Derek S. Wheeler
Hector R. Wong
Thomas P. Shanley
Editors

Pediatric Critical Care Medicine

Volume 3: Gastroenterological, Endocrine, Renal, Hematologic, Oncologic and Immune Systems

Second Edition

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For Cathy, Ryan, Katie, Maggie, and Molly

"You don't choose your family. They are God's gift to you…"

Desmond Tutu

Foreword to the First Edition

The practitioner of *Pediatric Critical Care Medicine* should be facile with a broad scope of knowledge from human developmental biology, to pathophysiologic dysfunction of virtually every organ system, and to complex organizational management. The practitioner should select, synthesize and apply the information in a discriminative manner. And finally and most importantly, the practitioner should constantly "listen" to the patient and the responses to interventions in order to understand the basis for the disturbances that create life-threatening or severely debilitating conditions.

Whether learning the specialty as a trainee or growing as a practitioner, the pediatric intensivist must adopt the mantle of a perpetual student. Every professional colleague, specialist and generalist alike, provides new knowledge or fresh insight on familiar subjects. Every patient presents a new combination of challenges and a new volley of important questions to the receptive and inquiring mind.

A textbook of pediatric critical care fills special niches for the discipline and the student of the discipline. As an historical document, this compilation records the progress of the specialty. Future versions will undoubtedly show advances in the basic biology that are most important to bedside care. However, the prevalence and manifestation of disease invariably will shift, driven by epidemiologic forces, and genetic factors, improvements in care and, hopefully, by successful prevention of disease. Whether the specialty will remain as broadly comprehensive as is currently practiced is not clear, or whether sub-specialties such as cardiac- and neurointensive care will warrant separate study and practice remains to be determined.

As a repository of and reference for current knowledge, textbooks face increasing and imposing limitations compared with the dynamic and virtually limitless information gateway available through the internet. Nonetheless, a central standard serves as a defining anchor from which students and their teachers can begin with a common understanding and vocabulary and thereby support their mutual professional advancement. Moreover, it permits perspective, punctuation and guidance to be superimposed by a thoughtful expert who is familiar with the expanding mass of medical information.

Pediatric intensivists owe Drs. Wheeler, Wong, and Shanley a great debt for their work in authoring and editing this volume. Their effort was enormously ambitious, but matched to the discipline itself in depth, breadth, and vigor. The scientific basis of critical care is integrally woven with the details of bedside management throughout the work, providing both a satisfying rationale for current practice, as well as a clearer picture of where we can improve. The coverage of specialized areas such as intensive care of trauma victims and patients following congenital heart surgery make this a uniquely comprehensive text. The editors have assembled an outstanding collection of expert authors for this work. The large number of international contributors is striking, but speaks to the rapid growth of this specialty throughout the world.

We hope that this volume will achieve a wide readership, thereby enhancing the exchange of current scientific and managerial knowledge for the care of critically ill children, and stimulating the student to seek answers to fill our obvious gaps in understanding.

Chicago, IL, USA — Thomas P. Green
New Haven, CT, USA — George Lister

Preface to the Second Edition

The specialty of pediatric critical care medicine continues to grow and evolve! The modern PICU of today is vastly different, even compared to as recently as 5 years ago. Technological innovations in the way we approach the diagnosis and treatment of critically ill children have seemingly changed overnight in some cases. Efforts at prevention and improvements in care of patients prior to coming to the PICU have led to better outcomes from critical illness. The outcomes of conditions that were, even less than a decade ago, almost uniformly fatal have greatly improved. Advances in molecular biology have led to the era of personalized medicine – we can now individualize our treatment approach to the unique and specific needs of a patient. We now routinely rely on a vast array of condition-specific biomarkers to initiate and titrate therapy. Some of these advances in molecular biology have uncovered new diseases and conditions altogether! At the same time, pediatric critical care medicine has become more global. We are sharing our knowledge with the world community. Through our collective efforts, we are advancing the care of our patients. Pediatric critical care medicine will continue to grow and evolve – more technological advancements and scientific achievements will surely come in the future. We will become even more global in scope. However, the human element of what pediatric critical care providers do will never change [1]. I remain humbled by the gifts that I have received in my life. And I still remember the promise I made to myself so many years ago – the promise that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for these gifts. It is my sincere hope that the second edition of this textbook will educate a whole new generation of critical care professionals, and in so-doing help me continue my promise.

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Cincinnati, OH, USA Derek S. Wheeler, MD, MMM

Preface to the First Edition

Promises to Keep

The field of critical care medicine is growing at a tremendous pace, and tremendous advances in the understanding of critical illness have been realized in the last decade. My family has directly benefited from some of the technological and scientific advances made in the care of critically ill children. My son Ryan was born during my third year of medical school. By some peculiar happenstance, I was nearing completion of a 4-week rotation in the Newborn Intensive Care Unit. The head of the Pediatrics clerkship was kind enough to let me have a few days off around the time of the delivery – my wife Cathy was 2 weeks past her due date and had been scheduled for elective induction. Ryan was delivered through thick meconium-stained amniotic fluid and developed breathing difficulty shortly after delivery. His breathing worsened over the next few hours, so he was placed on the ventilator. I will never forget the feelings of utter helplessness my wife and I felt as the NICU Transport Team wheeled Ryan away in the transport isolette. The transport physician, one of my supervising third year pediatrics residents during my rotation the past month, told me that Ryan was more than likely going to require ECMO. I knew enough about ECMO at that time to know that I should be scared! The next 4 days were some of the most difficult moments I have ever experienced as a parent, watching the blood being pumped out of my tiny son's body through the membrane oxygenator and roller pump, slowly back into his body (Figs. 1 and 2). I remember the fear of each

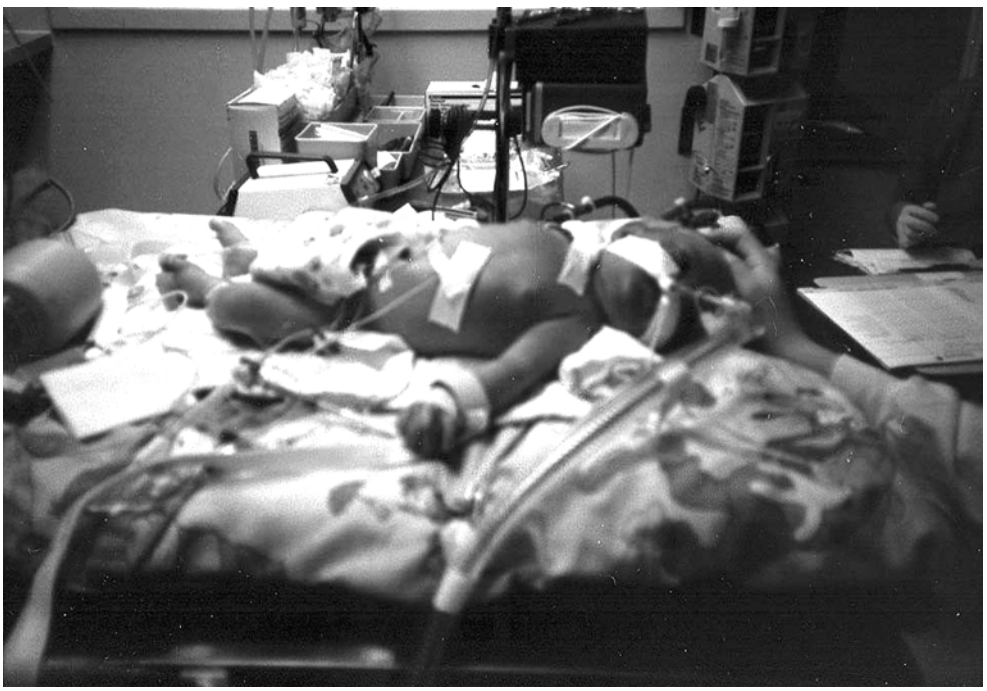

Fig. 1

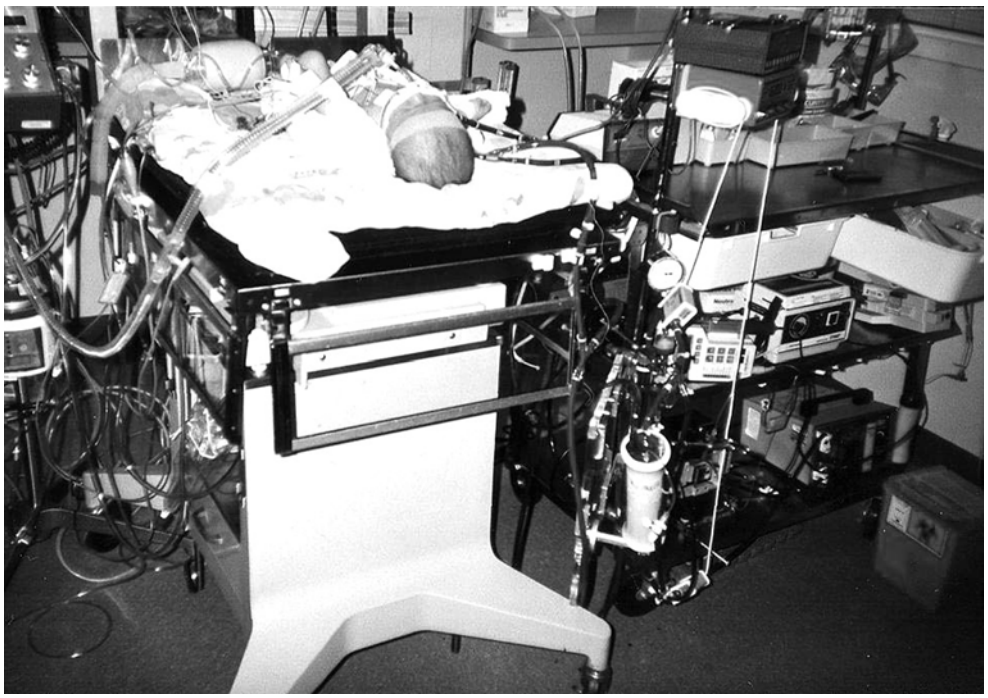

Fig. 2

day when we would be told of the results of his daily head ultrasound, looking for evidence of intracranial hemorrhage, and then the relief when we were told that there was no bleeding. I remember the hope and excitement on the day Ryan came off ECMO, as well as the concern when he had to be sent home on supplemental oxygen. Today, Ryan is happy, healthy, and strong. We are thankful to all the doctors, nurses, respiratory therapists, and ECMO specialists who cared for Ryan and made him well. We still keep in touch with many of them. Without the technological advances and medical breakthroughs made in the fields of neonatal intensive care and pediatric critical care medicine, things very well could have been much different. I made a promise to myself long ago that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for the gifts that we, my wife and I, have been truly blessed. It is my sincere hope that this textbook, which has truly been a labor of joy, will educate a whole new generation of critical care professionals, and in so-doing help make that first step towards keeping my promise.

Cincinnati, OH, USA Derek S. Wheeler, MD, MMM

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With any such undertaking, there are people along the way who, save for their dedication, inspiration, and assistance, a project such as this would never be completed. I am personally indebted to Michael D. Sova, our Developmental Editor, who has been a true blessing. He has kept this project going the entire way and has been an incredible help to me personally throughout the completion of this textbook. There were days when I thought that we would never finish – and he was always there to lift my spirits and keep me focused on the task at hand. I will be forever grateful to him. I am also grateful for the continued assistance of Grant Weston at Springer. Grant has been with me since the very beginning of the first edition of this textbook. He has been a tremendous advocate for our specialty, as well as a great mentor and friend. I would be remiss if I did not thank Brenda Robb for her clerical and administrative assistance during the completion of this project. Juggling my schedule and keeping me on time during this whole process was not easy! I have been extremely fortunate throughout my career to have had incredible mentors, including Jim Lemons, Brad Poss, Hector Wong, and Tom Shanley. All four are gifted and dedicated clinicians and remain passionate advocates for critically ill children, the specialties of neonatology and pediatric critical care medicine, and me! I want to personally thank both Hector and Tom for serving again as Associate Editors for the second edition of this textbook. Their guidance and advice has been immeasurable. I have been truly fortunate to work with an outstanding group of contributors. All of them are my colleagues and many have been my friends for several years. It goes without saying that writing textbook chapters is a difficult and arduous task that often comes without a lot of benefits. Their expertise and dedication to our specialty and to the care of critically ill children have made this project possible. The textbook you now hold in your hands is truly their gift to the future of our specialty. I would also like to acknowledge the spouses and families of our contributors – participating in a project such as this takes a lot of time and energy (most of which occurs outside of the hospital!). Last, but certainly not least, I would like to especially thank my family – my wife Cathy, who has been my best friend and companion, number one advocate, and sounding board for the last 22 years, as well as my four children – Ryan, Katie, Maggie, and Molly, to whom I dedicate this textbook and all that I do.

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Part I

The Gastrointestinal System in Critical Illness and Injury

Derek S. Wheeler

Gastrointestinal Bleeding

1

Brent Whittaker, Priya Prabhakaran, and Ujjal Poddar

Abstract

Gastrointestinal hemorrhage requiring admission to the intensive care unit is uncommon. An understanding of the etiologies of upper and lower gastrointestinal bleeding, many of which have a specific predilection to occur at certain ages, is crucial in using diagnostic techniques efficiently. The management of gastrointestinal hemorrhage should begin with a rapid but thorough assessment of the child's hemodynamic stability and amount of blood loss. Restoration of hemodynamic stability with volume expansion and appropriate use of blood products is the initial goal of therapy followed by measures to specifically localize and manage the bleeding. A multidisciplinary team approach including gastroenterologists and surgeons is essential in the treatment of these children. Endoscopy of both the upper and lower gastrointestinal tract are useful diagnostic and potentially therapeutic tools that should be performed in select cases after hemodynamic stability has been achieved. Critically ill children often have risk factors that make them prone to developing stress ulcers which can cause significant bleeding, and high-risk groups will benefit from acid-suppressive therapy with histamine receptor antagonists and/or proton pump inhibitors.

Keywords

Gastrointestinal bleeding • Endoscopy • Stress ulcer

Introduction

Gastrointestinal (GI) bleeding can run the spectrum from a positive test for occult blood to life threatening hemorrhage. As such, GI bleeding can be challenging to manage. The incidence of GI bleeding in a recent population-based survey of the frequency of upper gastrointestinal bleeding (UGIB) in children from 2 months to 16 years of age was 1–2 per 10,000 children annually. In another study of over 40,000 visits to the pediatric emergency department (ED), 0.3 % of all children presented with rectal bleeding [1]. Although the incidence of clinically significant GI bleeding is low, it requires urgent evaluation and management.

GI bleeding is more often present than appreciated in critically ill patients admitted to the pediatric intensive care unit (PICU). A study of patients transferred to the PICU demonstrated the prevalence of GI bleeding to be 17 % (194/1,114). Half of these cases of GI bleeding were acquired in the PICU. Most importantly, of the patients who acquired bleeding while in the PICU, 16 % had clinically significant bleeding [2].

Given the large volume of the GI tract, significant internal bleeding can occur prior to clinical presentation. This makes it imperative to keep a high index of suspicion for ongoing

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bleeding and a close watch on vital signs with serial examinations. Fortunately, the majority of these hemorrhages are not severe and do not require admission to the intensive care unit [3]. The incidence of GI bleeding has not been found to have any relationship to age, sex, or race [4]. Shock, prolonged surgery, and trauma have been identified as risk factors for clinically significant GI bleeding [5]. Coagulopathy, acute respiratory failure, and Pediatric Risk of Mortality Score (PRISM) greater than ten have also been found to be risk factors for severe UGIB. Children with clinically significant UGIB have an increased risk of mortality and prolonged PICU stay with attendant higher cost [5].

Definitions

Several definitions of GI bleeding are used in the medical literature. Upper GI bleeding (UGIB) is typically defined as bleeding arising proximal to the ligament of Treitz, near the end of the duodenum, while lower GI bleeding (LGIB) is typically defined as bleeding from a site distal to the ligament of Treitz, which includes the remainder of the small intestine, colon, and rectum [6]. Hematemesis is defined as the presence of bright red or coffee ground material in emesis. Melena is defined as the presence of dark, tarry black stools formed from the breakdown of blood in the GI tract. Hematochezia is defined as bright red or maroon colored blood per rectum. Hematemesis and melena are usually associated with UGIB, while hematochezia is typically a manifestation of LGIB. Hematochezia could represent brisk UGIB in up to 12 % of cases [7]. However, as a general dictum, the higher in the gastrointestinal tract the origin of the bleed is, the darker the stool.

Table 1.1 Hematemesis: well appearing or ill appearing patient

Age	Well appearing	Critically ill appearing
Neonate/ infant	Swallowed maternal blood, hemorrhagic disease of the newborn, immune mediated thrombocytopenia, milk protein allergy, clotting factor deficiency	Stress ulcer, sepsis, DIC
Children-adolescents	Epistaxis, Mallory-Weiss, gastritis, peptic ulcer, variceal bleeding due to Extra Hepatic Portal Venous Obstruction(EHPVO), caustic ingestion	Sepsis, DIC, variceal bleeding from liver disease, stress ulcers

Table 1.2 Melena or hematochezia: well appearing or ill appearing patient

Age	Well appearing	Ill appearing
Neonate/ infant	Anal fissure, swallowed maternal blood, vascular malformation	Necrotizing Enterocolitis(NEC), Sepsis, Disseminated Intravascular Coagulation(DIC), ischemic bowel, malrotation with volvulus, Hirschsprungs enterocolitis
Toddler	Meckel's diverticulum, polyps, vascular malformation, fissures intestinal duplications	Intussusception, volvulus, small bowel obstruction, infectious diarrhea
Children-adolescents	Polyps, vascular malformations, meckel's diverticulum, hemorrhoids	Henoch Schonlein Purpura (HSP), Hemolytic Uremic Syndrome (HUS), Sepsis, DIC

Etiology

The diagnostic approach to the evaluation of GI bleeding in children should be targeted to the most likely causes in each age group. It is also useful to classify these children based upon presentation into typically well appearing or ill appearing (Tables 1.1 and 1.2).

Specific Causes of UGIB

Hemorrhagic Disease of the Newborn

Neonates have low stores of vitamin K. Breast milk is low in vitamin K, and the contribution of gut flora to vitamin K production is not present at birth. Therefore the levels of the vitamin K dependent clotting factors can be low, and patients can present with bleeding, including severe GI bleeding. In the United States, vitamin K supplementation is routine in newborns, but parental refusal or delivery at home could result in no supplementation. Classic hemorrhagic disease of the newborn occurs between day 1 and 14, while the late variety presents between 2 and 12 weeks of life. Other causes of Vitamin K deficiency include maternal medication use (phenobarbital, phenytoin, or warfarin) [8], prolonged diarrhea, malabsorption, and antibiotic therapy. A prolongation of the Prothrombin Time (PT) which corrects with the administration of vitamin K is diagnostic. Lack of response to Vitamin K should prompt work-up for inherited disorders of coagulation.

Coagulation Disorders

Coagulation defects, inherited or acquired, are significant risk factors for GI bleeding. Patients with severe hemophilia type A or B have a lifetime risk of GI bleeding between 10 and 25 %, usually associated with gastric disease [9]. Patients with less severe hemophilia (mild, moderate or carrier) do not seem to share this risk. Disseminated intravascular coagulation (DIC) and liver failure are common acquired causes of coagulopathy in critically ill children.

Peptic or Esophageal Ulcerations

Ulcerations are not an uncommon cause of UGIB. One study identified gastric lesions in 83 % of full term infants undergoing Esophago Gastro Duodenoscopy (EGD) for evaluation of upper GI bleeding [10]. One of the major risk factors for GI bleeding due to peptic or esophageal ulcerations among children is exposure to non-steroidal anti-inflammatory drugs (NSAIDs) [11]. NSAIDs inhibit cyclooxygenase, which is vital in the synthesis of gastroprotective prostaglandins. Viral infections, such as herpes simplex virus (HSV), cytomegalovirus (CMV), and adenovirus can cause severe esophagitis with ulceration in immune-suppressed children. Candida esophagitis is also an important cause of UGI bleeding in immunocompromised hosts, and may also be an adverse effect of acid suppressive therapy [12, 13]. Identification of candida esophagitis beyond infancy should prompt an immune work up. *Helicobacter pylori* is frequently associated with peptic ulcers [11] and may have some influence in critical illness. It is now standard of care to treat *H. pylori* infections with triple therapy including Amoxicillin, Clarithromycin and a proton-pump inhibitor (PPI) for 1–2 weeks.

Mallory-Weiss Tears

Mallory-Weiss tears are shallow, horizontal tears in the esophagus, usually near the gastroesophageal junction and are caused by forceful and/or or recurrent emesis. Presenting symptoms include vomiting, hematemesis, and abdominal pain or painful swallowing. While not commonly seen in children, Mallory-Weiss tears can be seen in up to 13 % of pediatric patients being evaluated for upper GI bleeding [14].

Variceal Bleeding

Increased resistance to blood flow through the hepatic portal system increases blood flow through alternative vessels. These vessels include those in the esophagus, stomach and ano-rectal areas, leading to varices, which are exposed to higher flow and higher pressures than is normal. Resistance to flow can be caused by intrinsic liver disease leading to cirrhosis, or obstruction such as portal vein thrombosis [15]. Due to the higher pressure and thin walls, these vessels can bleed profusely. In addition, varices are at a high risk of rebleeding, even after sclerotherapy. Patients can have up to 9 % rebleeding rate at 3 years and 31 % rebleeding rate at 9 years [16, 17].

Specific Causes of LGIB

Blood in the stool in the context of diarrhea is concerning for an infectious or inflammatory etiology. An acute onset of diarrhea is suspicious for an infectious etiology (Table 1.3). Chronic diarrhea associated with weight loss or failure to thrive should raise the suspicion for Inflammatory Bowel Disease (IBD), such as Crohn's or Ulcerative Colitis, or may indicate an allergic colitis. Workup of suspected infectious diarrhea should include stool cultures, and evaluation for ova and parasites.

Table 1.3 Infectious causes of GI bleeding

Viruses (rotavirus)
Shigella
E. Coli
Salmonella
Yersinia
Giardia
C Difficile

Juvenile Polyps

Juvenile polyps are a common cause of LGIB in children. The prevalence of these hamartomatous lesions is at least 1 in 15 patients undergoing colonoscopy for a variety of indications [18]. In addition to juvenile polyps, children can also have polyps secondary to inherited polyposis syndromes such as Gardner syndrome and Peutz-Jeghers syndrome.

Henoch Schonlein Purpura (HSP)

HSP is a vasculitic disorder that usually presents with palpable purpura, usually of the lower extremities. Gastrointestinal vasculitis can present with severe abdominal pain, intussusception, and LGIB. In a study of 208 in patients with HSP only five children had LGIB that required a transfusion, while stool tested positive for occult blood in a significantly greater number of children [19].

Meckels Diverticulum

Meckel's diverticulum is a remnant of the omphalomesenteric duct during the development of the gastrointestinal system, which may contain heterotopic gastric mucosa. Meckel's diverticulum can be found in 2 % of the general population and is often asymptomatic. Most patients with symptomatic meckel's diverticulum tend to be males under the age of 2 years. Although it is more common in the pediatric population than in the adult population, it is still an infrequent cause of LGIB in the pediatric population (4 %) [20]. The LGIB that occurs in children with Meckels diverticulum can be profuse and is typically painless. Identification of a Meckels diverticulum is radiologically confirmed [20].

Intussusception

Intussusception is the most common cause of bowel obstruction in children, with a rate of 56 per 100,000 per year in the US. It has a peak incidence between ages 5 and 10 months, but is rarely seen in adults. The classic symptoms include severe, episodic abdominal pain, vomiting and bloody (currant jelly)

stools [21, 22]. Many of the symptoms are non-specific which can lead to an incorrect initial diagnosis [22].

Stress ulcers and their prevention

The gastric milieu is acidic to facilitate the action of proteolytic enzymes, which begin the digestion of food. The proteolytic activity of pepsin is greatest in an acidic environment, and activity is negligible at a neutral pH [23]. Even in a healthy population, the barrier between the gastric mucosa and the environment sometimes fails, resulting in peptic ulcers, gastritis, pain, and bleeding. In the critically ill patient, the gastric mucosa is exposed to ischemic challenges as well. The resultant breach of the protective barrier causes the digestive enzymes and acid to directly injure the gastric tissue. This is the postulated pathway for the development of stress ulcers. The most common risk factors that have been found to be consistently associated with the development of stress ulcers in the ICU are mechanical ventilation, anticoagulation, multi-organ failure, and head injury. Histamine-receptor blockers (H2 Blockers) and Proton Pump Inhibitors (PPI's) are frequently used for stress ulcers prophylaxis.

The acidic nature of the stomach plays a vital role in the defense of the body against pathogens and so there is some concern about the risks of modifying gastric pH in the critically ill patient. Raising the gastric pH may increase the risk of pneumonia in the mechanically ventilated patient (ventilator-associated pneumonia, or VAP). There is some literature that suggests that this may also increase the risk of acquiring infections due to *Clostridium difficile* [24]. Hence, while H2 blockers and PPIs are safe, well tolerated, and decrease the incidence of stress ulcers in the critically ill population, their use is not entirely without risk.

Additionally, early introduction of enteral feeds [25] has been found to be protective against stress ulcer development. While continuous enteral feeding does increase the gastric pH, it may also increase the risk of infection in critically ill patients [26]. For example, a recent meta-analysis showed higher hospital mortality for critically ill adults who were fed enterally and received an H2 blocker [27].

Proton pump inhibitors are more effective in raising gastric pH than histamine – receptor blockers alone. In addition there may be some tachyphylaxis to parenteral histamine-receptor blockers, lowering their efficacy after the first few days. In mechanically ventilated patients, the highest risk of stress ulcers is in those children who require mechanical ventilation for longer than 48 h. There is literature that suggests that 60 % of mechanically ventilated patients who develop GI bleeding do so on the first day of mechanical ventilation [28], therefore, if stress ulcer prophylaxis is warranted, it should be started with the onset of mechanical ventilation.

Management of GI Bleeding

Initial Management and Evaluation

The following questions should be answered in the child with possible GI bleeding after rapid assessment and stabilization of the patient. First, is it blood? Ingestion of dyes, berries, beets, licorice, iron, bismuth, charcoal or other foods can discolor the stool and mimic bleeding. Second, is it from the GI tract? Hematemesis, melena or hematochezia in the first 48–72 h of life may represent swallowed maternal blood. In breastfeeding patients, lesions in the breast or around the nipple also can be a source of maternal blood. The Apt test, which is used to confirm maternal origin of blood, is based on the ability of fetal hemoglobin to resist alkali denaturation [29]. Epistaxis and bleeding from the oral cavity can also masquerade as GI bleeding.

After identifying that the patient does indeed have a GI bleed, the next step is to evaluate the magnitude of the blood loss. Determination of volume of blood loss is based on history, physical exam and laboratory evidence. A focused history and physical exam can give valuable clues concerning the etiology of the bleed and the severity of the bleed. The physical exam should be rapid with special concern for the vital signs and a rectal examination should be performed in all cases of suspected lower GI bleeds (Tables 1.4 and 1.5). Some general caveats can be helpful:

- Blood streaking the outside of the stool may indicate minimal blood loss.
- Frank melena is associated with blood loss of at least 2 % of the total blood volume [9]

Table 1.4 History in GI bleeding

History	Conditions
Pain	Severe, intermittent pain: intussusception or bowel obstruction
	Painless: meckels, polyp, vascular malformation
Dysphagia/ odynophagia	Esophagitis-pill, peptic or infectious
Emesis	Mallory-Weiss tears
Epistaxis	Source of bleeding, or coagulopathy
Medications or ingestions	NSAIDs, steroids (peptic ulcers)
	Aspirin or warfarin
	Foreign bodies, ingestions of caustic substances
Breastfeeding	Ingested maternal blood
Diarrhea/sick contacts	Infectious diarrhea
	IBD
Stooling pattern	Acholic stool-biliary atresia with cirrhosis
	Lack of stools-Hirschsprung's disease
Dietary	Milk protein allergy
Umbilical vein catheter	Extra hepatic portal vein obstruction (EHPVO)
Weight	Chronic weight loss in adolescent-IBD

Table 1.5 Physical exam

Area	Findings	Concerns for
Vitals	HR, BP	Hypovolemia
General	Growth parameters	Chronic GI bleeding
	Edema	
Eyes	Icterus	Liver disease
	Pallor	Bleeding/anemia
Nose	Epistaxis	Coagulopathy, may be source of blood
Mouth	Perioral pigmentation/ freckling	Peutz-Jeghers syndrome
	Thrush	Esophagitis
	Trauma/recent tonsillar surgery	May be oral bleeding
Abdomen	Liver size or tenderness-liver disease	Liver disease
	Splenomegaly, caput medusae	Portal hypertension
	Lower Quadrant masses/tenderness Ascites	Intussusception
	Hyperactive bowel sounds	Liver disease
		Upper GI bleed
GU	Skin tags	May be the source for bleeding
	Fissures	Constipation
	Fistulas	Crohn's disease
Neuro	Mental status	Encephalopathy
Skin	Petechiae	ITP, TTP
	Purpura	HSP, DIC
	Jaundice	Liver disease
	Telangiectasia/spider angiomas	Liver disease
	Abnormal bruising	Coagulopathy or anticoagulant use

- Depending on the acuity of the loss, loss of up to 10–15 % of the blood volume may not be associated with any hemodynamic changes.
- Fifteen to thirty percent blood loss causes tachycardia and increased systemic vascular resistance.
- Acute losses of greater 30–40 % of total blood volume will cause hypotension [30]. In patients with chronic blood loss, compensation can maintain blood pressures with small fractions of normal hemoglobin levels.

Prompt assessment and support of the airway and breathing should be followed by circulatory support if needed. Evaluation of heart rate, capillary refill, peripheral pulses, and temperature of the extremities, blood pressure, and mental status may help to identify compensated or uncompensated shock. It is prudent to remember that hypotension is a late sign of shock and hypovolemia in children because of their robust ability to compensate for acute volume loss. In the setting of an acute hemorrhage, several compensatory mechanisms are activated. Systemic vascular resistance (SVR) increases due to vasoconstriction caused by a surge in circulating catecholamines, extravascular fluid is mobilized to the intravascular space to maintain preload and blood volume, heart rate increases which improves cardiac output and fluid is retained due to the secretion of anti-diuretic hormone.

Initial resuscitation with isotonic fluids should be followed with blood products as needed. Due to the marked decrease in oxygen carrying capacity due to anemia, administration of supplemental oxygen is beneficial. In emergencies, blood volume should be rapidly restored with O negative uncross-matched blood. Caution must be exercised to avoid the temptation to over resuscitate, because it can increase the severity of bleeding, particularly if it variceal in origin by increasing pressure in the splanchnic circulation Coagulopathy or thrombocytopenia, these should be corrected promptly.

Placement of a Nasogastric (NG) Tube

Analysis of the nasogastric aspirate is the traditionally accepted way of distinguishing between upper and lower gastrointestinal sources of bleeding, with frank blood or coffee ground aspirate being suggestive of UGIB. However, the lack of blood in an NG aspirate is neither sensitive nor specific. A negative NG aspirate does not preclude the necessity of upper endoscopy [31]. The presence of blood in the NG aspirate, or lack of clearing of the aspirate is predictive of high risk lesions (active bleeding or visible vessel) which may require endoscopic therapy, and improves endoscopic visualization [32].

NG insertion is generally a safe procedure, but is not without risk. Studies on adult patients have demonstrated a 0.3–2 % complication rate with pneumothorax being most common. Other complications are related to malpositioned tubes. Physical examination to confirm correct NG placement can be misleading and should be confirmed by additional techniques [33]. Although some practitioners feel that esophageal varices are a relative contraindication to the placement of an NG tube, there is data to support that it can be safely performed [34].

Laboratory Evaluation

Initial laboratory evaluation of the patient with a significant GI bleed should include hemoglobin/hematocrit, platelet count, MCV, BUN/Creatinine measurement and coagulation studies. Other pertinent studies such as liver function tests should be obtained based on the clinical context.

Laboratory tests may also give a few clues of the etiology of the bleeding, the severity of the bleeding, and the chronicity of the bleeding. Several studies have looked at the ratio of BUN/Creatinine in differentiating between an upper and lower GI bleeds in the pediatric population [35]. An elevated

BUN/creatine ratio (greater than 30) is usually reflective of partial digestion of blood in the GI tract and is somewhat predictive of UGIB, although it can rarely be seen with LGIB.

