (moist/sticky/dry, presence of lesions)
- Presence or absence of meningismus (nuchal rigidity, presence of Brudzinski or Kernig sign)
- Cardiovascular: presence of murmur, peripheral pulses
- Respiratory: work of breathing, auscultation for crackles, rhonchi, decreased breath sounds
- Abdomen: tenderness, hepatosplenomegaly, masses
- Skin: presence or absence of diaphoresis, pallor, petechiae, icterus, vesicular rash, any other lesions
- Neurologic
  - Level of alertness
  - Mental status, including orientation to person, place, and time; behavior, mood, affect, thought content, and cognition
  - Cranial nerve function
  - Sensation and motor function in extremities
  - Gait and cerebellar function, noting ataxia, dysmetria, and dysdiadochokinesia
  - Reflexes

CASE FOCUS

Physical Examination

At the time of your examination, Aria has an oral temperature of 38.3 °C (100.9 °F). Her heart rate is 112 beats/min, her blood pressure is 110/72 mm Hg, and her respiratory rate and oxygen saturation are normal. Her weight in the ED is documented as 61 kg (75th percentile).

Aria is sleepy but cooperative and in no acute distress. EEG leads are attached, but her head appears to be normocephalic and atraumatic. Her visual fields are full and equal, and her fundoscopic examination shows a normal optic disc bilaterally without bulging. Her mucous membranes are moist without lesions. Her neck moves easily with passive flexion, and Kernig and Brudzinski signs are negative. On her cardiovascular examination, she has normal heart sounds without murmurs, and radial and dorsalis pedis pulses are normal and equal bilaterally. On her respiratory examination, Aria is breathing comfortably, and her lungs are clear to auscultation bilaterally. Her abdomen is soft and nontender with normal bowel sounds. You do not appreciate any hepatosplenomegaly or masses. Aria's skin is warm and dry, without pallor, icterus, rashes, or other lesions.

Aria is awake and alert. She is oriented to person and place but reports a date from several weeks earlier. She speaks clearly and answers most questions appropriately but at times seems confused, and somewhat withdrawn with a flat affect. Aria's parents confirm this is a change from her baseline. Aria reports that her mood is "a little better" because she no longer has a headache. Cranial nerves II through XII are intact. Aria's muscle strength is a 5 on a scale of 0 to 5. She has normal muscle bulk and tone and intact sensation throughout her extremities. She has a normal gait and normal cerebellar function. Her patellar and Achilles reflexes are normal bilaterally.

Differential Diagnosis

Q: Thinking broadly, what is the differential diagnosis for an adolescent with headaches, fever, altered mental status, and suspected seizures?

The differential diagnosis for an adolescent with these symptoms is shown in Table 48.1 and is divided into causes that seem more and less likely based on Aria's presentation.

Table 48.1. Differential Diagnosis for an Adolescent With Headaches, Fever, Altered Mental Status, and Suspected Seizures

Diagnoses of highest suspicion	• CNS infection[a] — Bacterial (eg, those bacteria typically considered in meningitis, plus *Bartonella*, *Listeria*, *Mycoplasma*, *mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Cryptococcus*, *Rickettsia*) — Viral (eg, HSV, enterovirus, VZV, CMV, EBV, HHV-6, influenza, measles, HIV, rabies) — Other (fungal, parasitic) • CNS inflammation, such as postinfectious, demyelinating, or autoimmune disorders (MS, anti-NMDA receptor encephalitis, ADEM, anti-MOG-associated encephalomyelitis, steroid-responsive encephalopathy associated with autoimmune thyroiditis, anti-glutamic acid decarboxylase 65 encephalitis)[a] • Epilepsy/seizures • Primary or metastatic brain tumor, including CNS lymphoma
Other diagnoses to consider	• Acute ischemic or hemorrhagic stroke • CNS vasculitis (primary or secondary) • DKA • Eclampsia • Electrolyte derangement or hypoglycemia • Hypertensive encephalopathy • Metabolic/hepatic encephalopathy • Migraine disorder • Mycotic emboli • Nonepileptic pseudoseizure • Posterior reversible encephalopathy syndrome • Postinfectious cerebellitis • Psychiatric disorder • Sepsis • SLE • Toxic ingestion/exposure • Trauma causing subdural or epidural hemorrhage • Vitamin deficiency • Withdrawal

Abbreviations: ADEM, acute disseminated encephalomyelitis; CMV, cytomegalovirus; CNS, central nervous system; DKA, diabetic ketoacidosis; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMDA, N-methyl-d-aspartate; SLE, systemic lupus erythematosus; VZV, varicella-zoster virus.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: What diagnostic evaluation is needed for adolescents who present with headache, fever, altered mental status, and suspected seizures?

- Serum studies: The differential diagnosis for patients presenting with headache, fever, altered mental status, and suspected seizures is broad. Obtaining a CBC, chemistry panel, blood culture, and inflammatory markers may help narrow the list of possible diagnoses.
  - A point-of-care glucose test can be performed quickly to identify hypoglycemia as a causative or contributory factor.
  - A chemistry panel can quickly rule out electrolyte disturbances leading to seizures or altered mental status. Normal creatinine and blood urea nitrogen levels are also reassuring against renal disease as a cause of hypertension and subsequent stroke.
  - A CBC with differential may help support the diagnosis of an inflammatory, oncologic, or infectious etiology of symptoms, whereas inflammatory markers (CRP, erythrocyte sedimentation rate, procalcitonin), and blood culture can aid in prioritizing the patient's risk for a serious bacterial infection.
- A urinalysis may also help determine the presence of serious bacterial infection. A urine pregnancy test may also be sent, as presence of a fetus could change management of the patient and would raise suspicion for eclampsia.
- Cerebrospinal fluid (CSF) testing: Because central nervous system (CNS) infection and inflammation are high on the differential diagnosis for these symptoms, a lumbar puncture (LP) should be performed and CSF studies should be obtained in patients with this presentation.
  - If signs of elevated intracranial pressure are present on history or physical examination (papilledema, visual changes, vomiting), it is imperative to ensure coagulation studies and imaging of the head have been performed prior to performing an LP to look for evidence of hemorrhage or herniation.
  - Although it is preferable to perform an LP prior to starting antibiotics to avoid sterilization of CSF, antimicrobial treatment should not be significantly delayed, especially if suspicion for an infectious etiology is high.
  - CSF studies should include glucose, protein, leukocyte count with differential, erythrocyte count, opening pressure, Gram stain and bacterial culture, herpes simplex virus (HSV) polymerase chain reaction (PCR), varicella-zoster virus (VZV) PCR, and enterovirus PCR. A meningitis/encephalitis pathogen PCR panel should be considered if it is available. If possible, a small sample of CSF should be saved to hold in the laboratory in case future CSF studies are needed. For cases of suspected immune-mediated encephalitis or less common infectious etiologies, more specialized antibody or PCR testing on the CSF should be performed. Consultation with pediatric neurologists and infectious disease specialists can be useful in prioritizing the patient's diagnostic evaluation.
- EEG can be useful for localizing seizure activity, and identifying subclinical seizures, differentiating focal encephalitis from generalized encephalopathy, and localizing the area of encephalitic involvement.
- Imaging
  - A CT scan of the head is frequently obtained in patients presenting with altered mental status or focal neurologic findings and can be useful for identifying hemorrhage or significant cerebral edema leading to midline shift or herniation. However, CT is not sufficient to evaluate a patient with suspected encephalitis, as it typically is negative in cases of encephalitis.
  - Magnetic resonance imaging (MRI): Because it is much more sensitive than CT for identifying evidence of inflammation and encephalitis, a brain MRI should be performed with and without contrast.

CASE FOCUS

Diagnostic Evaluation

You review the initial laboratory studies obtained by the ED physician: CBC with differential, urinalysis, urine pregnancy test, urine drug screen, comprehensive metabolic panel, coagulation studies, and CT scan of the head. All test results are within normal limits. The first couple of hours of continuous EEG have been preliminarily read and show no active seizures but show possible focal dysfunction in the left temporal lobe. A blood culture is pending.

Because Aria has no definitive signs of increased intracranial pressure, has demonstrated improvement from initial presentation, and her CT scan of the head is grossly negative, your suspicion for significant increased intracranial pressure is low, and you decide it is safe to proceed with the LP; the preliminary results follow. Gram stain, bacterial culture, and meningitis/encephalitis PCR panel (including cytomegalovirus, enterovirus, HSV-1, HSV-2, human herpesvirus-6, human parechovirus, VZV, *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, Streptococcus agalactiae, *Streptococcus pneumoniae*, *Cryptococcus neoformans*, and *Cryptococcus gatti*) are still pending.

CSF studies		
Laboratory test	**Results**	**Normal range**
Glucose	55 mg/dL	>50 mg/dL
Protein	80 mg/dL	20–45 mg/dL
WBC count	95 cells/mm^3	≤5 cells/mm^3
RBC count	1 cell/mm^3	0 cells/mm^3
Polymorphonuclear leukocytes	7%	0%–6%
Lymphocytes	86%	40%–80%
Monocytes	7%	15%–45%
Opening pressure	12 cm H_2O	<28 cm H_2O

Abbreviations: CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

Arriving at a Diagnosis

Q: How do you develop an assessment for Aria?

In Aria's case, you must first ensure stability of her airway, breathing, and circulation. Once this is complete, you can then interpret the key findings from her history, examination, and diagnostic testing to generate a list of findings to arrive at her diagnosis.

1. **Assess airway, breathing, and circulation:** The first step in the assessment of a patient with altered mental status is to ensure stabilization of their airway, breathing, and circulation. Aria's airway, breathing, and circulation are intact during your assessment.
2. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Aria is a previously healthy, fully immunized adolescent with acute onset of daily headaches accompanied by photophobia who presents after acute mental status change and subsequent seizure-like activity. This triad of headache, altered mental status, and seizures suggests an intracranial pathology.

- Physical examination: Aria has been hemodynamically stable since admission, which is reassuring against a fulminant bacterial process like untreated meningitis or sepsis. She does, however, have a low-grade fever and tachycardia, which is concerning for an infectious etiology of her symptoms. Her examination is significant for acute encephalopathy, as evidenced by her altered mental status, including lack of orientation, confusion, and flat affect compared with baseline. Pertinent negative findings on physical examination include that she has no focal neurologic deficits.
- Diagnostic evaluation: Aria's CBC, comprehensive metabolic panel, CRP level, procalcitonin level, urinalysis, and coagulation studies are all unremarkable. CSF studies show an elevated protein level and an elevated white blood cell (WBC) count with lymphocytic predominance and are negative for organisms on Gram stain. These findings reinforce your suspicion that Aria is less likely to have a bacterial CNS infection and more likely to have a viral or postinfectious/inflammatory CNS process. The continuous EEG preliminary read shows a possible focal dysfunction in the left temporal lobe, which can be seen in HSV encephalitis.

3. **Develop the list of findings.**

Q: What major findings have you identified for Aria?

- Suspected focal seizure, now resolved
- Headache, now resolved
- Fever
- Tachycardia
- Acute encephalopathy
- Pleocytosis and elevated protein level in the CSF
- Focal abnormality on EEG

4. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and list of findings, are you able to choose one diagnosis to explain Aria's presentation?

When considering the information about Aria's condition obtained thus far, you think her constellation of symptoms is most consistent with a viral or autoimmune encephalitis. You are particularly concerned for HSV encephalitis given her continuous EEG findings. Revisiting your differential diagnosis, you are confident that you can eliminate many of the other diagnoses based on Aria's history, examination, and initial diagnostic evaluation. Her lack of neck stiffness, as well as reassuring vital signs and initial infectious diagnostic studies, make meningitis unlikely. She has no history or findings of head trauma or stroke. Her normoglycemia and lack of electrolyte derangements eliminate diabetic ketoacidosis and electrolyte abnormalities from the differential. She lacks the history to support a diagnosis of a rarer etiology of infectious CNS pathology (eg, rabies, Lyme disease), and she does not have the examination or diagnostic findings to support a systemic inflammatory syndrome (eg, systemic lupus erythematosus).

Q: What symptoms and signs can help you localize Aria's brain inflammation?

CNS infections often cause both meningeal and parenchymal inflammation, meaning meningitis and encephalitis can be difficult to differentiate. An illness may be termed *meningitis* if meningeal irritation is prominent or *encephalitis* if cognitive and sensory changes are prominent, but some clinicians prefer the broader term *meningoencephalitis*.

Q: How is the diagnosis of encephalitis made?

Encephalitis is largely a clinical diagnosis, based on the following criteria from the International Encephalitis Consortium, as shown in Box 48.1.

Box 48.1. Diagnostic Criteria for Encephalitis of Presumed Infectious or Autoimmune Etiology

Major criterion (required)
Presenting with altered mental status (decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours with no alternative cause identified
Minor criteria (2 are required for possible diagnosis; ≥3 are required for probable or confirmed diagnosis)
• Documented fever ≥38 °C (100.4 °F) within 72 hours before or after presentation • Generalized or partial seizures not fully attributable to preexisting seizure disorder • New onset of focal neurologic findings • CSF WBC count ≥5/mm^3 • Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset • Abnormality on EEG consistent with encephalitis and not attributable to another cause

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; WBC, white blood cell.

Adapted with permission from Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the International Encephalitis Consortium. *Clin Infect Dis*. 2013;57:1114–1128.

Based on these criteria, Aria meets the major criterion of altered mental status as well as 3 minor criteria: witnessed probable seizure, elevated CSF WBC count, and abnormality on EEG consistent with encephalitis.

Q: What factors in Aria's diagnostic evaluation help you decide between infectious, postinfectious, or autoimmune encephalitis?

In the majority of cases of pediatric encephalitis, a specific cause is never found; however, there are several clues as to whether there is an autoimmune, parainfectious, or direct pathogen-mediated cause for a patient's symptoms and findings. Table 48.2 outlines the symptoms and diagnostic findings most commonly seen in each of these 3 etiological categories.

Q: What components of a patient's history or physical examination might make you consider other common infectious etiologies of encephalitis, and what subsequent additional testing might you seek?

Encephalitis can be caused by many different infectious agents. The presenting signs and symptoms of a patient with encephalitis from an infectious etiology may vary depending on the underlying etiology. Table 48.3 explores possible findings on history and physical examination as well as additional testing to consider that may help uncover the etiology of the patient's illness.

5. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with acute encephalopathy with suspected viral or autoimmune encephalitis?

All patients with acute encephalopathy from suspected viral or autoimmune encephalitis require admission to the hospital for stabilization, determination of the underlying cause, and treatment initiation. When there is concern for CNS infection as evidenced by pleocytosis, bacterial etiologies should be definitively ruled out in the hospital setting.

Table 48.2. Common Symptoms and Diagnostic Findings in Infectious, Parainfectious, and Autoimmune Encephalitis

	Infectious	Parainfectious (eg, ADEM or acute cerebellar ataxia)	Autoimmune (eg, anti-NMDA receptor encephalitis)
Symptoms	Dependent on infectious agent Often fever and headache Seizures and encephalopathy possible	May have a viral prodrome or vaccination in prior 2 weeks Temporally separate, an encephalopathy and multifocal neurologic abnormalities (including cerebellar ataxia, cranial neuropathies, myelopathy) develop, with rapid progression during first week of symptoms.	May have prodrome of fever, headache, or viral-like illness occurring a few days prior Psychiatric symptoms, decreased level of consciousness, dyskinesias, autonomic instability, language dysfunction
CSF findings	Hemorrhagic pleocytosis can be seen with HSV, and atypical lymphocytes can be seen with EBV. No pathognomonic CSF findings help to differentiate among infectious causes of encephalitis.	Lymphocytic pleocytosis with or without oligoclonal bands	
EEG findings	Periodic high-voltage spike wave activity emanating from temporal regions and slow wave Complexes at 2- to 3-second intervals are highly suggestive of HSV.	Nonspecific, diffuse slowing, disorganized activity	
Brain MRI findings	Prominent temporal lobe lesions in HSV encephalitis	Multiple lesions in subcortical white matter characteristic of demyelination, often with brainstem or spinal cord involvement	Often normal, or contrast-enhancing cortical and subcortical abnormalities
Additional testing	Dependent on suspected causative agent (see Table 48.3)	CSF oligoclonal bands Serum IgG autoantibodies to AQP4 and MOG to rule out NMOSD and MOG antibody disease, respectively Consider spinal MRI.	CSF oligoclonal bands CSF and serum IgG antibodies to GluN1 subunit of the NMDA receptor Abdominal or transvaginal ultrasonography (see associations in the next row)
Associations	Dependent on suspected causative agent (see Table 48.3)	Predominance in winter and spring seasons	Associated with ovarian teratoma Can be triggered by HSV encephalitis

Abbreviations: ADEM, acute disseminated encephalomyelitis; AQP4, aquaporin-4; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; EEG, electroencephalogram; HSV, herpes simplex virus; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDA, N-methyl-d-aspartate; NMOSD, neuromyelitis optica spectrum disorder.