Testing for Occult Blood

These tests are based on the oxidation of alpha-guaiaconic acid to blue quinine by hydrogen peroxide. Hemoglobin has pseudo-peroxidase activity. The developer for the test contains hydrogen peroxide which, in the presence of hemoglobin, oxidizes the guaiac [36]. Several foods have peroxidase activity (horseradish, cauliflower, broccoli, and poorly cooked meat) and render the test falsely positive for occult blood. Alternatively, high doses of the anti-oxidant vitamin ascorbic acid can cause a false negative test by interfering with this reaction. Occult blood testing is also pH-dependent; pH <2 tends to give a false negative result, and pH of between 2 and 4 can cause the test to be falsely positive [37]. This renders gastric specimens unsuitable for evaluation by this method. Gastroccult ®(registered trademark) is a commercially available product for testing gastric aspirates for blood.

Radiologic Investigation

X-ray

The traditional flat plate or KUB has limited utility in the evaluation of an acute GI bleed. They are, however, quick and readily available, and can show free air, pneumatosis, air fluid levels, or in some cases intussusception. Helpful if positive, plain x-rays are not a sensitive test for most causes of GI bleeding.

Ultrasound

Ultrasound is non-invasive and does not involve radiation exposure, therefore it is the imaging modality of choice for diagnosis of intussusception. Unfortunately, it does not allow for therapeutic intervention (see below).

Air Contrast Enema

Air contrast enema is diagnostic and potentially therapeutic for intussusception. This has largely replaced barium enemas due to the risk of barium leaking in to the peritoneum in the event of perforation. The rate of reduction also may be higher in the air contrast reduction. Air contrast may be used with fluoroscopy or it is increasingly being used in conjunction with ultrasound [38].

CT Scan

The CT scan allows better visualization than a plain x-ray of the abdomen, but entails higher radiation exposure and possible exposure to intravenous contrast. The CT scan may be able to identify masses, obstructions, colitis or other complications from IBD.

Tagged Red Blood Cell Scan

A tagged red blood cell scan involves obtaining a specimen of blood from the patient, radiolabelling it, and re-injecting it back to the patient. With serial imaging over 60–90 min, the scans can localize slow bleeds (as little as 0.1 cc/min) The utility of this test is limited in hemodynamically unstable children due to the length of the study. This scan localizes the bleeding to an area rather than a specific vessel [39].

Meckel Scan

The Meckel scan uses technetium 99 which is taken up by heterotopic gastric mucosa. This appears on the nuclear scan as gastric tissue that is geographically separate from the stomach. To enhance the sensitivity of the Meckels scan histamine–receptor blocker such as ranitidine is injected prior to the technetium to allows uptake of the technetium, but decrease the secretion by the gastric mucosa [40].

Angiography

Angiography is useful to evaluate active bleeding at a rate of at least 0.5–1 cc/min. Bleeding can be treated during angiography with embolization of an arterial source of bleeding by coiling, glue or other modalities [41]. Risks of angiography include radiation exposure and contrast induced nephropathy.

Diagnostic Interventions (and Management)

Upper Endoscopy

The position statement for the North American Society for Pediatric Gastroenterology and Nutrition states that "After acute volume resuscitation has been initiated for gastrointestinal bleeding, endoscopy may be considered for active, persistent, or recurrent bleeding, for hemodynamically significant hemorrhage, or to distinguish between variceal and nonvariceal bleeding" [42]. Indications for urgent endoscopy include a sick, but hemodynamically stable patient and patients with ongoing bleeding. The presence of a perforation in the gastrointestinal tract is a contraindication for endoscopy. Due to the fact that a significant portion of patients with an upper GI bleed may present with melena and will have a negative NG aspirate [31], the EGD is often the initial modality in the evaluation of any GI bleeding. Endoscopy allows for definitive treatment of GI bleeding. Endoscopic band ligation of varices, application of clips to bleeding vessels, thermocauterization, and local injection of epinephrine or vasopressin, and foreign body or polyp extraction are therapeutic interventions during endoscopy to achieve hemostasis.

Colonoscopy

For most causes of lower GI bleeding, colonoscopy is the modality of choice. In addition to visualization, biopsy,

cauterization, clipping and polypectomy are all potential interventions.

In children with suspected colitis, colonoscopy is usually performed after the infection and inflammation have resolved.

Double Balloon Endoscopy

The double balloon endoscope adds an outer tube and balloon onto an endoscope also equipped with a balloon. After insertion into the small intestine, the outer balloon is inflated, and the scope is advanced as far as possible before inflating the balloon on the scope. At that point, the outer tube is advanced, the balloon is inflated and the outer tube is pulled back slightly, folding the small intestine like pleated fabric. This continues along the length of the small intestine. Between this approach from the upper, and a similar approach with the colonoscope which can be similarly advanced, the endoscopist is often able to view the whole small bowel. Advantages of this approach include the ability to intervene if lesions are noted, and the possibility of viewing the complete GI tract [43].

Capsule Endoscopy

One option that has gained increasing popularity recently is capsule endoscopy. A self contained camera is swallowed. It transmits images to a receiver, and makes it possible to evaluate the complete length of the intestines. Capsule endoscopy is frequently able to identify lesions [44].

In the best case, they are a minimally invasive, low risk option to identify lesions. In some cases they can replace the need for an EGD, but do not have any therapeutic interventions. In some smaller children, usually between the ages of 3 and 6, the children are unable or unwilling to swallow the capsule which necessitates an EGD for placement either in the stomach or the duodenum. The major risk of the procedure is retained capsule, which could necessitate surgical intervention.

Medical Therapy

The majority of all GI bleeding will stop spontaneously without intervention. However, medical management of GI bleeding may be required.

Proton Pump Inhibitors (PPI)

The use of acid suppressive medications is justified by the preponderance of peptic causes of UGIB. Omeprazole is frequently administered for this purpose. The metabolism of omeprazole is age-dependent, with low rates in infants less than 10 days of age, and increased metabolism between 1 and 6 years of age [45]. The dosing varies from 1 mg/kg IV once daily to 40 mg/1.73 m^2 daily to maintain gastric pH >4 [46]. Adult studies have shown that the combination of bolus and continuous drip of proton pump inhibitors keeps the pH higher than intermittent bolus dosing [47]. This has not been extensively studied in the pediatric population, but may be a consideration.

H-2 Blockers

Ranitidine is administered intravenously to raise the gastric pH to >4. The dose of ranitidine is also age dependent: 1.5 mg/kg IV every 8 h in term babies to 1.5 mg/kg IV every 6 h in older children [48].

Vasoactive Drugs

Early administration of vasoactive therapy prior to endoscopy is recommended for variceal bleeding in children. The Somatostatin analogue Octreotide is used in the treatment of UGI bleeding from varices in children with portal hypertension. It inhibits gastric acid secretion and diminishes splanchnic and azygous blood flow. Infused at 1–2 mcg/kg/h, it stopped UGI bleeding in 71 % of children with portal hypertension in one study; rebleeding after the infusion was discontinued occurred in 50 % of children with portal hypertension [49]. Cramps, nausea, and hyperglycemia are some of the side effects of octreotide. Vasopressin and somatostatin have also been used in the medical management of UGI bleeding.

Sucralfate

Although the mechanism of action is not totally understood, sucralfate is thought to form a protective barrier when exposed to an acidic environment which is protective for the gastric mucosa. Although there is no data on the addition of sucralfate to a PPI, the combination may be less effective than either medication alone because sucralfate requires an acidic pH to form the protective gel, although this is unproven [50].

Recombinant Activated Factor 7

FDA approved for use in hemophilia, recombinant Factor VIIa is being used for treatment of severe bleeding in other contexts. Factor VII is part of the extrinsic pathway in coagulation. After binding with tissue factor, it can directly activate factor 10, bypassing the intrinsic pathway. It has also been effective in patients with liver disease and GI bleeding. A dose of 90 mcg/kg every 2 h has been used [51]. In addition to the expense of this medication, and the extremely short half-life of only 2–4 h, side effects include thrombosis [52]. The administration of rFVIIa decreases the PT, but there are no established laboratory parameters to guide treatment, and treatment needs to be monitored clinically. As it is off-label use, treatment of GI bleeding with rFVIIa should be after failure of standard therapy [53].

Antibiotic Therapy

Antibiotic treatment of infectious diarrhea should be carefully considered. The treatment of E. Coli O157 H7 can

increase the risk of Hemolytic Uremic Syndrome (HUS) [54] and indiscriminate use of antibiotics may increase the risk of *C. difficile* colitis and prolonged shedding for salmonella. Absolute indications for the treatment of infectious diarrhea include children with immune compromise, a known etiology that requires treatment (Shigella or *C.difficile*), or critical illness.

Surgical Therapy

In severe cases of GI bleeding, a surgical consult should be obtained. Massive ongoing blood loss, bleeding Meckels diverticulum, volvulus, malrotation with obstruction, or bowel perforation may be some indications for surgery.

Management of Variceal Bleeding

The initial management of variceal bleeding is similar to the therapy of non-variceal UGI bleeding. Vasoactive medications should be started before endoscopy. Endoscopy can be performed safely in children by experienced operators [55]. Endoscopy is mandatory in cases of severe bleeding requiring transfusion or unexplained, recurrent bleeding [56]. While there are no randomized controlled trials addressing the timing of endoscopy in pediatric variceal bleeding, endoscopy should be performed as early as possible after the child has been stabilized. Prophylaxis against intestinal flora with a third-generation cephalosporin is recommended before endoscopy based on adult literature [57]. Endoscopic treatment of variceal bleeding includes endoscopic band ligation (EBL) or sclerothrerapy. A randomized controlled trial on 49 children with variceal bleeding showed that EBL achieved control of bleeding faster, with fewer complications and less rebleeding than sclerotherapy [58]. As an alternative, tissue adhesives like cyanoacrylate can also be injected endoscopically to control bleeding [59]. Sclerotherapy has been shown to be effective in eliminating varices and preventing subsequent bleeding in a RCT and some uncontrolled trials [60]. No survival benefit was detected and serious complications included bleeding prior to obliteration, esophageal perforation, and stricture formation [16, 17].

Balloon tamponade with a Sengstaken- Blakmore tube or a Foley catheter in infants may be used in the PICU setting for uncontrolled bleeding. In a retrospective study of 100 adult patients with variceal bleeding, the SB tube had an overall efficacy of 61 %. Tamponade was more likely to be successful without an increase in the risk of esophageal perforation if it had been preceded by sclerotherapy. Aspiration was the main complication [61]. Overall, inadequate pediatric evidence in the management of variceal bleeding leads to significant variability in the way physicians treat them [62].

Beta-blockers may be considered for prophylaxis against rebleeding in children with a prior variceal bleed. The benefits of this therapy should be weighed against the risks of beta blockade in the event of bleeding, The inability to mount appropriate tachycardia may lead to poor and delayed recognition of hemodynamic compromise and may interfere with the child's ability to compensate for hypovolemia in general.

Transjugular Intrahepatic Porto Systemic Shunt

For children with end stage liver disease and cirrhosis, one other option is the Transjugular intra-hepatic porto systemic shunt (TIPS) created between the portal vein and the hepatic vein. This can be used as a temporizing therapy prior to transplantation, or as a treatment in itself. The major benefit of the TIPS procedure is that it may replace a surgical shunt with its accompanying risks. The risks of the TIPS procedure include bleeding, and the shunting can cause encephalopathy if all blood bypasses the filtering effect of the liver [63, 64].

Summary and Recommendations

1. Clinically significant GI bleeding is rare in the pediatric population.
2. Initial treatment should focus on stabilization of the patient.
3. Focused physical examination and laboratory work up are essential after resuscitation.
4. Localization of the bleeding, with focused work-up while not always successful, is always beneficial.
5. Parenteral proton-pump inhibitors, H-2 blockers, and endoscopy are the mainstays of therapy of UGIB.
6. Supportive care and colonoscopy are important in managing LGIB.
7. Most bleeding, upper and lower, will resolve spontaneously.

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Liver Failure in Infants and Children

2

Ann E. Thompson

Abstract

Liver dysfunction is common in children requiring intensive care and is a common source of morbidity and mortality. Both primary disorders of the liver and complications of other underlying disorders may result in hepatic failure and life-threatening multisystem dysfunction. Slowly progressive liver disease may result from numerous disorders of infancy and childhood. The rate of progression and specific complications vary with the specific disorder, but most ultimately progress to cirrhosis and obstruction to portal venous blood flow, with variceal bleeding, intractable ascites, failed synthetic function, growth failure, severe coagulopathy, encephalopathy, and multiple organ dysfunction. Biliary atresia is the most common, but intrahepatic cholestasis, a variety of familial disorders, chronic viral infection, and parenteral nutrition induced cirrhosis are also relatively frequent.

Keywords

Acute liver failure • Fulminant liver failure • Hepatitis • Acetaminophen toxicity • Portal hypertension

Introduction

Liver dysfunction is common in children requiring intensive care and is a common source of morbidity and mortality. Both primary disorders of the liver and complications of other underlying disorders may result in hepatic failure and life-threatening multisystem dysfunction. Slowly progressive liver disease may result from numerous disorders of infancy and childhood (Table 2.1). The rate of progression and specific complications vary with the specific disorder, but most ultimately progress to cirrhosis and obstruction to portal venous blood flow, with variceal bleeding, intractable ascites, failed synthetic function, growth failure, severe coagulopathy, encephalopathy, and multiple organ dysfunction. Biliary atresia is the most common, but intrahepatic cholestasis, a variety of familial disorders, chronic viral infection, and parenteral nutrition induced cirrhosis are also relatively frequent.

Acute liver failure (ALF), also called Fulminant hepatic failure (FHF), is classically defined as massive liver necrosis with encephalopathy, developing within 8 weeks of the onset of illness. More recently it has been redefined as encephalopathy beginning less than 2 weeks after the onset of disease in patients without chronic liver disease. In children, FHF is a rare multiorgan system disorder, characterized by severe hepatic dysfunction with hepatocellular necrosis, which occurs in patients without underlying chronic liver disease, with or without encephalopathy [1]. Mortality is high, reported as 60–80 % in most series.

Etiology

Causes of fulminant hepatic failure are varied and numerous, and include infectious, metabolic, toxic, vascular, infiltrative, and autoimmune, as well as unknown processes

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Table 2.1 Etiology of chronic liver failure in infants and children

Cholestatic liver disease
Biliary atresia
Intrahepatic cholestasis, including Alagille's syndrome
Familial intrahepatic cholestasis (Byler disease)
Sclerosing cholangitis
Primary biliary cirrhosis
Parenteral nutrition-induced cirrhosis
Metabolic diseases (liver-based)
α1-Anti-trypsin deficiency
Wilson's disease
Tyrosinemia
Chronic active hepatitis/cirrhosis
Hepatitis B, C
Autoimmune
Neonatal hepatitis
Cryptogenic cirrhosis
Cystic fibrosis
Other/miscellaneous

(Table 2.2). In infants and children under the age of 2 years, metabolic disorders and infectious causes are most common, especially herpes viruses, adenovirus, and echovirus. Hepatitis A, B, and rarely C are more common, but many other infectious agents can cause fulminant disease. In older children infectious causes predominate, but metabolic and toxic causes remain important. Numerous drugs and environmental agents may be associated with toxic liver injury, either direct or indirect (e.g., hypersensitivity related).

In older children, especially adolescents, acetaminophen poisoning is a common cause of FHF. In adolescents it is most commonly the result of suicidal intent, though in younger children it results from accidental ingestion or inadvertent overdose. Of interest, several recent studies have suggested that many cases of FHF previously classified as "idiopathic" may in fact be due to unrecognized acetaminophen poisoning. For example, acetaminophen-containing protein adducts released by dying hepatocytes have been found in 20 % of children and adults with idiopathic FHF [2, 3]. Metabolism of acetaminophen is normally by three different pathways – conjugation with sulfate or glucuronide accounts for approximately 90 % of the metabolism, about 5 % is excreted unchanged in the urine, and 5–10 % is metabolized by cytochrome P450 mixed-function oxidase. The last of these is the primary mechanism of the hepatic toxicity. Acetaminophen is metabolized to N-acetyl-p-benzoquinoneimine (NAPQI) by the cytochrome P450 oxidase, which forms covalent bonds within the hepatocyte. Under normal circumstances, NAPQI is detoxified by addition of sulfhydryl groups, usually through conjugation by glutathione, but stores of glutathione may be exhausted by massive doses, and irreversible injury can occur. Treatment of acetaminophen poisoning is with the specific antidote, N-acetylcysteine. The initial dose is 140 mg/kg, followed by 70 mg/kg given po or pg every 4 h for 17 doses. Intravenous treatment may be more easily tolerated. Current recommendations are for a bolus dose of 150 mg/kg over 15–60 min, followed by a continuous infusion of 50 mg/kg/dose over 4 h, followed by 100 mg/kg/dose over 16 h. The management of acetaminophen poisoning is discussed further in the chapter on toxic ingestions.

Severe liver failure is associated with a microcirculatory disturbance causing tissue hypoxemia. N-acetylcysteine has been noted to have beneficial systemic hemodynamic effects in a variety of critical illnesses, serving as a means of reducing oxidative stress associated with inflammation and overwhelmed antioxidant mechanisms. This has suggested potential benefit in acute hepatic failure from a variety of other causes. A number of small studies have demonstrated improved oxygen consumption and indocyanine green clearance in patients with liver failure treated with N-acetylcysteine [4, 5]. In addition, as previously mentioned above, several studies have shown that many cases of idiopathic liver failure are actually due to acetaminophen poisoning. Given this information, N-acetylcysteine has been proposed as a potential treatment for all patients presenting with FHF. However, a multi-institutional study in children, conducted by the Pediatric Acute Liver Failure Group, unfortunately was unable to shown any improvement in survival at 1 year in non-acetaminophen acute liver failure. Moreover, liver transplant-free survival was significantly lower in the group that was treated with N-acetylcysteine [6]. Therefore, N-acetylcysteine is not currently recommended for treatment of non-acetaminophen acute liver failure in children.

Liver Failure and its Effects on Organ Function

Hepatic failure, whether acute or chronic, is associated with dysfunction of multiple organ systems. It is this constellation of system failures that characterizes most patients admitted to intensive care units and which are the most common causes of death [7, 8].

Hepatic Encephalopathy

Clinical Manifestations

Central nervous system dysfunction occurs in the majority of patients with both acute and chronic liver failure. Its etiology is multifactorial and not fully understood, and appears to differ somewhat between the two [9, 10]. For example, neurologic dysfunction develops rapidly in patients with acute liver failure, often progressing to coma, cerebral edema, and death from elevated intracranial pressure and herniation

Table 2.2 Causes of acute or fulminant hepatic failure

Infectious	
Hepatitis A, B, B and D, C, E	Measles
Cryptogenic	Yellow fever
Herpes simplex	Lassa
Adenovirus	Ebola
Echovirus	Marburg
Epstein-Barr	Dengue
Cytomegalovirus	Togaviruses
Varicella	Bacterial septicemia
Parvovirus B19	Leptospirosis
	Malaria
Toxic (direct or indirect)	
Acetaminophen	Isoniazid
Halothane	Cytotoxic agents
Valproate	Irradiation
Carbamazepine	Copper
Phenytoin	Amanita phalloides
Phenobarbital	Carbon tetrachloride
Tricyclic antidepressants	
Metabolic	
Galactosemia	Neonatal hemochromatosis
Fructosemia	Alpha-1 antitrypsin deficiency
Tyrosemia	Wilson's disease
Niemann-Pick II (C)	
Infiltrative	**Autoimmune**
Leukemia	Liver-kidney microsomal type I Ab (+) hepatitis
Hemophagocytic lymphohistiocytosis	Smooth muscle Ab (+) hepatitis
Hemangioendothelioma	Giant cell hepatitis with hemolytic anemia
Lymphangioendothelioma	
Ischemic/vascular (rare)	**Undefined**
Budd-Chiari syndrome	
Acute circulatory failure	
Septicemia with shock	
Heat stroke	

within days or even hours. Seizure activity and muscle twitching are commonly observed prior to the onset of coma. Cerebral edema occurs far more commonly in patients with acute or fulminant hepatic failure than in those with chronic hepatic insufficiency. It occurs in approximately 80 % of patients with acute disease and is a common cause of death [11]. Histological findings are consistent with cytotoxic edema – primarily severe swelling of astrocytes and astrocyte end feet. It is generally a reversible process, i.e. patients who recover spontaneously or undergo transplantation have resolution of the neurologic dysfunction if secondary damage has not occurred. However, secondary damage does occur frequently, and moderate to severe neurologic deficits are common. In contrast, in patients with cirrhosis and chronic liver failure, encephalopathy is much more insidious in both its onset and progression and may wax and wane. Episodes of gastrointestinal hemorrhage, sepsis, and sedative administration (among other events) may precipitate deteriorating mental status. Personality changes, motor dyscoordination, and asterixis usually precede the onset of stupor and coma. Histologic findings also reveal astrocytic rather than neuronal abnormalities, specifically Alzheimer type II astrocytosis, with swollen astrocytes, large pale nuclei, prominent nucleoli, and margination of chromatin.

Pathophysiology

The pathophysiology of hepatic encephalopathy needs to be further elucidated. Several hypotheses have been proposed to date, including the reduced synthesis (by the liver) of an essential substance for brain function, synthesis by the diseased liver of an encephalopathogenic substance, and/or reduced extraction and metabolism by the liver of encephalopathogenic substances or precursors. As investigation proceeds there is increasing evidence for activation of inflammatory mediators, alteration of gene expression in brain, and the effects of oxidative/nitrosative stress. In addition, multiple neurotoxins and false neurotransmitters, excessive levels of octopamine and serotonin, and deficient norepinephrine and dopamine are hypothesized to play important roles.

Accumulation of **ammonia** plays a major and presumed central role in the pathophysiology of both hepatic encephalopathy and cerebral edema, but is not the exclusive factor. The association between ammonia and hepatic encephalopathy has been recognized for over a century, and recent investigation continues to support its role. Positron emission tomography (PET) reveals increased blood-brain barrier permeability to ammonia as well as increased brain uptake and metabolism of the compound [12]. Excess CNS ammonia has multiple effects on brain function, not fully understood, which affect both excitatory and inhibitory function and contribute to edema formation. Elevated ammonia levels block chloride ion extrusion from post-synaptic neurons and render the inhibitory neurotransmitter ineffective [10]. However, ammonia also inhibits excitatory neurotransmission.

The **glutamine theory** proposes that glutamine, produced in the brain by deamination of ammonia, converting glutamate to glutamine, accumulates in astrocytes, where its osmotic effect is to promote edema formation (Fig. 2.1). It also causes acute egress of potassium, organic osmolytes, and methylamines through a volume activated channel. Magnetic resonance spectroscopy has provided support for the importance of the glutamine hypothesis [13]. Treatment with methionine sulfoximine, which inhibits glutamine synthesis, blocks accumulation of glutamine and water in experimental animals. In cell culture, free radicals form in astrocytes exposed to NH_3, leading to mitochondrial dysfunction which can be prevented by inhibition of glutamine synthetase. Inhibition of glutamine synthetase also prevents

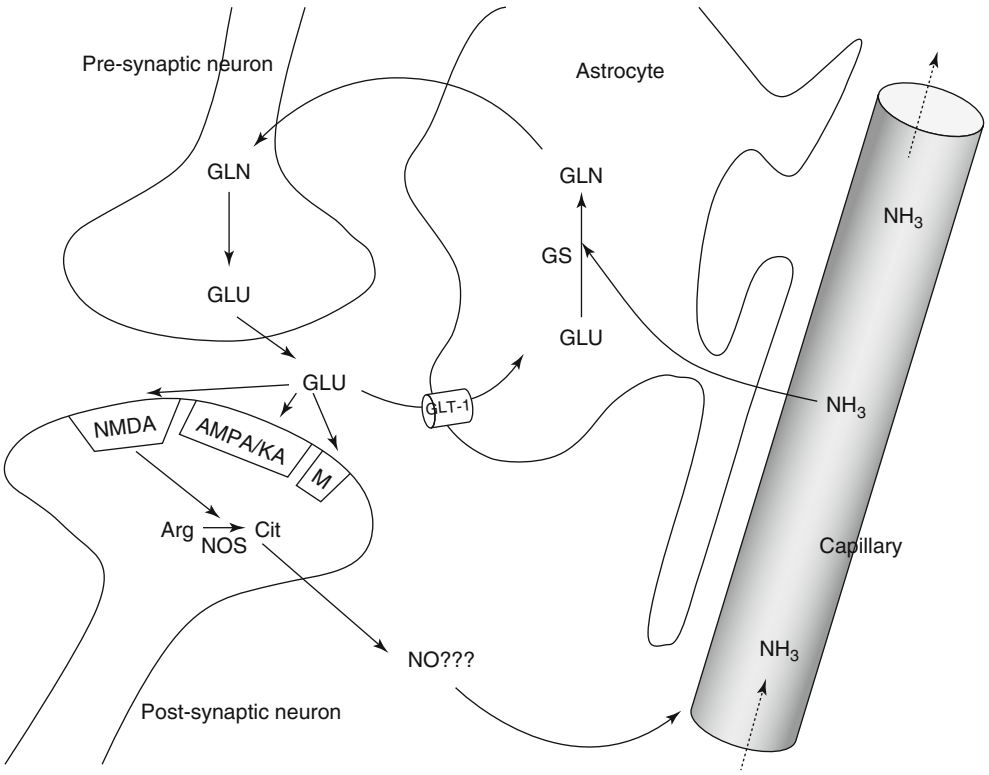

Fig. 2.1 Potential mechanisms for development of cerebral edema in acute hepatic failure. Ammonia (*NH3*) is taken up in abnormal quantities across an abnormally permeable blood brain barrier into the astrocyte. It promotes production of glutamine (*GLN*) from glutamate (*GLU*) by the action of glutamine synthase (*GS*) in the astrocyte. Elevated levels of glutamine lead to excess uptake of water into the astrocyte. Glutamine is pumped out of the astrocyte and taken up by the presynaptic neuron, where it is converted to glutamate. Nerve stimulation causes release of glutamate into the synaptic cleft where is acts as an excitatory neurotransmitter. Astrocytes rapidly take up glutamate via the glutamate transporter (*GLT-1*). Ammonia also blocks export of glutamine from the astrocyte which further increases astrocyte glutamine concentration and edema. Stimulation of NMDA receptors by glutamate may also stimulate nitric oxide synthase (*NOS*) and promote nitric oxide (*NO*) production with subsequent cerebral vasodilatation

edema formation and death in rats with hepatic failure [14, 15]. However, the effect on water content is not proportionate to the effect on glutamine accumulation, suggesting that other mechanisms are likely to be involved in development of cerebral edema.

Oxidative and nitrosative stress may be additional factors contributing to edema formation. Increased gene expression of brain heme oxygenase-1 and reduced expression of Cu/Zn superoxide dismutase are noted in rats in after portocaval shunts, and neuronal NOS is increased. Another theory of edema formation attributes edema formation to gradual vasodilatation, in which failed autoregulation occurs with uncoupling of $CMRO_2$ and CBF, loss of arteriolar tone, and vasogenic edema [16–19]. These two prevailing theories may, in fact, be interrelated. Once glutamine is produced in the astrocyte, it diffuses to presynaptic neurons where it is deaminated to glutamate, a critical excitatory neurotransmitter. The increased levels of glutamate may activate NMDA receptors, stimulating production of nNOS and nitric oxide, promoting vasodilatation and vasogenic edema [9, 14]. In addition to glutamate's potential effect on vascular tone, endotoxin and other vasoactive peptides from the gut or necrotic liver may contribute to vasodilation.

Measurement of cerebral blood flow (CBF) in patients indicates significant variability. Most appear to have decreased CBF, probably consistent with decreased energy consumption, but some are noted to have elevated flow which is associated with edema and higher mortality. Autoregulation may be impaired in late disease, especially in those with low systemic blood pressure [20], but is restored rapidly after transplantation, or during hypothermia. Limited experimental evidence indicates that both mild hypothermia and indomethacin can reduce CBF and prevent cerebral edema [21].

Brain energy metabolism is decreased in hepatic encephalopathy. The cerebral metabolic rate for glucose and $CMRO_2$ are proportionately decreased, apparently secondary to decreased energy demand [10, 22]. Neurologic dysfunction precedes depletion of high-energy phosphates in models of both acute and chronic encephalopathy, as well as in patients with mild encephalopathy associated with cirrhosis. Elevated CNS ammonia may contribute to cerebral energy failure, although this appears to be a *late* phenomenon. Its inhibition

of mitochondrial α-ketoglutarate dehydrogenase prevents pyruvate from entering the Kreb's cycle and results in excess lactate formation and decreased ATP production. Following the onset of intracranial hypertension, there may be evidence of cerebral hypoxia, probably secondary to the pressure-related decrease in cerebral blood flow.

Decreased energy consumption may be secondary to defects of neurotransmission which are associated with hepatic encephalopathy. Glutamate is the major excitatory neurotransmitter. It is released by the presynaptic neuron and stimulates receptors on postsynaptic cells. It is taken up by astrocytes and metabolized to glutamine by action of glutamine synthetase using ammonia from the circulation. Normally glutamine is actively extruded from the astrocyte and taken up again by the presynaptic neuron for conversion back to glutamate. In the setting of hyperammonemia, numerous alterations in this pathway occur [23]. Expression of multiple enzymes, including glutamine synthetase, is decreased. Nonetheless, elevated ammonia promotes production of glutamine, but impairs its release from astrocytes. The action of the glutamate transporter GLT-1, which is required for inactivation of glutamate in the synapse, is diminished [24]. Elevated levels of CNS glutamate have been noted in fulminant hepatic failure proportional to the degree of neurologic impairment. However, while seizures and hyperexcitability are seen in early acute hepatic encephalopathy and some congenital metabolic disorders, they are not common in patients with encephalopathy associated with chronic liver failure, as would be expected in the setting of excess excitatory neurotransmitters, casting doubt on the glutamate hypothesis as complete. The potential for ammonia to also *decrease* excitatory transmission, apparently by a post-synaptic mechanism, may partially explain these observations [25]. Glutamate receptors of all types are decreased on post-synaptic neurons, perhaps partially explaining the absence of neurological hyperactivity. The specific receptor most affected seems dependent on whether hepatic failure is acute or chronic.

GABA, **γ-aminobutyric acid**, is an inhibitory neurotransmitter found throughout the CNS. An alternative hypothesis to explain hepatic encephalopathy attributes neurologic dysfunction to excess GABA or heightened sensitivity to it [26, 27]. Increased blood-brain permeability allows increased amounts of GABA, derived from the gut, to enter the brain and bind to its receptor, producing neuronal inhibition and, presumably, hepatic encephalopathy. The GABA receptor is closed linked to the central benzodiazepine receptor ($GABA_A$). Drug-binding as well as binding by related compounds to these receptors enhances neuroinhibition. Furthermore, ammonia facilitates GABA-gated chloride currents and increases agonist ligand binding to the $GABA_A$/benzodiazepine receptor complex. This hypothesis predicts that patients with hepatic encephalopathy will be exquisitely sensitive to the benzodiazepines and endogenous benzodiazepine-like substances (which appears to be the case) and that benzodiazepine-antagonists such as flumazenil will improve the encephalopathy. Flumazenil does appear to decrease neurologic manifestations of chronic liver failure, but its effect is partial and transient, and there is no correlation with benzodiazepine receptor ligands in blood.

In addition to the GABA receptors coupled to central benzodiazepine receptors, peripheral-type benzodiazepine receptors (PTBR) on the outer mitochondrial membrane are noted to be increased in patients dying in hepatic coma, as well as in a variety of animal models of hepatic encephalopathy. Increased ammonia levels appear to upregulate astroglial PTBRs with increased production of neurosteroids. These neurosteroids have potent positive modulatory effects on the neuronal $GABA_A$ receptor which, combined with an ammonia-induced astroglial defect in GABA uptake may result in enhanced GABAergic tone [28, 29] and dysregulation of brain function through differential effects on neurotransmitter receptors [30]. In addition these substances may induce the morphological changes (Alzheimer type II) characteristic of hepatic encephalopathy [31].

Accumulation of **manganese**, particularly in the globus pallidus, has been shown to occur in patients with chronic liver failure and correlates with extrapyramidal symptoms in these patients, although not with the grade of encephalopathy [32–35]. MRI reveals signal hyperintensity in the globus pallidus on T1-weighted images, hypothesized to be related to deposition of paramagnetic Mn^{2+}, and autopsy demonstrates elevated tissue levels of manganese in patients dying in hepatic coma. Manganese appears to decrease glutamate uptake by astrocytes and increase glyceraldehydes-3-phosphate dehydrogenase, which suggests a role in the glutamatergic system as well as energy metabolism. In addition, its accumulation in astrocytes in non-human primates is associated with development of Alzheimer type II astrocytosis. Reversal of both symptoms and radiologic findings occurs after liver transplantation.

Management

Current treatment is very limited. Careful attention to details of general supportive care is essential (Table 2.3). Decreasing serum ammonia levels by administration of lactulose is considered the mainstay of therapy. Determining levels by arterial sampling is important, because arteriovenous difference of ammonia levels can be significant in hepatic failure. By-products of lactulose fermentation by gut flora decrease the pH in the intestinal lumen and trap ammonium in the colon for excretion. The osmotic load promotes rapid evacuation, but risks hypovolemia and hypernatremia. Even this routine approach to management, however, is of questionable value. For example, a recent meta-analysis questioned the beneficial effects of

non-absorbable disaccharides [36]. Antibiotics, e.g., neomycin or metranidazole, administered enterally alter gut flora and reduce bacterial production of ammonia and may be superior to lactulose [36].

Patients should be cared for with the head of the bed elevated to 30°. Controlled ventilation is indicated for those with absent protective airway reflexes and/or ineffective respiratory effort. Mannitol and loop diuretics are appropriate for patients with intracranial hypertension. Efforts to decrease external stimuli and control patient restlessness are difficult in the PICU setting, but important, and patients should be monitored for seizure activity. Sedation may be desirable in agitated patients, though the risk of exacerbating the encephalopathy must be considered (certainly the benzodiazepines should be avoided in these patients). Hyponatremia may worsen osmolar disequilibrium in the brain and should be corrected. Very limited experience supports use of hypertonic saline and maintenance of serum sodium level of 145–155 mEq/L [37]. Hyperglycemia may also increase intracranial pressure in hepatic failure [38]. Maintenance of normal serum glucose levels is recommended.

Intracranial pressure monitoring in these patients is controversial because of patients' coagulopathy and associated risk of intracranial hemorrhage. However, the correlation between clinical neurologic dysfunction and intracranial hypertension is poor, and numerous centers have reported experience with extradural monitoring devices. While the risk of CNS bleeding is real, the information gained has proved valuable in supporting these patients. It has also been used to help assess a patient's potential to survive and benefit from transplantation and to provide appropriate intraoperative intervention at the time of transplantation. Accumulated experience indicates that epidural monitoring, while somewhat less reliable, is significantly less risky than other approaches. With epidural monitoring, complications occur in approximately 4 % of patients with fatal hemorrhage in 1 %, as compared with 20 and 4 % with other types of monitors [39]. With the availability of Factor VIIa, it may be possible to further reduce the risk of bleeding in monitored patients [40].

Temperature control should help avoid increased cerebral blood flow and metabolism. In addition, induced hypothermia may be of some value. Several preliminary, small studies suggest that maintaining hypothermia (32–33 °C) may improve cerebral autoregulation and response to CO_2, and decrease cerebral edema and intracranial pressure [41–45]. Larger, better controlled studies are necessary, but hypothermia may be helpful in providing additional time to transplantation. The diagnosis, staging, pathophysiology, and management of hepatic encephalopathy is discussed further in the chapter on toxic/metabolic encephalopathy in this textbook.

Table 2.3 Hepatic encephalopathy: supportive care

Maintain normal serum electrolyte levels
Avoid hyponatremia
Maintain normoglycemia
Maintain hemodynamic homeostasis
Normovolemia
Normotension
Reduce serum ammonia levels
Lactulose
Non-absorbable antibiotics (e.g. neomycin)
Elevate head of bed 15–30°
Mechanical ventilation
Provide airway protection
Maintain mild hyperventilation
Consider mild-moderate sedation
Consider induction of mild hypernatremia
Consider epidural ICP monitor when coma > stage II
Maintain INR <1.5; platelets >50,000
Mannitol (0.25–0.5 g/kg IV) for elevated ICP, or
Loop diuretic
Consider therapeutic coma (with ICP monitoring)
Avoid hyperthermia
Consider hypothermia

Acute Kidney Injury

Pathogenesis of Hepatorenal Syndrome

Acute kidney injury occurs frequently in patients with both acute and chronic liver failure [46, 47]. Hepatorenal syndrome (HRS) is the most common cause of acute kidney injury in this population, but other causes include prerenal azotemia, acute tubular necrosis following episodes of hemorrhagic or septic shock, and direct renal toxicity (e.g. acetaminophen, radiocontrast-induced, hepatitis B or C). Forty to eighty percent of patients with fulminant hepatic failure develop HRS, and it occurs in up to 40 % of patients with cirrhosis and ascites. Two clinical presentations have been described. Type I is rapid in onset and progression, with a doubling of creatinine in less than 2 weeks (to >2.5 mg/dl in adults) and frequently follows an episode of hypovolemia or hypotension. Type II is more indolent with a less dramatic increase in serum creatinine. The primary manifestation is often diuretic-resistant ascites. In both types, onset often appears to be the consequence of an acute change in intravascular volume leading to an unstable renal circulation with cortical vasoconstriction and corticomedullary redistribution of blood flow. Renal histology is normal. Common precipitating events include gastrointestinal losses, hemorrhage, excessive diuresis, paracentesis without albumin replacement, or sepsis, especially spontaneous bacterial peritonitis. Some patients develop HRS in association with progressive hepatic deterioration in the absence of an obvious precipitating event. However, mild systemic hypotension is reliably

present. Multiple circulating vasoactive substances have been implicated in its pathogenesis including renin and angiotensin II, norepinephrine, arginine vasopressin, substance P, endotoxin, octopamine, and prostaglandins E_2 and I_2, among others.

In severe hepatic insufficiency the renal circulation is subject to complex hemodynamic effects of multiple vasoactive mediators [48, 49]. Hepatic failure itself and portal hypertension lead to extreme splanchnic vasodilatation secondary to increased local production (and decreased clearance) of vasodilating substances, especially nitric oxide, but including endotoxin and numerous cytokines. Ultimately systemic vasodilatation also occurs. Vasodilatation results in decreased *effective* intravascular volume and increased activation of vasoconstrictor mechanisms, especially the renin-angiotensin-aldosterone axis and sympathetic nervous system. Exposure to these endogenous vasoconstricting substances shifts the renal autoregulatory curve to the right. Although patients with severe hepatic insufficiency respond to the decrease in splanchnic and systemic vascular resistance with a compensatory increase in cardiac output, increased output is inadequate to normalize blood pressure. The resulting mean arterial pressure is on the pressure-dependent portion of the renal autoregulatory curve. Decreased renal blood flow leads to a further intense compensatory increase in renal vasoconstrictor and antinatriuretic mediator release, including renin, angiotensin, aldosterone, norepinephrine, and arginine vasopression, with resulting preglomerular vasoconstriction. Increased production of endothelin-1 in the renal vascular bed likely contributes to renal vasoconstriction [50]. Renal synthesis of nitric oxide and vasodilating prostaglandins is decreased.

The observation that renal blood flow is lower in some patients without HRS than in some with the syndrome suggests that mechanisms other than decreased RBF are important. Contraction of glomerular mesangial cells with reduction of the surface area available for glomerular filtration may be another important response to many of these agonists, particularly the endothelins, and an additional factor decreasing renal function [51]. This disturbance in vascular tone leads to hypofiltration, with sodium and water retention, while tubular function is preserved. High levels of circulating antidiuretic hormone further impair excretion of water by promoting reabsorption in the distal nephron. Of great interest is the fact that these derangements are functional: they are reversible after hepatic transplantation. Moreover, the kidneys function if *they* are transplanted into a recipient without liver dysfunction.

There are no specific clinical findings in the hepatorenal syndrome. Diagnosis follows exclusion of other causes of renal failure and absent diuretic response to volume loading (Table 2.4). It is supported by the presence of oliguria, elevated blood urea nitrogen (BUN) and serum creatinine, low urinary sodium (<10 mEq/L) and a ratio of urinary to plasma osmolality greater than 1 in the setting of adequate intravascular volume. Hyponatremia (<130 mEq/L) is virtually universal. Patients with hepatorenal syndrome have usually had sodium retention prior to development of renal insufficiency. Activation of antinatriuretic systems and impaired renal capacity to excrete solute-free water leads to disproportionate water retention and dilutional hyponatremia. In the face of severe hepatic insufficiency, however, BUN and serum creatinine, as well as apparent creatinine clearance, may be misleadingly low. Table 2.5 provides criteria for differentiating forms of renal insufficiency in patients with liver failure.

Table 2.4 Diagnosis of hepatorenal syndrome, based on International Ascites Club consensus, adapted for children

Major criteria
Chronic or acute liver disease with advanced hepatic failure and/or portal hypertension
Low glomerular filtration rate, as indicated by serum creatinine >2× baseline (normal for age)
Absence of shock, ongoing bacterial infection, or current or recent treatment with nephrotoxic agents. Absence of gastrointestinal fluid losses
No sustained improvement in renal function following diuretic withdrawal and volume expansion with 20 ml/kg isotonic fluid
Proteinuria <500 mg/dl and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Minor criteria
Urine volume <0.5 ml/kg/h × 24 h
Urine sodium <10 mEq/l
Urine osmolality greater than plasma osmolality
Urine RBC <50/hpf
Serum sodium concentration <130 mEq/l

Adapted from Arroyo et al. [52]. With permission from John Wiley & Sons, Inc.

Table 2.5 Differentiating causes of oliguria

	Prerenal	HRS	ARF
U [Na^+]	<10	<10	>30
U/P Cr	>30:1	>30:1	<20:1
U/P osm	>1	>1	1
FeNa	<1 %	<1 %	>2 %
Sediment	±	±	Casts, cells, etc.
PCWP	<10	>12	
Vol expansion	Diuresis	No diuresis	No diuresis

HRS hepatorenal syndrome, *ARF* acute renal failure

Management of Hepatorenal Syndrome

Treatment of hepatorenal syndrome is non-specific, but includes volume administration, titrated to central venous or pulmonary artery wedge pressure, and maintenance of adequate systemic arterial pressure. The age appropriate renal perfusion pressure necessary to maintain renal blood

flow is inadequately defined, but in adults is approximately 70–75 mmHg. Treatment with low dose (*renal dose*) dopamine is no longer recommended [53] – data supporting its use are absent, and the growing recognition of adverse effects of its use on pituitary function and lymphocyte numbers make its use less benign.

A combination of volume expansion and systemic vasoconstrictor administration appears beneficial. Presumably, overcoming splanchnic vasodilatation and increasing renal perfusion pressure lead to decreased production of local renal vasoconstrictors with improved renal perfusion and filtration. Effective agents include alpha-adrenergic agents (norepinephrine) and vasopressin and its analogues (terlipressin). Terlipressin, which acts on V1 vasopressin receptors, is best studied, although not in children. It is associated with a significant improvement in glomerular filtration rate with a much lower incidence of the ischemic complications seen with a similar, now abandoned agent, ornipressin [54–56]. At present terlipressin is not available in the U.S. Alpha-adrenergic agents, such as norepinephrine, are attractive because they are widely available, inexpensive, and apparently equally effective. However studies of efficacy and side effects are very limited. Octreotide, a somatostatin analogue, does not appear to be effective. The potential benefit of endothelin receptor antagonists and N-acetylcysteine is currently under investigation.

Once volume loading is adequate, diuretic therapy, particularly by steady infusion to avoid large fluid shifts, may be helpful. Unfortunately, achieving the desired solute-free water loss in these patients with available diuretics is difficult, and the natriuresis that occurs complicates the hyponatremia commonly already present. Two new experimental aquaretic agents offer a novel therapeutic approach to management of patients with cirrhosis with ascites and/or hepatorenal syndrome [57, 58]. Both selectively increase urine flow and solute-free water excretion. One group, the non-peptide AVP V2 receptor antagonists, selectively inhibit the water-retaining effect of AVP on renal tubules. Selective kappa opioid agonists comprise the second group. These agents both inhibit AVP release from the pituitary and have a direct effect on renal V2 receptors. Early clinical trials have been promising [59–62]. In addition to these new agents, discovery of aquaporins in the tubule has led to development of specific water channel blockers, which may also have a future role in management of HRS.

Nephrotoxic agents should be avoided, including NSAIDs and aminoglycosides, to the extent possible. Paracentesis may improve renal hemodynamics by improving perfusion pressure, but must be done extremely cautiously, with administration of intravenous albumin and careful attention to blood pressure. Renal replacement therapy is indicated for fluid overload, absence of adequate response to diuretics, acidosis, hyperkalemia, or severe hyponatremia. Continuous venovenous hemofiltration minimizes the risk of further destabilizing fluid shifts. Liver replacement is the only definitive treatment.

Coagulopathy and Bleeding Disorders

Coagulopathy is a hallmark of severe liver dysfunction and results from multiple derangements of hemostasis, including decreased production and clearance of coagulation factors, abnormal platelet production and function, increased fibrinolysis and dysfibrinogenemia, endothelial cell activation, and possible disseminated intravascular coagulation [63]. The liver is the primary site for synthesis of all coagulation factors and related inhibitory proteins except von Willebrand factor. Impaired hepatic synthetic function thus leads to decreased production of multiple factors in the coagulation pathway. Decreased factors II, V, VII, IX, and X result in prolongation of the prothrombin time (PT) and increased INR. Factors V and VII have the shortest half-lives and are, theoretically, the most sensitive indicators of hepatic dysfunction. However, they provide little advantage over the PT in practical terms and determination is far more expensive. Partial thromboplastin time (PTT) reflects abnormalities in all of the coagulation factors except VII and XIII. Prolongation occurs later in liver disease progression, but is common in severe dysfunction.

Unlike other components of the coagulation cascade, Factors VIII and von Willebrand factor are increased in these patients. This elevation of Factor VIII levels may help differentiate the coagulopathy of liver disease from DIC. Although the liver is the primary site of Factor VIII production, it is also synthesized in a variety of other tissues, including kidney, spleen, lymph nodes, and lung. While these alternate sites for synthesis may explain maintenance of Factor VIII levels, they do not provide an explanation for elevated levels. Factor VIII is stabilized under normal circumstances by complexing with von Willebrand factor. In liver disease von Willebrand factor is elevated, and partially explains increased levels of circulating Factor VIII. However, the elevation of Factor VIII exceeds that of von Willebrand factor, and other mechanisms are likely involved.

Nutritional deficiencies in some children with hepatic failure may result in decreased production of multiple vitamin K-dependent coagulation factors, including II, VII, IX, and X, as well as Proteins C and S, particularly in children with chronic hepatic insufficiency. Poor oral intake and cholestasis contribute to vitamin K_1 (phyllaquinone) deficiency, and use of broad-spectrum antibiotics that alter gut flora decreases synthesis of Vitamin K_2 (menaquinone), the primary source of liver vitamin K stores. A trial of intravenous vitamin K is warranted, but if there is no increased synthesis of the K-dependent factors, persistent coagulopathy is more

likely attributable to decreased hepatocyte function and increased consumption, rather than to vitamin K deficiency.

Low plasma fibrinogen, from decreased liver production and increased fibrinogenolysis, also contributes to coagulopathy in these patients. Tissue plasminogen activator and plasminogen activator inhibitor are increased. Plasminogen and α2-antiplasmin may be decreased. Disseminated intravascular consumption may develop in patients with FHF as a consequence of thromboplastic materials released from necrotic hepatocytes, expression of tissue factor on activation endothelial cells and subendothelium, failed clearance of endotoxins, and cytokine stimulation. In addition, some patients demonstrate dysfibrinogenemia, characterized by a defective form of fibrinogen with impaired fibrin polymerization, poor fibrin formation, and friable clots. The diagnosis is made by demonstrating normal fibrinogen levels, elevated fibrin degradation products, and prolonged thrombin time, uncorrectable with FFP.

Protein C and S production is also commonly decreased in patients with severe liver dysfunction. Hepatic production of ATIII is also decreased, and its consumption by thrombin is increased. The resulting deficiency has a major effect on heparin kinetics: the effect of an initial dose is increased, but the half-life of the anticoagulant in decreased. Decreased levels of these components of the coagulation cascade may explain the *paradoxical* phenomenon of frequent tubing occlusion during hemodialysis and continuous renal replacement therapies in coagulopathic patients.

Most patients are thrombocytopenic, and have deranged platelet function. In chronic liver disease thrombocytopenia commonly results from hypersplenism as well as decreased platelet production. In acute liver failure consumptive processes related to the underlying disease and decreased thrombopoeitin play a major role. Decreased platelet numbers and function interfere with formation of the primary hemostatic plug. Abnormal function results in failure to create the microenvironment necessary for production of fibrin and progression to a mature clot. Circulating platelets are smaller than normal, suggesting decreased release of young platelets from the marrow and impaired clearance of poorly functioning older ones by the reticuloendothelial system. Thrombocytopenia has been attributed to hypersplenism, accompanied by increased platelet sequestration, platelet destruction mediated by platelet-associated immunoglobulins, and diminished platelet production stimulated by thrombopoietin, which is produced predominantly (most likely exclusively) by the liver. The relative importance of each is unclear. Recent studies addressing the importance of thrombopoetin have yielded conflicting results [64–66]. However, following transplantation most patients have a prompt increase in platelet counts prior to appreciable change in spleen size [67]. Children with liver disease and thrombocytopenia been shown to have decreased hepatic thrombopoeitin mRNA, more severe in acute liver failure and decompensated cirrhosis than in compensated cirrhosis [68]. The role of recombinant thrombopoietin as a treatment for thrombocytopenia in liver disease requires investigation.

Platelet function is also impaired. Platelet aggregation is decreased: ADP-stimulated aggregation occurs in only 50 % of patients and requires a sixfold increase in the ADP dose when it does occur. Platelet adhesion is increased. Contributing factors include increased von Willebrand factor, altered membrane phospholipids, and increased platelet activation. Increased adhesiveness may explain the fall in platelet count often associated with hemodialysis and other renal replacement therapies in these patients, as well as frequent problems with continuous hemofiltration circuits.

Management of disordered hemostasis in these patients is difficult. Ultimate resolution depends on recovery or replacement of the failed liver. Gastrointestinal hemorrhage prophylaxis with H2 receptor antagonist, proton-pump inhibitors, and/or sucralfate is routine. Providing coagulation factors with intermittent or continuous infusions of FFP for active bleeding or for prophylaxis prior to or during invasive procedures is a temporizing measure. High volume plasma exchange and combined treatment with FFP and ATIII have been successful in restoring homeostasis and prolonging survival in the short term. Treatment with Factor IX concentrate may be useful, but there is controversy over the potential risk of promoting DIC. Thrombocytopenia and abnormal platelet function also predispose to catastrophic bleeding. While some recommend transfusion at a higher threshold, platelet transfusion at 20,000 cells/μL or less or for active bleeding is usually adequate. Treatment with DDAVP is of little value, since von Willebrand factor is already elevated in these patients. Synthetic Factor VIIa may be valuable addition to managing coagulopathy in patients with hepatic insufficiency. Experience in children remains limited but encouraging: it appears to be effective in correcting the INR in patients inadequately responsive to administration FFP or Vitamin K. It has the additional benefit of improving platelet function [69].

Variceal bleeding is a common reason for PICU admission of children with chronic liver disease. It is a complication of cirrhosis in most patients but can also occur secondary to extrahepatic portal hypertension in patients with normal liver function. Once variceal bleeding has occurred, recurrence is likely. Although coagulopathy may contribute to its severity, bleeding is less a complication of coagulopathy than one of altered splanchnic circulation secondary to resistance to portal venous flow. The mainstay of treatment of variceal bleeding is infusion of a vasoactive agent; in the U.S. octreotide is recommended. Somatostatin and vasopressin are alternatives. These agents decrease splanchnic blood flow and thus portal pressure, decreasing pressure within varices. Octreotide, a synthetic, long-acting form of somatostatin, selectively vasoconstricts splanchnic vessels and is

associated with fewer systemic side effects than vasopressin. It has a rapid onset of action and decreases portal pressure within minutes of administration.

Somatostatin receptors are found throughout the body. The effects of somatostatin and octreotide appear to be the consequence of binding to G proteins, with subsequent inhibition of adenyl cyclase. In the GI tract they decrease splanchnic blood flow, intestinal motility and gastric emptying, and increase intestinal absorption of water and electrolytes. They also decrease production of multiple gastrointestinal peptides and pancreatic enzymes, including insulin. Outside of the GI tract, side effects are numerous, including bradycardia and other ECG abnormalities, inhibition of growth hormone and thyrotropin release. They may also have an immunomodulatory role in the thymus [70]. Vasopressin activates V1 receptors on vascular smooth muscle cells and induces splanchnic and systemic vasoconstriction.

Correction of a severe co-existing coagulopathy is probably important, but normalizing clotting studies may be less critical than avoiding administration of excessive fluid that leads to increased variceal wall stress. Anti-secretory agents are recommended because of the high rate of associated peptic ulcer disease. A recent meta-analysis in adults indicates that sclerotherapy is not superior to vasoactive drugs (including terlipressin, somatostatin, and octreotide) for control of bleeding, rebleeding, blood transfusions, death, or other adverse events [71]. It does have advantages over vasopressin. It is associated with significantly more adverse events than somatostatin. Controversy remains over whether endoscopic therapy be added only in pharmacologic treatment failures or whether early combined therapy should be routine. Current recommendation is for endoscopy to determine the site of bleeding and potentially initiate endoscopic therapy, once initial hemostasis is achieved and visualization is optimized. In patients with recurrent life-threatening episodes of bleeding who fail endoscopic therapy, a TIPS procedure (transjugular intrahepatic portosystemic shunt) may be effective at reducing portal pressures.

Respiratory Dysfunction

Respiratory insufficiency in children with liver disease may result from abnormalities at any point in the ventilatory system, including the central nervous system, bellows apparatus, airways, and lung parenchyma. Progression of liver failure from mild to moderately severe is characterized by a respiratory alkalosis; late cirrhosis and deep coma are associated with the onset of metabolic acidosis [72]. Respiratory alkalosis is well described but not fully understood. It is most likely related to increased cardiac output and stimulation of intrapulmonary stretch receptors or intravascular baroreceptors, particularly during periods of increased intravascular (venous) volume. In addition, there is evidence that elevated levels of progesterone and estradiol are present in patients with cirrhosis and may contribute to respiratory alkalosis by activating progesterone receptors in the central nervous system [73]. Patients with hepatic encephalopathy usually maintain adequate (or increased) respiratory drive until severe cerebral edema develops, but may lose protective airway reflexes.

Respiratory mechanics are frequently impaired, particularly in very young infants and children with chronic liver disease. The diaphragm is commonly elevated and flattened secondary to abdominal distension and hence functions at a mechanical disadvantage. This, in combination with generalized muscle wasting from poor nutrition, places these patients at risk for respiratory failure with any increase load on the respiratory system. In patients with rickets as a result of Vitamin D malabsorption and abnormal liver metabolism, chest wall deformity and excessively flexible ribs, as well as hypophosphatemia may further compromise respiratory function.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a frequent complication of acute/fulminant hepatic failure and has a particularly high mortality rate in this population. Chronic liver disease (cirrhosis) is also a risk factor for its development and increased severity [74]. Failure of the diseased liver to clear or detoxify inflammatory mediators from the circulation contributes to its development. In addition, production and release of acute phase reactants, cytokines, and vasoactive agents from the injured liver most likely play a role [75]. Factors which may contribute to its development include increased pulmonary leukotriene B_4 and C_4 concentration, increased nitric oxide production, impaired systemic clearance of endotoxin, and altered systemic glutathione homeostasis. Under normal circumstances glutathione is produced by the liver, taken up by the alveolar type II cells from plasma, and maintained in the lung at concentrations far greater than in plasma. Decreased production of glutathione by the diseased liver limits pulmonary uptake. Subsequently decreased pulmonary clearance of oxidants and reactive oxygen species may contribute to the severity of ARDS [76, 77]. Liver transplantation often results in rapid resolution of ARDS.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is the triad of abnormal arterial oxygenation caused by intrapulmonary vasodilatation and shunting in the setting of liver disease or portal hypertension [78, 79]. Histologic findings include dilated pulmonary arterioles and capillaries, as well as dilated channels between pulmonary arteries and veins. Patients demonstrate arterial deoxygenation ($PaO_2 < 80$ mmHg on room air) and increased alveolar-arterial oxygen gradient ($\geq$15 mmHg), but normal $PaCO_2$. Contrast enhanced echocardiography with agitated saline reveals rapid appearance of microbubbles in the left heart, and technetium-99 macroaggregated albumin scan reveals extrapulmonary deposition. It occurs most commonly

in patients with cirrhosis, but has been recognized in both acute and chronic hepatitis, and in patients with prehepatic portal hypertension, as well as hepatic venous obstruction. Although uncommonly discussed in pediatrics, it is well documented to occur in children of all ages, especially in those with biliary atresia and polysplenia [80], and may account for 10 % of patients undergoing liver transplantation in some series [81, 82]. Its contribution to respiratory dysfunction in critically ill children may be under-recognized.

Arterial deoxygenation is related to rapid passage of pulmonary arterial blood through dilated pre- and post-capillary vessels, entering pulmonary venous channels without effective alveolar oxygenation. Pulmonary vessels demonstrated decreased tone and impaired hypoxic vasoconstriction. Early disease appears to be primarily characterized by V/Q mismatch, but with increasing severity intrapulmonary shunt and impaired oxygen diffusing capacity develop. The underlying mechanism is unclear, but is likely related to increased pulmonary nitric oxide production. Increased hepatic production of endothelin-1 is associated with increased pulmonary vascular expression of ET_B receptors in animal models. ET-1 binding to these receptors may stimulate NO production. Intravascular macrophage accumulation may further contribute to high NO levels.

Patients may be asymptomatic if hypoxemia is mild, but commonly have shortness of breath. They may have orthodeoxia (decrease in oxygenation with a change of position from supine to upright). Spider nevi, clubbing, and cyanosis may be present. Spongiform vascular lesions can sometimes be seen on chest radiographs. In adults, a hyperdynamic circulation is common but not consistent. In the limited number of children reported, portal hypertension and elevated cardiac output do appear to be constant findings. In most patients able to cooperate, spirometry is normal, but diffusing capacity is moderately to severely reduced. Diagnosis requires arterial blood gas sampling, ideally at room air and on 100 % O_2, in addition to demonstrating intrapulmonary shunting.

Hepatopulmonary syndrome is progressive, although the rate is variable. Aside from oxygen supplementation, the only effective treatment is liver transplantation. Although previously a contraindication to transplantation, current recommendations are to use progressive disease as an indication for transplantation prior to the development of severe hypoxemia. Outcome is fairly good, although complications, including wound infection and bile leak, are more common, and the mortality rate is higher than in patients without HPS [81]. Resolution of the pulmonary vascular disease occurs at a variable rate, ranging from days to years [80, 82, 83].

Respiratory Support

Goals of respiratory support are to assure generous oxygenation and avoid hypercapnia and its associated effects on cerebral blood flow and intracranial pressure. In the patient with respiratory alkalosis, providing sufficient minute ventilation to achieve the patient's spontaneous *set-point* appears prudent, although extreme hyperventilation may have deleterious effects on cerebral blood flow and oxygen delivery. High airway pressures may decrease jugular venous return and increase hepatic venous pressure, compromising cerebral and hepatic blood flow.

Treatment of ARDS in this population is nonspecific and should follow current general guidelines for its management. Treatment of hepatopulmonary syndrome is supportive and primarily focused on correcting hypoxemia with supplemental oxygen. There is limited evidence that infusions of methylene blue, which inhibits guanylate cyclase, and limits the effects of NO, can increase pulmonary vasoconstriction and improve oxygenation. This suggests potential benefit of NO inhibition, but there is no clinical application available at present.

Circulatory Derangements

Circulatory derangements in severe hepatic failure are significant and roughly proportional to the severity of liver disease [84, 85]. Portal hypertension appears to lead to splanchnic dilatation, at least in part mediated by nitric oxide [86–88], but the etiology of progressive systemic hemodynamic dysfunction is multifactorial. Evidence specifically related to children is very limited, but in adults there is evidence for left atrial and left ventricular enlargement (data related to right-side chamber size are conflicting), left ventricular hypertrophy, myocardial systolic and diastolic dysfunction, abnormalities of conduction (particularly prolonged QT interval), and autonomic dysfunction [89–91]. The systemic circulation is hyperdynamic, characterized by elevated cardiac output and increased heart rate, until very late in the course of disease, with low systemic vascular resistance and diminished response to vasopressor agents [92–95]. Low SVR and reduced afterload probably mask ventricular dysfunction, which can, however, be demonstrated during exercise testing and postural challenge in many patients.

Natriuretic peptide levels are elevated, consistent with the atrial and ventricular enlargement seen in many patients with chronic liver disease, and are known to be related to increased cardiac release, rather than decreased hepatic clearance. Recent evidence suggests they may be a marker of cardiomyopathy, rather than merely a reflection of volume overload [96, 97]. Increased sympathetic tone, increased intravascular volume and arteriovenous connections contribute to the high cardiac output state. In addition, chronic neurohumoral overactivity may stimulate cardiac tissue growth, including myocardial hypertrophy, but also cause injury, with development of fibrosis, and hinder ventricular relaxation. Observations in patients and experimental studies have shown decreased myocardial β-receptors as well as post-receptor defects in signal transduction [98, 99]. Elevated troponin I levels in

patients with cirrhosis but without a history of cardiac disease supports the possibility of ongoing injury [100].

Systemic arterial pressure is initially normal, but hypotension, especially diastolic, may develop with progressive disease and compromise blood flow to major organ systems. In patients with end-stage disease, vasodilation of the splanchnic circulation persists, but there is vasoconstriction of other tissue beds, including kidney, muscle, and skin. Decreased hepatic clearance of vasodilator substances arising in the gut may permit greater exposure of the systemic vasculature and subsequent vasodilatation. Increased circulating endotoxin from bacterial overgrowth increases cytokine production and nitric oxide synthesis. Decreased vascular tone may result from increased NO production, although, paradoxically, response to NO in patients with acute liver failure appears to be impaired [47]. Elevated levels of circulating cytokines triggered by hepatic necrosis may also contribute. Microvascular injury that results leads to capillary occlusion and shunting of blood away from nutritive vessels through precapillary arteriovenous channels. As severity of liver failure progresses and/or tissue perfusion decreases, a metabolic (lactic) acidosis develops, and represents premorbid circulatory deterioration.

Pulmonary hypertension is an uncommon complication of liver disease in children, usually associated with portal hypertension (portopulmonary hypertension) [101]. Histologic findings are consistent with plexogenic arteriopathy of the peripheral pulmonary arteries, including increased smooth muscle, increased thickness of the media, concentric luminal interstitial fibrosis and eventually fibrinoid necrosis. It is often rapidly progressive once the patient is symptomatic. Pharmacologic treatment has not been satisfying although newer agents may have benefit, and the benefit of liver transplantation is quite variable [102].

Optimizing cardiovascular function in patients with severe liver disease includes maintenance of an adequate circulating blood volume and initiation of vasoactive drug administration to increase diastolic and mean pressures to levels adequate for organ perfusion. Pure α-agonists are unlikely to be beneficial; norepinephrine or epinephrine is more likely to be effective. Treatment should be directed toward achieving a normal diastolic and mean arterial blood pressure. In some instances, however, it may be acceptable to tolerate lower than normal pressures if cardiac output and oxygen delivery are adequate, and there is no significant elevation of serum lactate. A trial of N-acetylcysteine can be considered for its non-specific effects on cardiac output, oxygen delivery, and oxygen consumption. These effects may be the result of N-acetylcysteine improving local production and effect of NO, or, alternatively acting as an antioxidant, reducing microcirculatory endothelial injury. As mentioned above, however, a multi-institutional evaluation of N-acetylcysteine in patients with non-acetaminophen induced liver failure was unable to show any benefit (and possibly worsened outcome) [4]. Overall, cardiovascular complications of liver disease resolve after liver transplantation.

Plasmapheresis in Fulminant Hepatic Failure

High-volume plasmapheresis or plasma exchange has the potential to remove circulating mediators and metabolic toxins from the circulation of patients with deranged liver function. Trials of plasmapheresis in adults with hepatic encephalopathy have demonstrated improved coma scores, increased cerebral perfusion pressure, increased cerebral oxygen consumption, and stabilization of systemic hemodynamics [103, 104]. The effect has been hypothesized to be due in part to removal of neuroinhibitory plasma factors. Experience in children indicates that plasmapheresis can be safely accomplished even in the neonatal period. Significantly improved coagulation can be achieved, without fluid overload, by way of increased levels of fibrinogen and factors II, V, VII, and IX. In most patients the prothrombin time can be maintained below 25 s with daily pheresis [105]. Because of this, it is an effective means of preventing life-threatening bleeding in these profoundly coagulopathic patients. Overall improvement in multiple organ dysfunction has also been noted. Improvement in neurologic status appears to be transient, and no effect on liver regeneration has been noted.

Liver Transplantation

Over the past 25 years, liver transplantation has matured from an experimental and innovative procedure to accepted treatment of end-stage liver disease, whether acute or chronic, for children of all ages. Overall outcome has improved steadily: 5–8 year patient survival is in the range of 75–90 % [106–108]. The outcome of transplantation in infants under a year of age has improved dramatically and is comparable to results in older children. Even the youngest recipients, those under 3 months of age, have acceptable short- and long-term survival rates. While there remains risk of long term disability after transplant, the need for lifelong immunosuppression in most patients and significant cost for long-term medical management, good overall quality of life can be anticipated [109].