Table 48.3. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children with Suspected Infectious Encephalitis

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Cryptococcal meningitis	Immunocompromised status or history of HIV	CSF/serum antigen detection, CSF fungal culture
Enterovirus encephalitis	Biphasic illness starting with systemic disease and progressing to CNS disease	Viral PCR panel of CSF, CSF EV PCR, CSF viral culture, viral stool culture
HSV encephalitis	May have a recent history of HSV oral lesion	CSF HSV PCR
Influenza-associated encephalitis	Prodrome of fever, malaise, myalgias, vomiting/diarrhea, tachycardia, diaphoresis, dry mucous membranes, delayed capillary refill	Respiratory pathogen panel (nasal swab)
Lyme encephalitis	History of tick bites or travel to tick-infested area, evidence of insect bites or erythema migrans	CSF lyme IgG
Rabies encephalitis	Interaction with feral animals or history of animal bite, rapid deterioration	CSF rabies neutralizing antibody, rabies-specific IgM
Subacute sclerosing panencephalitis, viral encephalitis (eg, varicella, measles, coxsackie virus)	Rash, lack of immunization, parotitis	Serum/CSF VZV, coxsackie, measles IgG

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; EV, enterovirus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

Derived from Tunkel AR, Glaser CA, Bloch KC, et al; Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47(3):303–327.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Aria is a 16-year-old previously healthy girl presenting with headache, acute encephalopathy, and new presumed seizure, with lymphocytic pleocytosis in her CSF suggestive of CNS inflammation and preliminary continuous EEG findings most consistent with viral or autoimmune encephalitis. She requires inpatient admission for further evaluation, monitoring, and empiric therapy.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

In preparing to treat Aria's symptoms, you review the literature to remind yourself about the management of acute encephalitis.

1. **Initial stabilization:** The first step in management of any case of encephalitis is to stabilize the patient if they are having any autonomic dysfunction, while working to mitigate the inflammatory effects of the disease. In Aria's case, her airway, breathing, and circulation are intact, and she is not acutely decompensating.
2. **Seizure management**
   - Acute management: Seizures, if uncontrolled, can be a life-threatening emergency. Impaired ventilation can lead to profound hypoxemia, acidemia, hypoglycemia, and hemodynamic instability. Because of Aria's altered mental status and abnormal movements in triage, the ED physician ordered a loading dose of levetiracetam, an appropriate step to control her suspected seizures. Additionally, the ED physician started Aria on a continuous EEG for monitoring. It is appropriate to monitor Aria for any additional seizure activity and dose rescue medications as needed to control any further seizures.
   - Chronic management: There is insufficient data to support the routine use of prophylactic antiseizure medications in patients with no seizures noted. Patients who have had seizures often receive antiseizure medications as neuroprophylaxis until the inflammation caused by encephalitis has abated and the seizure risk has diminished.
3. **Consultation with experts:** An infectious disease specialist can be helpful in guiding further infectious testing and empiric treatment based on the patient's risk factors and findings. Physical therapy, occupational therapy, and speech therapy can help rehabilitate patients with cognitive or physical effects of encephalitis inpatient and outpatient. Given Aria's change in mental status and suspected seizures, a pediatric neurologist should be consulted to assist with her diagnosis, EEG interpretation, and management.
4. **Antimicrobials:** Bacterial and some types of viral encephalitis can have a rapidly progressive and potentially fatal course. Therefore, empiric IV antimicrobial therapy should be carefully considered.
   - Antibiotics
     - When bacterial etiologies are suspected or have not yet been definitely ruled out in a patient with encephalitis, broad spectrum antibiotics should be urgently initiated. If there is clinical suspicion for encephalitis caused by *Rickettsia*, *Ehrlichia*, or *Bartonella henselae* infection, empiric IV doxycycline should be initiated.
     - Because bacterial etiology is not suspected, antibiotic therapy may have little utility for Aria's case; however, it would be reasonable to provide broad-spectrum antibiotic therapy (eg, a third- or fourth-generation cephalosporin and vancomycin) until her CSF PCR panel is negative for bacterial infection and/or her bacterial cultures are negative for at least 24 hours.
   - Antivirals
     - Acyclovir: Although the treatment of many different types of viral encephalitis is largely supportive, the morbidity and mortality of HSV encephalitis can be improved by early treatment with IV acyclovir. Because of this, acyclovir should be initiated immediately in all patients suspected of having viral encephalitis without waiting for the results of diagnostic testing. Additionally, because CSF HSV PCR and neuroimaging may be falsely negative early in the course, acyclovir should be continued until HSV has been definitively ruled out, sometimes by repeated CSF testing. Given Aria's EEG findings showing a possible focal dysfunction in the left temporal lobe, which can be seen in HSV encephalitis, it is appropriate to initiate IV acyclovir treatment.

    - Acyclovir can also be used to treat VZV encephalitis.
    - It is important to note that more than 80% of acyclovir in systemic circulation is excreted unchanged in urine, and therefore patients with renal impairment can quickly develop acyclovir toxicity. Renal function should be consistently monitored while patients are receiving the drug, and dose adjustments should be made for renal impairment. Adequate hydration is crucial to help prevent renal injury, and IV fluids should be strongly considered.
  - Oseltamivir should be initiated if influenza encephalitis is suspected.
- For targeted treatment recommendations of specific etiologies, including duration of treatment, consultation with an infectious disease specialist is recommended.

5. **Other medications:** Under the direction of a neurologist, if autoimmune or parainfectious encephalitis is suspected and infectious etiologies have been ruled out, treatment with immune-modulating therapy should be considered, including high-dose steroids, IV immunoglobulin, or plasmapheresis. If a patient's clinical status is not improved by these initial treatments, additional therapeutic options include rituximab and cyclophosphamide.
6. **Further diagnostics:** As soon as clinically feasible, patients should undergo an MRI of the brain to help distinguish among the different types of encephalitis.
7. **Monitoring:** Patients admitted with suspected encephalitis should be monitored closely for further mental status changes with neurologic assessments at least every 4 hours and vital sign changes (eg, new fever, bradycardia, hypertension). Given the risk of syndrome of inappropriate antidiuretic hormone secretion (or cerebral salt wasting), periodic monitoring of serum electrolytes is usually warranted.

   If presenting symptoms recur after initial recovery, providers should have high suspicion for autoimmune/anti-N-methyl-d-aspartate receptor encephalitis, which can have waxing and waning courses and can cooccur with infectious forms of encephalitis.

CASE FOCUS

Plan for Treatment and Monitoring

- **Seizure management:** After Aria's loading dose of levetiracetam in the ED, you continue a maintenance dose and expect this to continue as neuroprophylaxis until outpatient follow-up with neurology.
- **Consultation with experts:** You consult neurology for interpretation of Aria's EEG and management of her antiseizure medication. You decide to wait to consult an infectious disease specialist until Aria's preliminary infectious testing is known. You anticipate that Aria may experience some deconditioning and muscle atrophy and that she may have acute cognitive deficits from her illness. You request that physical therapy and occupational therapy evaluate her.
- **Antimicrobials:** Because of your suspicion for HSV, you initiate intravenous (IV) acyclovir. You have low suspicion for a bacterial infection but opt to start a third-generation cephalosporin (eg, ceftriaxone) and vancomycin for empiric coverage of *S pneumoniae*, *H influenzae* type b, and *N meningitidis*, because you know that rapid treatment for bacterial meningitis improves outcomes.
- **Other medications:** You wait to initiate immune modulating therapy for autoimmune or parainfectious encephalitis until further workup is completed.
- **Further diagnostics:** Continuous EEG is in process for Aria. You order an MRI of the brain.
- **Monitoring:** Your order strict monitoring of intake and output, vital signs with neurologic assessments every 4 hours, and repeat serum electrolytes for the following morning.

Case Resolution

Aria's test results include an EEG showing left temporal focal cerebral dysfunction without captured seizures and MRI showing a focal enhancing lesion in the left temporal lobe suggestive of infectious or inflammatory encephalitis. She meets the major criterion and 4 of the minor criteria set forth by the International Encephalitis Consortium for a clinical diagnosis of encephalitis. Her CSF also returns positive for HSV-1 PCR, and you are confident that her diagnosis is viral encephalitis caused by HSV-1. Her bacterial PCR tests return negative, so you discontinue antibiotics. You consult an infectious disease specialist to help with management of her antiviral course and outpatient follow-up. Aria's IV acyclovir is continued for a total of 14 days, and she receives occupational and physical therapy throughout her visit. After 14 days, she is discharged home near her neurologic baseline with maintenance levetiracetam. Close follow-up with a neurologist and an infectious disease specialist is scheduled.

Discharge Criteria

Q: How do you know when Aria is ready to go home?

You can feel comfortable discharging your patient with encephalitis when the following criteria are met:

- The patient is hemodynamically stable, seizures are controlled, and the patient has returned to baseline neurologic status.
- The patient is tolerating sufficient hydration and nutrition.
- A course of IV antimicrobials has been administered, if appropriate.
- Outpatient rehabilitation to regain strength and motor skills has been established.

Anticipatory Guidance

Q: What instructions should you provide to Aria's caregivers upon discharge?

- The ultimate neurological outcome for patients with encephalitis is extremely variable and is dependent on a number of factors, including underlying cause, and any complications that occurred over the course of the illness.
- Participation in rehabilitation can make a significant impact in clinical functional improvement.
- Return to care for any changes in mental status or personality, weakness, new seizures, fevers, worsening headaches, or vomiting.

Clinical Pearls

- Encephalitis as a diagnosis encompasses a wide-ranging variety of etiologies, symptoms, examination findings, and outcomes.
- History, physical examination, laboratory tests, and imaging can help narrow the differential, but these findings alone may not be sufficient to rule out infectious causes of encephalitis that can be rapidly progressive, and thus it is important to start empiric treatment early and maintain a high suspicion for infectious causes.
- The criteria for a diagnosis of encephalitis includes altered mental status (major criterion), seizures, focal neurologic findings, elevated WBC count in the CSF, and abnormalities of the parenchyma noted on MRI or EEG not otherwise known or explained (minor criteria).

Documentation Tips

- Use "encephalopathy" rather than "altered mental status" when changes in mental status are present (can also consider "lethargy," "somnolence," or "delirium").
- Transition to a specific diagnosis when possible (eg, encephalitis).
- Document the suspected or confirmed etiology when possible (ie, bacterial, viral, fungal).
- Document the frequency of neurologic assessments needed during the admission.

Suggested Readings

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Tomás, a 17-Month-Old Boy With Worsening Respiratory Status

CASE PRESENTATION

You are working an overnight shift on the pediatric acute care floor in December. During handoff you hear about Tomás, a 17-month-old, otherwise healthy boy who was admitted from the emergency department (ED) earlier in the afternoon with symptoms of rhinorrhea, cough, fever, and decreased urine output. He received 2 normal saline boluses and acetaminophen in the ED and was admitted to the wards where he was started on a nasal cannula at 2 L/min and intravenous (IV) fluids at a maintenance rate. Your colleague mentions that Tomás has some mildly increased work of breathing and tachypnea. The handoff assessment is acute viral bronchiolitis with dehydration.

Halfway into your overnight shift, Tomás's bedside nurse pages you to report that Tomás is "looking worse" and asks you to evaluate him.

Patient History and Review of Systems

Q: What information should you collect from Tomás's nurse, caregivers, and his medical record?

- History of present illness, as documented in the medical record, including presenting symptoms, duration of symptoms, and any associated symptoms
- Travel and exposure history
- Medical history and comorbidities, including birth history, prior hospitalizations (if any), and immunization status
- Interval history, including the following:
  - Fluid intake, urine output, and general activity levels over the previous days
  - Brief feeding history
  - Detailed description of bedside nurse's concerns and observations, including subjective changes since admission from nursing and parent perspectives
  - Objective changes since presentation, including the physical examination documented on admission for comparison and vital sign trends

CASE FOCUS

History and Review of Systems

In reviewing Tomás's medical record before entering his room, you learn that Tomás's father first noted congestion, cough, and fever up to 38.9 °C (102 °F) about 3 days ago. Tomás then had increasing fatigue over the past day. His father believes he drank only 2 cups of water and had only 1 wet diaper today (about 18 hours ago). His father also reports that Tomás had 2 episodes of nonbloody, nonbilious emesis earlier in the day just after attempting to drink oral rehydration solution but denies any diarrheal episodes. Tomás experienced some coughing fits over the last 3 days and just recently developed difficulty breathing, but his father does not recall any wheezing or stridor. His birth history and medical history are unremarkable, there is no significant travel or exposure history, and he is up to date on his vaccinations.

Tomás's clinical presentation documented in the medical record includes fever and tachycardia (heart rate of 162 beats/min), with resolution of the fever and modest improvement in his tachycardia after 2 normal saline boluses (20 mL/kg each) in the ED. Because of his clinical diagnosis of acute viral bronchiolitis, neither the ED physician nor the admitting team ordered a chest radiograph, and there was no indication for antibiotics or nebulized medication. The admission documentation of his physical examination notes "mild subcostal and intercostal retractions with mild tachypnea. Diffuse bilateral rales on auscultation." There is no personal or family history of chronic respiratory illness or cardiac conditions, and his father denies any feeding symptoms consistent with aspiration.

When you discuss Tomás's history with his nurse, he notes that Tomás's work of breathing has worsened over the past few hours. He also reports that Tomás seems more "ill appearing" than when he started his shift. Additionally, Tomás has had no urine output since his arrival on the acute care floor.

Physical Examination

Q: What parts of the physical examination should you focus on for Tomás?

- Complete set of vital signs
- Level of consciousness, ability to arouse
- Presence or absence of tears with crying
- Mucous membranes (moist, sticky, dry)
- Mouth/throat: ulcers, erythema, tonsillar hypertrophy
- Ears: tympanic membrane evaluation
- Skin turgor or cyanosis
- Presence and location of edema
- Accessory muscle usage with respiration, nasal flaring, grunting
- Lung auscultation: abnormal breath sounds, including quality, severity, and location
- Cardiac: heart rate, rhythm, gallop, rub, murmur, palpation of the precordium for point of maximal impulse (PMI)
- Peripheral perfusion: capillary refill time, temperature of extremities, quality of peripheral pulses
- Abdomen: ascites, organomegaly, tenderness, masses

CASE FOCUS

Physical Examination

Tomás is afebrile (rectal temperature: 36.8 °C [98.2 °F]) with tachycardia (heart rate: 170 beats/min), tachypnea (respiratory rate: 50 breaths/min), a normal blood pressure for age (82/47 mm Hg), and slightly low measured oxygen saturation of 90% on a 2-L nasal cannula.

Tomás is asleep but arouses and cries, producing tears, as you start your examination. He appears sleepy and is consolable. He does not have resistance or pain with neck movement. He has significant nasal congestion and rhinorrhea. His oral examination is unremarkable, with moist mucous membranes. His otoscopic examination reveals no abnormalities. Sitting upright, he has moderate subcostal and intercostal retractions, and auscultation reveals bilateral homogenous rales predominantly over the lower lobes. His cardiac examination is remarkable for tachycardia with a normal rhythm, normal S1 and S2, and no appreciable murmurs, gallops, or rubs. His precordium is hyperdynamic, but his PMI is nondisplaced. His distal upper and lower extremity pulses are palpable, and his extremities are warm, with a capillary refill time of 3 seconds. The abdomen has normal bowel sounds and is soft, and the edge of the liver is palpable 2 to 3 cm below the right costal margin. The remainder of his abdominal examination does not demonstrate any masses or tenderness. No rashes are visualized, he has normal skin turgor, and no prominent edema is noted.

Differential Diagnosis

Q: What is the differential diagnosis for a child with persistent tachycardia, worsening lower respiratory tract signs and symptoms, oliguria, and hepatomegaly?

For Tomás, you think that progression of his underlying bronchiolitis should be a significant consideration; however, because he is clinically worsening, you would like to think broadly about other possible causes of his symptoms. The differential diagnosis for a child with Tomás's symptoms is shown in Table 49.1 and is divided into causes that seem more and less likely based on his presentation.

Table 49.1. Differential Diagnosis for a Child With Persistent Tachycardia, Worsening Lower Respiratory Tract Signs and Symptoms, Oliguria, and Hepatomegaly

Diagnoses of highest suspicion	• Acute viral bronchiolitis • Acute viral syndromes, including influenza • AKI with oliguria • Cardiomyopathy: genetic (eg, from hypertrophic or dilated cardiomyopathy) or acquired (eg, from anomalous coronaries or cardiotoxic chemotherapeutics) • Myocarditis[a] • Pneumonia (viral or bacterial, including TB or aspiration)
Other diagnoses to consider	• Acquired valvular heart disease • Acute chest syndrome related to sickle cell disease • Airway foreign body • Arrhythmia • Bacteremia • Cardiac tamponade • CF • CHD with Eisenmenger syndrome • Hepatitis • Meningitis (viral, bacterial) • PE • Pericarditis • Pneumonitis • Pneumothorax/pneumomediastinum • Pulmonary hypertension • Reactive airway disease or asthma • Severe sepsis

Abbreviations: AKI, acute kidney injury; CF, cystic fibrosis; CHD, congenital heart disease; PE, pulmonary embolism; TB, tuberculosis.

[a] Diagnosis that seems most likely based on your patient's presentation.

CASE FOCUS

Urgent Intervention

Given Tomás's apparent change in clinical status, you advance his respiratory support to high-flow nasal cannula, starting at 8 L of flow at 35% fraction of inspired oxygen (FIO_2). With concern for dehydration and hypovolemia resulting in low urine output, you order a third normal saline bolus, this time at 10 mL/kg.

After the bolus finishes, you check on Tomás. He still has not voided, and he has developed worsening tachycardia and respiratory distress.

Diagnostic Evaluation

Q: What diagnostic evaluation might you pursue at this time?

- Uncomplicated acute viral bronchiolitis is a clinical diagnosis and does not require any specific imaging or laboratory workup; however, a few features of Tomás's case are concerning and should prompt further investigation. These concerning features include
  - Persistent tachycardia in the absence of fever that seems out of proportion to what would be expected with acute viral bronchiolitis.
  - Oliguria despite adequate fluid resuscitation.
  - Clinical worsening of his respiratory status after a fluid bolus.
  - Hepatomegaly.
- These findings, particularly in the setting of Tomás's clinical history, raise your suspicion for cardiac dysfunction, especially acute viral myocarditis or a cardiomyopathy. Suspicion of acute viral myocarditis should prompt immediate evaluation, including imaging and laboratory tests.
- Recommendations for the initial evaluation of patients in whom there is concern for cardiac dysfunction (eg, myocarditis) include the following:
  - Chest radiographs are useful to evaluate heart size, cardiac silhouette, pulmonary venous congestion, or pleural effusions. In children, cardiomegaly on upright nonportable chest radiograph is defined as a cardiothoracic ratio greater than 50%. It is important to remember, however, that only approximately half of pediatric patients with myocarditis demonstrate any abnormality on chest radiograph. Similarly, some patients with cardiomyopathy have a normal cardiac size and silhouette chest radiograph.
  - Electrocardiogram (ECG): ECG is an important part of the evaluation, as it may reveal arrythmias or voltage/interval changes that can be associated with certain diagnoses. The great majority of cases of myocarditis have abnormalities on ECG, although the specific changes vary by case and may include ST abnormalities, axis deviation, ventricular hypertrophy, heart block, infarction pattern, or decreased ventricular voltages. Likewise, the ECG for patients with cardiomyopathy is commonly abnormal, demonstrating ventricular hypertrophy and ST segment or T wave anomalies.
  - Echocardiogram: Echocardiography is an important tool to assess cardiac structure and function and to evaluate the etiology of heart failure. In myocarditis, the echocardiogram most frequently demonstrates decreased ejection fraction, valvular regurgitation, left ventricular dilation, or pericardial effusion. For cardiomyopathies, the echocardiogram is usually diagnostic.
  - Cardiac biomarkers (troponin, creatine kinase-MB [CK-MB], B-type natriuretic peptide [BNP]): These tests can indicate myocardial injury or strain. Only about half of pediatric myocarditis patients demonstrate elevated troponin I levels (>0.6 ng/mL [0.6 µg/L]) with a median of 2 ng/mL (2 µg/L). Troponin T has specificity of 86% and sensitivity of 71%. Elevations in CK-MB are less frequently associated with pediatric myocarditis. Normal biomarkers do not rule out cardiac dysfunction.
  - Serum chemistries: Heart failure may lead to decreased renal perfusion, resulting in kidney injury (elevated creatinine and blood urea nitrogen levels) and electrolyte abnormalities (eg, hyponatremia). Relatively nonspecific laboratory tests (eg, aspartate aminotransferase and alanine aminotransferase) also may be mildly abnormal related to secondary hepatic congestion.
  - Blood counts: White blood cell count may be abnormal, but it is a nonspecific test and may also raise concern for other conditions (eg, sepsis).
  - Inflammatory markers: Inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein) are nonspecific but may help distinguish inflammatory from noninflammatory etiology when a diagnosis is not established.
  - Blood culture: If bacterial infections are on the differential, a blood culture may be indicated.
  - Other imaging techniques: Depending on the suspected etiology, some patients with cardiac dysfunction may undergo cardiac computed tomography or magnetic resonance imaging (MRI); however, the need for these tests is generally determined by a pediatric cardiologist.

CASE FOCUS

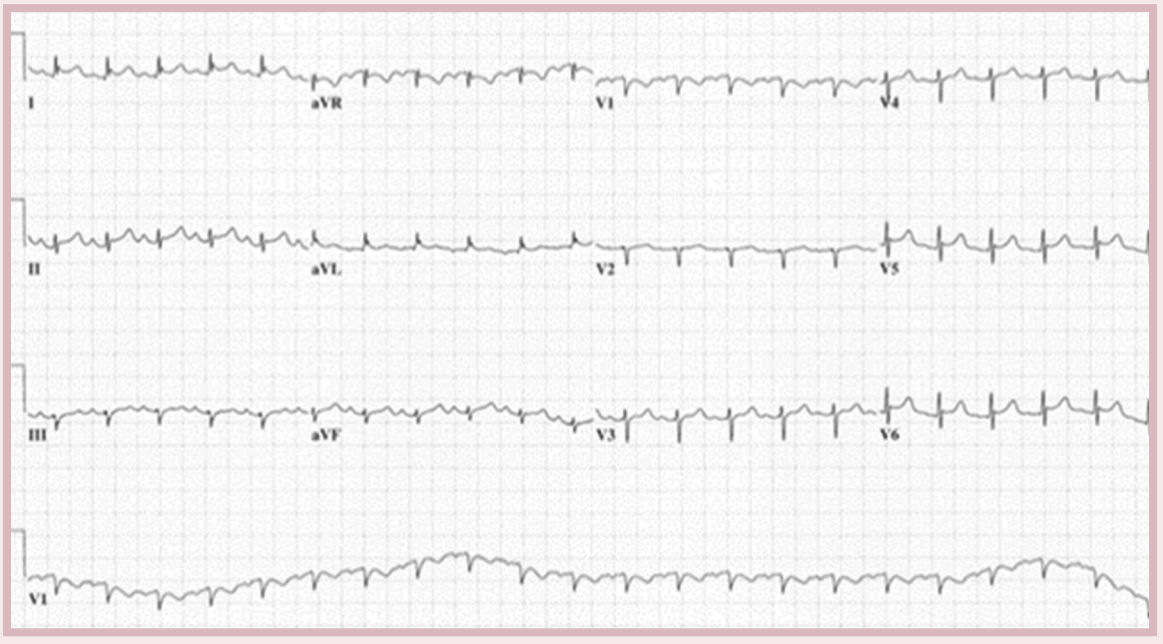
Diagnostic Evaluation

You order a portable anteroposterior chest radiograph, which demonstrates mild cardiomegaly and symmetric diffuse interstitial infiltrates, predominantly over the lower lobes. Tomás's serum chemistry results are as follows:

Laboratory test	Results	Reference range
Sodium	140 mEq/L (140 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Potassium	4 mEq/L (4 mmol/L)	3.5–4.7 mEq/L (3.5–4.7 mmol/L)
Chloride	110 mEq/L (110 mmol/L)	97–107 mEq/L (97–107 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)	18–24 mEq/L (18–24 mmol/L)
Anion gap	12 mEq/L (12 mmol/L)	4–12 mEq/L (4–12 mmol/L)
BUN	22 mg/dL (7.85 mmol/L)	5–18 mg/dL (1.78–6.43 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)	0.1–0.4 mg/dL (8.8–35.4 µmol/L)
Glucose	62 mg/dL (3.44 mmol/L)	60–100 mg/dL (3.33–5.55 mmol/L)

Abbreviation: BUN, blood urea nitrogen.

To evaluate Tomás's persistent tachycardia and moderately ill appearance, you obtain a 12-lead ECG, which is shown here:



CASE FOCUS

Diagnostic Evaluation *(continued)*

Tomás's ECG results are as follows: sinus tachycardia, leftward axis, diffuse nonspecific ST segment changes. Refer to Appendix Section VIII for a discussion of ECG interpretation.

You call the echocardiogram technician, and she is able to perform an immediate echocardiogram, which reveals moderate left and right ventricular dilation with normal wall thickness, dilated atria bilaterally, and reduced systolic function with a left ventricular ejection fraction of 23% (normal ejection fraction: 50%–70%) and qualitatively decreased right ventricular systolic function. There are no structural abnormalities or evidence of significant pulmonary hypertension. There is normal origin of the coronary arteries. There is no pericardial effusion.

In addition, you obtain troponin, CK-MB, and BNP levels, the results of which are as follows:

Laboratory test	Results	Reference range
Troponin I	1.8 ng/mL (1.8 µg/L)	< 0.06 ng/mL (0.06 µg/L)
CK-MB	2 ng/mL (2 µg/L)	0–1.7 ng/mL (0–1.7 µg/L)
BNP	150 pg/mL (150 ng/L)	< 40 pg/mL (40 ng/L)

Abbreviations: BNP, B-type natriuretic peptide; CK-MB, creatine kinase-MB.

Arriving at a Diagnosis

Q: How do you develop an assessment for Tomás?

To arrive at Tomás's final diagnosis, you will first interpret the key findings from his history, examination, and diagnostic studies, develop a list of findings, and then finalize your diagnosis.

1. **Interpret key findings from the history, physical, and diagnostic evaluation.**
   - History: Tomás has had 3 days of cough, congestion, and fever with 1 day of increasing work of breathing, decreased urine output, and progressive fatigue. His family history does not include any significant sudden cardiac death, congenital heart disease, or known cardiomyopathy.
   - Physical examination: Tomás's vital signs show persistent tachycardia and oxygen requirement, both worsening with fluid administration. His examination demonstrates bilateral homogenous rales over bilateral lower lung fields with tachypnea and significant accessory muscle usage. On cardiac examination, Tomás has a normal S1 and S2 and no murmur, rub, or gallop. He also has hepatomegaly and is appropriately hydrated on examination.
   - Diagnostic studies
     - Imaging: Tomás's chest radiograph demonstrates cardiomegaly with interstitial infiltrates predominantly over the lower lobes, consistent with cardiogenic pulmonary edema.
     - Initial laboratory tests: Tomás's basic metabolic profile demonstrates an elevated creatinine level consistent with stage II acute kidney injury (AKI) (creatinine equal to 2.0–2.5 times baseline).
     - ECG: Tomás's ECG shows sinus tachycardia, leftward axis, and diffuse nonspecific ST segment changes. His ECG does not show any findings concerning for a cardiac arrythmia.
     - Echocardiogram: His echocardiogram demonstrates depressed systolic function without structural abnormality and confirms congestive heart failure (CHF). Additionally, his echocardiogram rules out congenital heart disease, including anomalous coronaries, acquired valvular disease, cardiac tamponade, and pulmonary hypertension as etiologies.

- Cardiac laboratory tests: Elevated troponin I, CK-MB, and BNP levels indicate cardiac myocyte injury with evidence of stretched myocardium.

In this clinical scenario, the combination of poor renal perfusion and myocardial injury and stretch, with radiographic evidence of cardiomegaly, pulmonary infiltrates, and reduced ejection fraction, confirms your suspicion of acute CHF. Additionally, Tomás's echocardiogram decreases suspicion for hypertrophic, dilated, or restrictive cardiomyopathy.

2. **Develop the list of findings.**

Q: What major findings have you identified for Tomás?

- Systolic heart failure
- Compensated cardiogenic shock
- Pulmonary edema
- Elevated troponin
- Anuria
- AKI

3. **Revisit the differential diagnosis.**

Q: Based on your initial differential diagnosis and considering the list of findings, are you able to choose one diagnosis to explain Tomás's presentation?

Although there is not a single test to diagnose myocarditis, Tomás's history, clinical picture, laboratory findings, ECG findings, and echocardiogram are consistent with acute viral myocarditis resulting in symptomatic heart failure. Heart failure can develop as a result of viral myocarditis during or after the symptomatic period of an acute viral illness. Tomás initially had cough, congestion, and fever at presentation, indicating the myocarditis is likely concurrent with the viral illness.

Q: What is myocarditis?

- Myocarditis is an inflammatory disease of the myocardium that can be caused by a variety of etiologies (as described in detail in the next section), resulting in a large spectrum of clinical presentations. The diagnostic challenge of myocarditis comes from its overlap with more common clinical syndromes (eg, viral bronchiolitis, asthma, acute gastroenteritis). Despite the fact that myocarditis may cause greater morbidity and mortality than the syndromes it mimics, it often presents as the second diagnosis. Therefore, the diagnosis tends to hide behind the primary more common clinical presentation and becomes more obvious only as the clinical course veers from the expected progression of the initially diagnosed disease. Unfortunately, delays in recognizing myocarditis may cause additional harm, as the treatment strategies may be conflicting (ie, administering IV fluids to a patient who typically would be hypovolemic, when in fact they have volume overload and cardiac and pulmonary congestion).
- Epidemiologic data demonstrate that the presenting signs and symptoms of myocarditis vary based on severity and by age. The majority of patients younger than 10 years present with respiratory distress, tachypnea, or abnormalities on lung auscultation, whereas patients 10 years or older more frequently present with chest pain. Tachycardia is a common finding, but it may be absent in approximately 40% of patients. Other signs and symptoms that manifest in a smaller subset of patients include lethargy, hepatomegaly, abnormal heart auscultation, fever, cyanosis, and decreased peripheral perfusion.
- The spectrum of clinical presentation for acute viral myocarditis varies from asymptomatic, to acute CHF, to complete cardiovascular collapse and cardiogenic shock. There is no single symptom, sign, or laboratory test that reliably rules in or rules out the diagnosis. Thus, all front-line practitioners must recognize the constellation of signs, symptoms, and findings that increase clinical suspicion for acute viral myocarditis to facilitate an efficient diagnosis.

Q. What are the most common etiologies of myocarditis?

The most common etiologies of myocarditis in pediatric patients differentiate into infectious causes and noninfectious causes. Figure 49.1 demonstrates the most common etiologies.

- Infectious causes: Viral infection is the most common cause of myocarditis in North America, whereas rheumatic disease and *Trypanosoma cruzi* (Chagas disease) are the leading causes of myocarditis in resource-limited areas of the world. Classically, the most common viruses known to cause viral myocarditis were enteroviruses, most notably coxsackie group B, and influenza and respiratory syncytial virus. Most recently, studies have increasingly identified parvovirus B19, human herpesvirus 6, and adenovirus as common causes.
- Noninfectious causes can include autoimmune disease, medications (eg, chemotherapeutic agents), or postoperative complications.