Children with fulminant hepatic failure are at high risk of death. While some will recover liver function, many will progress rapidly to hepatic encephalopathy and death. Making the decision to proceed to transplantation is difficult and requires recognizing the very small window of time between *too soon* and *too late*. Progressive synthetic dysfunction, extrahepatic organ failure, and development of hepatic encephalopathy resulting from a disease process unlikely to

resolve spontaneously, are general issues that guide the decision. The specific criteria are more difficult. Increasing INR and bilirubin predict a poor outcome. Prothrombin time >90 s after Vitamin K administration predicts 100 % mortality without transplant, but is a very extreme marker. INR less than 4 has been associated with 73 % survival without transplant, while an INR greater than 4 predicts a survival rate of only 14 %. Young age is also a poor prognostic sign: patients under the age of 2 years have a much lower survival rate (8 % vs 50 % in children older than 2 years).

British criteria for transplant in non-acetaminophen-induced liver failure include three of the following: non-A, non-B hepatitis or drug-induced injury; age less than 10 years; jaundice to encephalopathy time less than 7 days; serum bilirubin greater than 17.5 mg/dL; and prothrombin time longer than 50 s. For those with acetaminophen-induced disease, occurrence of three of the following indicates a need for transplantation: pH less than 7.3 24 or more hours after ingestion; serum creatinine greater than 3.4 mg/dL; stage 3 encephalopathy; and prothrombin time longer than 100 s. While not routinely used in U.S. practice, these guidelines provide a useful framework for decision-making.

Transplantation has greatly altered the outcome of fulminant hepatic failure [110]. However, the availability of organs remains the primary limiting factor. Whole organs rarely become available quickly enough to help these patients. Split organ transplantation, typically of the left lateral segment, makes transplantation possible much more quickly. Living related donation is also possible, but presents complex ethical issues, particularly in this setting where parent decision-making must be so pressured. Other options include transplantation of an auxiliary liver to allow regeneration of the native liver and potential removal of the transplanted liver if not needed in the future. Overall outcome of transplantation is not as good as in other transplant recipients, with early mortality of 20–40 %. Younger children and those requiring mechanical ventilation are at particularly high risk.

Artificial Support Devices

There is currently no widely available hepatic equivalent of renal dialysis or ventricular support device. A variety of devices have been used or are under development, including charcoal hemoperfusion, hemodiabsorption, hemoperfusion through hepatocytes, extracorporeal whole liver perfusion, bioartificial liver, and extracorporeal liver assist device. Ideally such support would have multiple capabilities including removal of toxins; synthesis of coagulation factors, albumin, and other proteins; and reversal of the inflammatory processes involving the liver and other organ systems. At present none of the devices has provided the support needed for long-term management.

Charcoal hemoperfusion is an effective means of removing water-soluble toxins but not ammonia or protein bound compounds and has not been helpful in hepatic failure. More recently developed systems have had greater ability to remove protein-bound substances, using hemodiabsorption, which combines hemodialysis with adsorption using charcoal or albumin. These include the BioLogic-DT and the MARS systems, which may explain their greater impact on hepatic encephalopathy [111–114]. Including biologic components in these systems, specifically living hepatocytes, holds additional promise, but multiple technical details have limited their value to date. One very recently published study of a bioartificial liver appears to show a survival benefit in fulminant/subfulminant hepatic failure [115].

A recent metanalysis of 12 randomized clinical trials of artificial and bioartificial liver support systems to evaluate their possible beneficial and harmful effects in acute and acute-on-chronic liver failure provided only limited encouragement [116]. Overall, support systems had no significant impact on mortality or bridging to liver transplantation, but did reveal a beneficial effect on hepatic encephalopathy. In patients with acute-on-chronic liver failure there did appear to be a benefit on mortality (33 % reduction), but not in those with acute liver failure Multicenter, prospective, controlled trials of extracorporeal liver assist devices are essential before their value can be known. In addition to determining whether such devices can truly prolong good survival, such studies will need to determine the best source of functioning hepatocytes and the number required to support patients of varying sizes, markers of improving or deteriorating native hepatic function, and the frequency and nature of complications in infants and children [117, 118].

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Acute Pancreatitis

3

Raffaele Pezzilli

Abstract

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. Clinically, two forms of acute pancreatitis are recognized: the mild form associated with minimal organ dysfunction and uneventful recovery, and the severe form associated with organ failure and/or local complications such as necrosis, walled-off pancreatic necrosis and pseudocysts. Due to the rareness and heterogeneous symptoms of acute pancreatitis in children, the disease is often misdiagnosed. Acute pancreatitis in children is often found after abdominal trauma, biliary or pancreatic malformation, drugs, biliary stones, viral or bacterial infections, systemic illnesses and metabolic diseases. In more than 20 % of cases, no clear etiological factors can be detected; thus, many young patients have an idiopathic form of pancreatitis. The percentage of severe pancreatitis in children is about 15 %; death occurs in about 5 % of cases. Improvements in diagnostic and imaging methods and growing awareness cannot account for the recent increases observed in the incidence of pediatric acute pancreatitis. Regarding treatment, the pain must be alleviated, and fluids and electrolytes should be administered immediately. After the acute pancreatitis is resolved, genetic tests should be carried out in cases of patients having a disease of unknown origin.

Keywords

Pancreatitis, acute necrotizing pancreatitis • Diagnostic techniques and procedures • Routine diagnostic tests • Severity of illness index, trypsinogen

Abbreviations

BUN	Blood urea nitrogen
CFTR-gene	Cystic fibrosis transmembrane conductance regulator gene
CRP	C-reactive protein
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
IL-1	Interleukin 1
IL-10	Interleukin 10
IL-6	Interleukin-6
IL-8	Interleukuin-8
LDH	Lactate dehydrogenase
MR	Magnetic resonance
PRSS-1	Protease-serine gene-1
PSTI	Pancreatic secretory trypsin inhibitor
SPINK1	Serine proteases inhibitor–Kazal type 1
TAP	Trypsinogen activation peptide
TNF-alfa	Tumor necrosis factor-alfa
TPN	Total parenteral nutrition

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Introduction

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems [1]. From a pathological point of view, the findings of acute pancreatitis range from microscopic interstitial edema and fat necrosis of the pancreatic parenchyma to macroscopic areas of pancreatic and peripancreatic necrosis and hemorrhage [1]. From a clinical point of view, the disease is accompanied by upper abdominal pain with variable abdominal symptoms, ranging from mild tenderness to rebound; it is also often accompanied by vomiting, fever, tachycardia, leukocytosis and the presence of elevated pancreatic enzymes in the blood and/or urine [1]. Clinically, two forms of acute pancreatitis are recognized: the mild form associated with minimal organ dysfunction and uneventful recovery, and the severe form associated with organ failure and/or local complications, such as necrosis, walled-off pancreatic necrosis, and pseudocysts [1].

Acute pancreatitis, especially if severe, can lead to several potential local complications. *Pancreatic necrosis* is a focal or diffuse area of non-viable parenchyma, which typically is associated with peripancreatic steatonecrosis. Computed tomography (CT) with intravenous contrast bolus is currently the best diagnostic method (accuracy 80–90 %). The necrosis may become infected in 10–30 % of cases. The distinction between sterile and infected pancreatic necrosis is important because the therapeutic approach (mainly medical therapy in sterile pancreatic necrosis and surgical in the infected type) and prognosis (mortality rate about three times higher in infected pancreatic necrosis) differ considerably. The diagnostic gold standard for suspected infection of pancreatic necrosis is represented by microbial cultures of material from percutaneous needle aspiration. *Acute fluid collection* is a localized effusion in or near the pancreas, without a fibrotic wall. It tends to appear early and regresses spontaneously in most cases. It is not considered a sign of disease severity unless it becomes infected.

Pseudocysts are collections of pancreatic juice enclosed by a non-epithelial wall. The maturation of a pseudocyst after acute pancreatitis requires at least 4 weeks after the onset of the disease. A post-acute pancreatitis pseudocyst is also an acute fluid collection persisting more than 4 weeks and surrounded by a well-defined wall. Finally, a *walled-off pancreatic necrosis* is an intra-abdominal collection of pus (usually near the pancreas), appearing after an attack of acute pancreatitis or after pancreatic trauma. Pus predominates and there is only a small amount of necrotic tissue, distinguishing it from infected pancreatic necrosis. A pseudocyst containing pus is also correctly defined as walled-off pancreatic necrosis [2].

Epidemiology

Acute pancreatitis is a rare disease in children; unfortunately, there are no epidemiological data on the incidence of the disease in childhood. Early published series reported five to ten patients per year at major children's hospitals and pediatric referral centers [3], even if an increasing number of children with this disease have been seen in large teaching hospitals where a number ranging from 30 to more than 100 children per year may be treated [3, 4]. No ethnic groups seem to be overexpressed [4]. As regards gender, the male:female ratio ranges from 0.7:1 to 2:3 [5]. The mean age at onset varies from 8 to 14 years; all ages, from under 1–18 years of age, seem to be involved [3, 6, 7]. The median duration of hospitalization per episode ranges from 8 to 13 days [3, 6].

Pathophysiology

Three phases characterize the pathophysiology of acute pancreatitis, as shown in Fig. 3.1. The concept that the cause of the pathophysiological changes in acute pancreatitis lay in the autodigestion of the pancreas mediated by the pancreatic enzymes is still generally accepted [8], and the intra-cellular activation of trypsin seems to play a key role in initiating acute pancreatitis. Furthermore, this event induces a variety of local and systemic responses, mainly mediated by the production of cytokines.

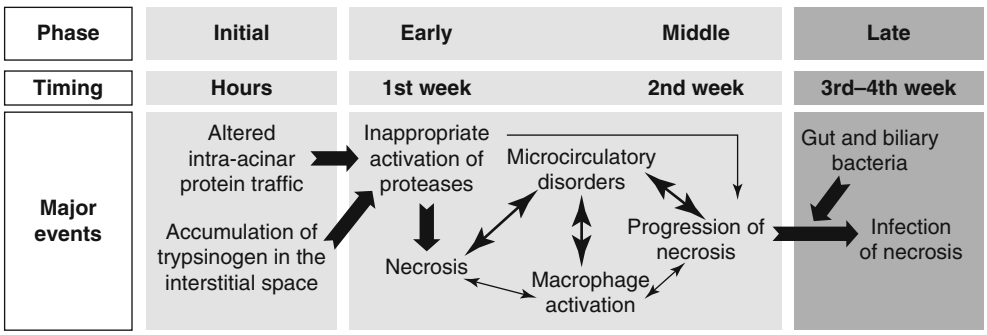

Fig. 3.1 Pathophysiological and clinical phases of acute pancreatitis

Trypsin is synthesized as an inactive proenzyme called trypsinogen in the endoplasmatic reticulum and is then transported to the Golgi system where the protein is sorted, together with other pancreatic enzymes, into core particles. In acute pancreatitis, according to the co-localization theory, trypsin activation occurs within cytosolic vacuoles containing both digestive enzymes and lysosomal enzymes. One of the lysosomal enzymes, cathepsin B, seems to be able to transform trypsinogen into trypsin by removing the TAP region from trypsinogen [9], as demonstrated by the detection of immunoreactivity against trypsinogen activation peptide (TAP) in vacuoles positive for lysosomal markers [10, 11]. Another possible mechanism in the activation of trypsinogen involves intracellular calcium. In fact, it has been demonstrated that premature trypsin activation takes place in the apical cells in response to supramaximal cholecystokinin stimulation, and that this activation is dependent on the spatial and temporal distribution of Ca^{2+} release within the same subcellular compartment [12].

Finally, as protective mechanisms against active trypsin and other proteinases, there are several inhibitors secreted by the pancreas, such as the pancreatic secretory trypsin inhibitor; when the balance between proteases-antiproteases is optimal, the pancreatitis does not progress but, when the balance is in favor of the activated trypsin, the pancreatitis progresses to the necrotizing form of the disease.

The destruction of the pancreatic parenchyma following acute pancreatitis quickly induces an inflammatory reaction at the site of the injury. The initial cellular response involves the infiltration of polymorphonuclear leukocytes into the perivascular regions of the pancreas. Within a few hours, macrophages and lymphocytes accumulate and phagocyte-derived oxygen radicals participate in a primary injury to the pancreatic capillary endothelial cells. The increased microvascular permeability facilitates margination and extravascular migration of additional neutrophils and monocytes amplifying the inflammatory process. Following an experimental insult, there is rapid expression of tumor necrosis factor-alfa (TNF-alfa) and interleukin-1 (IL-1) [13]; these two substances are primary inducers of pro-inflammatory interleukin 6 and 8 (IL-6 and IL-8) production and are known to initiate and propagate many consequences including fever, hypotension, acidosis and acute respiratory distress syndrome (ARDS). Finally, in severe forms of acute pancreatitis, there is also a reduced production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) a chemokine capable of blocking the action of the pro-inflammatory cytokines [14].

Etiology

The possible causes associated with an attack of acute pancreatitis are reported in Table 3.1. Acute pancreatitis in children is often found after abdominal trauma in (15 % of the cases), followed by biliary or pancreatic malformation (13 %), drugs (10 %), biliary stones (9 %), viral of bacterial infections (7 %), systemic illnesses (7 %) and metabolic diseases (5 %). A variety of medications have been hypothesized to be causative agents of acute pancreatitis, such as anticonvulsant agents [15], asparaginase [16], and mercaptopurine [17]. The mechanism for drug-induced pancreatitis is not fully understood; disruption of the cellular metabolism by drugs or their metabolites may be the initial trigger point. However, in more than 20 % of the cases, no clear etiological factors can be detected; thus, many young patients have an idiopathic form of pancreatitis.

Genetics

Genetic evaluation constitutes a diagnostic challenge, especially in patients with recurrent attacks of acute pancreatitis or in those with an unknown etiology of the disease. The hereditary pancreatitis locus was narrowed to the long arm of chromosome 7, and the gene responsible was identified no more than 10 years ago [18]. The mutation was identified in the third exon of the gene which transcribes cationic trypsinogen (Protease-Serine-1 gene, PRSS-1), and it is the result of an arginine to histidine substitution (R122H "classic" mutation). Subsequently, other family members with a similar phenotype who tested negative for this mutation were found positive for other less frequent mutations, namely the N91I and the A16V mutation [19]. The suggested pathomechanism of hereditary pancreatitis is related to the block of intracellular trypsin autolysis which prevents pancreatic autodigestion; the PSSR-1 mutation eliminates the initial hydrolysis site, thus preventing the destruction of the trypsin prematurely activated in the pancreas and, in turn, leading to generalized zymogen activation, autodigestion and pancreatitis [20]. The median age of symptom onset of hereditary pancreatitis is 12 years of age with no difference between patients presenting different PSSR-1 mutations [19]; the median number of attacks was two per year, and nearly 30 % of these patients had surgery at a median age of 24 years (about 15 years after the onset of symptoms). Hereditary pancreatitis should be investigated in families with at least two first-degree relatives, or three or more second-degree relatives, over two or more generations, having acute relapsing pancreatitis and/or chronic pancreatitis for which there were no causative or precipitating factors. In the U.S., it is estimated that at least 1,000 individuals are affected by hereditary pancreatitis [20].

A strong association between mutations in a gene encoding the serine protease inhibitor-Kazal type 1 (SPINK1); also known as pancreatic secretory trypsin inhibitor (PSTI) and idiopathic pancreatitis has also been reported. The human gene has four exons and is located on chromosome 5 [21].

Table 3.1 Study period, gender, age at onset of pancreatitis, etiology, severity, recurrences and mortality of acute pancreatitis in ten studies

Author	Eichelberger et al. [53]	Jordan and Ament [54]	Tam et al. [55]	Ziegler et al. [56]	De Banto et al. [7]	Weizman et al. [34]
Study period	1957–1979	1965–1975	1971–1983	1974–1986	1976–1977	1978-1984
No. of cases	24	54	29	49	301	61
Gender						
Males	13	27	15	27	126	27
Females	11	27	14	22	175	34
Age at onset						
Mean (years)	8	NR	7.5	NR	8 years	10.2
Range (years)	2–18	1 week to 21 years	3–14	1 month to 18 years	1 month to 16 years	1–18.5
Etiology						
Idiopathic	4	10	13	3	103	15
Trauma	10	7	5	16	41	9
Malformation	–	5	–	8	5	6
Drugs	3	16	–	–	33	2
Biliary	4	5	1	16	32	–
Infectious	3	5	5	–	9	–
Systemic disease	–	–	–	6	–	22
Others	–	6	1	–	19	–
Metabolic	–	–	4	–	24	6
Familial	–	–	–	–	25	1
Post-ERCP	–	–	–	–	10	–
Transplantation	–	–	–	–	–	–
Severity						
Mild	NR	47	21	45	249	NR
Severe	NR	7	8	4	52	NR
Recurrences	NR	4	7	10	NR	20
Mortality	NR	14	0	1	6	13

Author	Haddock et al. [57]	Pezzilli et al. [6]	Werlin et al. [3]	Suzuki et al. [37]	Total	Frequency
Study period	1978–1992	1998–1999	1996–2001	1983–2007		
No. of cases	49	50	180	135	932	100
Gender						
Males	15	25	83	54	412	44.2
Females	34	25	97	81	520	55.8
Age at onset						
Mean (years)	7.4	10.5 (median)	NR	7.5		
Range (years)	1–16	2–17	1–18	1–16		
Etiology						
Idiopathic	12	17	13	14	204	21.9
Trauma	7	5	25	13	138	14.8
Malformation	4	8	6	76	118	12.7
Drugs	–	1	22	15	92	9.9
Biliary	2	6	16	–	82	8.8
Infectious	20	6	13	5	66	7.1
Systemic disease	–	–	25	12	65	7.0
Others	3	3	20	–	52	5.6
Metabolic	–	1	11	–	46	4.9
Familial	1	3	5	–	35	3.8
Post-ERCP	–	–	10	–	20	2.1
Transplantation	–	–	14	–	14	1.5
Severity						
Mild	46	41	NR	121	570	85.5

(continued)

Author	Haddock et al. [57]	Pezzilli et al. [6]	Werlin et al. [3]	Suzuki et al. [37]	Total	Frequency
Study period	1978–1992	1998–1999	1996–2001	1983–2007		
No. of cases	49	50	180	135	932	100
Severe	3	9	NR	14	97	14.5
Recurrences	5	14	22	NR	82	17.4
Mortality	0	1	11	2	48	5.2

NR not reported

SPINK1 inhibits approximately 20 % of the total trypsin activity within the pancreas, thus providing an important defense against prematurely activated trypsinogen [22]. Whether an N34S mutation should be considered a causative factor of pancreatitis per se or simply a disease modifier is uncertain [23–25].

The most commonly inherited disease of the pancreas is cystic fibrosis, inherited as an autosomal recessive illness [26]. The cystic fibrosis transmembrane conductance regulator-gene (CFTR-gene) is located on chromosome 7q3.1, existing as a single copy in the human genome, and encoding a 170,000 molecular-weight glycoprotein. A deletion of three base pairs of the CFTR-gene, resulting in the loss of phenylalanine residue (ΔF508 mutation), has been shown to be responsible for the disease in approximately 70 % of patients [27, 28]. Many other mutations have been reported, and more than 800 disease-causing lesions have been identified in the CFTR-gene [29]. The suggested underlying pathogenetic mechanism involves a defect in the regulation of the apical membrane-chloride channels of epithelial cells, resulting in highly viscous secretions having an inability to maintain luminal hydration. From the clinical standpoint, cystic fibrosis is the only hereditary disease in which pancreatic involvement can be expressed by both exocrine insufficiency (without pancreatic inflammatory disease) and pancreatitis [30]. Symptoms of acute relapsing pancreatitis develop in approximately 2 % of patients with cystic fibrosis diagnosed on clinical grounds and they occur in adolescence or adulthood, but only in patients with pancreatic sufficiency.

Diagnosis

The diagnosis of acute pancreatitis still depends on clinical suspicion and requires confirmatory laboratory and imaging studies [3, 4, 6, 7]. The most common clinical symptoms and signs are abdominal pain in almost all patients, followed by vomiting and abdominal tenderness with abdominal distension [5]. Other less common clinical signs include fever, tachycardia, hypotension, jaundice and abdominal signs, such as guarding, rebound tenderness and decreased bowel sounds [5]. The determination of amylase and lipase levels remains the most commonly used laboratory tests. Although serum levels of lipase and amylase over three times the upper reference limit suggest pancreatitis, the level of elevation is not diagnostic. Both enzymes can be elevated in conditions unrelated to pancreatitis (e.g., salivary diseases, uremic syndrome, ketoacidosis, macroamylasemia, macrolipasemia), and both can be normal in the presence of imaging evidence of acute pancreatitis. CT images of the pancreas are useful not only in confirming the presence of acute inflammation of the pancreas, but also in identifying the complications of acute pancreatitis and in diagnosing a possible biliary origin of the disease. It is reasonable to avoid a CT scan early in the course of pancreatitis because the presence of necrosis requires up to 48 h to be visualized [31]. In the near future, findings similar to those obtained with a CT scan may be obtained using magnetic resonance (MR) [32]. An ultrasound examination can demonstrate the presence of gallstones, biliary sludge, dilated common and intrahepatic ducts, and choledochal cysts.

Outcome

As in adults, acute pancreatitis in children can be life-threatening. In children, death occurs in about 5 % of the cases ranging from 0 to 27 % of all pancreatitis cases [3, 6]. As reported in Table 3.1, the percentage of severe pancreatitis in children is about 15 %; this figure is similar to that reported in adult patients [33]. The early causes of death are shock and respiratory failure, whereas late life-threatening complications of pancreatitis are generally associated with infected pancreatic necrosis due to colonic bacteria translocation.

About one-fifth of children may experience recurrent attacks of acute pancreatitis [6, 34] ranging from 7.4 to 32.7 % and, in most cases (about 50 %), the etiology of the disease is unknown. This figure is similar to that reported in the adult population [35]; of course, the causes of recurrent acute pancreatitis in adults are quite different (about 60 % of adult patients are alcoholics whereas only 10 % of adults had unrecognized causes). In the era of genetic tests, it has been reported that mutations of CFTR, SPINK1, and PRSS1 genes can be found up to 40 % of children with recurrent acute pancreatitis [36].

Table 3.2 Clinical and laboratory criteria for identifying the severity in acute pancreatitis in children. This score is evaluated as the number of criteria satisfied; the presence of three or more criteria indicates a severe attack of acute pancreatitis

On admission	Under 7 years of age
	Weight less than 23 Kg
	Leukocyte count greater than 18,500 mmc
	LDH greater than 2,000 U/L
During the initial 48 h after admission	Calcium less than 8.3 mg/dL
	Albumin less than 2.6 mg/dL
	Fluid sequestration greater than 75 ml/kg/48 h
	BUN greater than 5 mg/dL

Adapted from DeBanto et al. [7] with permission from Nature Publishing Group

Assessment of Severity

The clinical course and the outcome differ significantly between mild and severe cases; the physician must make a rapid assessment of the patient's condition and evaluate the risk of a severe clinical course. Several scoring systems have been developed to assist the physician in this decision; in adults; a scoring system has been developed and validated in children [7] (Table 3.2). However, other authors demonstrated that this score was useful in excluding severe pancreatitis (positive predictive value 26 %, negative predictive value 96 %) in a retrospective study on 135 patients with acute pancreatitis [37]. In addition, it seems that clinicians caring for children with acute illness of the pancreas do not generally apply the multiple score systems in clinical practice [6]. The determination of a unique index of severity, such as C-reactive protein (CRP) determination may be an alternative tool; in fact, this marker of inflammation at a level greater than 150 mg/dL is able to distinguish the mild from the severe forms of childhood pancreatitis in a fashion similar to that found in adults [6]. Another possibility is to determine the IL-6 in the serum; this cytokine is able to detect the severity of acute pancreatitis in adults earlier than CRP [38].

Treatment

Objectives and Methods of Conservative Treatment

The primary objectives to be achieved in the treatment of acute pancreatitis are essentially: (1) pain control, (2) electrolyte support and energy intake, (3) removal of the causal agent, when possible, (4) attenuation of inflammatory and autolytic processes at the glandular level ("specific" therapy) and (5) prevention and eventual treatment of the local and systemic complications of the necrotizing forms. For mild forms of the disease, in most cases, the first three steps are sufficient for clinical resolution. In severe forms, the therapeutic engagement is more complex and patients may, with reasonable frequency, require periods of hospitalization in intensive care units. The therapeutic approach to severe acute pancreatitis is reported in Fig. 3.2.

The control of pain must be swift and effective [39]. Supportive therapy is mandatory because it counterbalances the loss of fluids and hypercatabolism. The maintenance of cardiovascular, renal and respiratory parameters can, in many cases, prevent the onset of multisystem complications. Pancreatic hypoperfusion, secondary to the inadequate maintenance of plasma volume, is indeed able to trigger and increase the phenomena of pancreatic necrosis. Patients with mild forms, for which oral refeeding is expected within 4–6 days of hospitalization, do not need an aggressive nutritional approach [39]. In contrast, in the severe forms, total parenteral nutrition (TPN) must be used, which must take into account any metabolic imbalances (such as acidosis or alkalosis, hyperglycemia, hypocalcemia, hypokalemia and hypomagenesemia) and cardiovascular complications in its formulation [39]. Recently, enteral nutrition using a jejunal feeding tube has been used with good results in patients with severe acute pancreatitis instead of TPN. The pathophysiological assumption is that the TPN does not provide all essential nutrients (e.g. glutamine) and does not protect intestinal mucosa trophicity, and this phenomenon, in turn, can increase intestinal permeability to toxins and bacterial translocation.

The early removal of the causative agent makes it paramount to reach a sufficiently precise etiologic diagnosis and early intervention. The removal of a biliary obstruction using endoscopic techniques has now entered into the routine treatment of these patients [31]. The use of systemic antibiotics for the prevention of pancreatic infections is one of the cornerstones of the conservative treatment of the severe forms of acute pancreatitis. Several studies have shown a significant reduction in the incidence of pancreatic and extrapancreatic infections in patients treated with imipenem-cilastatin [40]; this measure does not reduce the mortality of patients with severe acute pancreatitis.

Objectives and Indication of Surgical Treatment

The infection of pancreatic necrosis in the course of acute pancreatitis is a very serious medical condition, and its presence is associated with a marked increase in risk of death; it develops in percentages varying from 15 to 70 % of all patients with acute necrotizing pancreatitis and accounts for more than 80 % of deaths from acute pancreatitis. The risk of infection increases with the extent of necrosis and the days after the initiation of acute pancreatitis, reaching a peak

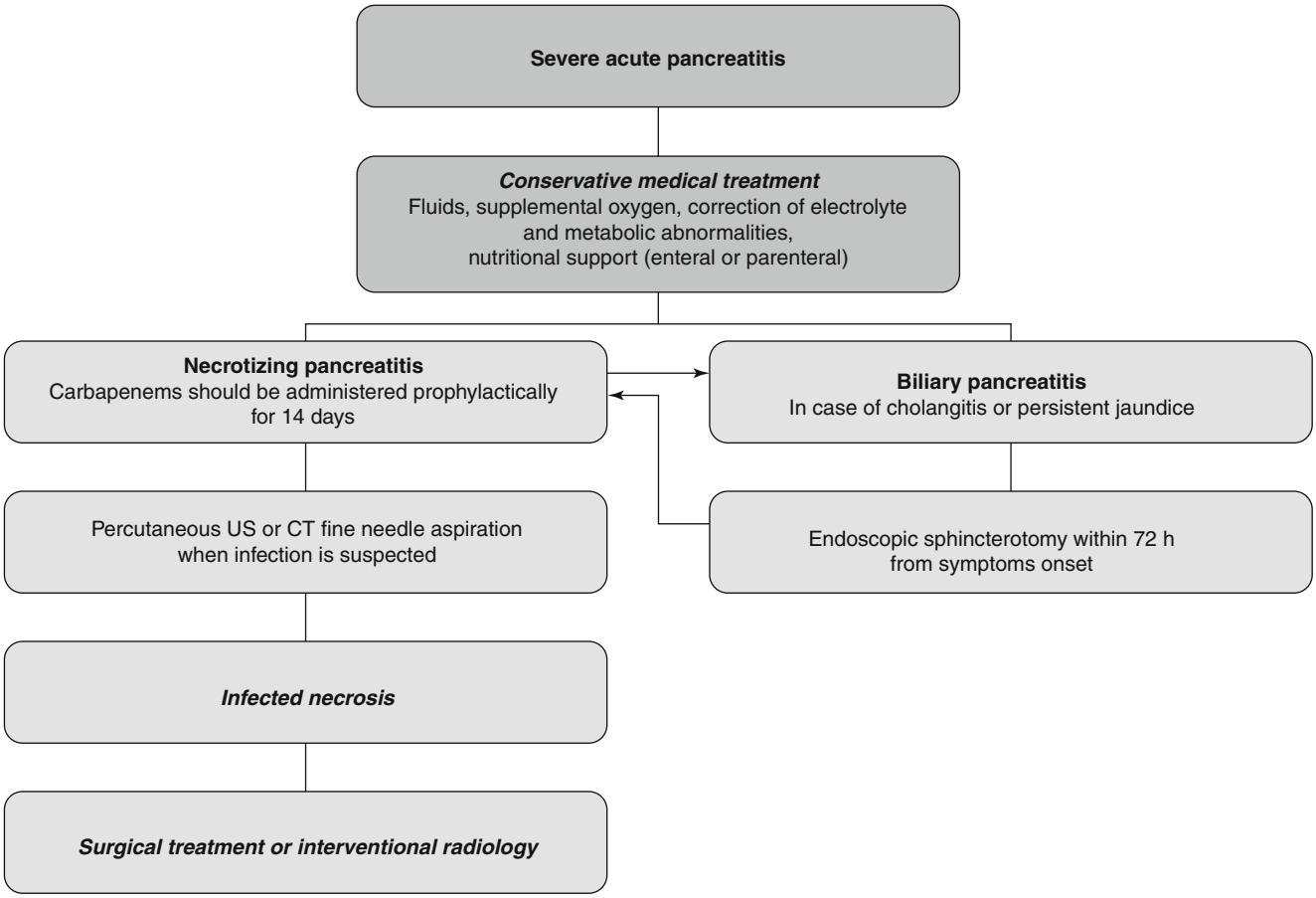

Fig. 3.2 Therapeutic approach to severe acute pancreatitis

incidence (70 %) after 3 weeks [41]. In most cases, the infection is caused by Gram-negative bacteria of enteric origin, and about two-thirds of the infections are caused by a single microbiological agent. In some cases, fungi can be found [42]. From a clinical point of view, acute pancreatitis with sterile necrosis can be difficult to distinguish from a form with infected necrosis, because both can give fever, leukocytosis and abdominal pain. However, this distinction is very important since mortality in patients with infected necrosis who did not undergo early surgery is high. Computer tomography or ultrasound-guided percutaneous suction of the necrotic material and/or peripancreatic fluid collections, with a fresh microscopic examination and bacterial culture, is safe and accurate (sensitivity and specificity exceeding 95 %). It must be used, even repetitively, usually from the second week of illness, in patients whose clinical condition worsens or does not tend to improve, despite the removal of any causative agent and the implementation of a vigorous supportive treatment. Debridement is the surgical treatment of choice for infected necrosis and the only therapeutic doubt concerns which type of intervention to be performed (necrosectomy with drainage-washing or an open packing technique). Recently, other treatment options, such as percutaneous, endoscopic or minimally invasive surgery have been proposed [43–45]. These methods require highly experienced operators.

The treatment of patients with sterile pancreatic necrosis remains controversial and it should be reserved for selected cases, such as those patients in whom repeated attempts at oral re-feeding after 5–6 weeks of therapy are associated with abdominal pain, nausea, vomiting or the recurrence of pancreatitis. At this stage of the disease, however, necrosis is more demarcated and surgery is easier. In other cases, supportive care associated with prophylactic antibiotic treatment should be the primary treatment [46–50]. It is, therefore, very important that a cholecystectomy be carried out in due time (possibly during the same hospitalization for mild forms, usually at a distance of 3–4 weeks for severe forms) in the case of gallstones in order to prevent the recurrence of acute episodes [31].

Refeeding in the Mild Form of Acute Pancreatitis

The recommendation is to initiate refeeding when pain disappears, using a low-fat solid diet; in fact, in mild acute pancreatitis, immediate oral feeding is feasible and safe and may

accelerate recovery without adverse gastrointestinal events [51]. There is also the need to know the exocrine pancreatic function in patients who have experienced an acute episode of pancreatitis in order to cure possible maldigestion [52].

Conclusion

The following points should be kept in mind in the case of acute pancreatitis: (1) in a child with unexplained abdominal pain, we must think about acute pancreatitis, (2) the severity and the etiology of the disease should be rapidly assessed, (3) the pain must be alleviated, and fluids and electrolytes should be administered immediately. After the acute pancreatitis is resolved, genetic tests should be carried out in cases of patients having a disease of unknown origin.

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Abdominal Compartment Syndrome in Children

4

Ori Attias and Gad Bar-Joseph

Abstract

Abdominal compartment syndrome (ACS) is a clinical syndrome resulting from increased intra-abdominal pressure (IAP) and characterized by progressive end-organ dysfunction and failure, affecting mainly the hemodynamic, respiratory, renal and gastrointestinal systems. If untreated, ACS can deteriorate rapidly to critical organ failure and death. On the other hand, rapid relief of the elevated IAP often reverses the adverse pathophysiologic changes promptly.

Consensus definitions of intra-abdominal hypertension (IAH) and ACS have been published for adult patients, but similar definitions for children are lacking (See Appendix). For adults, ACS is defined as sustained increase of IAP >20 mmHg associated with new organ dysfunction or organ failure. ACS may be primary – resulting from an intra-abdominal cause (abdominal trauma, post abdominal surgery, ascites etc.) or secondary – caused by extra-abdominal causes, typically in conditions requiring massive fluid resuscitation. The reported incidence of ACS among critically ill children is relatively low compared to adults, though it may be under-recognized.

The diagnosis of ACS requires a high index of suspicion, and a comprehensive management approach consists of IAP monitoring, prevention, and medical and surgical measures. IAP monitoring can be easily and reliably achieved through measurement of the urinary bladder pressure using simple bedside techniques. Prevention consists of prophylactic use of incomplete, temporary abdominal closure following surgery and avoidance of excessive fluid resuscitation. Medical management includes measures to reverse fluid overload, improve abdominal wall compliance and the non-operative evacuation of excessive intra-abdominal contents. Once these measures fail to relieve IAH and ACS, decompressive laparotomy (DL) is crucial and should not be delayed.

DL often results in dramatic stabilization of the patient's condition. However, the overall outcome of pediatric patients who have developed ACS and required DL remains poor, with reported 40–60 % mortality rates.

Keywords

Abdominal compartment syndrome • Intra-abdominal pressure • Abdominal hypertension • Decompressive laparotomy

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Introduction

Compartment syndrome occurs when the pressure within a confined space increases to a point where the vascular inflow is compromised and the function and viability of the tissues within the compartment are threatened. Abdominal Compartment Syndrome (ACS) is defined as a pathological

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increase of the intra-abdominal pressure (IAP) with consecutive dysfunction of one or several organ systems leading to adverse hemodynamic, respiratory and renal effects [1]. If untreated, ACS can deteriorate and lead rapidly to critical organ failure and death. On the other hand, immediate relief of the elevated IAP – through evacuation of a "pathological" volume (blood, transudate, ascitic fluid, etc.) or through decompression of the abdominal cavity – usually reverses the adverse pathophysiologic changes promptly. Therefore, every clinician taking care of critically ill children should be familiar with the unique characteristics of this relatively common clinical entity, as a high index of suspicion, timely recognition and prompt intervention can be lifesaving.

As reviewed by Schein [2], the clinical effects of increased IAP, were first mentioned in 1863 by Marey and in 1870 by Bert, who have described the respiratory effects caused by increased IAP. The first description of the ACS was published by Kron et al. in 1984 [3], and the term ACS was coined by Fietsam et al. in 1989 [4]. The syndrome has come to the forefront of the adult surgical practice since the late 1980s, and the introduction of laparoscopic surgery in the 1990s was followed by further extensive experimental and clinical research.

However, the roots of the ACS are clearly found in the pediatric surgery arena, as its clinical characteristics were observed in the 1940s following surgical interventions for the repair of omphaloceles and gastroschisis. In 1948, Gross [5] noted that although it was often possible to forcefully close the abdominal wall in these neonates, they died shortly following surgery with respiratory failure and cardiovascular collapse. This clinical picture was attributed to "abdominal crowding", and methods to avoid these complications were developed by pediatric surgeons [6, 7]. In fact, the surgical techniques currently used to treat ACS, namely temporary abdominal closure (TAC) with synthetic materials and staged abdominal repair, were pioneered by these surgeons [8].

Unfortunately, publications on ACS in children have lagged greatly behind those involving the adult population [9]. The first series on ACS in pediatric (non-neonatal) patients were published only in 2000 [10] and in 2001 [11], and less than 100 pediatric cases were described in small case series since that time [12–19]. This reflects not only a lower incidence but also less awareness, knowledge, or interest among pediatric health care practitioners [9, 20]. Consequently, most of our knowledge on ACS in children still originates from the adult literature.

Definitions

The World Society on the Abdominal Compartment Syndrome (WSACS) was created in 2004 and has been instrumental in the development of consensus definitions (Table 4.1) [1]. It should be stressed that there are no specific definitions for the pediatric age group and there is no evidence that the adults' criteria also apply to children (See Appendix).

Intra-abdominal Pressure and Abdominal Perfusion Pressure

IAP is the steady-state pressure concealed within the abdominal cavity [1]. The values of IAP range from sub-atmospheric to 0 mmHg in normal individuals [21–23], and they are slightly positive in patients receiving positive pressure ventilation due to transmission of the intra-thoracic pressure to the abdomen [24]. The IAP increases with inspiration and decreases with expiration [1, 21], and there is a positive

Table 4.1 Consensus definitions and abbreviations

IAP	The steady-state pressure concealed within the abdominal cavity
Normal IAP	Lower than 5 mmHg in resting healthy adults 5–7 mmHg in critically ill adults
IAH	A sustained or repeated pathologic elevation of IAP ≥12 mmHg IAH is graded as follows: Grade I: IAP 12–15 mmHg, Grade II: IAP 16–20 mmHg, Grade III: IAP 21–25 mmHg, Grade IV: IAP >25 mmHg
APP	MAP-IAP
ACS	A sustained IAP >20 mmHg (with or without APP<60 mmHg) associated with new organ dysfunction or failure
Primary ACS	Condition associated with injury or disease in the abdominal-pelvic region that frequently requires early surgical or interventional radiologic intervention
Secondary ACS	Conditions that do not originate from the abdominal-pelvic region
Recurrent ACS	Condition in which ACS redevelops after previous surgical or medical treatment of primary or secondary ACS

ACS abdominal compartment syndrome, *APP* abdominal perfusion pressure, *IAH* intra-abdominal hypertension, *IAP* intra-abdominal pressure, *MAP* mean arterial pressure. Reproduced with permission from The World Society of the Abdominal Compartment Syndrome (WSACS)

correlation between IAP and body mass index [23]. The IAP also varies with body position (higher in vertical vs. horizontal, higher in prone vs. supine) and with the contraction of the abdominal musculature [21]. IAP typically is expressed in millimeters of mercury and conversion from centimeters of water may be necessary (1 mmHg = 1.36 cmH_2O).

The "critical IAP" that causes organ dysfunction varies individually due to differences in physiologic reserve and comorbidities [25]. For this reason, there is no clear-cut IAP threshold that clinicians can use to definitively decide if a patient is suffering end-organ dysfunction from elevated IAP. In an effort to improve predictability of the impact of IAP on patient's outcome, the concept of abdominal perfusion pressure (APP) was developed. APP, calculated as mean arterial pressure (MAP) minus IAP, has been proposed as an accurate index of visceral perfusion and as a useful parameter to guide clinicians in the resuscitation and management of patients suffering from ACS [25, 26]. APP was shown to be superior to IAP, pH, base deficit, and arterial lactate in predicting outcome in these patients [25]. In adults, APP values higher than 60 mmHg were associated with improved survival in patients with IAH and ACS [1, 26].

Intra-abdominal Hypertension (IAH)

IAH is defined as a sustained or repeated pathologic increase in IAP ≥12 mmHg [1]. To stratify patients according to the severity of IAH and guide therapy, IAH may be graded as I–VI on the modified Burch scale [1, 27] (Table 4.1). Comorbidities, such as chronic renal, pulmonary or cardiac disease, may aggravate the deleterious effects of IAH and lower the threshold at which organ dysfunction occurs [1]. IAH may also be subclassified according to the duration of symptoms [1]: Hyperacute – lasting seconds to minutes – usually during activities such as coughing, sneezing, performance of Valsalva maneuver and defecation; acute – developing in hours and usually seen in surgical patients as a result of abdominal trauma; subacute – developing over days and seen mainly in medical patients; chronic – lasting months or years as a result of pregnancy, morbid obesity, chronic ascites or cirrhosis.

Abdominal Compartment Syndrome

The WSACS Consensus Conference defined ACS as a sustained increase of IAP >20 mmHg (with or without APP <60 mmHg), associated with new organ dysfunction or organ failure [1]. ACS represents the natural progression of end-organ dysfunction caused by increased IAP, and develops if IAH is not recognized and treated appropriately [1]. In contrast to IAH, ACS is not graded, but is rather considered an "all or none" phenomenon [28]. It should be stressed that this definition represents a "consensus" agreement. To define "ACS" in the clinical setting, the entire individual patient's clinical status and IAP should be considered.

An IAP >20 mmHg relates to the "adult" definition of ACS. In children, MAP is lower than in adults and it varies with age. Therefore, the APP of a small child may be compromised and ACS may develop at lower IAP's. Beck et al. [11] found IAP's of 15 mmHg high enough to cause ACS in children. Ejike et al. [29] evaluated IAP in a cohort of critically ill children and concluded that pressures of >10 mmHg were potentially dangerous. Sukhotnik et al. [30] showed that neonates may develop ACS at IAP's in the range of 9–13 mmHg. Baroncini et al. [31] investigated hemodynamic function in children undergoing laparoscopic procedures and reported substantial cardiopulmonary compromise at very low IAP's in neonates and at slightly higher levels in older children. They recommend a maximal IAP of 6 mmHg in neonates and of 12 mmHg in older children during laparoscopy. Ejike et al. recently suggested that pediatric ACS should be defined as an IAP of >12 mmHg associated with new dysfunction or failure of two or more organ systems [16] (See Appendix). Again, the IAP value should be considered only as one component of the entire clinical picture.

According to its cause and duration, ACS may also be classified as primary, secondary, or recurrent (Table 4.1) [1]. Primary ACS is characterized by the presence of acute or subacute IAH resulting from an intra-abdominal cause (e.g., abdominal trauma, post abdominal surgery, ascites, abdominal tumor). Secondary ACS is caused by extra-abdominal causes, typically in conditions requiring massive fluid resuscitation, such as septic shock and major burns. Recurrent ACS represents a redevelopment of ACS following resolution of an earlier episode of either primary or secondary ACS (a "second-hit" phenomenon) and may occur despite of an open abdomen or as a new ACS episode following definitive closure of the abdominal wall [28].

Incidence

Among adult patients, the incidence of IAH is variable, ranging between 18 and 80 % of ICU patients, depending on the definition threshold used and on the type of the patient population [32]. In a 1-day-point prevalence study, Malbrain et al. [33] found that 50.5 % of ICU patients had IAH and 8.2 % had ACS. Among 265 medical/surgical ICU patients, the same group observed a 32.1 % incidence of IAH on ICU admission [34].

Very scant data exist regarding the occurrence of ACS in children. Earlier studies by Beck et al. [11] and Diaz et al. [19] calculated an incidence of severe ACS, requiring decompressive laparotomy (DL) of around 1 % among critically ill children. Ejike at al., defining ACS as an IAP of >12 mmHg associated with new dysfunction or failure of two or more

organ systems [16], found ACS to be present in 4.7 % of ventilated PICU patients. However, only five of their 294 (1.7 %) eligible patients underwent laparotomy, three of them for 'bowel perforation'. In a recent study, Pearson et al. [14] described 26 children who have undergone DL for ACS. The occurrence rate was calculated as 0.56 % of the ventilated patients in their PICU (Meyers RB 2012, personal communication).

This lack of consensus definition makes the true incidence of ACS among pediatric patients difficult to determine [16]. The higher incidence of ACS – when defined as a certain threshold pressure combined with significant physiological deterioration – has a profound clinical importance as it serves to awaken the critically crucial index of suspicion. If unrecognized – and therefore untreated – this 'early' ACS may rapidly evolve and deteriorate to 'full blown' ACS requiring emergency DL and resulting in a very high mortality rate. Unfortunately, ACS is still grossly under-recognized by pediatric intensive care personnel [9].

Etiology and Risk factors of ACS

Although primarily thought of as surgical diagnoses, IAH and ACS pose a risk to both medical and surgical patients [34, 35]. In principle, two basic mechanisms can lead, independently or in combination, to IAH and ACS. The first is the accumulation of excessive mass within the limited capacity of the abdominal cavity [36]. The second is a tense, low compliant abdominal wall (Table 4.2).

Primary ACS derives from intra-abdominal pathology and is most often seen in trauma or in postoperative patients. It has been identified as one of the major causes of morbidity and mortality in patients with a traumatic injury [37–39]. Secondary ACS, associated with an extra-abdominal etiology, is encountered mostly in medical or burn patients [40, 41], usually as a result of edema fluid accumulation. It is often viewed as an "unavoidable" sequelae of aggressive fluid (crystalloid) resuscitation for various etiologies (e.g., sepsis, post trauma, burns) [11, 18, 37, 42–44].

In adults, the most common cause of primary ACS is abdominal injury with intra-abdominal bleeding. Aside from the accumulated blood in the peritoneal or retroperitoneal spaces, the situation may be aggravated by edema formation, bowel distention and tense abdominal wall. Consequently, a damage control approach has become an established routine, consisting of hemorrhage control with or without abdominal packing, leaving of an 'open abdomen' and delaying definitive abdominal wall closure ('staged celiotomy') [45–48]. Other relatively frequent causes of ACS in adults are major abdominal surgeries such as abdominal aortic surgery, especially if

Table 4.2 Conditions associated with IAH and ACS

Increased intra-abdominal content	Hemoperitoneum (blunt or penetrating abdominal trauma)
	Intra-abdominal or retroperitoneal masses (tumor, hematoma, abscess)
	Ascites (liver failure, nephrotic syndrome etc.)
	Peritoneal dialysis
	Pneumoperitoneum (during laparoscopy)
	Gastrointestinal tract dilatation
	Gastroparesis and gastric distention
	Ileus
	Volvulus
	Colonic pseudo-obstruction
	Necrotizing enterocolitis (NEC)
	Small bowel perforation
Decreased abdominal wall compliance	Abdominal surgery, especially with tight abdominal closures
	Abdominal wall bleeding or rectus sheath hematomas
	Surgical correction of large abdominal hernias, gastroschisis, or omphalocele
	Major burns (with or without abdominal eschars)
	Mechanical ventilation, with PEEP >10 cmH_2O
	Prone positioning
Combination of decreased abdominal wall compliance and increased intra-abdominal content	Massive fluid resuscitation
	Sepsis, severe sepsis, and septic shock
	Cardiogenic shock
	Complicated intra-abdominal infection
	Obesity
	Severe acute pancreatitis

ACS abdominal compartment syndrome, *IAH* intra-abdominal hypertension, *PEEP* positive end-expiratory pressure

associated with coagulopathies. In contrast to adults, primary ACS due to abdominal trauma has been reported in only a minority of the pediatric cases [11–19], in whom ACS is associated with a diversity of other acquired, non-congenital etiologies, such as enteropathies, intestinal perforation, peritonitis, post abdominal surgery for various conditions and malignancies (Table 4.2).

In recent years, the role of massive fluid resuscitation and capillary leak emerges as a major – if not the major – contributor or cause of ACS [37, 42, 49–51]. In the multicenter study by Malbrain et al., massive fluid resuscitation and polytransfusion were used almost twice as frequently among patients who have developed IAH than in patients who did not [34]. In children, ACS was associated with massive fluid resuscitation for the treatment of various etiologies [11, 14, 18, 19, 52]. Marked capillary leak, characterizing conditions such as sepsis, burns or bone marrow transplantation, predispose to the development of secondary ACS [11, 52]. This secondary ACS adds significant morbidity and mortality, and it may be predicted and possibly avoided by more judicious fluid resuscitation [37, 42, 49–51].

Major burns have been increasingly recognized as a risk factor for IAH and ACS due to massive (initial) fluid resuscitation and due to capillary leak leading to ascites, bowel edema and abdominal wall edema [32, 43, 44, 53, 54]. It should be stressed that ACS developed not only in patients with full-thickness circular burns of the abdomen, but also following proper escharotomy or in the absence of any abdominal burns.

Pathophysiology of ACS

IAP and APP may be considered analogous to the Monro – Kelly doctrine relating to the intra-cranial pressure (ICP) and cerebral perfusion pressure (CPP), respectively (Fig. 4.1). The abdominal pressure – volume curve consists basically of two arms: At low intra-abdominal volumes, the abdominal wall is very compliant and relatively large increases in "pathologic" volumes will lead to only minor increases in IAP [55]. Subsequently, once a critical excessive volume has been attained, compliance of the abdominal cavity decreases abruptly and small changes in volume will lead to large changes in IAP. Further distension beyond this "knee" of the curve will result in a rapid rise in IAP, decreased organ perfusion, development of clinical ACS and, if untreated, in multiple organ failure (MOF) and death.

Regardless of the primary initial insult or pathological event, three main processes are always secondarily involved in the pathogenesis of IAH and its progression to ACS: tissue ischemia/hypoxia followed by reperfusion injury, inflammatory response and increased capillary permeability. The combination of these processes is augmented by massive

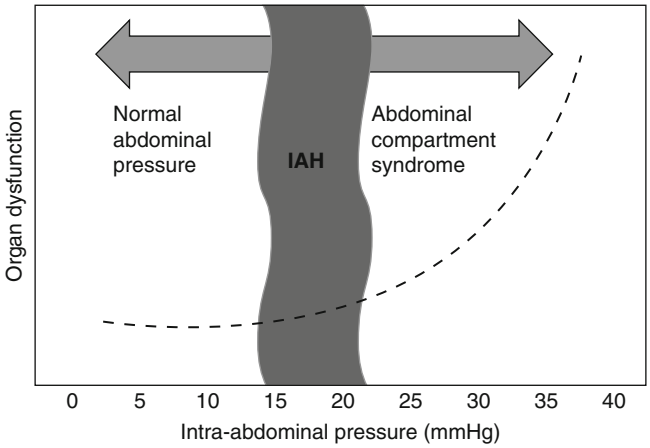

Fig. 4.1 Distinctions between normal intra-abdominal pressure, intra-abdominal hypertension (*IAH*) and abdominal compartment syndrome (*ACS*) in adults, depicted over the abdominal volume-pressure curve. The area illustrating IAH may undergo shifts to the right or left depending on the clinical scenario (Reproduced with permission from the World Society of the Abdominal Compartment Syndrome – www.wsacs.org)

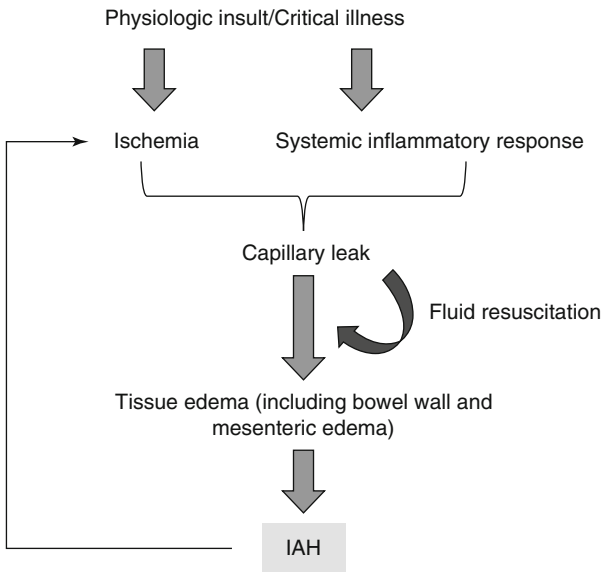

Fig. 4.2 The vicious cycle of inflammatory response, fluids resuscitation and intra-abdominal hypertension. Abbreviations: *IAH* intra-abdominal hypertension (Adapted and reproduced with permission from AbViser® Medical, LLC, by Dr. Tim Wolfe)

crystalloid resuscitation, which activates a vicious cycle that results in tissue edema – involving both abdominal wall and intra-abdominal tissues and organs, and often in free fluid sequestration and ascites accumulation (Fig. 4.2).

The inflammatory response is a predominant component of the primary conditions associated with IAH and ACS (Table 4.2). Inflammation follows tissue ischemia, cellular hypoxia and reperfusion – the hallmark of traumatic shock [56]. It involves, among others, the release of cytokines,

formation of oxygen free radicals and decreased cellular production of adenosine triphosphate (ATP) [57]. The pro-inflammatory cytokines promote vasodilatation and increase capillary permeability, leading to edema formation [58]. Tissue reperfusion promotes the generation of oxygen free radicals that have a toxic effect on cell membranes. Insufficient oxygen delivery limits ATP production and impedes energy-dependent cellular activities, particularly the sodium-potassium pump. Pump failure causes cellular swelling, lose of membrane integrity and spilling of intracellular contents into the extracellular space, thus promoting further inflammation [57, 59]. Capillary leakage, edematous intestines and accumulation of ascitic fluid elevate IAP that impairs venous return and intestinal lymphatic outflow and thereby increases capillary filtration pressure and worsens gut edema [56, 60, 61]. As pressure mounts, intestinal perfusion is impaired, and the cycle of cellular hypoxia and damage, inflammation and edema formation continues in a vicious cycle [57].

Efforts aimed at restoring abdominal organs' perfusion with large amounts of crystalloid solutions or blood products further aggravate the clinical condition. Aside from their effect on the capillary filtration pressure, crystalloids decrease plasma protein concentration and reduce plasma oncotic pressure. These combined effects of the Starling forces serve to overwhelm the anti-edema safety factors (lymph flow, plasma oncotic pressure) and the vicious cycle is further augmented by the "futile crystalloid preloading" [32, 62]. Other organ specific pathophysiologic processes are discussed in the relevant sub-sections below.

Organ System Dysfunction and the Clinical Presentation of ACS

ACS and IAH affect all critical body systems, most notably the cardiac, respiratory, renal, and neurologic systems, as well as the hepatic and intestinal systems [28, 32] (Fig. 4.3).

Cardiovascular Effects

With advancing ACS, the patient presents a rapidly deteriorating clinical picture of profound shock, unresponsive to fluid resuscitation and to vasoactive drugs [11, 52, 63, 64]. Cardiac output (CO) decreases primarily due to decreased venous return: The inferior vena cava (IVC) and the portal vein are compressed by the elevated IAP [38, 64–68]. Cephalad deviation of the diaphragm increases intrathoracic pressure, impedes superior vena cava (SVC) flow and possibly causes direct cardiac compression, reducing ventricular compliance and contractility [28, 64, 66, 67]. In small children undergoing laparoscopy, an IAP of 12 mmHg may lead to regional cardiac

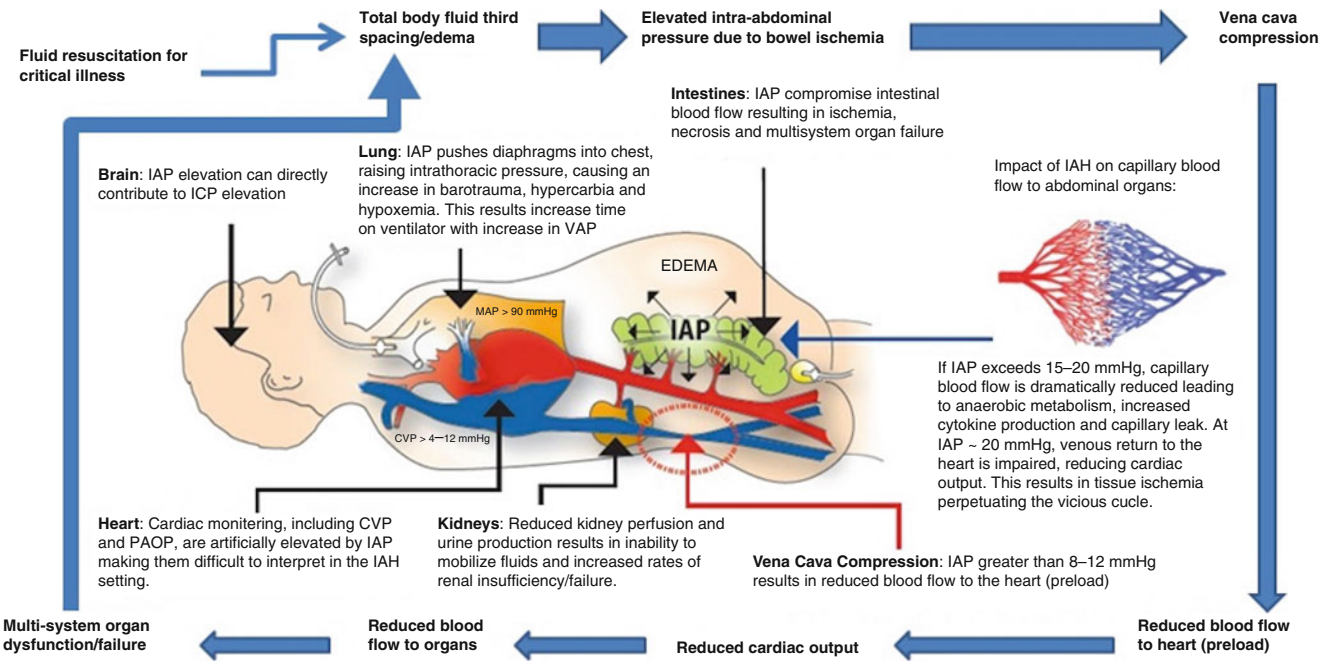

Fig. 4.3 The vicious cycle nature of the pathopysiologic processes leading to abdominal compartment syndrome (*ACS*) and multi-organ system failure. Abbreviations: *IAH* intra-abdominal hypertension, *CVP* central venous pressure, *MAP* mean arterial pressure, *PAOP* pulmonary artery occlusion pressure, *ICP* intra-cranial pressure, *VAP* ventilator associated pneumonia (Adapted and reproduced with permission from AbViser® Medical, LLC, by Dr. Tim Wolfe)

wall motion abnormalities, especially to septal hypokinesia [69]. Mechanical compression of the abdominal vasculature increases systemic vascular resistance and cardiac afterload.

In this setting, straightforward interpretation of hemodynamic data may be misleading, as the elevated intrathoracic pressure 'falsely' increases all other manometric measurements, including central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP) and pulmonary artery pressure [24, 38, 68, 70], potentially leading to erroneous management decisions. Therefore, alternative methods of preload evaluation, like the measurement of right ventricular end-diastolic volume by echocardiography, reflect more accurately the intravascular volume status as it is less affected by changes in the intrathoracic pressure [21, 28, 71–74]. Alternatively, the falsely elevated CVP and PAOP can be 'corrected' by using the following formula [28, 72]:

$$\text{Corrected CVP} = \text{Measured CVP} - \text{IAP} / 2 \qquad (4.1)$$

$$\text{Corrected PAOP} = \text{Measured PAOP} - \text{IAP} / 2 \qquad (4.2)$$

The compressed IVC and the impaired venous drainage from the lower extremities promotes the formation of peripheral edema and may place the patient with IAH/ACS at an increased risk for developing of deep vein thrombosis [28, 41, 75].

Respiratory Effects

Acute respiratory failure is a major component of ACS. The elevated IAP causes upward displacement of the diaphragms, resulting in increased intrathoracic pressure, compression of the lungs and progressively low compliant, stiffer chest [11, 28, 38, 52, 68, 76, 77]. The resultant pathophysiologic picture is characterized by alveolar atelectasis, decrease in all lung volumes mimicking severe restrictive lung disease, hypoxemia and hypercarbia [11, 28, 38, 52, 64]. Parenchymal compression impairs pulmonary capillary blood flow, leading to increased alveolar dead space and ventilation – perfusion (V/Q) mismatch [78]. In the ventilated patient, progressively higher positive end expiratory pressure (PEEP), peak inspiratory and plateau pressures are required to maintain gas exchange [11]. Mechanical ventilation at high inflation pressures can cause alveolar barotrauma triggering the release of inflammatory mediators that enhance capillary leakage and may aggravate preexisting lung injury [21, 41].

Renal Effects

Acute kidney injury (AKI) characterized by oliguria progressing to anuria – both unresponsive to fluid therapy and diuretics – is one of the hallmarks of ACS and is usually its first clinical manifestation [10, 11, 38, 64, 79]. Location of the kidneys deep within the retroperitoneal space makes them especially vulnerable to the deleterious effects of increased IAP. In adults, oliguria usually develops at IAP's >15–20 mmHg and anuria at IAP's >30 mmHg [80, 81]. Parallel values for pediatric patients are not available, though it should be expected that renal impairment will be manifested at lower IAP's [11].

Oligo-anuria results mainly from the combined effects of reduced renal perfusion and direct compression of both renal parenchyma and the renal veins, leading to severe reduction in the renal filtration gradient (FG) [70, 82–84]: FG is the mechanical force across the glomerulus and is equal to the difference between the glomerular filtration pressure (GFP) and the proximal tubular pressure (PTP). GFP is equal to renal perfusion pressure and is calculated as MAP minus renal venous pressure that equals IAP, while PTP is equal to the IAP.

$$\begin{aligned} \text{FG} &= \text{GFP} - \text{PTP} = \left(\text{MAP} - \text{IAP}\right) - \text{IAP} \\ &= \text{MAP} - 2\text{IAP} \end{aligned} \qquad (4.3)$$

Thus, elevations in IAP will have a far greater impact on renal function and urine production than that caused by reduction in MAP alone – such as seen in shock states – and the IAH-induced renal dysfunction is responsive to neither volume expansion nor vasopressors and loop diuretics, but rather improves dramatically by prompt release of the increased IAP [4, 11, 81, 85, 86]. Ureteral compression has been excluded as the cause of diminished urine production with IAH since oliguria was not prevented by the placing ureteral stents [80].

Gastrointestinal Effects

The gastrointestinal (GI) tract is very sensitive to elevations in IAP. A dog's model showed that an IAP of 20 mmHg significantly decreases blood flow to the entire GI tract and other intra-abdominal organs with the exception of the adrenal glands that were spared, probably as a survival mechanism supporting catecholamine release in the presence of hypoperfusion [87]. Animal models also showed significant decreases in intestinal mucosal blood flow with the development of tissue ischemia and intra-mucosal acidosis at IAP levels above >20 mmHg [88, 89]. In the setting of hemorrhagic shock and fluid resuscitation, the adverse effects of increased IAP on intra-abdominal organs may manifest even at IAP's lower than 20 mmHg due to the combined effects of reduced CO and splanchnic vasoconstriction [90]. Moreover, IAH also compresses the mesenteric venous system, causing venous congestion, intestinal edema and ascites, further

increasing IAP and worsening intestinal hypoperfusion and ischemia. Intestinal hypoperfusion leads to bacterial translocation and may contribute to the development of sepsis and MOF in patients with ACS [75, 89, 91].

Aside from the markedly swollen, tense abdomen, the GI manifestations of ACS include paralytic ileus, feeding intolerance, systemic lactic acidosis, exacerbation of NEC and not infrequently gut necrosis and significantly increased mortality [11, 30, 34, 44, 92–94]. Lactic acidosis is often the first sign of intestinal ischemia as a result of IAH, and should never be ignored. The abdominal wall blood flow is dramatically reduced by the elevated IAP, resulting in impaired wound healing and high rates of fascial dehiscence or surgical site infection [28, 95].

CNS Effects

Increased intracranial pressure (ICP) is a well recognized component of the ACS [41, 96–100]. The elevated IAP increases intra-thoracic pressure that interferes with internal jugular venous drainage, causing intracranial congestion and intracranial hypertension (ICH) [77, 96, 98, 101, 102]. Multiple studies described prompt reductions of ICH following DL [97, 103–105]. It was therefore recommended that IAP monitoring should be considered in all traumatic or non-traumatic patients with non-responsive ICH, and a lower threshold for DL should be considered in patients who have sustained combined abdominal and head trauma [55]. As diagnostic laparoscopy may increase ICP, it should be avoided in evaluating patients with severe head injuries [55].

Diagnosis

Considering the high mortality rate associated with ACS, early and prompt recognition of ACS is mandatory and a high index of suspicion is crucial. In general, ACS should be suspected in any patient with the appropriate clinical setting and risk factors, whose organ dysfunction worsens or does not improve following adequate supportive therapy [106]. Physical examination, including palpation of the abdomen and measuring abdominal girth has been shown to be highly unreliable, with sensitivity and positive predictive values of around 40–60 %, thus making it a poor diagnostic tool for the diagnosis of ACS [107–109]. Imaging studies are of very limited value because they are neither sensitive nor specific for ACS and they should not be considered as independently adequate modalities for its diagnosis [110]. Therefore, reliable measurement of IAP is the first step in the diagnosis and management of patients with IAH/ACS [106], though, because of individual variability, no single IAP value can reliably diagnose ACS. According to the WSACS recommendations, patients with two or more risk factors for ACS (Table 4.2) should undergo baseline IAP measurement, and if IAH is present, serial IAP measurements should be performed every 4–6 h throughout the patient's critical course, until IAP remains <12 mmHg for at least 24 h in the absence of organ dysfunction [106, 111].