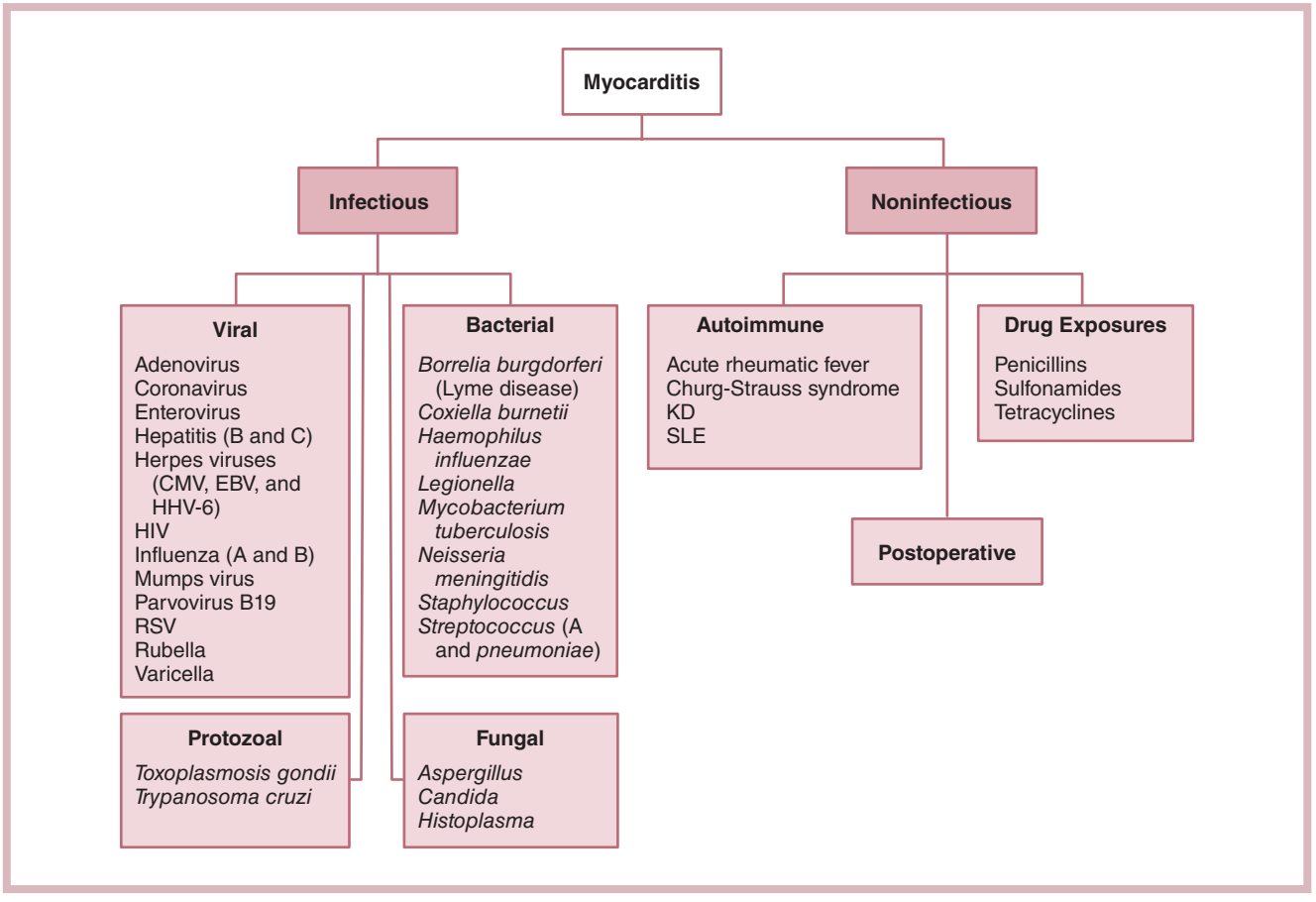


Figure 49.1. The most common etiologies of pediatric myocarditis.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; KD, Kawasaki disease; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with suspected myocarditis?

Although Tomás is already hospitalized, it can be helpful to consider the following admission criteria for patients with suspected myocarditis:

- Any suspected case of acute myocarditis will likely require admission for monitoring and management.
- Patients with a viral syndrome and persistent tachycardia in the absence of fever or dehydration may be admitted for further monitoring and evaluation given that these findings raise suspicion for myocarditis.
- More relevant for Tomás are indications to transfer to a higher level of care (eg, pediatric intensive care unit [ICU], pediatric cardiac ICU). These indicators may include
  - Respiratory failure.
  - Hypotension.
  - Fluid overload.
  - Altered mental status.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Tomás is a 17-month-old boy who was admitted with presumed viral bronchiolitis after presenting with acute onset of viral respiratory symptoms, tachycardia, and oliguria. He has now developed compensated cardiogenic shock, systolic heart failure, myocardial injury, pulmonary edema, and AKI with anuria, likely secondary to acute viral myocarditis. He requires ongoing admission for further treatment and monitoring.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Treatment of acute viral myocarditis is focused on providing supportive care in a closely monitored setting. Patients with myocarditis should always be managed in close consultation with a pediatric cardiologist.

1. **Supportive care**
   - Treatment of myocarditis is always dependent on the clinical scenario, as supportive care is the first-line therapy. This may include respiratory support, which can help with afterload reduction, and tightly controlled fluid management with diuretics while initiating appropriate therapy for heart failure (when present).
   - Patients who develop hemodynamic instability and cardiogenic shock from myocarditis require intensive care admission for intubation, mechanical ventilation, and hemodynamic support with vasopressors, inotropes, and diuretics.
   - Therapy for refractory cardiogenic shock may progress to extracorporeal membrane oxygenation or a ventricular assist device, depending on the expected time to recovery.
   - Arrhythmias or heart block can be sequelae of myocarditis; therefore, some patients may also require antiarrhythmics or pacemaker placement.
   - Once patients are hemodynamically stable, guideline-directed medical heart failure therapy ensues.

Q. What are the medical management options for pediatric heart failure?

- Myocarditis that leads to dilated cardiomyopathy is the most common myopathic process causing heart failure in children. Because of limited pediatric data, the current practice for treating pediatric heart failure extrapolates recommendations from adult studies and adult guidelines. As a patient's heart failure progresses, the pediatric cardiology team may recommend pharmacologic interventions (eg, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers, β-blockers, digoxin, diuretics).
  - These medications are relatively uncommon in general pediatric practice. The most common adverse effects for these heart failure medication classes to assist with appropriate medication titration and drug effect monitoring include
    - ACEIs: hyperkalemia, worsening of renal function, angioedema, dry cough.
    - β-blockers: symptomatic bradycardia, hypoglycemia.
    - Loop diuretics: electrolyte derangements (hypokalemia, hypomagnesemia, hyperuricemia), ototoxicity (dose dependent).
    - Aldosterone antagonists: hyperkalemia, gynecomastia.
    - Digoxin: life-threatening arrhythmias, hyperkalemia.
  - Advanced heart failure medications and antiarrhythmic therapies have unique side effect profiles and are not reviewed here.

2. **Immunomodulating therapy:** Treatment with IV immunoglobulin and systemic steroids is not routinely recommended; however, decisions should be individualized and made in conjunction with a pediatric cardiologist.
3. **Monitoring**
   - Heart failure signs and symptoms (eg, shortness of breath, fatigue, edema) are helpful in the diagnosis of heart failure and are also integral to monitoring the patient's response and recovery. Although many pediatric patients completely recover, a small number may go on to have chronic heart failure and may even require cardiac transplant.
   - In the hospital, the care team may utilize cardiorespiratory monitoring and/or telemetry for monitoring of vital signs and to evaluate for potential arrhythmias.
   - Follow-up studies, including BNP trend, repeat echocardiography, and repeat chest radiographs, can all be used in monitoring progression of disease and response to therapy.
   - Monitoring fluid status is critical to inpatient management of heart failure. In the ICU setting, this may be done with invasive monitoring, whereas in the acute care setting this is more likely to be done by clinical examination and daily trending of the patient's weight.
4. **Nutritional therapy:** Ensuring adequate nutrition is an important component of pediatric heart failure. Patients may require fluid restriction to minimize cardiac overload, but they may also have increased caloric requirements as a result of heart failure.
5. **Further diagnostic testing**
   - Once diagnosed, further workup of myocarditis may include testing for possible etiologies using nasopharyngeal swab viral polymerase chain reaction (PCR) testing or serum serologies. However, viral PCR testing may be negative if symptomatic myocarditis presents after the viremic phase. Although serology results do reliably identify viral infections, studies demonstrate they may not necessarily correlate with endomyocardial biopsy findings.
   - Additional specialized testing may be used to further diagnose and manage myocarditis, including cardiac MRI and endomyocardial biopsy. Cardiac MRI reveals high-quality images in the evaluation of cardiomyopathy or myocarditis but often requires sedation, which carries a higher risk in an acutely ill child. The standard of reference for the diagnosis of myocarditis is an endomyocardial biopsy with histopathologic examination, but it is an invasive test that also requires sedation. In most cases, the clinical presentation, laboratory findings, and echocardiogram negate the need for cardiac MRI or biopsy for the diagnosis of myocarditis. Therefore, clinicians reserve cardiac MRI and/or endomyocardial biopsy for cases in which the results may offer prognostic or therapeutic value.

CASE FOCUS

Plan for Treatment and Monitoring

- **Supportive care:** You order a dose of IV furosemide in an attempt at diuresis and simultaneously increase Tomás's high-flow nasal cannula to 12 L. Additionally, you page the on-call cardiologist for advice on Tomás's care. In the meantime, you work with your nursing team to attempt to secure a second site of IV access and with your respiratory therapy team to increase Tomás's high-flow rate and titrate his F_{IO_2} as needed to keep his measured oxygen saturation at 92% or higher.
- **Immunomodulator therapy:** None is indicated at this time, but you will discuss this possibility with cardiology.
- **Monitoring for response to therapy:** You continue Tomás on continuous pulse oximetry and also place telemetry monitoring. While awaiting consultation with the cardiologist, you will frequently assess his respiratory status based on his work of breathing, tachypnea, and oxygen saturations.
- **Nutritional therapy:** Tomás is made nil per os (nothing by mouth) until he can be stabilized. Given his fluid overload, you hold off on starting IV fluids.
- **Further diagnostic testing:** You order a nasal swab for a respiratory pathogen panel by PCR but will await consultation with pediatric cardiology before performing any specialized testing for infection.

Case Resolution

Over the next hour and despite the dose of IV furosemide, Tomás requires 70% F_{IO_2} to maintain his measured oxygen saturations around 91% pulse oxygen saturation. His tachycardia and tachypnea persist, and his hands and feet are cooler than they were on your previous examination, with a capillary refill time of 4 seconds. You recognize the need for increased cardiopulmonary support and urgently contact the pediatric critical care team.

Tomás is transferred to the pediatric ICU and eventually requires intubation with mechanical ventilation, inotropic support, and aggressive diuresis with invasive hemodynamic monitoring. He stabilizes and shows recovery with a slow wean of intensive care support. He is then able to transition to oral furosemide and oral enalapril and transfer back to the acute care floor 12 days after admission to the ICU. A specific infection etiology of his acute myocarditis is never determined; however, the course of his illness remained consistent with your diagnosis of acute viral myocarditis. After he demonstrates euvolemia and normal electrolyte levels, he is eventually discharged home on a stable dose of oral enalapril with close follow-up in the pediatric cardiology clinic.

Discharge Criteria

Q: How do you know when Tomás is ready to go home?

You can feel comfortable discharging a patient recovering from acute viral myocarditis when the following criteria are met:

- The patient does not require oxygen.
- The patient is taking sufficient fluids orally to maintain appropriate hydration.
- The patient no longer requires IV medications or IV fluids.
- The patient has stable daily weights and is euvolemic on examination.
- The patient's echocardiogram has demonstrated stably decreased or improved biventricular systolic function.

- The home medication regimen has been initiated in the hospital. The patient has normal and stable electrolytes without unacceptable adverse effects on this regimen.
- The patient's caregivers understand home medications and return precautions.
- Appropriate follow-up care has been established, including cardiology and rehabilitation services as needed due to prolonged hospitalization and intensive care.

Anticipatory Guidance

Q: What instructions should you provide to Tomás's caregivers upon discharge?

- In some cases, acute myocarditis leads to dilated cardiomyopathy and chronic heart failure. Medications should be taken daily as directed, and it is important to follow up as directed with the pediatric cardiologist.
- Return to care for respiratory distress, rapid or uncontrolled increase or decrease in weight, temperature above 38.3 °C (100.9 °F), persistent vomiting, lethargy, presyncope, or syncope.

Clinical Pearls

- Myocarditis can present in many different ways, with various levels of severity, masquerading behind many different diseases upon presentation, including but not limited to viral bronchiolitis, asthma exacerbation, sepsis, or acute gastroenteritis. History and physical examination may help reveal clues that prompt further investigation. When accepting a handoff case, clinicians should allow the working diagnosis to guide treatment while also noting clinical changes or developments and being prepared to alter or develop the working diagnosis as needed.
- Tachycardia that does not respond to appropriate hydration, antipyretics, or pain control should prompt consideration of myocarditis.
- A thorough family history is an important aspect of history taking and initial evaluation, especially when distinguishing between risk of hereditary versus acquired illness.
- In the United States, myocarditis is most commonly caused by viruses, whereas in resource-limited areas, Chagas disease and rheumatic disease are the most prevalent causes.
- Myocarditis is a clinical diagnosis. There is no single test to rule it in or out, but cell counts; electrolytes; renal function evaluation; troponin, CK-MB, and BNP levels; chest radiography; ECG; and echocardiography assist in the diagnosis. In some cases, more advanced testing (eg, cardiac MRI, endomyocardial biopsy [standard of reference]) may impact the course of treatment.
- Treatment of myocarditis is largely supportive and may require admission to an intensive care unit.
- Heart failure management in children derives from a few small pediatric studies and data extrapolation from adult guidelines. Medical therapy may include ACEIs, angiotensin receptor blockers, β-blockers, diuretics, or digoxin.

Documentation Tip

- If heart failure is present, document whether it is acute, chronic, or acute on chronic, and mention the underlying etiology if known.

Suggested Readings

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CASE 50

Anna, an 11-Year-Old Girl With Medical Complexity, Fever, Increased Secretions, and Increased Seizure Frequency

CASE PRESENTATION

Anna is an 11-year-old girl with a medical history of extreme prematurity, intraventricular hemorrhage, and cerebral palsy. Her underlying diagnoses include chronic respiratory failure with tracheostomy and ventilator, severe dysphagia and reflux with gastrojejunostomy (GJ) tube, hydrocephalus with ventriculoperitoneal (VP) shunt, spasticity treated with enteral baclofen, scoliosis, and intractable epilepsy for which she is on multiple antiseizure medications (ASMs). She is nonverbal and nonambulatory. She does not take feeds or medications by mouth.

Anna's parents, along with her home health nurse, have brought her to the emergency department (ED) because of new-onset fever, increased oral secretions, poor feeding tolerance evidenced by retching, increased seizure frequency, and general discomfort. The physician in the ED notes that Anna has an increased oxygen requirement, and she has obtained basic laboratory tests and imaging prior to calling you to assess Anna for admission.

Patient History and Review of Systems

Q: What information should you collect from Anna and her caregivers?

Children with medical complexity are often unable to communicate in traditional ways, and therefore input of caregivers is important. Some children with medical complexity understand more than they are able to express, and therefore assumptions should not be made about their ability to be involved their care. Patients who are old enough should be questioned directly and involved in their care if they are able.

- History of present illness
  - Duration, timeline, order, and description of symptoms
  - Recent sick contacts
- Associated symptoms, including fever, cough, congestion rhinorrhea, changes in urine (presence of blood, changes in frequency or volume), or changes in stools (frequency, consistency, presence of blood)
- Recent changes in social factors that might impact medical care (eg, disruption of living situation, finances, medication and medical equipment supply, home nursing)

- Baseline health status, including any frequent illnesses and their characteristics, baseline medication and airway clearance regimen and any recent changes to them, specialists involved in regular care, and most recent dental evaluation
- Effects of current illness on chronic health issues, including the following:
  - Comfort, sleep, and alertness, including any recent changes in level of arousal, interactivity, or wakefulness, expressions of discomfort or distress, and any recent changes to her sleep-wake cycle
  - Seizures: Change in frequency, manifestations, or severity; any missed doses of ASMs
  - Spasticity: any worsening, tolerance of baclofen
  - Dysphagia/reflux: tolerance of GJ tube feeds, any recent feed or free water adjustments, any leakage or irritation at tube site, vomiting and any association of respiratory symptoms with vomiting, abdominal distention, pain
  - Chronic respiratory failure: ability to clear respiratory secretions on her own; management of tracheostomy tube during the day and at night; suctioning requirements and frequency, including any need for more frequent suctioning or changes in baseline airway clearance plan; any changes in consistency of tracheostomy tube secretions; oxygen requirements, including increased need for respiratory support and any change in ventilator use
  - Hydrocephalus: last evaluation of VP shunt, appearance of the VP shunt tract, history of VP shunt malfunction, behaviors during any previous VP shunt infection or malfunction, and any constipation, which can obstruct the distal end of the VP shunt

CASE FOCUS

History and Review of Systems

In the ED, your initial history is acquired from Anna's parents, who are her primary caregivers, and also her home health nurse. You also have access to her outpatient clinic notes.

You learn that Anna has been acting more restless and uncomfortable for the last 3 days. Anna's mother has also noted thick yellow secretions coming out of the tracheostomy tube during routine tracheostomy care. Anna has been trying to cough, but her mother reports that she "doesn't ever cough very well." Normally, her tracheostomy is placed on a heat and moisture exchanger (HME) during the day, and she has ventilator support at night without supplemental oxygen, but over the last 2 nights, she has required 0.5 to 1 L/min of oxygen to maintain oxygen saturations levels between 90% and 99%. In addition, Anna's home health nurse noted a temperature of 38.9 °C (102 °F) today, which is what prompted Anna's parents to call her pediatrician and then bring her to the ED.

Anna's review of systems is positive for increased seizure frequency for 1 day. Anna typically has 1 or 2 brief, self-resolving generalized tonic-clonic seizures per day on her current medication regimen; however, today she has already had 3 such seizures. Anna's mother reports adherence to prescribed ASMs. With regard to her cerebral palsy, Anna is tolerating her antispasticity medication as well, although her mother states that Anna seems to be "a little more tight" over the last few days. Anna's mother has also noticed some retching with feeds. She does state that her daughter will often display similar behavior when she is in pain, upset, or has an acute illness. Anna's mother slowed her feeding rate last night, but this did not seem to help. Anna's home health nurse notes that her urine has become more yellow in color and has a "strong" odor. Her nurse also reports that Anna has been voiding her usual quantity and frequency for the last few days. Her mother reports no leakage or irritation at her GJ tube site. Anna has not had any vomiting, diarrhea, or constipation. There has been no blood in her urine or stool. She has no significant changes in her sleep-wake cycle. Anna has not had any recent sick contacts, and she has not started having periods.

Anna's medical history also includes 2 prior hospitalizations for acute illnesses, one for a bacterial respiratory tract infection (tracheitis) and the second for a urinary tract infection (UTI). She had a shunt infection shortly after it was placed when she was a neonate, but she has had no further infections. She has had shunt revisions by neurosurgery as she has grown, with the last surgical procedure being 2 years ago. She has had no major changes to overall health status recently. On review of her most recent outpatient clinic note from her primary care pediatrician, you review her list of home medications and therapies closely, noting that she has had no changes to her medication or healthcare regimen in the last 6 months, nor has she experienced any changes in social factors that might impact her care.

BACK TO BASICS

HME

A tracheostomy bypasses much of the upper airway, including the nose and sinuses, which typically serves to warm and moisturize incoming air. An HME is a device that is placed over the tracheostomy tube. It collects moisture from exhaled air and returns some of it during inhalation, thus partially replacing the function of the upper airway.

Physical Examination

Q: What parts of the physical examination should you focus on for Anna?

Given that Anna is nonverbal and has abnormal physical examination findings at baseline, it is very important to perform a thorough physical examination and to ask her caregivers about any changes from her baseline to help determine the cause of her symptoms.

- Complete set of vital signs
- General appearance: comfort level and level of alertness, especially as compared to baseline
- Head: scalp lesions, assessment of VP shunt site
- Eyes, ears, nose, and throat: pupillary response as compared to baseline; intraoral or intranasal erythema or lesions (if able to assess oral cavity, given spasticity); tympanic membranes (bulging, redness, presence of fluid)
- Neck/tracheostomy site: range of motion, presence of lymphadenopathy or jugular vein distention; status of tracheostomy (patent, capped vs uncapped, positioning); changes to skin surrounding tracheostomy site; leakage at tracheostomy site; presence, color, and thickness of sputum
- Cardiovascular: murmurs, changes in capillary refill time and pulses
- Respiratory: work of breathing; symmetry of chest expansion; presence of crackles, rales, or wheezing; focality of any abnormal findings
- Abdomen: distension; presence and characteristics of bowel sounds; organomegaly; discomfort; guarding; palpable masses; status of GJ tube site, including patency, appearance of surrounding skin, leakage, presence of granulation tissue, and tube mobility
- Genitourinary: including Tanner staging, presence of vaginal bleeding, discharge, or lesions
- Skin: diaphoresis, lesions, rashes, or other abnormalities; signs of pressure injury to high-pressure areas (eg, sacrum)
- Extremities: range of motion, presence of gross deformity, contractures, level of mobility, discomfort on repositioning
- Neurologic: irritability and responsiveness; overall muscle tone as compared to baseline; reflexes, including presence of clonus; facial symmetry

CASE FOCUS

Physical Examination

Anna's vital signs show that she is febrile (temperature: 38.8 °C [101.8 °F]), mildly tachycardic (heart rate: 103 beats/min) and also tachypneic (respiratory rate: 42 breaths/min). She is normotensive (blood pressure: 107/94 mm Hg). She has mild hypoxia (oxygen saturation: 88% on tracheostomy collar).

Anna is a small girl and is sitting up in her wheelchair. She appears slightly uncomfortable and will groan but will also smile occasionally. Per Anna's mother, she is at her baseline wakefulness and alertness. Anna has surgical scarring on her posterolateral right scalp and mild scalp deformity noted with VP shunt valve and tubing palpable subcutaneously. Otherwise, she is normocephalic. Her pupils are equal, round, and reactive to light. She has normal-appearing tympanic membranes bilaterally, and nasal mucous membranes that are normal without drainage. Her intraoral cavity is difficult to examine given her jaw spasticity, but her teeth, gums, and posterior oropharynx appear normal.

Anna has limited neck range of motion due to spasticity. Her tracheostomy is in place and appropriately positioned, and the surrounding tissue is without irritation or erythema. When Anna's mother removes her tracheostomy cap, you note thick yellow secretions in the lumen of the tube. There is no lymphadenopathy or jugular venous distension.

On cardiovascular examination, Anna has mild tachycardia with a regular rhythm. You do not hear any murmurs. She has normal radial and dorsalis pedis pulses and brisk capillary refill.

On respiratory examination, you note that her left chest wall is smaller than the right due to curvature of the spine. She has decreased chest movement with respiration on the left side compared to the right. She has some increased work of breathing, with mild tachypnea and mild subcostal retractions. Auscultation reveals diffuse coarse breath sounds bilaterally, with decreased breath sounds in the bases. There is no wheezing.

External abdominal examination reveals a GJ port that is in place and appropriately mobile. The surrounding tissue is nonerythematous. There is a 5-mm border of granulation tissue lining the lateral half of the stoma. The stoma is draining a small amount of thin yellow fluid. Her abdomen is not distended. Palpation reveals no organomegaly, no palpable stool, and no guarding. Anna appears to be more uncomfortable during the abdominal examination, but her mother states that "Anna doesn't really like people touching her, and that is a normal reaction for her."

Genitourinary examination shows that Anna is Tanner stage 2, and her external genitalia appears normal. There is no blood or discharge noted.

Her skin is warm and dry, with no rashes. Anna's mother assists you with lifting her so you can visualize her sacrum and buttocks. There is mild blanching erythema to the sacrum, but the examination is otherwise normal.

Anna has diffuse spasticity and limited passive range of motion in the proximal and distal joints of the upper and lower extremities. No gross deformity is present. Anna is at her neurologic baseline per her mother's report. She is nonverbal, and she does not make purposeful eye contact. Her pupils are reactive as previously noted. You are unable to assess cranial nerves III through X because of her baseline neurologic status. Her palate is elevated symmetrically. Her muscle tone is increased in all extremities. Her bicipital and patellar reflexes are 3+ (very brisk). Her ankle reflex is 4+ with 4 beats of clonus. She withdraws to noxious stimuli.

Differential Diagnosis

Q: What is the differential diagnosis for a child with medical complexity who presents with increased respiratory secretions and increased oxygen requirement, poor feeding tolerance, increased seizure frequency, and general discomfort?

The differential diagnosis for a child with medical complexity who presents with nonspecific signs and symptoms is broad. Anna is experiencing increased respiratory secretions and an increased oxygen requirement, in addition to poor feeding tolerance, increased seizure frequency, and general discomfort. This combination of signs and symptoms makes a respiratory illness more likely, but not certain. The differential diagnosis is shown in Table 50.1 and is divided into causes that seem more and less likely for Anna.

Table 50.1. Differential Diagnosis for a Child With Medical Complexity and Nonspecific Signs and Symptoms including Increased Secretions, Oxygen Requirement, and Seizure Frequency; Poor Feeding Tolerance; and General Discomfort

Diagnoses of highest suspicion	• Aspiration pneumonia • Baclofen withdrawal • Bacterial pneumonia • Bacterial tracheitis[a] • Viral LRTI, including SARS-CoV-2[a] • VP shunt malfunction or infection[a]
Other diagnoses to consider	• Acute infectious gastroenteritis • ASM toxicity or side effects • Bone or joint infection • Bowel obstruction • Constipation • Dysautonomia • Dysmotility • Femur fracture with fat embolism syndrome • Ileus • Infected pressure ulcer • Odontogenic Infection • Pancreatitis • UTI • Worsening intractable epilepsy

Abbreviations: ASM, antiseizure medication; LRTI, lower respiratory tract infection; UTI, urinary tract infection; VP, ventriculoperitoneal.

[a] Diagnoses that seem most likely based on your patient's presentation.

Diagnostic Evaluation

Q: The differential diagnosis for Anna is extensive. To narrow the list of clinical possibilities, what diagnostic evaluation is warranted?

- It is essential to consider the full range of common pediatric illnesses when evaluating a child with medical complexity. Based on your evaluation, these more common diagnoses are less likely.
- Diagnoses that are more relevant in children with medical complexity or technology dependence are shown in Table 50.2, along with their common clinical features and recommended diagnostic evaluation.

Table 50.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Medical Complexity and Nonspecific Signs and Symptoms

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Respiratory		
Aspiration pneumonia	Fever, increased work of breathing, increased oxygen requirement, focal crackles, clinical history of aspiration event, oral feeding, frequent retching or reflux symptoms	Chest radiography
Bacterial pneumonia	Fever, increased work of breathing, increased oxygen requirement, focal crackles	Chest radiography
Tracheitis	Fever, increased work of breathing, increased secretions, increased oxygen requirement, nonfocal lung examination; presence of tracheostomy	Respiratory Gram stain and culture from tracheostomy tube
Viral LRTI	Fever, increased work of breathing, increased oxygen requirement, nonfocal lung examination with diffuse crackles	Respiratory virus panel (PCR)
Gastrointestinal		
Constipation	Decreased stool frequency, hard stools, pain with defecation	Clinical history, abdominal radiography
Dysmotility	Retching; change in feeding tolerance from baseline; abdominal distention, particularly with feeding	Gastric emptying study (nuclear medicine study, abdominal radiography timed after feeding)
Ileus	Retching, change in feeding tolerance from baseline, abdominal distention, change in stooling	Clinical history, abdominal radiography
Pancreatitis	Retching, pain especially with feeding; history of ASM use	Lipase level

Table 50.2. Possible Diagnoses, Associated Clinical Features, and Diagnostic Evaluation in Children With Medical Complexity and Nonspecific Signs and Symptoms *(continued)*

Diagnosis	Possible clinical features and/or risk factors	Diagnostic evaluation to consider
Neurologic		
ASM toxicity or side effects	Although variable based on drug and dosing, can include altered mental status, somnolence, behavioral change, worsening seizures, discoordination, hematologic abnormalities, electrolyte disturbances, transaminitis/liver failure, pancreatitis, hyperammonemic encephalopathy, DRESS syndrome, or SJS	ASM levels Depending on symptoms and which ASMs are taken, further testing may include CBC with differential, CMP, lipase level, and serum ammonia level.
Baclofen withdrawal	Increased muscle tone, increased seizure frequency, poor feeding tolerance, fever; can progress to rhabdomyolysis and multiorgan failure	Test dose of baclofen to evaluate for improvement CK level to evaluate for rhabdomyolysis
VP shunt malfunction	Fever, headache, change in behavior, vomiting or retching, increased seizure frequency; can progress to vital sign changes and physical examination consistent with increased intracranial pressure (Cushing triad: hypertension, bradycardia, and respiratory depression)	Head CT scan or fast-acquisition MRI[a] and shunt series radiographs
Worsening intractable epilepsy	Increased seizure frequency in the absence of acute infection	Clinical history, EEG, MRI of the brain
Musculoskeletal		
Bone or joint infection	Fever, focal bone or joint tenderness, swelling or erythema, or change in range of motion, elevated inflammatory markers	Radiography, US, or MRI as indicated, ESR/CRP level, CBC Bone scan may be helpful if unable to localize symptoms.
Fracture (accidental or intentional)	Focal bone tenderness or swelling, change in circulation distal to possible fracture site, history of decreased bone density with regular care needs (eg, diaper and positional changes)	Radiography as indicated
Pressure ulcer	Erythema or ulceration on skin examination	Clinical examination
Genitourinary		
UTI	Fever, dysuria, change in urination, diarrhea; risk of UTI increased in patients with urinary retention or incomplete voiding	UA, urine culture

Abbreviations: ASM, antiseizure medication; CBC, complete blood cell count; CK, creatine kinase; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CT, computed tomography; DRESS, drug reaction with eosinophilia and systemic symptoms; ESR, erythrocyte sedimentation rate; LRTI, lower respiratory tract infection; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SJS, Stevens-Johnson syndrome; UA, urinalysis; US, ultrasonography; UTI, urinary tract infection; VP, ventriculoperitoneal.

[a] Some VP shunt valves require reprogramming after an MRI.

CASE FOCUS

Diagnostic Evaluation

Based on the information you have collected, you order a complete blood cell count, chest radiograph, sputum culture and smear of tracheal secretions, erythrocyte sedimentation rate, and C-reactive protein (CRP) level, the results of which are as follows:

Laboratory test	Results	Normal range
CBC		
WBC count	21,400/μL (21.4 × 10^9/L)	4,000–13,000/μL (4.0–13.0 × 10^9/L)
Hemoglobin	11.5 g/dL (115 g/L)	11.5–14.5 g/dL (115–145 g/L)
Hematocrit	35% (0.35)	33%–43% (0.33–0.43)
MCV	85 μm^3 (85 fL)	76–90 μm^3 (76–90 fL)
Platelet count	390 × 10^3/μL (390 × 10^9/L)	150–400 × 10^3/μL (150–400 × 10^9/L)
Neutrophils	85% (0.85)	54%–62% (0.54–0.62)
Bands	2% (0.02)	0%–3% (0–0.03)
Inflammatory markers		
ESR	65 mm/h	0–10 mm/h
CRP	21.2 mg/dL (212 mg/L)	<1 mg/dL (<10 mg/L)

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; WBC, white blood cell.

- **Posteroanterior/lateral chest radiograph: no focal opacity on evaluation of the radiograph. The radiologist's read is as follows: Viral versus reactive airway disease, with slightly increased bibasilar opacities. Low lung volumes make basilar lobar pneumonia difficult to exclude in the appropriate clinical setting.**
- **Sputum culture and smear from the trachea: gram-negative rods and abundant white blood cells (WBCs); final culture results are pending.**

You also collected the following studies, the results of which were reassuring:

- **Urinalysis and urine culture**
- **Abdominal radiograph**
- **Comprehensive metabolic panel**
- **Venous blood gas**
- **Lipase level**
- **Viral respiratory panel**
- **ASM levels**
- **Shunt radiograph series**
- **Fast-acquisition magnetic resonance imaging (MRI)**

Arriving at a Diagnosis

Q: How do you develop an assessment for Anna?

To arrive at a diagnosis, you must be thorough in your assessment and rely heavily on objective evidence, including objective details from Anna's history, vital signs, extensive and thorough physical examination, laboratory tests, and diagnostic imaging. In children with medical complexity, in addition to acute and chronic medical conditions, clinicians must be aware of their multiple medications and the technology that they rely on, because related complications must be considered in the differential diagnosis.

1. **Interpret key findings from the history, examination, and diagnostic evaluation.**
   - History: Anna has a history of spastic cerebral palsy requiring a VP shunt, intractable epilepsy, chronic respiratory failure requiring tracheostomy tube and ventilation at night, GJ tube feedings, and regular enteral baclofen dosing. Her current symptoms include 3 days of restlessness, thick yellow tracheostomy tube secretions, retching, new oxygen requirement, increased spasticity, and increased seizure activity compared to her baseline.
   - Physical examination: On examination, you note fever, tachycardia and tachypnea, hypoxia, mild increased work of breathing, and increased secretions at the tracheostomy site. Although you were initially concerned about abdominal tenderness, her mother reassures you that this finding is normal for Anna, and you will continue to monitor Anna's abdomen.
   - Diagnostic evaluation: Anna's diagnostic evaluation shows a leukocytosis and respiratory culture with increased WBC count and gram-negative bacteria. Her chest radiograph does not show a focal opacity, and the respiratory viral polymerase chain reaction panel is negative.
2. **Develop the list of findings.**

Q: In addition to her chronic medical conditions, what major findings have you identified for Anna?

- Fever, tachycardia, and leukocytosis with a source of infection, concerning for sepsis
- Increased oxygen requirement and secretions (acute on chronic respiratory failure)
- Increased seizure frequency
- Increased muscle tone (ie, worsening spasticity)
- Concern for feeding tolerance

3. **Revisit the differential diagnosis.**

Q: Reviewing your differential now within the context of Anna's examination and laboratory findings, how does this change your list of likely diagnoses?

Because of the complexity of Anna's case, you decide to systematically consider the evidence that supports or refutes the diagnoses that are highest on your differential.

- Respiratory (tracheitis): Anna has fever, an increased oxygen requirement, increased tracheal secretions, and increased work of breathing. Her diagnostic evaluation is significant for an elevated WBC count with left shift and a positive sputum Gram stain. Tracheitis is usually associated with a normal or nonfocal chest radiograph and can be bacterial or viral. Either infection can trigger reactive airway disease in a patient like Anna, leading to atelectasis and the bibasilar opacities seen on Anna's chest radiograph. These findings can also be attributed to her baseline anatomy and poor expansion causing atelectasis. For all of these reasons, tracheitis remains high on your differential diagnosis.
- Gastrointestinal (GJ) tube malfunction: Anna's nonspecific signs of pain and your initial concern for abdominal pain during your examination warrant consideration of GJ tube malfunction. Anna's mother believes that Anna's reaction to your examination is her baseline reaction and that Anna is not experiencing abdominal pain. Anna also has had normal urine and stool output and no frank vomiting, making GJ malfunction less likely.