IAP Measurement in Children

IAP can be measured directly – through a needle or catheter inserted into the abdomen, or indirectly – using transduction of urinary bladder, gastric or colonic pressure via a balloon catheter [111, 112]. Transvesicular measurement of abdominal pressure (TVAP), initially described by Kron et al. in 1984 [3] and later modified by Cheatham and Safcsak [113], is the most widely used method due to its simplicity, low risk and minimal cost [111, 112, 114]. The WSACS recently advocated its use as the "gold standard" method for IAP measurement [1].

TVAP measurement techniques utilize the patient's indwelling urinary catheter, and may be performed with or without electronic devices. An age and weight-adjusted amount of saline (1 mL/kg for young children [22, 115], up to a maximum of 25 mL for older children and adults [116]) is injected into the bladder via a T-connector or a 3-way stopcock and the fluid is then allowed to rise in the tubing, with the pressure determined by the height of the fluid above the midaxillary line (Fig. 4.4). Alternatively, TVAP can be continuously monitored through a pressure transducer connected to the urinary catheter. Of note: injection of larger volumes should be avoided as this may falsely elevate IAP [22, 115, 116]. IAP should be

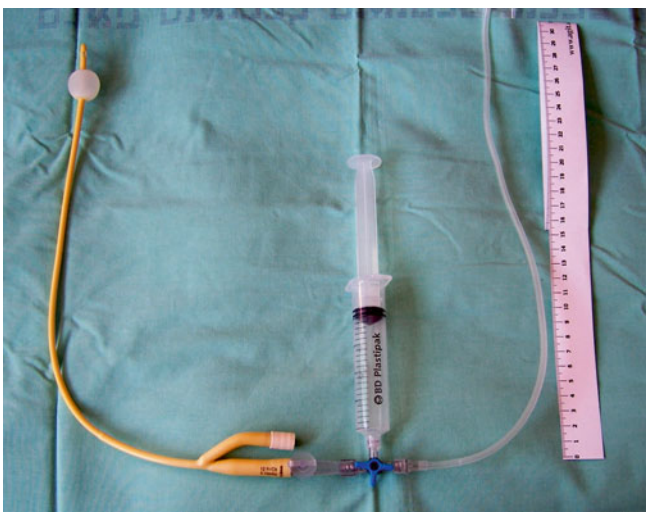

Fig. 4.4 Transvesicular abdominal pressure (TVAP) measuring system, consisting of a urinary catheter, T connector, 3-way stopcock, 20 ml syringe, open-end extention tube and a measuring tape

measured 30–60 s after installation to allow detrusor muscle relaxation, in the complete supine position and at end-expiration. If initially measured in cmH_2O, IAP should be converted to mmHg.

Imaging Findings

Plain radiography of the abdomen is insensitive to the presence of IAH [117]. Typical abdominal CT findings in children [118] and adults [119] with IAH and ACS include rounded abdomen, elevated diaphragm, narrowing of the IVC and renal veins, direct renal compression or displacement and bowel wall thickening, and it can assist in the diagnosis of ACS. Narrowing of the IVC and portal veins were recently documented in adult volunteers with induced IAH [120].

Management of IAH and ACS

For a long time, surgical DL was considered the only treatment for IAH and ACS, but nonoperative medical management strategies are now recognized as playing a vital role in the prevention and treatment of IAH and ACS [18, 28, 70, 121]. Based mainly on clinical observations and expert consensus rather than on proven outcome studies, the WSACS has proposed a graded approach to the management of IAH/ACS (Fig. 4.5). This approach consists of four elements (1) serial IAP monitoring (as discussed above); (2) prevention of IAH and ACS; (3) medical management and (4) surgical management.

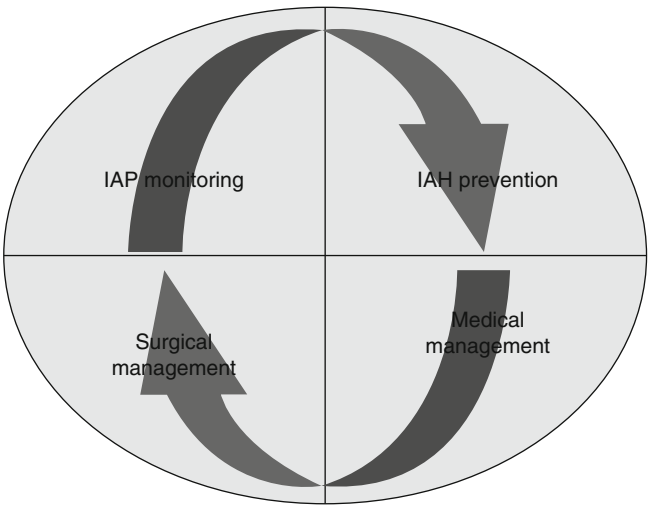

Fig. 4.5 Graded approach to the management of IAH/ACS consisting of four elements: *1* serial IAP monitoring, *2* prevention of IAH and ACS, *3* medical management, *4* surgical management

Prevention of IAH and ACS

The best treatment of ACS is prevention, and the first step in prevention is recognition of the patient at risk (Table 4.2), followed by IAP monitoring and early recognition of IAH that allows early interventions [122]. In high risk, mainly trauma patients, who undergo emergent laparotomy for damage control, the prophylactic use of incomplete, temporary abdominal closure techniques that allow the abdominal contents to expand more freely, was shown to be highly beneficial in preventing primary ACS [38, 123]. This approach was pioneered and is used extensively in the repair of congenital abdominal wall defects [3, 5, 7].

Appropriate fluid resuscitation with avoidance of excessive amounts of fluids is crucial for the prevention of ACS. Therefore, once goal-directed resuscitation end points (i.e., decrease in lactate and base deficit, adequate mixed venous oxygen saturation) are achieved, ongoing aggressive resuscitation should be stopped [56, 107, 122].

In burn patients, fluid resuscitation with colloids or hypertonic saline was shown to reduce the amount of fluids needed and to decrease the incidence of ACS when compared with crystalloids resuscitation [124, 125]. Thus, the consensus of specialists has proposed that hypertonic saline and colloids should be considered for resuscitation in patients with IAH to avoid the progression to secondary ACS [106]. Other patient populations who may benefit from reduced volume resuscitation include patients with end-stage liver or renal disease and congestive heart failure.

Medical Management of IAH (Fig. 4.5)

Nonoperative management is the first line treatment for grades I through III IAH, while immediate DL is the treatment for grade IV IAH/ACS [28, 106, 126]. Medical management aims at optimizing systemic and regional (abdominal) perfusion and at reversing three causative factors: fluid overload, decreased abdominal wall compliance and increased abdominal and intraluminal contents [126]. Recently, Cheatham and Safcsak demonstrated that an integrated approach with this stepwise algorithm can improve outcome and decrease hospital costs [127]. (To view the nonoperative management algorithm see https://www.wsacs.org/education/algorithms.html).

Optimizing Fluid Balance

As already discussed, excessive fluid resuscitation should be avoided. Diuretics in combination with albumin may be used in hemodynamically stable patients to mobilize third space edema into the intravascular space and thereby improve abdominal wall compliance and reduce intra-abdominal contents [106]. For unstable patients or for those with impaired

renal function, fluid removal by renal dialysis or by continuous renal replacement therapy (CRRT) may be helpful in reducing IAP and improving organ function [106, 128]. It is crucial to ensure that fluid removal does not result in impaired systemic or local perfusion or in reduced oxygen delivery.

Improving Abdominal Compliance

Body Positioning: As elevation of the head of the bed above 20° significantly increases IAP, maintaining it at less than 20° is important [106, 119, 120, 123]. Prone positioning was shown to increase IAP and its use in patients with respiratory failure and IAH should be carefully considered [129].

Abdominal Musculature Tension: Increased abdominal muscles tension due to voluntary muscle contraction, pain or agitation, patient-ventilator dys-synchrony and intrinsic or extrinsic positive end-expiratory pressure (PEEP) reduce abdominal wall compliance and contribute to IAH [34, 126, 130]. Neuromuscular blockade was shown to significantly reduce IAP [130, 131]. Therefore, the levels of sedation and analgesia should be optimized and neuromuscular blockade may be attempted mainly in patients with mild to moderate IAH [106, 130, 131].

Decreasing Intraluminal and Abdominal Contents

Evacuation of Intraluminal Contents: Paralytic ileus, a common finding in critically ill patients, causes accumulation of air and fluid within the hollow viscera, resulting in elevation of IAP [132]. Therefore, all patients at risk for IAH should have a nasogastric tube that enables the removal of excess air and fluid from the stomach and partly from the intestinal lumen [106]. The administration of prokinetic agents such as metoclopramide or erythromycin may facilitate the evacuation of intraluminal contents [106, 132]. Electrolyte abnormalities, such as hypokalemia, hypercalcemia, hypophosphatemia, and hypomagnesemia that may contribute to ileus should be corrected [126]. Enteral nutrition must often be minimized or completely discontinued [126]. When colonic ileus is most pronounced, the use of cathartics, enemas, rectal tubes and even colonoscopic decompression may be helpful [106, 126].

Evacuation of Abdominal Contents: Ascites and blood are the most common components of abdominal space-occupying lesions, but abscesses and free air also can increase IAP [70]. Since small changes in intra-abdominal volume may have a pronounced effect on IAP, patients with ascites, hemoperitoneum or large retroperitoneal collections often benefit from ultrasound guided, bedside, percutaneous drainage that decrease IAP, improve organ function and may avoid surgical intervention [70, 106, 133, 134]. Continuous drainage is preferable and more effective then single-needle drainage paracentesis [133, 135]. Although ultrasound guidance is preferable, under emergency situations and when a large amount of fluid has accumulated, "blind" catheter insertion at one third the distance between the left superior anterior iliac crest and the umbilicus ("left" McBurney's point) is safe. Rapid removal of even a large volume of peritoneal fluid is safe in patients who are not volume depleted [136]. Generally, success with catheter drainage is early and dramatic; therefore, if ACS persists after catheter drainage, DL should not be delayed.

Often no designated drainage catheter is available and a single end hole catheter is ineffective. We use rather routinely a single lumen, 0.8 mm ID polyurethane intravenous catheter (Leader Cath 115.11, Vygon, France) to which we add four or five side holes (Fig. 4.6). Using a sterile technique and when the metal guidewire is inserted into the catheter, holes are carefully cut in a swiping motion, starting about 1 cm from the catheter tip. To ensure mechanical stability, the catheter is "rotated", so that the holes are cut along it in a spiral fashion.

Surgical Management

Decompressive Laparotomy (DL)

If nonoperative measures fail to reduce IAH and relieve ACS and organs dysfunction continues to deteriorate, DL, in which the peritoneal cavity is left open, is the only definitive treatment for ACS [106, 137]. Due to the relatively small capacity of the abdominal cavity in children and the exponential nature of the volume-pressure curve, the child's condition may deteriorates extremely rapidly. Thus, DL often represents a true emergency, life-saving procedure, and its performance should not be delayed. Not infrequently, emergency DL is performed in the ICU [11, 14, 138].

The potentially catastrophic clinical course of ACS, the relative unawareness of ACS among caretakers of pediatric patients [9, 14] and the reluctance of some physicians to perform DL out of concern for causing permanent disability or mortality [127], probably contribute to the very high mortality of ACS in children. On the other hand, once performed, DL often results in immediate and dramatic improvement in all affected organ functions and in stabilization of the patient's condition [10, 11, 14, 139].

Indications and timing of DL: There is no uniform consensus regarding the indications or the IAP threshold that should prompt DL in ACS [79, 106, 137, 140]. According to the WSACS guidelines for adults, DL should be performed for all primary ACS with IAP >20 mmHg and for secondary ACS with IAP >25 mmHg, when accompanied with progressive organ failure or failure to maintain APP ≥60 mmHg despite of all medical measures [106, 141]. No parallel recommendations have been defined for children (See Appendix). A therapeutic algorithm described by Steinau et al. [12] defines ACS as IAP >20 mmHg or IAP >16 mmHg with organ dysfunction, and recommends immediate DL for primary ACS, and delaying DL

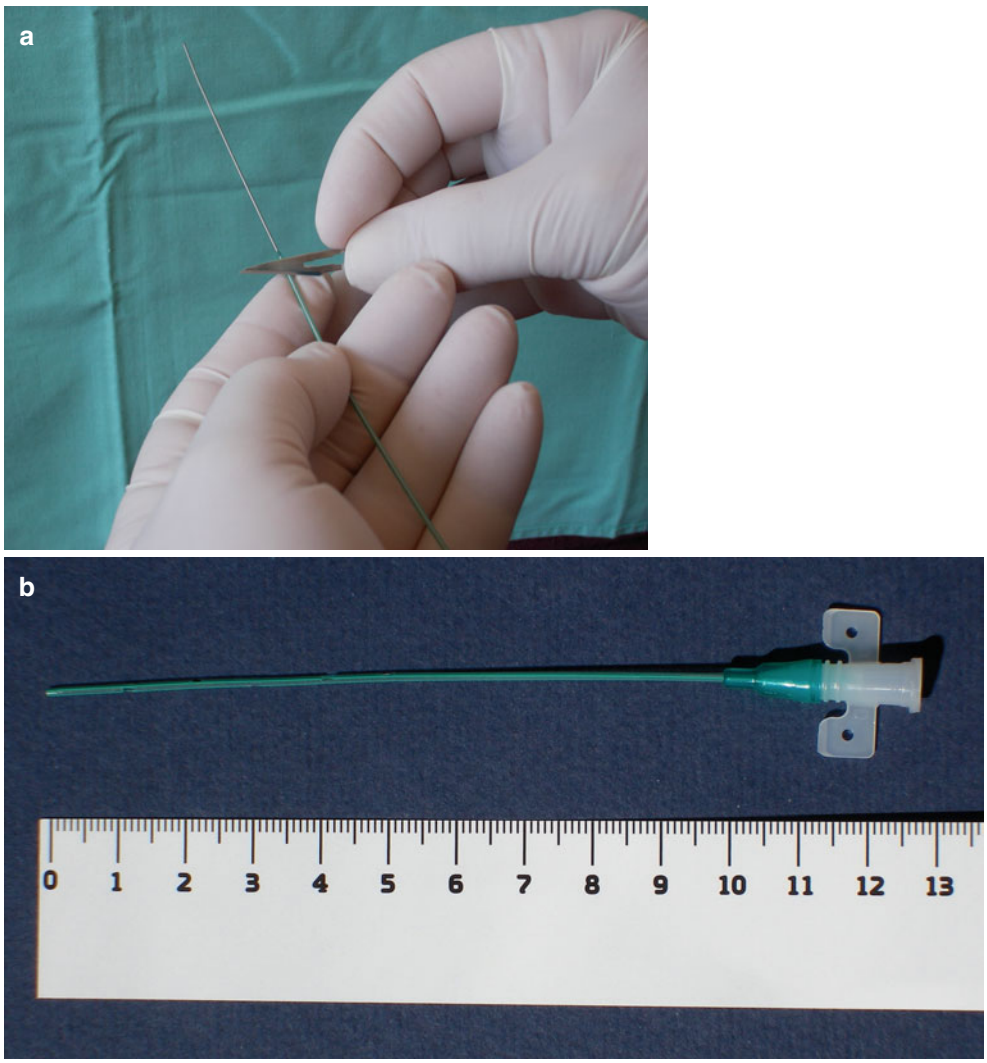

Fig. 4.6 "Makeshift" abdominal drainage catheter (Leader Cath 115.11, Vygon, France): (**a**) preparation of the catheter: side holes are cut in a swiping motion when the metal guidewire is inserted into the catheter. (**b**) drainage catheter with four side holes cut along it in a spiral fashion

until medical therapy is exhausted for secondary ACS. Pearson et al. [14] recommend DL in any child with a IAP >20 mmHg, lactate >3 mg/dL, persistent oliguria, elevated ventilatory pressures and an increasing vasopressor score. Our approach – similar to that of 70 % of surveyed members of the Society of Critical Care [20] – is to reach at a decision based on the comprehensive clinical picture combined with the IAP value. In the presence of IAH, when organ functions continue to deteriorate despite of all appropriate medical measures, DL should be considered and performed without additional delays [38, 106, 138].

Techniques of DL: The selection of the optimal technique for DL will be decided by the responsible surgeon. In cases of ACS following a recent abdominal surgery or in a case of recurrent ACS, the existing abdominal incision will usually be re-opened. For primary ACS, a full-thickness, longitudinal midline or subcostal transverse laparatomy will be performed.

Temporary abdominal closure (TAC) techniques are used following DL to avoid evisceration and protect the underlying viscera, to prevent abdominal infection and to allow for faster abdominal wall closure [55, 70, 142]. The most commonly used methods are the placement of a temporary absorbable mesh (e.g. Vicryl) (see Fig. 4.7), the "Bogata bag" [117, 142–145] and the vacuum-assisted closure (VAC) [142, 146]. The "Bogota bag", consisting of a plastic sheet cut from a sterile infusion fluids bag sewn to the fascia or skin edges [143], is always readily available and allows easy visualization of the abdominal organs – a helpful adjunct in evaluating the patient following DL.

Recurrent ACS is possible with any of the TAC techniques, especially if they are applied in a fashion that does not allow continued visceral expansion during resuscitation. Patients who develop "open-abdomen" ACS have a high mortality, and IAP monitoring should be continued after the procedure [147]. If recurrent ACS develops, the abdomen should immediately be reopened.

Following the resolution of ACS, definitive abdominal closure should not be delayed, since the incidence of failed

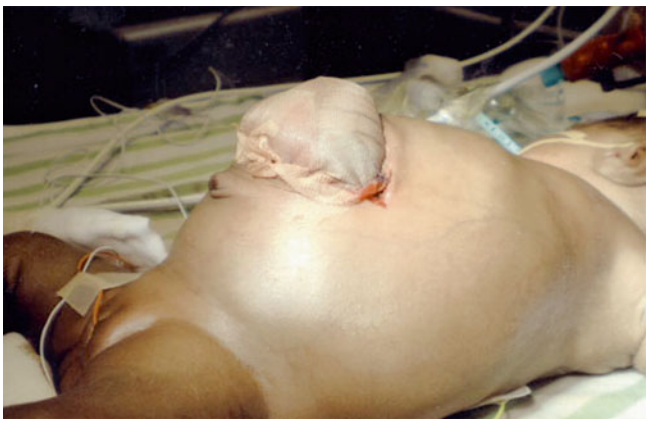

Fig. 4.7 Temporary abdominal closure (TAC) of the open abdomen with a Vicryl mesh following decompressive laparotomy (DL) for abdominal compartment syndrome (ACS) (Adapted from Steinau et al. [12]. With permission from Springer Science + Business Media)

closure and additional complications increases with time. The time window for successful primary fascial closure is usually 5–7 days [106, 122]. Beyond this time, adhesions and early granulation tissue often preclude fascial closure, resulting in the need for split-thickness skin grafting or cutaneous advancement flaps [11, 106, 122]. In children, however, even with prolonged use of a TAC, skin grafting is only rarely needed [146].

Complications of DL: DL can result in significant fluid and heat losses [70, 148, 149]. Postoperative bleeding and infection are rare [137], although Pearson et al. mentioned that bleeding occurred in 22 of 26 children who have underwent DL [14]. Enterocutaneous fistulas may form due to exposure of the bowel to the specific TAC used, inflammation, and/or infection [150, 151]. Extensive bowel swelling, adhesions between the bowel and the abdominal wall and sustained fistulas can prevent and delay definitive closer of the abdomen [148–150, 152]. Cosmetic concerns and physical and psychological discomfort with the scar area can complicate DL among children [12, 70].

The effects of DL on organs dysfunction: De Waele et al. [150] analyzed 18 adult studies (a total of 250 patients) for the effects of DL: The mean IAP fell from 34.6 mmHg before DL to 15.5 mmHg after DL. The hemodynamic effects of DL were somewhat non-uniform, but in general blood pressure and cardiac output increased, CVP and PAOP decreased significantly following DL. In all of the reviewed studies, PaO_2/FIO_2 ratios significantly increased and PIP's significantly decreased following DL. In most – but not in all – reviewed studies, urinary output increased dramatically after DL.

Pearson et al. [14], recently analyzed the effects of DL among 26 pediatric patients with ACS: Oxygen index, mean airway pressure and vasopressor score gradually decreased toward normal within 12 h of DL. Lactate levels dropped postoperatively by an average of 56 % and the hourly fluid requirement after DL decreased by 43 % compared to that before DL. On the other hand, urine output continued to be low with no return to normal by 12 h after DL, 11 patients had persistent renal failure and 20 required hemodialysis.

Critical Care Management of the Child with ACS

Critical care management of the patient with ACS consists of supporting the failing organ systems until definitive therapy is instituted and the patient's basic problem is brought under control. Cardiovascular function should be supported by judicious use of fluid resuscitation to avoid volume overload and further aggravation of ACS, combined with inotropic support. Traditional measures of preload, such as CVP, may be misleading due to the concomitant elevated intrathoracic pressure. APP may serve as a resuscitation endpoint, though it was not subjected to a prospective clinical trial [106, 122]. In adults, the WSACS recommended APP above 50–60 mmHg as a resuscitation endpoint [106]. No parallel recommendation was published for children, but given their lower physiologic perfusion pressures, APP threshold of 40–50 mmHg may be suggested, with infants at the lower end and adolescents at the upper end of this range.

Most patients will require mechanical ventilation, and as IAP rises, higher ventilatory pressures and FiO2 will be required. As IAH and ACS represent an extreme low-compliance state, pressure regulated, volume controled (PRVC) modes in conjunction with prolongation or reversal of the I/E ratio may help maintaining oxygenation while controlling PIP's. High PEEP may be required to counteract lungs compression, but should be applied judiciously, as it may further decrease venous return to the heart.

Improving renal perfusion with fluid resuscitation and inotropic support and high-dose furosemide (often as continuous intravenous infusion), may preserve urinary output and renal function in mild or early cases of ACS. Acidosis should be corrected, attempting to maintain arterial pH >7.20. These measures, however, will result, at best, in temporary improvement, as they do not alleviate the basic problem. Therefore, treatments directed at resolving ACS are mandatory and should not be delayed.

Outcome of ACS

The outcome of patients with ACS depends primarily on the basic clinical situation as well as on the delay in relieving the IAH. In both critically ill adults and children, the occurrence of ACS during ICU stay is an independent predictor of mortality [16, 21]. When left unrecognized and untreated, ACS is almost uniformly fatal. Deaths associated with ACS are usually due to multiple organ failure or sepsis. Mortality

among adult patients with documented ACS occurred in 10–68 % of patients [3, 39, 79, 140]. The mortality rate of children who underwent DL for ACS ranged between 40 and 60 % [11, 14, 16, 19].

Summary

ACS is a clinical syndrome resulting from IAH and characterized by rapidly progressive organ system failure, involveing the cardiac, respiratory, renal, gastrointestinal and central nerve systems. High index of suspicion, timely recognition and prompt intervention can be lifesaving. No specific definitions of IAH and ACS, nor specific treatment guidelines for the pediatric population have been published by the WSACS. Stepwise approach including medical management and DL may alleviate ACS and improve outcome, though the overall mortality even with surgical intervention is still very high (See Appendix).

Appendix

Following completion of this Chapter, updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome were published in July 2013 [153, 154].

The Pediatric Sub-Committee of the WSACS reviewed the (adult) main management guidelines in regard to their applicability and suitability for children, but could not make firm recommendations and proposed pediatric specific definitions:

1. ACS in children is defined as a sustained elevation in IAP of greater than 10 mmHg associated with new or worsening organ dysfunction that can be attributed to elevated IAP.
2. The reference standard for intermittent IAP measurement in children is via the bladder using 1 mL/kg as an instillation volume, with a minimal instillation volume of 3 mL and a maximum installation volume of 25 mL of sterile saline.
3. IAP in critically ill children is approximately 4–10 mmHg.
4. IAH in children is defined by a sustained or repeated pathological elevation in IAP >10 mmHg.

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Obesity in Critical Illness

5

Michael Hobson and Jennifer Kaplan

Abstract

Obesity continues to be a major health concern facing today's youths. With the ongoing rise in obesity, clinicians will increasingly care for more obese children struck with critical illness. Clinical management in these patients often becomes complicated, as obesity adversely impacts numerous organ systems. As such, pediatric intensivists should recognize these children as a unique patient population that merit special attention.

Keywords

Obesity • Inflammation • Critical illness

Introduction

Obesity is one of the most widespread and substantial health concerns facing today's children. Obesity in adulthood is defined as a body mass index (BMI) of ≥30 kg/m^2, whereas pediatric obesity is characterized by a BMI at or above the 95th percentile for age and gender. At present, it is estimated that 17 % of children and adolescents are obese [1]. Furthermore, nearly one-third of youths are overweight, based on a BMI greater than the 85th percentile [1]. As the obesity epidemic rages onward, its economic burden continues to have significant impact [2–4]. It is estimated that the Medicare costs associated with obesity could be as high as $85 billion per year [5]. In 2008, the National Association of Children's Hospitals and Related Institutions (NACHRI) convened a group to investigate the needs and barriers to pediatric obesity programs [6]. Executive sponsors of the 47 NACHRI member hospitals that completed an application were invited to complete a survey. Nearly 75 % of the respondents reported that obesity programs were integrated into their hospitals' strategic plans. Children's hospital administrators also reported that managing childhood obesity is an integral part of the goal of caring for children. With such an emphasis from hospital administration, the care of the obese child will become more apparent in pediatric hospitals. Furthermore, with the increasing number of obese children being managed at children's hospitals, the number of critically ill obese children will increase.

With the rise in pediatric obesity across society, clinicians must continue to familiarize themselves with the unique challenges that accompany caring for the obese child. Obesity leads to a wide array of comorbidities (Table 5.1), and an understanding of the many medical and surgical pathologies seen in these patients is paramount for their proper care in the critical care setting. At the present time, there is a paucity of literature regarding the care of obese pediatric patients in the ICU, and clinical guidance in large part must be extrapolated from adult studies. This chapter will provide an overview of the care of the critically ill obese child.

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Table 5.1 Comorbidities associated with pediatric obesity

Cardiovascular:
Hypertension
Dyslipidemia
Early atherosclerotic disease
Pulmonary:
Obstructive sleep apnea
Obesity hypoventilation syndrome
Gastrointestinal:
Nonalcoholic steatohepatitis
Gastroesophageal reflux disease
Cholelithiasis
Endocrine:
Diabetes mellitus, impaired glucose tolerance
Metabolic syndrome
Hyperandrogenism
Accelerated linear growth, early onset of puberty
Neurologic:
Idiopathic intracranial hypertension
Psychosocial:
Depression, anxiety, poor self esteem

General Considerations for Dealing with the Critically Ill Obese Patient

Difficulties with Routine Bedside Care and Procedures

An obvious but important notion is that the sheer size of obese pediatric patients, particularly adolescents, presents challenges for customary medical care. Pediatric hospitals specifically may not be equipped with properly sized blood pressure cuffs, patient beds, imaging modalities and operating room tables. Routine nursing care is made more difficult and often requires additional staff to assist with routine care. Furthermore, the lack of mobility associated with an ill obese patient increases the risk of venous thromboembolism and pressure ulcers [7]. Everyday diagnostic radiologic procedures are also made problematic in obese patients because of a large body habitus. The image quality of radiographs is reduced, particularly with portable x-ray machines, often making it difficult to distinguish between infiltrates and overlying soft tissue. Diagnostic imaging with ultrasound is hindered by a greater distance to be penetrated by the sound waves, and changing patient position to obtain better acoustic windows may be even more difficult in the obese patient. Utilizing CT and MRI studies may be prohibited by patient size, particularly in pediatric hospitals. These same factors may exclude interventional procedures such as ultrasound or CT-guided abscess drainage [8]. Lastly, peripheral intravenous access may not be obtainable in these patients, and central venous access is made more difficult by disruption of the normal anatomical landmarks and an increased distance of the vessels from the skin surface. However, the use of ultrasound guidance has increased success of central venous cannulation and decreased complication frequency in obese patients [9].

Effects of Obesity on Pharmacology

Clinicians must also be aware of pharmacologic adjustments which may be needed for obese patients. Many sedative and analgesic agents are extremely fat soluble, and thus their volume of distribution becomes altered in obese patients. An increase in total blood volume, cardiac output and an alteration in plasma protein binding can affect the pharmacokinetic profile of medications in the obese patient [10–12]. Obesity may also cause changes in hepatic and renal function which may modify drug metabolism and clearance [13].

Dosing regimens for obese patients include dosing on total (actual) body weight (TBW), ideal body weight (IBW), percent ideal body weight, adjusted body weight [IBW + 0.4 (TBW − IBW)], body mass index, and body surface area. Another method used to predict the expected normal weight of an obese patient is called the predicted normal weight (PNWT). The PNWT is equal to the sum of an individual's lean body weight and a fraction of the individual's excess fat content that represents the predicted normal fat mass [14]. Unfortunately, there is no consensus regarding the appropriate drug dosing method to use in obesity. However, in general, hydrophilic agents should be dosed based on ideal body weight; whereas lipophilic drugs should be dosed based on total body weight.

In obese pediatric and adult patients, basing drug dosing on total (actual) rather than ideal body weight may lead to undesired prolonged effects of the medication. For example, when rocuronium was dosed based on total body weight versus ideal body weight, obese patients demonstrated a significant increase in the duration of action of rocuronium [15, 16]. In contrast, Purhinger et al. demonstrated no difference in the duration of action of rocuronium when dosed by total body weight [17]. Still, it is recommended that rocuronium be dosed based on ideal body weight to avoid prolonged duration of action.

Alternatively, using an ideal body weight for obese patients may undertreat patients. In a multicenter study evaluating vancomycin dosing, adequate initial dosing was achieved in only 28 % of obese patients compared with 99 % of normal weight patients [18]. In a separate study, actual versus ideal body weight dosing of vancomycin did not result in increased serum trough levels in obese children [19]. Therefore it is recommended that in obese adult and pediatric patients vancomycin dosing should be based on total versus ideal body weight. Total weight based dosing

was utilized for a study examining cefoxitin kinetics in obese surgical patients in which patients weighing ≥80 kg received a 2 g dose versus a 1 g for patients weighing <80 kg [20]. The doubling of the dose in obese patients resulted in a two-fold higher plasma concentration of cefoxitin. However, tissue penetration was lower in the obese patient and there was an inverse relationship between cefoxitin tissue penetration and body mass index. This "underdosing" of antibiotics may contribute to the increased surgical site infections demonstrated in obese patients. Clearly studies are needed to determine appropriate dosing in obese patients. A more detailed description of the pharmacokinetic considerations in obese patients can be found in these excellent reviews [13, 21, 22].

Airway Management and Obesity

Airway management of obese children can present the pediatric intensivist with an arduous task and clinicians skilled in the management of difficult airways should be readily available in these circumstances. Subcutaneous fat deposits and fatty infiltration of pharyngeal muscles can obscure airway anatomy and make laryngoscopy difficult [23]. A laryngeal mask airway should be quickly accessible should this situation arise. Brodsky et al. prospectively evaluated morbidly obese surgical patients to determine factors which might complicate direct laryngoscopy and tracheal intubation [24]. Using logistic regression analysis, neck circumference was the only patient characteristic that had a significant effect on the probability of problematic intubation.

Proper positioning of the obese patient is critical for successful tracheal intubation. Morbidly obese patients undergoing elective bariatric surgery were evaluated to determine the effect of patient position on the view obtained during laryngoscopy [25]. Patients were randomized to a conventional "sniff" position which utilized a firm 7-cm cushion underneath the patient's head or a "ramped" position which was achieved by arranging blankets underneath the patient's upper body and head until horizontal alignment was achieved between the external auditory meatus and the sternal notch (Fig. 5.1a, b). Collins et al. demonstrated that a grade 1 view was visualized in 18/27 (67 %) patients with the "sniff" position compared with 29/33 (88 %) patients with the "ramped" position, $p = 0.037$ [25]. Another technique called the HELP maneuver (Head Elevated Laryngoscopy Position) may also improve the view of the glottis during laryngoscopy. Therefore it is recommended that obese patients be positioned in which the upper body, neck and head are elevated to a point where an imaginary horizontal line can be drawn from the sternal notch to the ear to improve the view of the larynx during laryngoscopy (Fig. 5.1b) [25]. Increased abdominal pressure and a higher incidence of gastroesophageal reflux place obese patients at an increased risk for aspiration. Additionally, obese patients desaturate rapidly in the supine position (see below), and thus preoxygenation in the sitting position is beneficial prior to attempting intubation [26]. Lastly, in the event of an airway emergency, cervical adipose tissue can greatly obscure laryngeal anatomy, thus hindering cricothyrotomy or emergent tracheostomy, should that be needed.

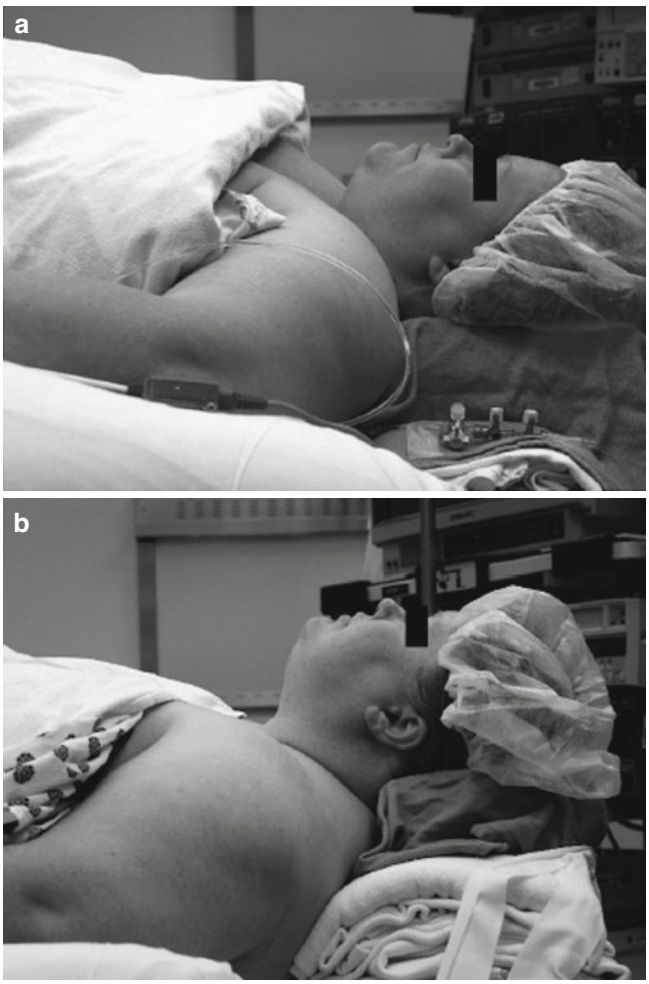

Fig. 5.1 (**a**) Patient positioned supine with 7-cm headrest under occiput. (**b**) Patient positioned with folded blankets under upper body, head and neck (Reprinted from Collins et al. [25]. With permission from Springer Science + Business Media)

Pulmonary Physiology and Obesity

Basic respiratory mechanics are significantly altered in the patient with an obese body habitus, and this presents challenges in the management of respiratory failure in this patient population. Adipose tissue overlying the chest wall coupled with increased intra-abdominal pressure reduces chest wall motion and diaphragmatic excursion, thereby decreasing overall pulmonary compliance. This, in turn, yields decreased

Table 5.2 Respiratory physiology associated with obesity

Respiratory mechanics:
Reduced respiratory system compliance
Increased airway resistance
Lung volumes:
Reduced functional residual capacity
Reduced forced vital capacity
Tendency toward atelectasis and V:Q mismatch
Work of breathing:
Reduced tidal volume, higher respiratory rate
Increased oxygen consumption
Gas exchange:
Increased $PaCO_2$
Reduced PaO_2
Increased A-a gradient

tidal volume, alveolar hypoventilation, and increased ventilation/perfusion (V/Q) mismatch [27]. Clinically, obese patients breathe with a higher respiratory rate resulting in an increased oxygen consumption [2]. This increased oxygen consumption has detrimental implications when obese patients present with respiratory failure or in shock. Table 5.2 summarizes the alterations in respiratory function associated with obesity.

It has been well established that obese patients are at risk for post-operative respiratory complications. This is in large part due to the above described physiologic changes associated with their body habitus. Pelosi et al. showed that sedated, mechanically ventilated patients following elective abdominal surgery had significantly decreased functional residual capacity (FRC) (0.67 L vs. 1.7 L), decreased static compliance, and a threefold higher lung resistance compared to normal-weight controls [28]. Furthermore, obese patients undergoing mechanical ventilation with general anesthesia and paralysis showed an increased tendency toward hypoxemia, most often due to a heightened propensity toward atelectasis [29]. Fortunately, clinicians can adopt mechanical ventilation strategies to help abate these complications. The consequences of obesity on lung compliance is exacerbated when patients are in the supine position; this may be partially overcome by placing sedated, ventilated obese patients in the reverse Trendelenburg position. Higher levels of positive end-expiratory pressures (PEEP) may be needed to overcome increased abdominal pressure, and greater plateau pressures may be seen in the face of diminished respiratory system compliance. However, these higher plateau pressures should not be viewed as injurious to the alveoli, as transpulmonary pressure is not increased [26]. However, obese patients may also have a tendency toward airway obstruction, due in part to mechanical air-trapping and overactive airway responsiveness. In the obese critically ill patient mechanical ventilation should be adjusted to achieve a tidal volume based on predicted body weight to prevent overdistension, and clinicians should be mindful of the development of intrinsic PEEP [26].

Cardiovascular Physiology and Obesity

The physiologic consequences of obesity have a negative impact on the function of both the right and left ventricle. Sleep apnea and chronic hypoxia can lead to pulmonary hypertension and eventual right heart failure. Early coronary artery disease and systemic hypertension are other ill effects of long-standing obesity. Additionally, the high metabolic activity of excess adipose tissue leads to an increased total blood volume and increased cardiac output. Over time, this may lead to left ventricular dilation, increased left ventricular wall stress, and eventually compensatory hypertrophy with diastolic dysfunction. Such combined systolic and diastolic dysfunction under this circumstance has been dubbed "the obesity cardiomyopathy" [30]. Patients with this condition are at increased risk for congestive heart failure and sudden death. In Framingham Heart Study participants, it was demonstrated that for every 1 kg/m^2 increase in BMI, the risk of heart failure increased by 5 % in men and 7 % in women [31].

Recent evidence suggests that the adverse effects of obesity on the heart may begin as early as childhood. A retrospective review of healthy children undergoing routine echocardiography showed a positive correlation between BMI and left ventricular mass index [32]. Similarly, Saltijeral et al. prospectively performed echocardiography on obese children (mean age of 13 years) with no other cardiovascular risk factors; compared to normal-weight controls, these children had increased left ventricular septal and posterior wall thickness, as well as increased left ventricular strain patterns [33]. Left ventricular hypertrophy has been further categorized based on the left ventricular mass and relative wall thickness. These categories include concentric hypertrophy (increased left ventricular mass and increased relative wall thickness), eccentric hypertrophy (increased mass and normal relative wall thickness), concentric remodeling (normal mass and increased relative wall thickness) and normal geometry (normal mass and normal relative wall thickness) [34, 35]. In a cohort of predominantly African-American adolescent subjects obesity, hypertension, and concentric hypertrophy were independent predictors of diastolic dysfunction [36]. In adults, concentric hypertrophy is associated with increased odds for total cardiovascular events and all-cause mortality [34, 35]. Fortunately, in adolescent patients these cardiovascular changes are reversible and can improve after weight loss. Ippisch et al. evaluated cardiac abnormalities in 38 morbidly obese adolescents before and after bariatric surgery [37]. The prevalence of concentric left ventricular hypertrophy improved from 28 % pre-operatively to 3 %

post-operatively (p = 0.007). Furthermore, left ventricular geometry and diastolic function also improved following weight loss.

Despite these potential obesity-related cardiovascular complications, many studies have demonstrated that overweight and obese heart failure patients have a better prognosis than normal weight patients. This condition is termed the "obesity paradox" [38, 39]. In an analysis of 1,203 patients with advanced heart failure, patients with a higher BMI had a trend toward improved survival [38]. This finding has been confirmed in other studies in which a higher BMI conferred better survival in patients with heart failure [40, 41]. In a large study with 5,255 participants, obese patients with heart failure had a lower risk of cardiac death and all-cause mortality [42]. Using data from the Acute Decompensated Heart Failure National Registry, Fonarow et al. demonstrated that in-hospital mortality rates decreased with higher BMI quartiles (5 % for BMI 16–23.6 kg/m^2 vs 2.2 % for BMI 33–60 kg/m^2) [43]. Furthermore, for every 5-unit increase in BMI, these authors demonstrated that the odds of risk-adjusted mortality decreased by 10 % [43]. In a meta-analysis performed by Oreopoulos et al. to examine the relationship between increased BMI and mortality in patients with CHF, both overweight and obesity groups were associated with lower all-cause mortality (RR 0.84, 95 % CI 0.79–0.90 and RR 0.67, 95 % CI 0.62–0.73, respectively) compared to individuals without elevated BMI levels [44]. Molecular mechanisms to explain the epidemiological findings for the obesity paradox have not been elucidated. In addition, the obesity paradox has not been extensively studied in children.

Additional Disease-Specific Considerations for the Critically Ill Obese Patient

In morbidly obese adults the main reasons for PICU admission are obstructive airway disease, pneumonia and sepsis [45]. Critically ill morbidly obese PICU patients have higher rates of complications including sepsis, nosocomial pneumonia, ARDS (acute respiratory distress syndrome), catheter related infection, tracheostomy, and acute renal failure [46, 47]. Although the complication rate is higher in obese patients, the influence of excess body weight on ICU mortality remains controversial. There is no definitive association, either positive or negative, on obesity and ICU mortality. Several studies have shown increased mortality in obese ICU patients [45, 46, 48] while others demonstrate no difference [49, 50] and others demonstrate a decreased mortality [51, 52].

Mechanical Ventilation

The physiologic alterations associated with obesity place obese patients at risk for longer days on mechanical ventilator support. The need for mechanical ventilation significantly increases in hospitalized patients with increasing BMI [47]. Patients with a BMI > 40 kg/m^2 were more likely to require mechanical ventilation compared with patients with a BMI 30–40 kg/m^2 [46]. The mean lengths of mechanical ventilation and ICU stay were longer for morbidly obese patients (7.7 ± 10.6 days and 9.3 ± 13.5 days, respectively) compared to non-obese patients [4.6 ± 7.1 days (p = 0.0004) and 5.8 ± 8.2 days (p = 0.007), respectively] [45].

Acute Lung Injury/ARDS

Obese patients with acute lung injury (ALI) or ARDS demonstrate increased morbidity but not increased mortality. Analysis from the ARDS Network found no significant increase in the adjusted odds for mortality in overweight or obese patients suffering acute lung injury [53]. Morris et al. conducted a prospective cohort study of 825 patients with ALI across a range of BMI categories in an adult intensive care unit and demonstrated no mortality difference between overweight and obese patients compared to those with normal weight [54]. However in severely obese patients (BMI > 40 kg/m^2) duration of mechanical ventilation and ICU and hospital stays were longer [54].

Data suggests that about 14 % of obese patients require re-intubation after undergoing prolonged (>48 h) mechanical ventilatory support [55]. The use of non-invasive ventilation in obese patients following extubation may improve extubation success rates. In a study of 62 adult obese patients with a BMI ≥ 35 kg/m^2 the initiation of post-extubation non-invasive ventilation resulted in a 16 % absolute risk reduction in the rate of respiratory failure. This resulted in shorter ICU and hospital length of stays [55].

Asthma

While the prevalence of both obesity and asthma have risen dramatically over the past few decades, the significance of the association between these two diseases is currently unclear [56]. Cross-sectional and prospective studies have established a link between obesity and asthma in both children and adults [57]. Furthermore, these studies have shown that obesity frequently precedes the development of asthma and also increases the risk of childhood asthma persisting into adulthood [57]. A recent meta-analysis investigating the relationship between weight and asthma showed that a high birth weight along with an increased weight through childhood resulted in a higher risk of asthma in adolescence, particularly in females [58]. However, several confounding factors have prohibited a definitive causality between obesity and asthma. For example, the dyspnea on exertion that may

result from obesity-related deconditioning can potentially be falsely interpreted as exercise-induced asthma.

The obese pediatric patient with asthma is at risk for more severe exacerbations relative to non-obese asthmatics. In an inner-city cohort of 1,322 children with asthma, obese patients reported a higher rate of medication use, reported more wheezing, and were more likely to seek care in the emergency department [59]. A recent retrospective study of children admitted to the intensive care unit with status asthmaticus found that obese patients had a longer requirement for continuous albuterol, intravenous corticosteroids, and supplemental oxygen, and thus ultimately a longer stay in the ICU [60]. Several factors have been proposed to explain this phenomenon. As described above, obese patients have a propensity toward mechanical air trapping as well as diminished respiratory system compliance with a subsequent reduction in lung volumes. Under reduced tidal volumes less retraction is exerted on the airways from the surrounding lung parenchyma, thereby allowing the airway smooth muscle to contract more readily when activated by various broncho-constricting stimuli [61]. Despite their worse disease severity, obese patients with asthma have not demonstrated increased airway inflammation or airway hyper-responsiveness [62, 63]. For example, exhaled nitric oxide, a highly reproducible indicator of airway inflammation, is not increased in obese asthmatics [62]. Thus, it appears that the increased severity of disease in obese patients with asthma may be more attributable to mechanical factors than airway inflammation. If this is indeed the case, it is not surprising that bronchodilator and corticosteroid therapies appear less efficacious in this patient population [64].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is another condition which may complicate the care of an obese child in the PICU. Children with obesity are four to five times more likely to have sleep disordered breathing [65]. There is a positive correlation between obesity and the apnea index, defined as the number of respiratory events divided by the sleep time [65]. A large neck circumference coupled with an abnormal upper airway results in partial or complete airway obstruction while sleeping, causing intermittent hypoxia, hypercapnia, and sleep fragmentation. Patients with OSA display apnea, snoring, paradoxical chest/abdominal motion, and may suffer from daytime somnolence as well as mild cognitive impairment. Positive pressure ventilation for the correction of OSA in pediatric patients is associated with a decreased apnea index and less severe oxygen desaturations; however, compliance with such therapy has shown to be difficult for children [66]. Obese children with accompanying adenotonsillar hypertrophy have improved sleep physiology and improved quality of life following adenotonsillectomy [67]. Children with obesity and severe OSA have an altered ventilatory response to carbon dioxide stimulation, and thus are prone to post-operative respiratory complications [68]. Obese and overweight children who underwent adenotonsillectomy were more likely to be admitted following surgery compared with normal weight children [69]. Furthermore, length of stay positively correlated with BMI. Nafiu et al. demonstrated that overweight/obese children had more frequent peri-operative complications such as desaturation, multiple laryngoscopy, and laryngospasm compared with healthy weight subjects [69]. Therefore, the obese patient undergoing adenotonsillectomy may merit hospital observation with a consideration for ICU-level care on the first post-operative night. The economic implications may be substantial for this patient population, as obese children undergoing tonsillectomy have higher hospital costs compared to normal-weight counterparts [70].

The obesity-hypoventilation syndrome (OHS) is a related but distinct entity from OSA. The classic triad encompassing this condition consists of obesity, daytime hypoxemia, and diurnal hypoventilation [2]. While the exact pathogenesis of OHS remains to be elucidated, contributing factors include abnormal respiratory system mechanics, blunted central chemoresponsiveness to hypoxia and hypercapnia, and neurohormonal abnormalities [71]. Patients with obesity hypoventilation syndrome are more likely to require hospitalization for hypercapnic respiratory failure compared to patients with obesity alone, and the management of this disorder involves titration of noninvasive positive pressure ventilation. Additionally, these patients are prone to other clinical problems such as polycythemia, pulmonary hypertension, and cardiac dysrhythmias. Hospitalized patients with OHS required more ICU admissions (40 % vs. 25 %) compared to eucapnic morbidly obese hospitalized patients [72]. Patients with obesity hypoventilation syndrome have a higher mortality rate and are 2.5 times more likely to die than obese patients lacking this comorbidity [2].

Cardiopulmonary Arrest

Recovery after in-hospital cardiopulmonary arrest in obese pediatric patients is worse than in non-obese pediatric patients [73]. Obese pediatric patients who receive cardiopulmonary resuscitation (CPR) following an in-hospital cardiopulmonary arrest are less likely to be successfully resuscitated. In a review of the American Heart Association National Registry of Cardiopulmonary Resuscitation, 213 (17 %) of the 1,268 pediatric patients who suffered in-hospital cardiac arrest were obese [73]. The authors noted that obese patients were more often pulseless throughout the event and had a first documented rhythm of asystole

compared with non-obese patients. Obese patients received more epinephrine doses compared with non-obese groups (4 vs. 3 respectively, $p<0.005$). Additionally, obese patients were less likely to receive extracorporeal membrane oxygenation therapy (ECMO). Obesity was independently associated with worse rates of event survival as well as survival to hospital discharge [73]. The reasons for these differences may be explained in the effectiveness of the resuscitation efforts. The authors cite the following as reasons for suboptimal resuscitations in the obese child: deviation in effective team function, difficulties with vascular access, difficulties with airway management, ineffective force and depth of chest compressions, confusion over proper medication dosages, and uncertainty regarding defibrillation energy dosages [73]. Advances in medical simulation involving scenarios with the obese critically ill child may alleviate many of these shortcomings.

Venous Thromboembolic Disease

Venous thromboembolic (VTE) disease in children was historically thought to occur infrequently but is becoming more prevalent in the pediatric population [74, 75]. Data obtained from a large retrospective cohort study of children <18 years of age from the Pediatric Health Information System database demonstrates that the annual rate of VTE increased from 2001 to 2007 (from 34 to 58 cases per 10,000 hospital admissions) [76]. Furthermore, the majority (63 %) of children with VTE in this study had at least one coexisting chronic complex medical condition. Additionally, children admitted to the PICU and who have a central venous catheter are at even more risk of developing an VTE [77]. Obesity also places hospitalized children at higher risk for thromboembolic events. Using the Health Care Cost and Utilization Project Kids' Inpatient Database, Vu et al. showed that obesity was a significant risk factor for deep venous thrombosis (DVT) (prevalence ratio 2.1; 95 % Confidence Interval, 1.5–2.8) in patients aged 15–17 years who were hospitalized for four or more days [78]. Traumatically injured obese children are also more likely to develop a DVT compared to non-obese children [79].

Unfortunately, the appropriate prophylactic and treatment dose of enoxaparin, the low molecular weight heparin of choice, is not well established in the obese patient. Enoxaparin dosing should be dosed based on total body weight as recommended for venous thromboembolism prophylaxis in the 2008 American College of Chest Physicians guidelines [80]. Furthermore, while the dose of enoxaparin for prophylaxis of thromboembolism has been established in adults, a recent review of several pediatric cases suggest that higher doses than that recommended for adults may be necessary [81]. Monitoring of anti-factor Xa levels and targeting the dose to achieve a 4-h dosing level of 0.5–1 U/ml are necessary to determine the proper enoxaparin dose [80]. More studies are necessary to provide definitive recommendations for enoxaparin dosing in obese children.

Obesity and Infection

It has been recognized that obesity bestows an increased risk for the development of infection in critically ill patients [82]. Obesity is an independent predictor of bloodstream infections in older adults [83]. A recent systematic review confirmed a correlation between a higher BMI and worse outcomes from bacterial infections in hospitalized patients [84]. Following a bacterial infection obese patients had higher mortality, longer duration of mechanical ventilation, and longer length of ICU and hospital stays [84]. This trend is seen across an array of various infectious insults [85]. Obese patients are at increased risk for aspiration pneumonia secondary to higher volume of gastric secretions, increased intra-abdominal pressure, and a higher incidence of gastroesophageal reflux [85].

Obese ICU patients are also at increased risk for nosocomial infections during their hospitalization, particularly ventilator-associated pneumonia, urinary tract infections, and catheter-associated bloodstream infections [46]. The reasons for this trend are likely multifactorial. Obese patients are at an increased risk for respiratory complications and prolonged mechanical ventilation. Successful attainment of central venous access often requires a greater number of punctures in this population, and these catheters may serve a longer duration due to the inability to establish adequate peripheral intravenous lines. Another contributing factor is that at baseline obesity is associated with an underlying chronic inflammatory state. Many cells within adipose tissue can contribute to the inflammatory response in obesity and include adipocytes, endothelial cells, leukocytes and monocytes/macrophages [86]. In an animal model of sepsis even short duration high fat feeding increases mortality and organ injury following polymicrobial sepsis [87]. Furthermore, obesity is often accompanied by diabetes mellitus, which in turn weakens the immune response via impaired neutrophil chemotaxis and phagocytosis [88].

Surgical Site Infections

Obese patients had higher rates of surgical-site infections in a variety of surgical procedures including spinal, coronary artery bypass, and digestive tract surgeries [89–92]. Obese surgical patients are at increased risk for surgical site infections for a variety of reasons including lengthened operative time, increased local tissue trauma related to surgical retraction devices, and an impaired blood supply to adipose tissue which may result in a decrease in the

delivery of antimicrobial agents [85]. Additionally, obesity was independently associated with *Staphylococcus aureus* nasal carriage and may contribute to the post-surgical infection risk [93]. Bacterial cellulitis and necrotizing fasciitis are more severe in obese patients, owing in large part to an increase in lymphedema and impaired host immune defenses in adipose tissue [94].

Obesity and H1N1

The effect of obesity on infectious outcomes has been further scrutinized in light of the H1N1 influenza pandemic of 2009. In multiple studies obesity was a leading comorbidity in adults and children with severe influenza [95–97]. In an observational case-control study during the 2009 pandemic, obese patients with H1N1 were more likely to require ICU admission compared to the general population [98]. In a large prospective, multicenter study involving 144 intensive care units across Spain, Diaz et al. found that obese and morbidly obese adult patients requiring ICU admission for respiratory failure had a longer duration of mechanical ventilation and ICU length of stay compared to patients of normal body weight A recent meta-analysis suggests that obesity is associated with a higher risk of ICU mortality in influenza A patients [99]. Morbid obesity (BMI $\geq$ 40 kg/m^2) significantly increased the risk of ICU admission or death in this population (OR 2.01, 95 % CI 1.29–3.14, P<0.002) [99]. Of adult cases with H1N1 reported to the California Department of Public Health over a 17-month period during the 2009 pandemic, extreme obesity (BMI $\geq$ 40) occurred in 22 % of the 425 fatal cases [100]. In Europe, obesity and diabetes were the most frequent identified underlying conditions associated with H1N1 fatalities and occurred in 57/193 patients with comorbidities [101]. Furthermore, data suggests that the obese ICU patients with influenza utilized more hospital resources compared to their non-obese counterparts [100, 101].

Trauma

Obese patients have increased morbidity after sustaining multi-system trauma compared to non-obese patients. In a review of 1,167 adult trauma patients admitted to an ICU over a 2 year period Bochicchio et al. demonstrated that patients with a BMI greater than 30 kg/m^2 had nearly twice the rate of respiratory, blood, and urinary tract infections [82]. This resulted in significantly longer ICU and hospital stays in obese patients [82]. Additionally, when controlled for premorbid risk factors, obesity was an independent predictor for increased mortality in these trauma patients. Similarly, Brown et al. retrospectively compared 870 non-obese and 283 obese patients admitted to the ICU following blunt traumatic injury. Despite equivalent Injury Severity Scores, mechanism of injury, and admission vital signs, obese patients had a higher rate of complications compared to non-obese patients. These complications included multi-organ failure, ARDS, renal failure, vasopressor usage, and extubation failure [102]. In the pediatric cohort, Brown et al. found that obese children suffering blunt trauma had an increased risk of sepsis (15 % vs 4 %, p = 0.007) and wound infection (26 % vs 8 %, p = 0.03) compared with non-obese patients but no difference in mortality [103]. This effect seems to be pronounced in patients undergoing damage-control laparotomy, often due to obesity necessitating longer operating times and a longer time to abdominal closure.

Obese patients are at risk for injuries that differ from non-obese patients. Patients with an elevated BMI sustain an increased rate of rib fractures, pulmonary contusions, and pelvic and extremity fractures [104] Not all injuries sustained during multi-trauma occur more frequently in obese patients. Children with obesity sustained less severe traumatic head injuries compared with non-obese patients [103]. Injuries related to MVC in obese children also vary by age. Examination of data obtained from the National Automotive Sampling System Crashworthiness Data System for occupants involved in a motor vehicle collision (MVC) demonstrated that obese teenagers have a decreased risk of severe head and abdominal injury compared to non-obese teenagers after MVC [104]. Furthermore, obesity increases the risk of thoracic injuries in young children (ages 2–9 years of age) and increases the risk of severe lower extremity injuries in older children (ages 14–17 years of age) [104]. Obese children (2–13 years) have severe injuries which involve more body regions than the obese teenager [104].

Burn Injury

Historically, in the treatment of patients who have suffered burn injuries, total body surface area of the burn and the age of the patient have been the greatest predictors of patient outcome. However, in a recent review of patients treated in a dedicated burn center over a 2 year time period, greater than expected mortality was observed in patients with a body mass index $\geq$35 kg/m^2 when compared with their calculated risk of mortality as predicted by the Abbreviated Burn Severity Index [105]. Moreover, in this study, 13/14 (92 %) morbidly obese patients developed complications during treatment. Obese children suffered a burn injury to a high-risk area more frequently than non-obese children (72.8 % vs 60.8 %, p = 0.03) and had full thickness burns to $\geq$5 % body surface area more frequently [106]. The length of stay for obese children who suffered burn injury was almost 2 days longer than non-obese children [106]. Ongoing study is underway to discover better methods of care for these challenging patients.

Cancer

Pediatric cancer patients are another population where obesity increases the risk of poor outcomes. Lange et al. conducted the first study to show increased mortality among overweight pediatric oncology patients [107]. In their review of 768 children undergoing therapy for untreated acute myelogenous leukemia, patients with a BMI ≥95th percentile for age were more likely to present with higher leukocyte counts and to have unfavorable marrow cytogenetics [107]. Even when adjusting for these two factors, overweight children still had a significantly higher rate of mortality compared to normal-weight children. This treatment-related mortality was in large part due to infectious complications, with infection causing 18 % of obese patient deaths versus 8 % of normal-weight patient deaths ($p=0.002$) [107]. Of patients surviving childhood leukemia, nearly 50 % may develop obesity later in life [108], thus placing them at risk for hypertension and cardiovascular sequelae [109].

Bariatric Surgery

While nutritional and behavioral strategies have traditionally been the mainstays of therapy for overweight children, the frequency of bariatric surgery in the obese adolescent population has been increasing [110]. Current procedures for carefully selected patients with significant obesity-associated comorbidities include adjustable gastric banding, sleeve gastrectomy, biliopancreatic diversion, and the Roux-en-Y gastric bypass. Gastric bypass is a surgical procedure which is a combination of restrictive and malabsorptive procedures and is the operation currently most commonly performed [110]. The success rate of bariatric surgery in the adolescent population parallels that of adults, and a recent review noted that laparoscopic gastric bypass on average decreased obese adolescents' BMI by 37 % at 1 year [111]. Furthermore, the metabolic derangements associated with obesity such as diabetes mellitus can often be reversed after these procedures [112].

Paralleling the successful outcome for adolescent bariatric surgery is fortunately a low rate of complications. In a nationwide review of adolescent patients undergoing weight-loss procedures, complication rates were similar to adult patients (roughly 5 %, mostly respiratory complications), there was no pediatric mortality, and pediatric patients had shorter lengths of hospitalization compared to adults [110]. However, as the frequency of bariatric surgery in the adolescent population continues to increase, it will become paramount for the pediatric intensivist to become familiar with its complications. Following gastric bypass, dilation of the gastric remnant from distal intestinal obstruction can lead to sepsis and increased liver enzymes. Post-gastric bypass anatomy predisposes to internal hernias with subsequent bowel ischemia and infarction [113]. Additionally, there have been reports of pressure-induced rhabdomyolysis in obese patients undergoing bariatric surgery [114], often manifested initially as subtle shoulder or hip pain, and thus a high index of suspicion for this complication is needed. Finally, one of the most feared complications postoperatively is an anastomic leak with subsequent intra-abdominal sepsis. Due to increased thickness of subcutaneous adipose tissue and the greater omentum, obese patients often lack classic signs of peritonitis such as guarding and rebound tenderness [113]. Signs of an anastomotic leak include tachycardia, shortness of breath, tachypnea, and anxiety. These symptoms are nonspecific and often concerning for a pulmonary embolism; in fact, the presence of respiratory symptoms in a study of bariatric surgery patients admitted to an adult ICU with sepsis led to a misdiagnosis in over half of the patients [115]. Contrast studies often have low utility in the diagnosis of an anastomotic leak, and thus early contact with the patient's surgeon for a diagnostic laparoscopy should be undertaken when there is clinical concern for this complication.

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Nutrition in the PICU

6

Nilesh Mehta

Abstract

Nutritional therapy is recognized as an important cornerstone in the management of the critically ill child. However, optimal nutrient delivery in the PICU is challenging and results in nutritional deterioration and negatively impacts on clinical outcomes. There is increasing evidence that energy and protein intake in the PICU are far lower than their estimated requirement during critical illness. Recent data show an association between decreased macronutrient intake and mortality in mechanically ventilated children. Hence, optimal energy and protein intake in the PICU needs to be prioritized.

Enteral nutrition (EN) is the preferred mode of feeding in the PICU. Current evidence suggests benefit of early initiation of EN, followed by rapid advancement using a protocolized strategy and subsequent maintenance of uninterrupted EN. While the gastric route is preferred, patients at risk of aspiration or those who have failed gastric feeding may benefit from transpyloric feeding in centers with available resources and expertise. The role of routine prokinetics in the PICU is unclear. EN is probably safe in hemodynamically stable patients on a single vasopressor agent. Both avoidable and unavoidable barriers to EN exist, and need to be addressed by multidisciplinary commitment. Immunonutrition has been inadequately studied in critically ill children, and its role needs further clarification with the help of well-designed clinical trials. In the current era of limited evidence base for most nutrition practices, uniform consensus based strategies might be prudent. Protocols that provide guidelines for early initiation, rapid advancement and maintenance of EN in the PICU have been shown to improve the ability to reach nutrition goals and their use is associated with improved clinical outcomes. Future studies must examine strategies to optimize EN, improve protein intake to preserve lean body mass, role of supplementary PN, and clarify the role of immunontrition in the PICU.

Keywords

Nutrition • Enteral • Parenteral • Energy • Protein • Outcomes • Immunonutrition

Introduction

Nutritional therapy is recognized as an important cornerstone in the management of the critically ill child. The provision of optimal energy, protein, and micronutrients via the appropriate route is a fundamental goal of critical care and is expected to improve patient outcomes. The metabolic response to stress alters macronutrient requirements and the handling of nutrient substrate by the host. These alterations

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Table 6.1 A.S.P.E.N. guidelines paper – evidence based table of suggested guidelines

Nutrition support guideline recommendations in the critically ill child		
#	Guideline recommendations	Grade
1	1A) Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition and those who are nutritionally-at-risk	D
	1B) A formal nutrition assessment with the development of a nutrition care plan should be required, especially in those children with premorbid malnutrition	E
2	2A) Energy expenditure should be assessed throughout the course of illness to determine the energy needs to critically ill children. Estimates of energy expenditure using available standard equations are often unreliable	D
	2B) In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help to prevent overfeeding and underfeeding in this population	E
3	There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon understanding of protein metabolism and carbohydrate- and lipid- handling during critical illness	E
4	4A) In critically ill children with a functioning gastrointestinal tract, enteral nutrition (EN) should be the preferred mode of nutrition provision, if tolerated	C
	4B) A variety of barriers to EN exist in the pediatric intensive care unit (PICU) Clinicians must identify and prevent avoidable interruptions to EN in critically ill children	D
	4C) There are insufficient data to recommend the appropriate site (gastric vs. post-pyloric/transpyloric for enteral feeding in critically ill children. Post-pyloric or transpyloric feeding may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding	C
5	Based on the available pediatric data, the routine use of immunonutrition or immune-enhancing diets/nutrients in critically ill children is not recommended	D
6	A specialized nutrition support team in the PICU and aggressive feeding protocols may enhance the overall delivery of nutrition, with shorter time to goal nutrition, increased delivery of EN, and decreased use of parenteral nutrition. The affect of these strategies on patient outcomes has not been demonstrated	E

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are not easily estimated and prescription of optimal nutritional support during critical illness can be challenging. Furthermore, the severity of illness and complexities of critical care often impede nutrition intake goals during this vulnerable period. The resultant deficits in macronutrient and micronutrient intake may be associated with poor clinical outcomes, especially in children with existing nutritional deficiencies. Hence, there has been increasing interest in the field of pediatric critical care nutrition in recent years. The desire to optimize nutrition intake with the aim of improving clinical outcomes has driven many ongoing clinical and translational studies in the pediatric intensive care unit (PICU). Until the results of these trials are available and instruct nutrition therapy, clinicians are left with the task of adopting best practices, based on scant evidence (Table 6.1). In this chapter some of the key issues around feeding the critically ill child will be addressed, highlighting the evidence where available and outlining directions for the future.