- Neurologic
  - VP shunt malfunction, including obstruction or infection: Anna is experiencing increased muscle tone and increased seizure frequency, which can be associated with VP shunt malfunction. The fact that she is otherwise at her baseline mental status and her shunt radiographs and fast-acquisition MRI were both unchanged from baseline make VP shunt malfunction less likely. Also, you suspect Anna's increased seizure frequency is associated with fever, lowering her seizure threshold, and not attributable to VP shunt malfunction. Her increased muscle tone is also likely due to her acute illness and discomfort.
  - Baclofen withdrawal: Baclofen withdrawal can be associated with increased muscle tone, fever, and increased seizure frequency, all of which Anna is experiencing. Arguing against this diagnosis, however, is Anna's normal creatine kinase level and no history of missed baclofen doses.
  - Worsening of baseline epilepsy: It is important to consider a worsening of baseline epilepsy because of Anna's increased seizure frequency; however, because the increase in seizures is acute in the setting of a febrile illness and not chronically worsening, this is less likely.
  - ASM toxicity: Increased seizure frequency can also be seen in ASM toxicity. Patients with this diagnosis, however, often have changes in mental status or recent medication dose changes, neither of which applies to Anna.
- Musculoskeletal
  - Bone or joint infection: Children with complex medical needs are at increased risk for bone or joint infections due to osteopenia, sedentary lifestyles, and skin breakdown, along with relative immunosuppression from poor nutrition and chronic disease. Children presenting with bone or joint infections may have nonspecific signs of infection or pain. Although Anna's presentation is nonspecific, there are no focal joint findings on examination. Although bone or joint infection remains on your differential, it is lower on your list.
  - Pressure ulcers: Patients like Anna, with a history of impaired mobility, are at an increased risk for pressure ulcers. Although Anna does have some sacral erythema, she does not have any ulceration on examination. Blanching erythema indicates a stage 1 pressure injury. This should be addressed, but it is not severe enough to explain Anna's symptoms.
  - Fracture: Having a history of impaired mobility also places patients at an increased risk of fracture. Fractures can present with nonspecific signs of pain. Anna has no focal findings on musculoskeletal examination. Extremity radiographs could be considered during her evaluation.
- Genitourinary: Patients who are chronically incontinent or wear diapers are at an increased risk of UTI. Because Anna is at increased risk of UTI and has nonspecific signs of infection, it is important to consider a UTI as a potential diagnosis. Anna, however, has a negative urinalysis.

Q: Based on your initial differential diagnosis and list of findings, are you able to choose a primary diagnosis to explain Anna's presentation?

Based on Anna's clinical history, physical examination, and laboratory evaluation, her diagnosis is most consistent with tracheitis. Although bacterial colonization of tracheostomy tubes is common, the presence of fever and increased purulent secretions, WBCs on the Gram stain of her tracheal secretions, and lack of evidence of other bacterial or viral infection make tracheitis infection most likely.

4. **Consider admission criteria.**

Q: What are reasonable admission criteria for a patient with medical complexity in whom there is concern for bacterial tracheitis?

- The patient has sepsis.
- The patient has respiratory distress or respiratory support requirements above baseline.
- The patient has seizure activity inadequately controlled by outpatient therapies.
- The patient is unable to tolerate the home feeding regimen.

- There are signs and symptoms of dehydration refractory to acute interventions in the outpatient setting or ED.
- There has been failure of outpatient treatment (eg, antibiotic therapy).

You decide that Anna requires hospitalization related to her increased oxygen requirement and increased work of breathing compared to her home baseline. In addition, her fever, tachycardia, and leukocytosis, along with the fact that she has a suspected source of infection, are concerning for possible sepsis.

CASE FOCUS

Arriving at a Diagnosis: Your Assessment Statement

Anna is an 11-year-old girl with medical complexity who has a history of extreme prematurity and cerebral palsy complicated by dysphagia and reflux with a GJ tube in place, chronic respiratory failure with tracheostomy and ventilator dependence, spasticity, scoliosis, and epilepsy. She presents with fever, increased seizure frequency, increased oxygen requirement, increased tracheal secretion burden, leukocytosis, and generalized discomfort. A Gram stain of her tracheostomy tube secretions shows WBCs and gram-negative bacteria. She likely has bacterial tracheitis.

She requires admission related to her need for increased respiratory support, the potential for rapid decompensation, feed adjustment or intravenous fluids, and antimicrobial treatment.

Developing a Plan for Treatment and Monitoring

Q: What is your plan for further treatment and monitoring?

Children with medical complexity often have complex care plans. Care plans include their acute medical concerns as well as their complex daily care. Given their complex care needs, often involving multiple medications, these children are at greater risk of iatrogenic errors in the hospital setting. When caring for children with medical complexity, it is important to have a systematic way to develop and monitor their treatment plan. This can be done based on body systems or by use of an organized list of findings. For Anna, you prefer to address concerns based on organ systems.

1. **Respiratory**
   - Acute on chronic respiratory failure due to tracheitis: For patients with a tracheostomy tube, supplemental oxygen can be provided via the tracheostomy through an oxygen adapter. Likewise, oxygen can be provided through the ventilator. For patients on supplemental oxygen or other forms of respiratory support, oxygen saturations should be monitored on continuous pulse oximetry. If there is concern about the need for increased ventilatory support, a blood gas analysis may be obtained. Anna's mother and home health nurse have increased Anna's oxygen supplementation, and she is currently stable on her home ventilator, as evidenced by the venous blood gas obtained during her diagnostic evaluation, which was within normal limits.
   - Airway clearance: To help improve oxygenation and facilitate removal of excess pulmonary secretions, there are multiple respiratory treatments including frequent suctioning, inhaled β-agonists and inhaled corticosteroids in the case of increased reactive airway symptoms, and multiple chest physiotherapy and cough augmentation techniques that can be employed.

2. **Neurologic**
   - Epilepsy on multiple ASMs: Although patients with epilepsy should be continued on their outpatient ASMs while hospitalized, there are additional treatment options for patients experiencing increased seizure frequency in the setting of an intercurrent illness. A common option is to provide rescue benzodiazepines as needed for seizures lasting longer than 5 minutes or occurring in clusters; however, clinicians can also consider temporarily increasing the dose of the patient's maintenance ASMs or providing a scheduled long-acting benzodiazepine for the duration of their illness. Consultation with the child's neurologist can help with this decision. Because Anna has only had a slight increase in seizure frequency, it is reasonable to continue her home ASM regimen but to also have a rescue seizure medication plan in place.
   - Shunted hydrocephalus: VP shunts can malfunction in multiple ways, including obstruction, breakage, malposition, and infection. The history and physical examination are important to determine whether VP shunt malfunction exists. Imaging to diagnose shunt malfunction includes MRI or computed tomography to evaluate for increased ventricle size and radiographs to evaluate the length of shunt tubing. To definitively determine the presence of a VP shunt infection, cerebrospinal fluid must be obtained in consultation with neurosurgery. Once a VP shunt has been in place for at least 6 months, the incidence of infection decreases significantly. Because VP shunt malfunction is low on your differential, it is reasonable to not obtain cerebrospinal fluid at this time.
   - Hypertonicity on enteral baclofen: When there is concern that a patient is not receiving their full baclofen dose, it is reasonable to consider baclofen withdrawal as a cause of hypertonicity. Baclofen withdrawal can also present with altered mental status, including agitation and delirium. When Baclofen withdrawal is suspected, a test dose of baclofen can be administered to see if there is symptomatic improvement. Because baclofen withdrawal seems unlikely in Anna, it is reasonable to continue to monitor for signs of withdrawal and not perform this intervention.
   - Immobility: When children with medical complexity are hospitalized, home therapies (speech, physical, occupational) should be continued. It is especially important that patients continue these therapies while sick or further immobilized to prevent regression or deterioration.
3. **Cardiovascular:** Tachycardia can be a result of fever, dehydration, anemia, agitation, or pain. The etiology of tachycardia should be determined by the patient's history, physical examination, and diagnostic workup. Anna's intake and output should be measured carefully.
4. **Fluids, electrolytes, nutrition, and gastroenterology**
   - Retching with GJ feeds: GJ tubes may be used when patients do not tolerate gastric feedings due to severe gastrointestinal reflux or aspiration. Typically, GJ tubes include a port for gastric access and an additional tube to the jejunum for feeding. There is a risk of malfunction with these tubes, including obstruction and malpositioning. The most common imaging modality to check for appropriate tube placement is a radiograph.
   - Reflux: Severe gastrointestinal reflux disease may contribute to poor feeding tolerance in children with medical complexity. Patients experiencing reflux may be treated with acid suppression, and they may also require additional medications for dysmotility.
5. **Infectious disease:** Children with tracheostomies are at risk of tracheitis because their tracheostomies bypass some of the respiratory tract's normal immunologic protection. The diagnosis of tracheitis can be difficult to differentiate from bacterial pneumonia and viral lower respiratory tract infection. There are no national guidelines for the diagnosis and treatment of bacterial respiratory tract infection, so the diagnosis must be made using the best available evidence. Antibiotic therapy must also be chosen carefully, with consideration of both the known bacterial colonization of a particular patient and likely acute infectious organisms. It is important to review Anna's past respiratory cultures for previously treated organisms and their antibiotic susceptibilities. A reasonable empiric regimen may include vancomycin plus a third-generation cephalosporin or ampicillin-sulbactam.
6. **Skin:** Children with medical complexity are at an increased risk of pressure ulcers due to decreased mobility, altered neurologic responsiveness, and the presence of medical devices. Pressure ulcers can cause pain, are an infection risk, and can prolong hospitalization. Pressure ulcers are classified based on their depth and severity. Pressure ulcers should be promptly addressed with appropriate wound care when identified.

CASE FOCUS

Plan for Treatment and Monitoring

- **Respiratory:** You place Anna on her home ventilator settings around the clock and continuous cardiorespiratory monitoring. You escalate her airway clearance regimen to include frequent suctioning, regular chest percussive therapy, cough assist therapy, inhaled hypertonic saline, and inhaled short-acting β-agonist treatments (eg, albuterol). You consult Anna's primary pulmonologist and will consider consulting the intensive care team if Anna's respiratory status decompensates and you are concerned that she needs ventilator adjustment.
- **Neurologic:** You continue Anna's home ASM regimen and order seizure rescue medications and seizure precautions. You also continue her home regimen for spasticity. You will consider consulting the neurology team if Anna continues to have increased seizure frequency to discuss potential ASM adjustment or coverage while she is ill. Additionally, you plan to request that both a physical therapist and an occupational therapist assess Anna during hospitalization and ensure that her home therapy is being maintained to the extent possible.
- **Cardiovascular:** You plan to continue to monitor and check a complete set of Anna's vital signs every 4 hours.
- **Fluids, electrolytes, nutrition/gastrointestinal:** You write orders to continue Anna's home GJ tube feeds and home care regimen. You will closely monitor Anna's intake and output, as her fever and increased work of breathing may contribute to dehydration.
- **Infectious disease:** You order empiric antibiotics (vancomycin and ceftriaxone) to cover for typical community-acquired gram-positive and gram-negative tracheitis organisms and bacteria that have grown in Anna's prior respiratory cultures, particularly any of those that may have antibiotic resistance. You plan to narrow antibiotic therapy based on culture results and antibiotic sensitivities when the results return. Additionally, you plan to trend Anna's fever curve, oxygen requirement, and inflammation markers to monitor for clinical improvement.
- **Skin:** You consult the wound care team for evaluation of Anna's sacral erythema and plan to adjust her home skin care regimen. You order frequent repositioning while she is hospitalized.

Case Resolution

Approximately 36 hours after her admission to the hospital and initiation of broad-spectrum antibiotics to cover both gram-positive and gram-negative organisms, Anna symptoms begin to improve significantly. Her fever resolves, her respiratory status returns to baseline, and her seizure activity decreases. Her tracheal culture results return positive for methicillin-resistant *Staphylococcus aureus*. You transition her to oral antibiotics and determine that she is stable for discharge home to complete a 7-day course.

Discharge Criteria

Q: How do you know when Anna is ready to go home?

Children with medical complexity often have complex discharge needs. It is important to include their primary caregivers and hospital case managers in daily discussions regarding discharge planning. Shared decision-making with the patient's caregivers and primary care pediatrician will be important in determining when the patient is ready for discharge, because caregivers can indicate when they are comfortable caring for the patient in the home setting. Many children with medical complexity have respiratory medications and equipment at home as well as home nursing care; therefore, they are often able to be at home even when they are not fully recovered from their illness.

You can feel comfortable discharging a patient with bacterial tracheitis and medical complexity when the following criteria are met:

- The patient has shown clear clinical improvement.
- The patient's home care resources are in place, including home health nursing and follow-up appointments with the primary care pediatrician and subspecialists.
- The patient no longer requires respiratory support that cannot be provided at home.
- The patient is tolerating an enteral antibiotic that targets their acute infection.
- The patient is tolerating their maintenance medications.
- The patient's seizure disorder is sufficiently controlled such that it can be managed safely by primary caregivers with the available home regimen.
- The patient is tolerating enteral feeds sufficiently to maintain hydration. Families and home health nurses often can adjust or advance home feeding regimens at home as needed with support from the patient's primary care pediatrician.
- The patient has appropriate transportation home. Often children with medical complexity, particularly those with home tracheostomies/ventilators, require ambulance transportation.

Anticipatory Guidance

Q: What instructions should you provide to Anna's caregivers upon discharge?

- Monitor for return of the symptoms that prompted the initial hospital evaluation, including new fevers, new oxygen requirement, or concern for worsening respiratory status.
- If there are new clinical changes (eg, new ventilator settings, adjustments to home medications) determined during hospitalization, follow up to ensure that Anna's primary care physician is aware of changes and can help monitor care at home.

Clinical Pearls

- Children with medical complexity are often unable to communicate in traditional ways; therefore, a broad, detailed history with the input of caregivers is important.
- Children with medical complexity often have abnormal physical examination findings at baseline, so it is important to determine any changes from baseline.
- Given the complexity of these patients, it is important to maintain effective, multidisciplinary care and communication for the duration of their hospitalization. This may include multidisciplinary care conferences and/frequent communication with primary care providers and subspecialists.
- Families and home health nurses usually know patients with complex medical needs best, including what they as caregivers reasonably can and cannot take care of in the home setting.

Documentation Tips

- Document all active diagnoses, as these can often contribute to a more prolonged hospitalization due to medical complexity.
- Documentation of early medication reconciliation inclusive of prescribed and nonprescribed medications and treatments is an important part of care and patient safety.
- The diagnosis of chronic respiratory failure should be documented for patients who are tracheotomy/ventilator dependent or on chronic oxygen.
- The diagnosis of dysphagia and aspiration risk should be documented for patients who are dependent on tube feeding.
- Do not document "history of" a diagnosis if the diagnosis is active. This would signify that the issue has been resolved.

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Wallace AN, McConathy J, Menias CO, Bhalla S, Wippold FJ II. Imaging evaluation of CSF shunts. *AJR Am J Roentgenol*. 2014;202(1):38–53 PMID: 24370127 https://doi.org/10.2214/AJR.12.10270

Appendix

Section I: Pediatric Vital Signs

Table A.1. Normal Pediatric Vital Signs by Age

Age	Heart rate (beats/min)	Blood pressure (mm Hg)[a,b]	Respiratory rate (breaths/min)
0–3 mo	110–160	65–85/45–55	30–60
3–6 mo	100–150	70–90/50–65	30–45
6–12 mo	90–130	80–100/55–65	25–40
1–3 y	80–125	90–105/55–70	20–30
3–6 y	70–115	95–110/60–75	20–25
6–12 y	60–100	100–120/60–75	14–22
>12 y	60–100	100–120/70–80	12–18

[a] Hypotension is a systolic blood pressure <5th percentile and is commonly approximated as <60 mm Hg (for neonates), <70 mm Hg (for ages 1 month–1 year), <70 + (age × 2) mm Hg (for ages 2–10 years), <90 mm Hg (for age >10 years).

[b] Refer to the 2017 American Academy of Pediatrics "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents" for the age, sex, and height-based definitions of normal blood pressure, prehypertension, and hypertension: https://pediatrics.aappublications.org/content/140/3/e20171904

Adapted with permission from Kleinman K, McDaniel L, Molloy M, eds. *The Harriet Lane Handbook*. 22nd ed. Elsevier; 2021.

Section II: Fluids and Hydration

Table A.2. The Centers for Disease Control and Prevention Dehydration Assessment

Symptom	Minimal or no dehydration (<3% loss of body weight)	Mild to moderate dehydration (3%–9% loss of body weight)	Severe dehydration (>9% loss of body weight)
Mental status	Well, alert	Normal, fatigued, restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; may refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in the most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, impalpable
Breathing	Normal	Normal, fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skin fold	Instant recoil	Recoil in <2 seconds	Recoil in >2 seconds
Capillary refill	Normal	Prolonged	Prolonged, minimal
Extremities	Warm	Cool	Cold, mottled, cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Adapted from King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52(RR-16):1–16.

Table A.3. Components of Commonly Used Intravenous Fluids as Compared to Human Plasma

Fluid	Glucose (g/dL)	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg (mg/dL)	Buffer (mEq/L)	Osmolarity (mOsm/L)
Human plasma	0.07–0.11	135–145	95–105	3.5–5.3	4.4–5.2	1.6–2.4	23–30 bicarbonate	308
D5 normal saline (0.9% NaCl)	5	154	154	–	–	–	–	308
D5 half-normal saline (0.45% NaCl)	5	77	77	–	–	–	–	154
D5 0.2 normal saline (0.2% NaCl)	5	34	34	–	–	–	–	78
D5 lactated Ringer solution	5	130	109	4	3	–	28 lactate	273

Abbreviations: Ca^{2+}, calcium; Cl^-, chloride; K^+, potassium; Mg, magnesium; Na^+, sodium; NaCl, sodium chloride.

Table A.4. Holliday-Segar Method of Determining Maintenance Fluid Requirements in Children

Body weight	Daily fluid requirements (mL/kg/d)	Hourly fluid requirements (mL/kg/h)
First 10 kg	100	approximately 4
Second 10 kg	50	approximately 2
Each additional kg	20	approximately 1
Example for a patient weighing 26 kg	(100 mL/kg/d × 10 kg) + (50 mL/kg/d × 10 kg) + (20 mL/kg/d × 6 kg) = 1,620 mL/d	(4 mL/kg/h × 10 kg) + (2 mL/kg/h × 10 kg) + (1 mL/kg/h × 6 kg) = 66 mL/h

Section III: Chest Radiograph Interpretation

Box A.1. Chest Radiograph Interpretation Steps for Beginners

1. Verify the patient's identifiers and the image study date and time.
2. Evaluate image quality.
   a. Penetration: Evaluate the penetration by inspecting the visibility of the spaces between the vertebral bodies. Ideally, the thoracic spine should be visible through the cardiac shadow and below the diaphragm. An underpenetrated film may make pulmonary markings appear more prominent than they are and may hide disease in the left lower lung field. Viewing a lateral film can help with diagnosis in these cases. Overpenetration may prevent visibility of subtle findings (eg, pulmonary nodules).
   b. Inspiration: Ensure the radiograph is an inspiratory film by counting the posterior ribs (8–10 ribs above the diaphragm). Poor inspiratory effort may crowd lung markings and can be misinterpreted as lower lobe pneumonia. Viewing a lateral film can help with visualization of lower lobes.
   c. Rotation: Evaluate for evidence of rotation by looking at symmetry in distance between the spinous process and the medial ends of each clavicle. Significant rotation will alter the appearance of the cardiac silhouette, the hila, and the hemidiaphragms.
   d. Magnification: Anteroposterior films will magnify the heart slightly. The cardiac size on posteroanterior films is more accurate.
   e. Angulation: The medial end of the clavicle should superimpose on the third or fourth rib. An angulated film will project anterior structures higher on the radiograph than posterior structures.
3. View a lateral image to review the spine, diaphragms and posterior costophrenic sulci, anterior/retrosternal clear space (in older children), and retrocardiac space.
4. View posteroanterior or anteroposterior image to evaluate the following:
   a. Bones and soft tissues for abnormalities.
   b. Mediastinum. In infants and young children, the thymus should make the mediastinum appear large compared to older children and adolescents.
   c. Cardiac silhouette and cardiomegaly (by measuring the cardiothoracic ratio).
   d. Diaphragms, including air below diaphragms. The right diaphragm is normally higher than the left diaphragm. Small pleural effusions may be appreciated by evaluating for blunting of the costophrenic sulcus.
   e. Airway and lungs: Airway (including trachea and bronchi), hila (left hilum is slightly higher than the right), lung parenchyma, and lung pleura. Chest radiograph densities may be recognized as atelectasis based on a shift of the trachea, heart, or interlobar fissures toward the area of atelectasis. Additionally, the hemidiaphragm will commonly be displaced upward in atelectasis. The contralateral lung may also be overinflated to compensate for the volume loss.
5. Review radiologist interpretation as soon as it is available.

Derived from Herring W. *Learning Radiology: Recognizing the Basics*. 4th ed. Elsevier; 2019.

Section IV: Systemic Inflammatory Response Syndrome and Sepsis

It is important to note that adult definitions of sepsis changed in 2016 (Sepsis-3), with *sepsis* defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and *septic shock* subsequently defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality. However, formal revisions to the 2005 Goldstein pediatric sepsis definitions have not yet been adopted, and so this publication has continued to utilize the 2005 definitions.

Box A.2. Definitions of Systemic Inflammatory Response Syndrome, Sepsis, Severe Sepsis, and Septic Shock

- Systemic inflammatory response syndrome (SIRS): SIRS is defined as the presence of at least 2 of the following 4 criteria, one of which must be abnormal temperature or leukocyte count. The age-based SIRS criteria for heart rate, leukocyte count, and respiratory rate can be found in Table A.5.
  - Core temperature of >38.5 °C (101.3 °F) or <36 °C (96.8 °F).
  - Tachycardia, which is defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or an otherwise unexplained persistent elevation over a ½- to 4-hour time period.
  - For children <1 year, an abnormal heart rate may also be represented by bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, blocker drugs, or congenital heart disease; or an otherwise unexplained persistent depression over a ½-hour time period.
  - Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
  - Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or 10% immature neutrophils.
- Sepsis: SIRS in the presence of or as a result of a suspected or proven infection.
- Severe sepsis: Sepsis plus 1 of the following: cardiovascular organ dysfunction *or* acute respiratory distress syndrome *or* 2 or more other organ dysfunctions. Organ dysfunctions are defined in Table A.6.
- Septic shock: Sepsis and cardiovascular organ dysfunction, as defined in Table A.6.

Adapted from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8.

Table A.5. Age-Based Systemic Inflammatory Response Syndrome Criteria

Age group	Heart rate (beats/min)		Respiratory rate (breaths/min)	WBC count ($\times 10^3/\mu L$ [$\times 10^9/L$])
	Tachycardia	Bradycardia		
0 d–1 wk	>180	<100	>50	>34,000/μL (34 × 10^9/L)
1 wk–1 mo	>180	<100	>40	< 5,000/μL or > 19,500/μL (< 5 × 10^9/L or > 19.5 × 10^9/L)
1 mo–1 y	>180	<90	>34	< 5,000/μL or > 17,500/μL (< 5 × 10^9/L or > 17.5 × 10^9/L)
>1–5 y	>140	NA	>22	< 6,000/μL or > 15,500/μL (< 6 × 10^9/L or > 15.5 × 10^9/L)
6–12 y	>130	NA	>18	< 4,500/μL or > 13,500/μL (< 4.5 × 10^9/L or > 13.5 × 10^9/L)
13 to <18 y	>110	NA	>14	< 4,500/μL or > 11,000/μL (< 4.5 × 10^9/L or > 11 × 10^9/L)

Abbreviations: NA, not applicable; WBC, white blood cell.

Adapted from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8.

Table A.6. Definitions of Organ Dysfunction

Organ system	Definition of dysfunction
Cardiovascular	One of the following criteria despite administration of isotonic intravenous fluid bolus ≥40 mL/kg/h: ● A decrease in blood pressure (hypotension) <5th percentile for age or systolic blood pressure <2 SD below normal for age ● Need for vasoactive drug to maintain blood pressure in normal range (dopamine >5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) ● Two of the following: — Unexplained metabolic acidosis (base deficit >5.0 mEq/L [5 mmol/L]) — Increased arterial lactate level >2 times upper limit of normal — Oliguria (as defined by urine output <0.5 mL/kg/h) — Prolonged capillary refill (>5 seconds) — Core to peripheral temperature gap of >3 °C (5.4 °F)
Respiratory	Any of the following: ● Pao_2/Fio_2 <300 in absence of cyanotic heart disease or preexisting lung disease ● $Paco_2$ >65 torr or 20 mm Hg over baseline $Paco_2$ ● Proven need or >0.5 Fio_2 to maintain saturation ≥92% ● Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic	Either of the following: ● GCS score ≤11 ● Acute change in mental status with a decrease GCS score ≥3 points from abnormal baseline
Hematologic	Either of the following: ● Platelet count <80 × 10^3/µL (80 × 10^9/L) or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients) ● INR >2
Renal	Serum creatinine level ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine level
Hepatic	Either of the following: ● Total bilirubin level ≥4 mg/dL (not applicable for newborns) ● ALT level 2 times upper limit of normal for age

Abbreviations: ALT, alanine aminotransferase; Fio_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; INR, international normalized ratio.

Adapted from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8.

Section V: Common Procedures

Table A.7. Selected Medical Procedures in Pediatric Hospital Medicine

Procedure	Indications	Contraindications or cautions	Risks	Important considerations
Bladder catheterization[a]	The need to collect a sterile urine sample for analysis and culture; to alleviate urinary retention; to perform bladder irrigation; to measure postvoid residual urine volumes; to monitor urinary output	Pelvic trauma, recent reconstructive surgery of the bladder or urethra, urethral stricture	UTI; hematuria; urethral stricture development; with indwelling catheter, urinary obstruction from sediment clogging tubing; creation of false passage from urethral tear or perforation	Sterile technique; adequate lubrication and anesthetic jelly should be used to minimize pain with the procedure.
Incision and drainage[a]	Drainage of purulent material from an abscess cavity or to obtain fluid for diagnostic studies (ie, Gram stain and culture)	Nonfluctuant cellulitis; surgical consultation recommended for abscesses on the face or hands (except paronychia)	Pain, bleeding, injury to adjacent structures, recurrence of abscess, scar or fistula formation	Use of procedural sedation may be needed.
LP[a]	To obtain CSF sample for diagnostic studies, to measure opening pressure or therapeutically reduce intracranial pressure	Overlying skin/tissue infection; risk of herniation based on clinical status or imaging (midline shift, posterior fossa mass, loss of cisterns); coagulopathy; brain abscess; unstable vital signs	Pain at the site, spinal epidural or subdural hematoma, post-LP headache (postural), meningitis from introduction of bacteria into the CSF, brain herniation	Sterile procedure; use of local anesthetic is recommended; lateral recumbent position necessary for opening pressure; to decrease the risk of post-LP headache, maintain the needle's bevel parallel to the long axis of the spine.
PICC	Difficulty maintaining IV access; need for prolonged IV access (eg, for prolonged antibiotic therapy); need for a central venous access to deliver IV nutrition, need to administer certain medications, or perform frequent blood draws	Cellulitis or burn over insertion site, injury or thrombosis of proposed vein, caution should be used for patients in hypercoagulable states or with bleeding diathesis.	Thrombosis, air embolism, bleeding, infection, pneumo- or hydrothorax, guidewire fragment embolus, injury to other structures, cardiac dysrhythmias	Sterile procedure; insertion facilitated by use of procedural sedation and US guidance; placement confirmed with fluoroscopy or radiography

Table A.7. Selected Medical Procedures in Pediatric Hospital Medicine *(continued)*

Procedure	Indications	Contraindications or cautions	Risks	Important considerations
Procedural sedation	Need for anxiolysis or sedation to facilitate medical procedures (eg, incision and drainage, PICC insertion, dressing changes, echocardiogram)	Caution is advised in patients with preexisting respiratory, cardiac, or neurologic conditions.	Cardiac and respiratory depression, hypotension, nausea/vomiting; paradoxical reaction, urinary retention, or laryngospasm, depending on the agent	Providers should follow institutional guidelines for sedation credentialing, medication administration, and patient monitoring.

Abbreviations: CSF, cerebrospinal fluid; IV, intravenous; LP, lumbar puncture; PICC, peripherally inserted central catheter; US, ultrasound; UTI, urinary tract infection.

[a] For the detailed steps of performing these procedures, the American Academy of Pediatrics online video resource *Common Pediatric Medical Procedures* is available at https://shop.aap.org/common-pediatric-medical-procedures-video-series.

Derived from Fowler GC. *Pfenninger and Fowler's Procedures for Primary Care*. 4th ed. Elsevier; 2020; Caleon L, McFarlin A, Zeretzke-Bien CM. Procedure pearls. In: Zeretzke-Bien C, Swan T, Allen B, eds. *Quick Hits for Pediatric Emergency Medicine*. Springer; 2018:63–76.

Section VI: Rashes

Table A.8. Characterization of Rashes

Characteristic	Examples
Morphology	Macule, plaque, nodule, bullae, pustule, vesicle, scale, petechiae, purpura
Configuration	Linear, annular, nummular, target, serpiginous, reticulated, herpetiform, zosteriform
Color	Red/erythematous, yellow/jaundiced, violet/violaceous, black, silver Note: Rashes will present differently in different skin tones; avoid using descriptors that may only be accurate for a specific skin tone
Distribution	Random or patterned, symmetric or asymmetric, glove and stocking
Texture	Verrucous, lichenification, induration, umbilicated, xanthomas, desquamation
Progression	Centripetal spread: extremities to trunk; centrifugal spread: trunk to extremities; descending: head to toe; ascending: feet to head
Blanching	Erythema that diminishes with pressure Note: Blanching may not be observed in patients with darker skin tones
Other clinical signs	Dermatographism, Darier sign, Nikolsky sign, Auspitz sign, Koebner phenomenon

Derived from Bender NR, Chiu YE. Dermatologic evaluation of the patient. In: Kliegman RM, St Geme J. *Nelson Textbook of Pediatrics*. 21st ed. Elsevier; 2020:3441–3451.e1; Kang JH. Febrile Illness with skin rashes. *Infect Chemother*. 2015;47(3):155–166.

Section VII: Adolescent History

Table A.9. The HEADSS Assessment: Home/safety, Education/employment, peer group Activities/eating, Drugs, Sexuality, Suicide/depression

Components	Example statements/questions
Introduction	I am going to ask you some very personal questions. I ask these questions to every teenaged patient I care for. The things you tell me are private unless you give me permission to share them, or unless I feel that you are in any danger based on your answers.
Home/safety	Where do you live? Who lives at home with you? Is there anyone at home you can talk to about things that are bothering you? Is there any violence at home? Have you been the victim of violence at home? What time do you go to sleep and wake up in the morning? Do you often wake up in the middle of the night? Is your sleep refreshing? Do you feel safe at home? Are there any guns or other weapons at home? Do you have access to them? Do you feel safe in your neighborhood? From 0% to 100% of the time, how often do you wear your seatbelt in the car? If you drive, how often do you use your phone while driving? Have you ridden in the car with someone who was drunk or high? Do you ever feel the need to carry a weapon to protect yourself?
Education and employment	Where do you go to school? What grade are you in? Do you feel comfortable at school? Have you ever been bullied at school or online? Do you have a group of friends at school, or do you prefer to be alone? What are your grades like? Have there been any recent changes in your grades? What do you want to do after graduating high school? Do you have a job? If so, what is your workplace like?
Activities/eating	What do you do for fun? What do you and your friends do together? Do you play sports or participate in any clubs? Do you participate in any religious or spiritual activities? How much time do you spend online? What do you do online? How do you feel about your weight and body shape? Has your weight changed recently? What is your diet like? Have you ever dieted or intentionally tried to lose weight? What do you do for exercise? Have you ever felt like your eating was out of control? Have you ever made yourself vomit?
Drugs	Do any of your friends or family members smoke cigarettes, vape, use drugs, or drink alcohol? Have you ever tried any of those things? If so, how often? What about pills or medications that are not prescribed to you? (For patients who endorse substance use, consider the use of the CRAFFT[a] questionnaire to screen for drug and alcohol abuse.)

Table A.9. The HEADSS Assessment: Home/safety, Education/employment, peer group Activities/eating, Drugs, Sexuality, Suicide/depression *(continued)*

Components	Example statements/questions
Sexuality	How would you describe your gender identify? What pronouns (he/she/they) do you use? Many people your age begin to have attractions physically or romantically. Have you thought about that? Who are you attracted to? Have you ever had sex? What sort of contact was it? Oral, vaginal, or anal? From 0% to 100%, how many of your encounters are protected? What do you use for protection? Has anyone ever forced you to do something you did not want to do? Are you currently in a relationship? Do you feel safe around your partner? Have you ever traded money or drugs for sex?
Suicidality/ depression	Do you feel stressed, sad, or anxious? Have you ever been so sad that you thought about ending your life? Have you ever tried to end your life? Do you ever cut yourself? (For patients who endorse depressed mood, hopelessness, or anhedonia, consider the use of PHQ-9[b] to screen for depression.)

Abbreviations: CRAFFT, Car, Relax, Alone, Forget, Family/Friends, Trouble; PHQ, Patient Health Questionnaire.

[a] The CRAFFT questionnaire is a brief screening tool for drug and alcohol abuse and is available at https://crafft.org.

[b] PHQ-9 is a screening tool for depression and can be accessed at https://www.phqscreeners.com. A version of PHQ-9 modified for adolescents can be accessed at https://www.aacap.org/App_Themes/AACAP/docs/member_resources/toolbox_for_clinical_practice_and_outcomes/symptoms/GLAD-PC_PHQ-9.pdf.

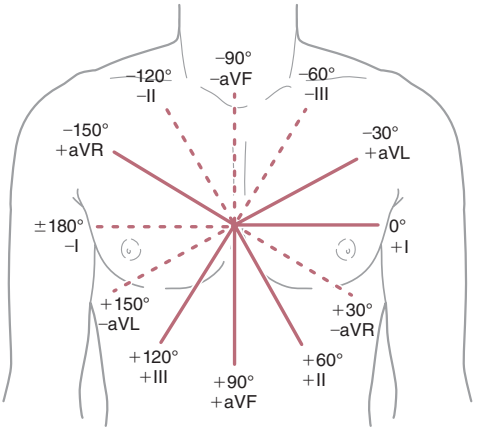
Derived from Doukrou M, Segal TY. Fifteen-minute consultation: communicating with young people—how to use HEADSSS, a psychosocial interview for adolescents. *Archives of Disease in Childhood—Education and Practice* 2018;103:15–19; Goldenring JM, Rosen DS. Getting into adolescent heads: an essential update. *Contemp Pediatr*. 2004;21(1):64–90.

Section VIII: Electrocardiogram Primer

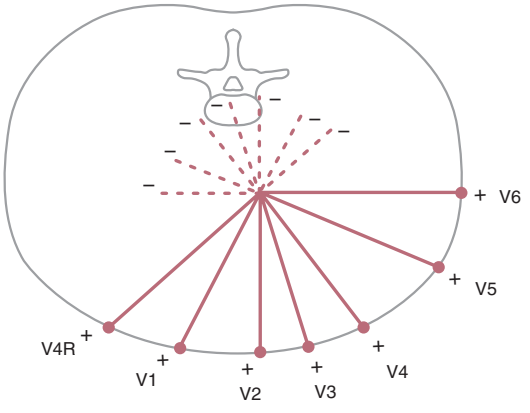
Box A.3. Primer for Electrocardiogram Interpretation

Electrocardiogram basics

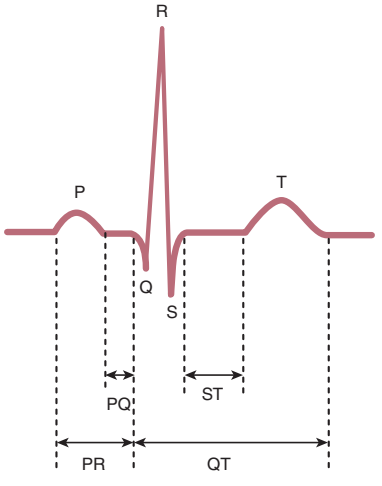
- Hexaxial reference system: Six limb leads (I, II, III, aVR, aVL, aVF) provide information in the left-right and superior-inferior relationships.



- Horizontal reference system: Six precordial leads (V1–V6) provide information about the anterior-posterior and left-right relationships.



- The various ECG waveforms (P wave, QRS complex, T wave), intervals (PR and QT), and segments (PQ and ST) are shown in the following graphic.



Box A.3. Primer for Electrocardiogram Interpretation *(continued)*

Evaluation of heart rhythm

Normal sinus rhythm is indicated by

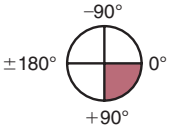
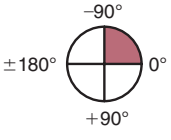
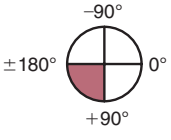
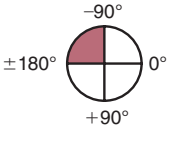
- P wave prior to each QRS complex with constant PR interval
- Normal P wave axis, which is defined as between 0 and +90 degrees (ie, P waves are upright in leads I and aVF)

Determination of heart rate

- Standard ECG speed is 25 mm/s; therefore, 1 mm (small square) = 0.04 seconds and 5 mm (big square) = 0.2 seconds
- Heart rate (beats per minute) can be calculated by dividing 60 by the RR interval (in seconds)

Evaluation of QRS axis and T wave axis

- QRS axis: The QRS axis is determined using the hexaxial reference system.
  - First step: The axis quadrant can be determined based on positive or negative R wave deflections in leads I and aVF.

R Wave Deflection		QRS Axis	Interpretation
Lead I	aVF		
+	+	0 to +90 	Normal
+	−	0 to −90 	Left axis deviation (LAD)
−	+	+90 to ±180 	Right axis deviation (RAD)
−	−	−90 to ±180 	Indeterminate axis

(continued)

Box A.3. Primer for Electrocardiogram Interpretation *(continued)*

Evaluation of QRS axis and T wave axis *(continued)*

  - Second step: Find the lead with an equiphasic QRS complex (ie, the height of the R wave and the depth of the S wave are equivalent). Using the hexaxial reference system diagram and the axis quadrant as determined by step 1 above, the QRS axis can be approximated as perpendicular to the equiphasic lead. For example, if the axis quadrant is 0 to +90 and lead aVL is equiphasic, the axis is +60°.
  - Normal QRS axis values
    - Age 1 week to 1 month: +110° (range +30° to +180°)
    - Age 1 month to 3 months: +70° (range +10° to +125°)
    - Age 3 months to 3 years: +60° (range +10° to +110°)
    - Age >3 years: +60° (range +20° to +120°)
- The T wave axis is determined in a similar manner to the QRS axis. The normal T wave axis is 0 to +90 degrees; therefore, the T wave should be positive in leads I and aVF.

Duration of waves and intervals

- PR interval
  - Short PR interval is seen in preexcitation (eg, WPW syndrome), Duchenne muscular dystrophy, glycogen storage disorders, and Friedrich ataxia.
  - Prolonged PR interval (first-degree AV block) is seen in myocarditis, some congenital heart defects, and hyperkalemia.
  - Variable PR interval is seen in Wenckebach (Mobitz type 1) second-degree AV block.
- QRS duration: Prolonged QRS is indicative of ventricular conduction disturbances (eg, BBB and WPW syndrome).
- Corrected QT interval: $QTc = QT/\sqrt{RR}$. Normal QTc is ≤0.44 seconds in children 6 months and older, ≤0.47 seconds in the first week after birth, and ≤0.45 seconds from age 1 week to 6 months.
  - Prolonged QT is seen in LQTS, hypocalcemia, myocarditis, and cardiomyopathy.
  - Drugs known to prolong the QT interval include antiarrhythmics, antipsychotics, antidepressants (eg, tricyclics), organophosphates, and antibiotics (eg, azithromycin).

Atrial enlargement

- RAE is suggested by P wave amplitude >3 mm in leads II, V1, or V2.
- LAE is suggested by P wave duration >0.1 seconds in any lead.
- Bilateral atrial enlargement is when both RAE and LAE criteria are met.

Ventricular hypertrophy

- VH produces abnormalities in the QRS axis, QRS voltages, R/S ratio, and T wave axis.
- RVH (neonate) is suggested by a QRS with RAD (>180°), persistent upright T wave in V1 after 3 days after birth, S wave in lead I that is ≥12 mm, R wave in V1 that is >10 mm with no S wave, R wave in aVR that is ≥8 mm, or a qR pattern in V1.
- RVH (nonneonate) is suggested by RAD; increased R voltages in leads V1, V2, or aVR; increased S voltages in lead I and V6; upright T wave in lead V1 (for ages 3 days to 5 years); presence of Q wave in lead V1; high R/S ratio in leads V1 or V2; or R/S ratio <1 in lead V6.
- LVH is suggested by LAD; increased R voltages in leads I, II, III, aVL, aVF, V5, or V6; increased S wave amplitudes in leads V1 or V2; Q wave in V5 or V6 that is >5 mm along with tall symmetric T waves; deep Q waves in the inferior leads; or an abnormal R/S ratio favoring LVH.

Box A.3. Primer for Electrocardiogram Interpretation *(continued)*

Q waves

- Normal Q waves are narrow (0.02 seconds) and < 5 mm in amplitude in the left precordial leads and aVF. They are normally absent in the right precordial leads.
- Deep or wide Q waves may suggest LVH, myocardial infarction, or myocardial fibrosis.
- Q waves in the right precordial leads may suggest certain congenital heart anomalies or RVH.

ST segment

- The ST segment should be isoelectric but may appear abnormal in early repolarization.
- Early repolarization is characterized by elevated ST segments in leads with upright T waves and depressed ST segments in leads with inverted T waves. Terminal slurring of the QRS complex, with or without a "fish-hook" pattern in V4, and asymmetric T waves may be present. In general, the height of the ST segment elevation is < ¼ of the height of the T wave (ie, ST to T wave ratio < 0.25).
- Pathologic ST segment changes may be seen in myocarditis, pericarditis, myocardial ischemia, or myocardial infarction.

Conduction disturbance

- RBBB is suggested by RAD, prolonged QRS with QRS terminal slurring (ie, the prolonged QRS complex is related to prolongation in the S or R' wave), and ST depression with T wave inversion. (Note: RSR' in V1 is normal in infants, toddlers, and young children if QRS duration and voltage are normal.)
- WPW syndrome is diagnosed by a shortened PR for age, the presence of a delta wave (ie, slurring of the initiation portion of the QRS complex), and a wide QRS duration for age.

Abbreviations: AV, atrioventricular; BBB, bundle branch block; ECG, electrocardiogram; LAD, left axis deviation; LAE, left atrial enlargement; LQTS, long QT syndrome; LVH, left ventricular hypertrophy; RAD, right axis deviation; RAE, right atrial enlargement; RBBB, right bundle-branch block; RVH, right ventricular hypertrophy; VH, ventricular hypertrophy; WPW, Wolff-Parkinson-White.

(a) Box derived from Electrocardiography. In: Park MK, Salamat M, eds. *Park's The Pediatric Cardiology Handbook*. 6th ed. Elsevier; 2022:38–69; (b) images adapted with permission from Vectorial approach. In: Park MK, Gunteroth WC, eds. *How to Read Pediatric ECGs*. 4th ed. Mosby; 2006: 1–9; Basic Measurements. In: Park MK, Guntheroth WG, eds. *How to Read Pediatric ECGs*. 4th ed. Mosby; 2006: 10–34.

Table A.10. Pediatric Electrocardiogram Reference Values by Age

Age	Heart rate (beats/min)	QRS axis (degrees)	PR interval (ms)	Q wave in III (mm)	Q wave in V_6 (mm)	R wave in V_1 (mm)	S wave in V_1 (mm)	R/S ratio in V_1	R wave in V_6 (mm)	S wave in V_6 (mm)	R/S ratio in V_6	S wave in V_1 plus R wave in V_6 (mm)	R wave plus S wave in V_4 (mm)
<1 d	94–155 (122)	58–168 (+135)	79–160 (107)	5	2	5–27 (14)	0.5–23 (9)	0.2–9.8 (2.3)	0–12 (5)	0.2–10 (4)	0.5–9 (2.5)	2–27 (13)	12–52 (32)
2–3 d	91–158 (124)	65–171 (+134)	81–139 (108)	5	2	5–27 (15)	0.5–21 (10)	0.2–6.0 (2.0)	0.1–12 (5)	0.2–10 (3)	0.5–11 (3)	2–28 (14)	17–53 (33)
4–7 d	90–166 (128)	76–168 (+133)	75–137 (104)	5	3	3–25 (13)	0.5–17 (7)	0.2–9.8 (2.8)	0.5–12 (5)	0.4–10 (4)	0.5–10 (2.5)	2–25 (12)	13–48 (31)
8–30 d	106–182 (148)	65–159 (110)	73–138 (101)	4	3	3–22 (11)	0.5–12 (4)	1.0–7.0 (2.9)	3–17 (8)	0.2–10 (3)	0.5–12 (4)	3–22 (12)	15–48 (31)
1–3 mo	120–179 (149)	31–115 (75)	73–130 (98)	5	3	3–19 (10)	0.5–13 (5)	0.3–7.5 (2.3)	5–22 (12)	0.3–7 (3)	0.5–12 (4.5)	6–29 (17)	22–58 (36)
4–6 mo	105–185 (142)	7–105 (60)	74–145 (106)	7	3	3–20 (10)	0.5–17 (6)	0.2–6.0 (2.4)	6–23 (14)	0.2–10 (3)	0.5–18 (6.5)	7–35 (19)	21–58 (38)
7–12 mo	107–168 (132)	7–98 (54)	73–156 (156)	6	3	2–20 (9)	0.5–18 (7)	0.1–3.9 (1.8)	6–23 (13)	0.2–8 (2)	0.5–22 (8)	7–33 (19)	21–50 (34)
1–3 y	90–151 (119)	8–100 (55)	82–148 (114)	5	3	3–18 (9)	1–21 (9)	0.1–4.2 (1.4)	6–23 (14)	0.1–7 (2)	0.5–28 (9.5)	7–38 (22)	17–48 (33)
4–5 y	73–137 (108)	7–104 (55)	85–161 (118)	4	3	2–18 (8)	2–22 (10)	0–2.8 (0.9)	9–25 (15)	0.1–6 (2)	0.8–30 (11)	13–42 (25)	17–52 (35)
6–8 y	65–133 (100)	10–140 (66)	90–164 (124)	3	5	1–13 (7)	3–24 (12)	0–2.0 (0.8)	9–27 (17)	0.1–4 (1)	1–30 (12)	13–47 (28)	20–53 (36)
9–12 y	63–129 (92)	9–115 (61)	87–171 (128)	3	3	0.5–10 (6)	3–26 (12)	0–1.9 (0.6)	10–26 (17)	0–4 (1)	2–33 (14)	15–45 (28)	21–50 (35)
13–16 y	66–120 (86)	11–133 (58)	92–175 (135)	3	3	0.5–10 (5)	3–22 (11)	0–1.8 (0.5)	7–23 (15)	0–4 (1)	2–39 (15)	11–42 (25)	12–49 (29)

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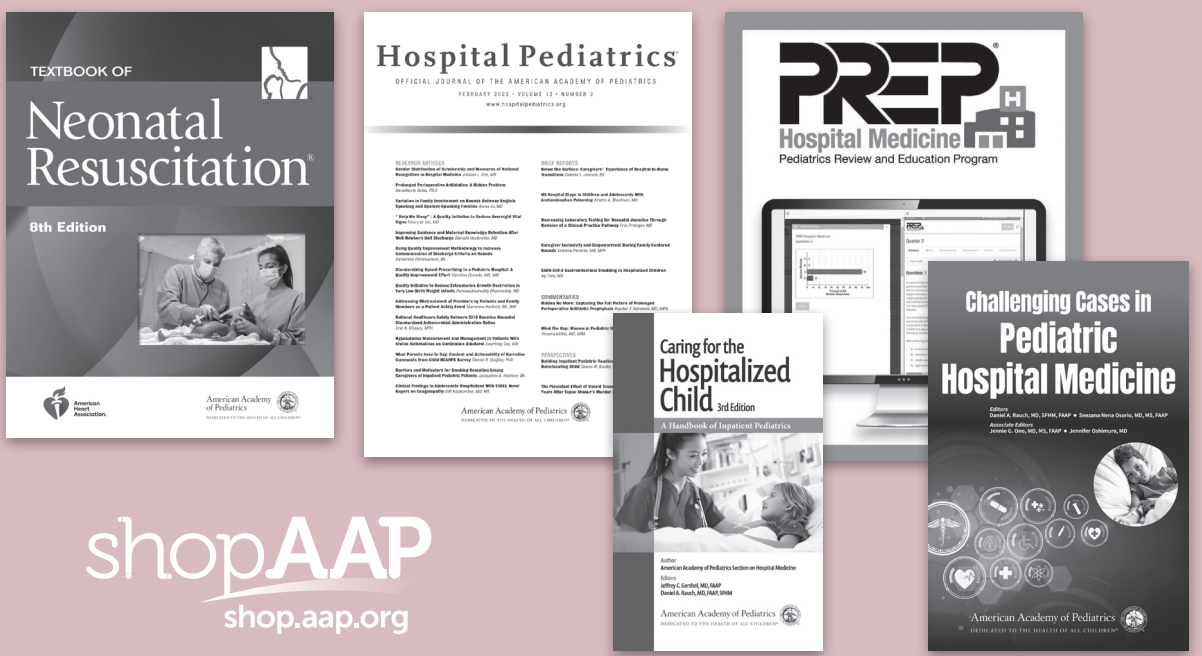

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