Nutritional Deficiencies During Critical Illness

Over the past three decades, there has been no change in the prevalence of malnutrition in children on admission to the PICU [1–3]. Furthermore, critically ill children are at a risk of suboptimal prescription of macronutrients and failure to deliver the prescribed goal. These factors result in uncorrected energy and protein imbalances that contribute to further deterioration of nutritional status during the PICU stay [4, 5]. Poor nutritional status impacts both patient outcomes as well as utilization of healthcare resources in the intensive care unit [6, 7]. Physiologic alterations in the malnourished host and the effect of further nutritional deterioration during critical illness may influence clinical outcomes, such as mortality, length of hospital stay, and acquired infections [1]. Hence, detection of malnutrition on admission and serial monitoring of nutritional status is desirable in the PICU, but has largely been neglected.

Nutritional Assessment

Nutritional assessment is best undertaken by a dedicated PICU dietician or other trained personnel. A combination of anthropometric and laboratory parameters has been used to allow identification of patients with existing malnutrition. Common anthropometric measurements including weight, recumbent length (for children younger than 2 years) and height (for age 2 years or older) are obtained with standard equipment and technique and plotted for age on the Centers for Disease Control and Prevention (CDC) revised 2000 growth charts for United States, where the child is graphically

ranked along percentiles ranging from 3rd to 97th [8]. The use of variables such as weight for height or body mass index (BMI), in children older than 2 years, may provide a better indication of body composition and help distinguish between wasting (acute malnutrition) and stunting (chronic malnutrition). Z score is increasingly used as a way to interpret the anthropometric variables, and it denotes units of standard deviation from the median reference value [9]. Cut offs at −2 and +2 Z scores indicate severe malnutrition. Unfortunately, critically ill children frequently have fluid shifts, with capillary leak and edema that make most of the anthropometric measurements, including weight, unreliable. Furthermore, commonly used laboratory markers of nutritional state, such as serum albumin and prealbumin are influenced by disease state. Hence, nutritional assessment in the PICU population can be challenging.

Despite some of its limitations, serial nutritional assessment will allow early detection of anthropometric deterioration, and some patient groups in the PICU are particularly vulnerable. Some centers have used scoring systems to identify patients at risk of nutritional deficiency and hence likely to benefit most from nutritional interventions [10–12]. Preterm infants are particularly at risk for developing nutritional deficiencies and loss of lean body mass during critical illness. During the course of illness, this group of patients demonstrates a higher likelihood of anthropometric deterioration compared to older patients [4]. Newborns with congenital heart disease have a high incidence of PEM manifested by low weight-for-age Z scores on admission [13]. Progressive nutritional deterioration continues after discharge from the hospital, and a significant proportion of these patients are severely underweight on readmission for subsequent major cardiac surgery. Aggressive nutritional support has been associated with better nutritional status on readmission. Critically ill children with burn injuries manifest a prolonged hypermetabolic stress response and poor intake, which results in energy deficits, decreased lean body mass, and delayed linear growth that persist for months after injury [14, 15]. Malnutrition and subsequent anthropometric deterioration are independently associated with poor clinical outcomes, such as prolonged mechanical ventilation in the PICU population [16]. Prevention of nutritional deterioration, especially preservation of lean body mass, by optimizing nutrient intake during critical illness is crucial. The initial and ongoing nutritional assessment of critically ill children is discussed in greater detail elsewhere in this textbook.

Macronutrient Goals During Critical Illness

Energy Goals

A sound understanding of the metabolic profile during critical illness and individual macronutrient handling is required in order to prescribe optimal nutrition in the PICU. The nature, severity, and duration of this response is unpredictable, and energy needs may vary during throughout the course of illness. In certain disease conditions, such as burn injury or severe dysautonomia, energy expenditure may increase significantly from baseline [17, 18]. Therapeutic interventions such as mechanical ventilation, administration of vasoactive or sedative agents may have metabolic effects that are superimposed on illness-related factors. For example, the use of neuromuscularblocking agents in severe head trauma markedly decreases energy expenditure in patients who typically react with an increase in resting energy expenditure (REE), resulting in a lower than predicted total energy expenditure [19, 20].

Many predictive equations for REE in critically ill children have been developed. However, these equations have a wide range of predicting REE within 37–65 % of the measured values. As a result, a significant proportion of critically ill children in the PICU are either underfed or overfed when energy prescription is based on these equations [21]. Predictive equations based on age and gender do not account for illness severity, [22, 23] the dynamic changes in the underlying medical condition, or ongoing therapeutic interventions, all of which may influence the REE over time in individual patients [24, 25]. Furthermore, these standard age or gender-based equations represent reference data from several years ago and were derived from a healthy population with few young children [26]. They fail to incorporate measurements of body composition [27], often including only weight which is estimated [23]. Finally, most predictive equations require an accurate measurement of body weight, which is often not feasible in the PICU due to the patient conditions and the fluid shifts during acute illness. It is not surprising therefore, that a poor agreement has been reported between measured REE and energy expenditure predicted by the Schofield equation, Food and Agriculture Organization/World Health Organization/United Nations University equation, and Harris-Benedict equation [23, 28].

In general, many of the pediatric studies report a positive mean bias when using predictive equations, resulting in significant risk of overestimation of needs and resultant overfeeding [29, 30]. This lack of a hypermetabolic response has been seen even in children undergoing major surgery, extracorporeal membrane oxygenation, and cardiac surgery, including cardiopulmonary bypass. In their longitudinal study of energy balance in 46 patients during the first 7 days of critical illness, Oosterveld et al. reported that patients were underfed on 60 % of days and overfed on approximately 30 %. Although underfeeding was predominant, patients with sepsis were reported to have positive cumulative balance at the end of 1 week and were more likely to be overfed. It is becoming increasingly clear that the anticipated hypermetabolic response to injury or illness is either absent or muted in critically ill children.

Measured resting energy expenditure (REE) using indirect calorimetry provides accurate estimation of energy expenditure and guides energy prescription during critical illness. Indirect calorimetry is uniformly viewed as the gold-standard measurement and the most accurate measurement of the energy needs in ICU patients. Despite advantages of measured REE in the PICU, only a handful of centers regularly use indirect calorimetry (IC). A majority of centers rely on estimations from equations when prescribing daily energy goals [31]. Newer compact metabolic monitors may allow easier calibration, portability, and ability to use in patients requiring frequent respiratory interventions or different ventilator modes [32, 33]. In an era of resource constraints, IC may be targeted to patients who are at risk of metabolic instability, in which equation estimates are often unreliable and likelihood of energy imbalance is high [34]. Although the cost– benefit ratio of using IC for energy prescription needs to be further examined, it may have a role in preventing cumulative energy imbalances during critical illness.

Energy Balance in the PICU

Optimal energy homeostasis should be an important goal in the PICU, as both underfeeding and overfeeding are deleterious. Cumulative negative energy balances, accrued as a result of underfeeding, have been correlated with higher mortality and increasing number of infectious complications in critically ill adults [35–37]. Significant anthropometric changes, especially loss of lean body mass, have been shown in infants after critical illness [38]. As discussed above, systematic underfeeding of previously malnourished children and infants is associated with increased morbidity and must be avoided. On the other hand, many patients in the PICU may be at risk of cumulative positive balance, with up to 8,000 kcal excess over 1 week in a single center study [5]. While the problems with underfeeding have been well documented, overfeeding remains underdetected and has deleterious consequences too [29, 39]. It increases ventilatory work by increasing carbon dioxide production and can potentially prolong the need for mechanical ventilation [40]. Overfeeding may also impair liver function by inducing steatosis and cholestasis, and increase the risk of infection secondary to hyperglycemia. Hyperglycemia associated with caloric overfeeding has been associated with prolonged mechanical ventilatory requirement and PICU LOS [41]. There has been some enthusiasm for the concept of hypocaloric feeding in critically ill adults. However, there are no data in general or critically ill pediatric populations for the role of hypocaloric feeding. The application of hypocaloric feeding in a select group of chronically ill children at high risk of obesity is currently sporadic.

Table 6.2 Protein intake recommendations in the PICU

Suggested protein requirements in children	
Age (years)	Protein (g/kg/day)
0–2	2–3
2–13	1.5–2
>13	1.5

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Protein Goals

Once energy goals have been determined, the next step is to ensure adequate protein intake to account for the muscle catabolism and the general trend towards negative protein balance during critical illness (Table 6.2). In a recent review of studies reporting protein balance in mechanically ventilated children, we observed a direct correlation between both protein and energy intake and likelihood of achieving a positive protein balance [42]. In general, protein balance improved as protein intake increased [43–48]. Positive balance was achieved in enterally fed infants with viral bronchiolitis with as little as 1.5 g protein/kg/day [45]. While the lowest protein intake associated with a positive balance was 1.5 g/kg/day, individual and grouped thresholds for protein intake associated with achieving a positive protein balance were varied. In parenterally fed, hypermetabolic subjects an intake of 2.8 g protein/kg/day was required to achieve positive nitrogen balance [49, 50]. Severely ill, catabolic patients may be unable to maintain protein balance even with increasing amounts of protein and energy intake during the early and most critical stages of illness [48, 51]. Provision of nutrients during this time is often technically challenged by fluid restriction, interruptions or intolerance to feeding, and difficulty in obtaining enteral or parenteral feeding access [52, 53]. Due to the fixed protein: energy ratio of available enteral nutrition formula, failure to deliver nutritional prescription results in cumulative deprivation of both energy and protein, and anthropometric deterioration. In a recent multicenter study of nutrition practice in mechanically ventilated children, average enteral protein intake in the first 10 days in the PICU was less than 50 % of prescribed [54]. Lean body mass loss from cumulative negative protein balance is particularly concerning in children with pre-existing malnutrition, patients with compromised respiratory reserves and muscle function, and preterm infants with low reserves. Based on our review, protein intake for critically ill infants and children should reach a minimum of 1.5 g/kg/day, which is consistent with the recommendation in the recent American Society for Parenteral and Enteral Nutrition pediatric critical care nutrition guidelines [34]. Groups with a positive protein balance reported a minimum energy intake of 57 kcal/kg/day. The association between energy intake and protein balance in these studies might be

independent of protein intake. However, existing studies lack uniform study design, consistent methodology for measuring protein balance, and as such, do not allow meaningful interpretation from pooled data. There is an urgent need for studies with clearly defined interventions, larger samples, uniform and reproducible methodology, and longitudinal data points. Future research should consider the effect of increased protein provision on measures of lean body mass, while accounting for energy balance.

Nutrient Delivery in the PICU

Enteral Nutrition: Practical Considerations

The preferred route of nutrient delivery in critically ill children and adults is via a functional gastrointestinal tract [55]. Enteral nutrition (EN) is recommended in patients with hemodynamic stability and is generally considered to be more physiologic, cost-effective, and with a lower risk of nosocomial infection compared to parenteral nutrition (PN). In adult critically ill patients, EN is associated with beneficial effects on intestinal mucosal permeability, a lower rate of infectious complications, and decreased length of hospital stay [56–58]. To realize the potential benefits of EN in the PICU, both early initiation and maintenance of enteral feeding is recommended. Although the perceived benefits of early EN have not been backed by randomized control trials, it has been uniformly promoted by consensus-based guidelines in pediatric populations, mainly by extrapolation from adult literature [55, 59].

Role of Transpyloric Enteral Feeding in the PICU

The optimal site of enteral feeding (gastric vs. postpyloric) remains unclear. In general, gastric feedings are preferred because of ease of administration and reduced costs and expertise required in comparison to transpyloric feedings. In patients with poor gastric emptying or in cases where a trial of gastric feeding has failed, transpyloric or postpyloric (small bowel) feeding may be used to decrease the risk of aspiration and to improve EN tolerance [60]. However, there is no evidence of benefit for routine use of small bowel feeding in all patients admitted to the PICU. In a study examining the role of small bowel feeding in 74 critically ill children randomized to either gastric or postpyloric feedings, there was no significant difference in the incidence of microaspiration, tube displacement, and feeding intolerance between the two groups [61]. The study was not powered to detect differences in mortality. Although caloric goals were only met in a small percentage of the population studied, the proportion of subjects who achieved their daily caloric goal was higher in the small bowel group compared with the gastric fed group.

The evidence for benefits of postpyloric feeding remains equivocal, even in the adult critical care population [62]. It may be prudent to consider postpyloric feedings in selected patients who do not tolerate gastric feeding or those who are at a high risk of aspiration. Patients with depressed mental status, absent or depressed gag reflexes, severe respiratory distress, recurrent emesis, gastroesophageal reflux, history of aspiration, and delayed gastric emptying are deemed at high risk of aspiration [63]. Successful placement of transpyloric tubes requires the availability of experienced and expert operators, and backup support from radiologists in case bedside placement cannot be achieved. A variety of procedural techniques for transpyloric feeding tube placement have been described, including the use of modified tubes; air insufflation; videoscopic, echocardiographic, or external magnet assistance; and pH-assisted and spontaneous passage with or without promotility agents [64–67]. No single method has been shown to be superior and centers use techniques based on available local experience and expertise. The advent of percutaneously placed gastric and jejunal tubes has minimized cost, time, and morbidity [68]. Tube tip malposition is frequently encountered with any of these devices either at placement or during the course of use [69, 70]. Bedside screening methods for achieving correct tip position range from auscultation during air insufflation to ultrasound-guided tip localization. However, feedings should be held when malposition of tip is suspected, and when in doubt, radiographic confirmation of correct tip position must be obtained before recommencing feedings. Overall, transpyloric feeding is well tolerated in critically ill children and may allow early goal caloric intake by improving tolerance in carefully selected patients [61]. The benefit of transpyloric enteral feeding compared with PN, in terms of decreased complications and costs, must be further examined [71].

Barriers to EN in the PICU

Prospective cohort studies and retrospective chart reviews have reported the inability to achieve daily caloric goal in critically ill children. The most common reasons for suboptimal enteral nutrient delivery in these studies are fluid restriction, interruptions to EN for procedures, and EN intolerance due to hemodynamic instability. The percent of estimated energy expenditure actually administered to these subjects was remarkably low. In a study examining the endocrine and metabolic response of children with meningococcal sepsis, goal nutrition was achieved in only 25 % of the cases [12]. Similar observations have been made in a group of 95 children in a PICU where patients received a median of 58.8 % (range 0–277 %) of their estimated energy requirements. In this

Table 6.3 Barriers to optimal EN and suggested management

Barriers to enternal nutrition (EN) in the PICU		
Barrier	Reason	Suggested approach
Interruptions to EN	Intolerance	Apply uniform definition, algorithmic guideline
	Procedures	Review fasting guidelines for procedures
		Resume feeding if procedure delayed, canceled or complete
	Enteral access issues	Request specialized team for enteral access, radiology collaboration, prompt replacement of displaced enteral tubes
Fluid restriction	Patients with cardiac or renal conditions	Consider concentrated formulae
		Review ***other*** fluids
		Anticipate and plan with dietitian
Patient on vasoactive drug(s)	Concerns for gut ischemia	Prudent to hold EN when actively resuscitating with fluid, hemodynamics worsening or multiple vasoactive drugs required
		Consider EN if no fluid resuscitation for over 12 h and on single or stable vasoactive support
		Monitor closely while advancing feeds
Delayed EN initiation	Failure to prioritize	Educate, develop institution-specific, uniform guidelines for nutrition delivery
General reluctance to address nutrition delivery	Failure to prioritize nutrition support	Create nutrition support teams
		Request dietitian dedicated to the ICU
		Involve key stakeholders and develop multiprofessional consensus for nutritional therapy goals

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review, EN was interrupted on 264 occasions for clinical procedures. In another review of nutrition intake in 42 patients in a tertiary-level PICU over 458 ICU days, actual energy intake was compared with estimated energy requirement. Only 50 % of patients were reported to have received full estimated energy requirements after a median of 7 days in the ICU [53].

Diagnostic and therapeutic interventions in the PICU often require a fasting state, and hence compete with EN delivery goals. In addition, a significant number of eligible patients are deprived of EN during critical illness because of avoidable factors such as suboptimal nutrient prescription, failure to initiate EN early, and prolonged interruptions to enteral feeding [53, 72, 73]. Delayed initiation and subsequent interruptions contribute to suboptimal EN administration in the PICU. Patients with avoidable EN interruptions in one study experienced significant delays in reaching the prescribed caloric goal and were more likely to be exposed to the higher cost, infectious risks, and other morbidities associated with PN use [52]. Following initiation, EN was interrupted in 24 (30 %) patients at an average of 3.7 ± 3.1 times per patient (range, 1–13), for a total of 88 episodes, accounting for 1,483 h of EN deprivation in this study. A majority of EN interruptions in this study were deemed as avoidable, and nearly a third of the patients did not receive any EN during their PICU course. Fasting for procedures and intolerance to EN were the most common reasons for prolonged EN interruptions. Interventions aimed at optimizing EN delivery must be designed after examining existing barriers to EN and directed at high-risk individuals who are most likely to benefit from these interventions (Table 6.3).

In some patients, EN may not be feasible, especially due to intolerance or hemodynamic instability during acute illness. EN is generally initiated once hemodynamic stability has been achieved. In most centers, ongoing fluid resuscitation, escalating vasopressor medications, and worsening shock may be contraindications for initiating EN. The administration of EN in patients on single vasoactive medications for hemodynamic support in the PICU is probably safe [74]. The interaction between nutrient administration in patients receiving vasoactive and inotropic infusions on gut mucosal perfusion and the risk of mucosal ischemia are complex. In an effort to minimize the likelihood of intestinal ischemic necrosis, EN administration in this group of patients requires a thoughtful approach and robust monitoring for early signs of intolerance. EN intolerance is another challenging bedside dilemma in the PICU. The condition is variably defined, and the use of markers of intolerance such as gastric residual volume (GRV) is not based on sound evidence. The absence of bowel sounds, abdominal distension, vomiting, diarrhea and discomfort are other markers that are used to assess for intolerance to EN. Bedside practice is heterogeneous and EN is interrupted due to perceived intolerance in a large proportion of patients [52].

Strategies to Optimize Macronutrient Intake in the PICU

In a large multicenter study of mechanically ventilated children in the PICU, lower energy and protein delivery in relation to estimated requirements was significantly associated with increased mortality [54]. The use of protocolized nutrient delivery was associated with decreased acquired infections in this group. Protocols that provide

guidelines for early initiation, rapid advancement and maintenance of EN in the PICU have been shown to improve the ability to reach nutrition goals in several centers [75, 76]. These protocols guide bedside management of intolerance and provide surveillance for safe delivery of enteral nutrients. Figure 6.1 shows an example of a step-

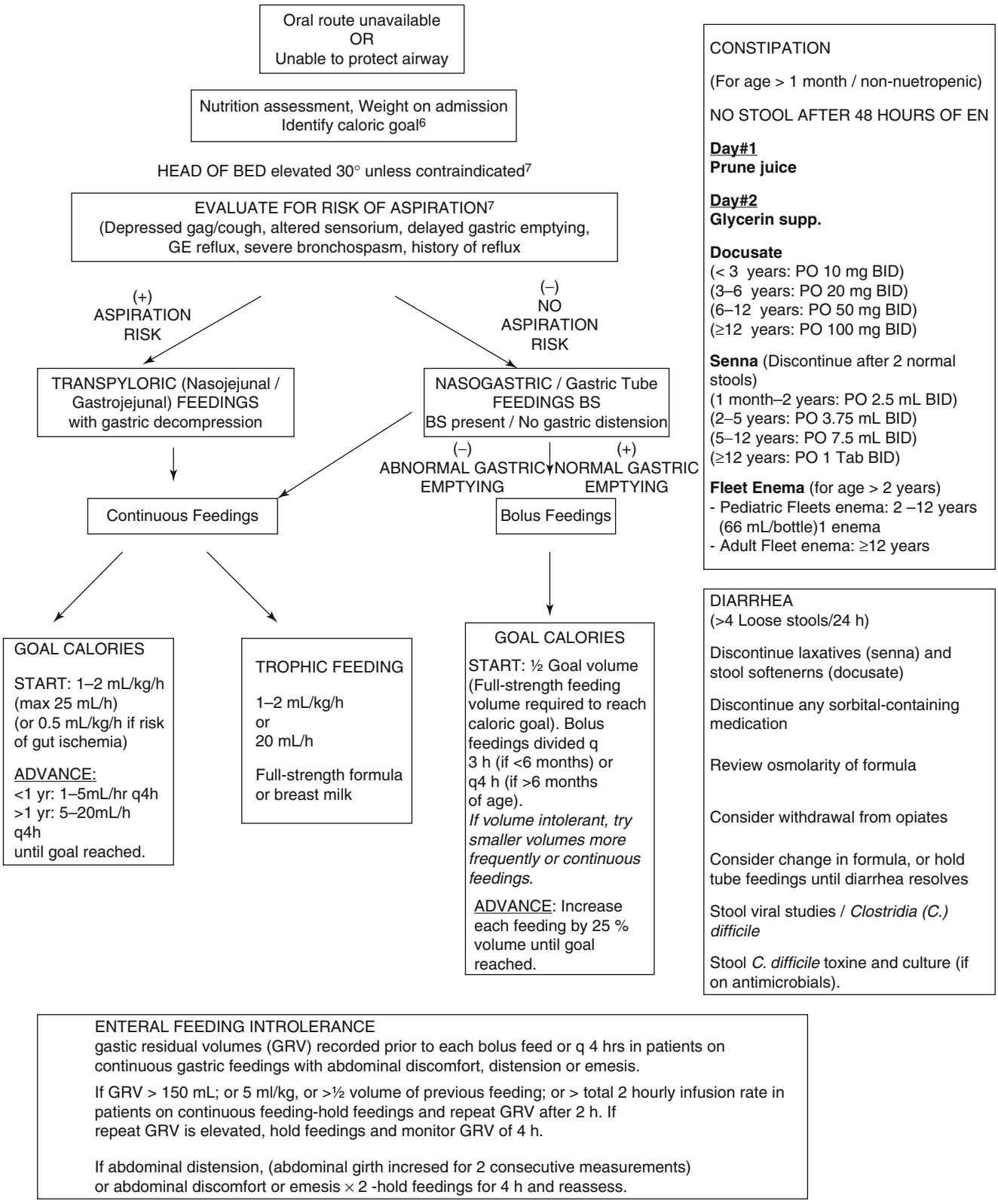

Fig. 6.1 Approach to EN paper (NCP) – CHB EN algorithm (Reprinted from Mehta [87]. With permission from SAGE Publications)

wise algorithm for delivering EN in the PICU. In addition, educational intervention and practice changes targeted at high-risk patients and addressing institution-specific deficiencies in practice may decrease the incidence of avoidable interruptions to EN in critically ill children. The role of transpyloric feeding especially in children at risk of aspiration or those who have failed an attempt at gastric feeding has been discussed earlier. Some centers use continuous gastric feeds in an effort to increase tolerance, and the strategy is generally well tolerated [77]. There is not enough evidence to recommend the use of prokinetic medications or motility agents (for EN intolerance or to facilitate enteral access device placement), prebiotics, probiotics, or synbiotics in critically ill children. The use of PN to supplement suboptimal EN in select patients with unavoidable EN interruptions may be reasonable [78]. The safety and efficacy of a mixed EN and PN strategy to reach nutrition goals in critically ill children need to be examined. A recent study in critically ill adults did not show any benefit of early PN introduction in the ICU population, which was associated with higher complication rates when compared to the group where PN was initiated only after 7 days [79]. Optimal enteral delivery of nutrients can only be realized with multidisciplinary commitment to prioritize EN and a specialized nutrition support team has been shown to benefit this goal [80, 81].

Immunonutrition in the PICU

The potential of specific nutrients as modulators of the inflammatory or immune response has generated great enthusiasm in employing them in the critically ill population. The properties of nutrients such as arginine, glutamine, aminopeptides, ω -3 fatty acids and antioxidants, have promoted the concept of immunonutrition and elevated nutrition in the ICUs from a supportive to a therapeutic strategy. Unfortunately, several RCTs examining the role of immunonutrition in adult critically ill patients have shown conflicting results. These studies tested immune enhancing diets as a combination of a variety of nutrients administered to heterogeneous patient populations. As a result, the studies do not allow meaningful interpretation of the safety or efficacy of individual nutrients and fail to detect significant differences in relevant clinical outcomes. Systematic reviews of immunonutrition studies in adults seemed to suggest a beneficial role for parenteral glutamine in patients receiving parenteral nutrition, and enteral glutamine in burn and trauma patients [82]. Antioxidants, particularly selenium, have also generated some interest [83]. However, in a recent international trial in critically ill adults, glutamine supplementation was associated with worse outcomes. In this blinded, 2×2 factorial trial, 1,223 critically ill adults from 40 centers were randomized to receive glutamine, antioxidants, both or a placebo within 24 h of admission to the intensive care unit. Patients on mechanical ventilatory support and with multi-organ failure were eligible for enrollment. The results revealed a trend towards higher 28-day mortality in the group receiving glutamine versus those that did not receive glutamine (32.4 % vs. 27.2 %; adjusted odds ratio, 1.28; 95 % confidence interval [CI], 1.00–1.64; P = 0.05). Furthermore, there was a significant increase in mortality while in the hospital and at 6 months, in the glutamine group. Early provision of antioxidants did not improve outcomes in this study. The results of this study are compelling and preclude any attempts to supplement glutamine in high doses early in the course of critical illness. Enteral formulas enriched with fish oils are recommended in patients with acute respiratory distress syndrome. The role of arginine-supplemented diets is controversial and not recommended in septic patients. In general, the data are insufficient to make recommendations on the optimal route, timing, duration and dosage of each nutrient.

The role of immune-enhancing EN in children during critical illness has not been extensively studied. Briassoulis et al. randomized mechanically ventilated children in the PICU to receive either a formulation containing glutamine, arginine, ω -3 fatty acids, and antioxidants or standard age-appropriate formulation [43]. No difference in outcome was noted in the 25 children in each arm, although a trend toward a decrease in nosocomial infection rates and positive gastric aspirate culture rates in the treatment arm was noted. The use of a specialized adult immune modulating enteral formula in pediatric burn victims has been associated with improvement in oxygenation and pulmonary compliance in a retrospective review [84]. The immunologically active formulae used in these studies were not specifically tailored for children. A recent RCT of glutamine supplementation in critically ill pediatric population was terminated for futility [85]. In this comparative effectiveness trial, 293 critically ill pediatric patients were randomized to receive a combination of enteral glutamine (0.3 g/kg/day), zinc, selenium and intravenous metoclopramide (GZSM); or enteral whey protein. There were no differences between the groups with respect to time until acquiring nosocomial infection or sepsis (13.2 days whey protein vs. 12.1 days GZSM; p = 0.29). Future pediatric studies in this field might need to focus on examining the effects of single (vs combination of) nutrients, in large (multicenter) trials, on homogeneous PICU populations designed to detect differences in important outcome measures. The adult trials, especially the recent glutamine and antioxidant trial, are cautionary and perhaps hint at a careful investigative approach. The temptation to adopt these strategies prematurely in the heterogeneous PICU population should be avoided, pending a definite evidence of safety and benefit [86, 87].

Conclusions

Optimizing nutrition therapy is a low cost intervention with potential for improved outcomes during critical illness in children. Increased awareness of the role of nutrition during critical illness and a multidisciplinary effort will ensure that nutrition goals are reached in the PICU population. There is increasing evidence that failure to reach nutrition goals during critical illness is associated with poor patient outcomes. Screening on admission to detect patients who are either malnourished or at risk of nutritional deterioration is the first step. Accurate and sequential assessment of energy and protein requirements, delivery of nutrients early via enteral route when feasible and attention to common hurdles, are prudent measures to ensure optimal nutrient delivery. In recent years, the possibility of modulating immune response by the specific functions of individual nutrients has sparked widespread interest. Future studies must use sound clinical design and multicenter collaboration to elucidate the impact of immunonutrients on outcomes from pediatric critical illness. Other areas needing urgent clarification include, defining and managing intolerance to EN, role of energy balance on clinical outcomes, protein supplementation and balance, and the indications as well as benefits of small bowel feeding. Protocols that provide guidelines for early initiation, rapid advancement and maintenance of EN in the PICU have been shown to improve the ability to reach nutrition goals and their use is associated with improved clinical outcomes. In the interim, it is important to adhere to prudent nutrition practices at the bedside derived by consensus. Nutrition must be recognized as a critical component of care, a discrete discipline, in which all intensivists should reach a minimum level of competence.

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Part II

The Endocrine System in Critical Illness and Injury

Jefferson P. Piva

Diabetic Ketoacidosis

7

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Abstract

The current concepts of physiopathology, diagnosis and treatment of diabetic ketoacidosis (DKA) in childhood, as well as preventive measures to avoid cerebral edema are reviewed in this chapter. Based on the reviewed literature and on the author's experience, the most efficient and recommended measures for DKA management are presented.

Among the main findings we would remark: (a) Normal saline solution (NaCl 0.9 %) remains as the preferred hydration solution. Hypotonic (diluted) solutions are avoided in the treatment of DKA. (b) there is a consensus regarding the contraindication of sodium bicarbonate administration to repair metabolic acidosis in DKA. (c) Regular insulin should be used as continuous infusion (0.1 IU/kg/h) without the need of a loading dose. In small babies with KAD and new onset diabetes, low insulin infusion rates (0.05 IU/kg/h) has been associated with few hypoglycemic episodes as well as with lower impact on the osmolarity, being protective for cerebral edema; (d) For fast corrections of glucose oscillations during DKA treatment, a practical scheme using two bags of electrolytic solutions is presented. (e) Cerebral edema, associated with DKA is a multifactorial process with different pathophysiological mechanisms. Depending on the associated risk for cerebral edema the most efficient treatment measures are reviewed.

In conclusion: continuous infusion of regular insulin associated with adequate water and electrolyte replacement using isotonic solutions, besides being an effective treatment for DKA, preserves plasma osmolarity and prevents cerebral edema.

Keywords

Diabetes in children ketoacidosis • Hyperglycemia and cerebral edema

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Introduction

Diabetic ketoacidosis (DKA) is a frequent cause of admission to the Pediatric Intensive Care Unit (PICU). DKA is a life-threatening condition affecting patients with Diabetes Mellitus (DM) type 1 and less frequently in patients with DM type 2, manifested by hyperglycemia (generally higher than 200 mg/dL), acidosis (pH <7.3 or serum bicarbonate <15 mmol/L), ketonemia (ketonuria) and dehydration (mild to severe degree). Depending on the geographic region, between 15 and 70 % of children with new-onset diabetes mellitus type 1 (DM1) will establish their diagnosis after a DKA hospital admission. Nowadays, close to 25 % of adolescents and young adults with DM2 will have their diagnosis confirmed after a DKA hospital admission [1–15]. DKA is commonly observed in young children (<5 years of age) with DM1 and belonging to families without ready access to medical care. Moreover, the prevalence of DKA is inversely associated with the effectiveness of the health system and with the prevalence of DM in the community [1–3, 5]. As such, DKA may be considered as an important measure of the overall quality of care in a community.

Despite all therapeutic advances, DKA is still the main cause of death in children and adolescents with DM1. After the discovery of insulin in the early twentieth century, the mortality declined from 100 % to 0.15–5 % [1–12]. Most fatal cases are related to the development of cerebral edema, which is present in 0.5–3.1 % of patients with DKA, with mortality rate between 40 and 90 %. Cerebral edema is also largely responsible for the long-term complications of DKA in approximately 10–25 % of survivors [1–5, 16–20]. In less developed countries, delayed admission to the hospital is associated with a higher incidence of refractory septic shock, cerebral edema, and mortality [21, 22]. Other important causes of morbidity and mortality are hypokalemia, hyperkalemia, hypoglycemia, infections and changes in the central nervous system (CNS) [1–5, 12, 13].

In small children, it is often difficult to identify the classical signs of DM, such as polyuria, polydipsia, and weight loss. Some of these symptoms are often attributed to other more prevalent diseases, thus delaying the diagnosis. Although a significant part of patients have DKA as an initial manifestation of DM, exclusion and/or identification of one or more triggering factors is needed. It is crucial to perform a thorough and detailed history and clinical examination, with the aim of identifying possible triggering factors (see below). The fact that morbidity and mortality of DKA are associated with the type of intervention and treatment used over the first hours of presentation has been well documented [1–5, 12, 14–18].

In patients with previously diagnosed DM, DKA is usually associated with inadequate use of insulin. Adolescents have problems adhering to treatment and diet, as well as psychological factors associated with eating disorders that could trigger up to 20 % of cases of recurrent DKA. In patients on insulin pump therapy, inappropriate interruption of the insulin pump, even if transient, leads to DKA due to low serum levels of insulin [1–3, 5, 9, 10, 12].

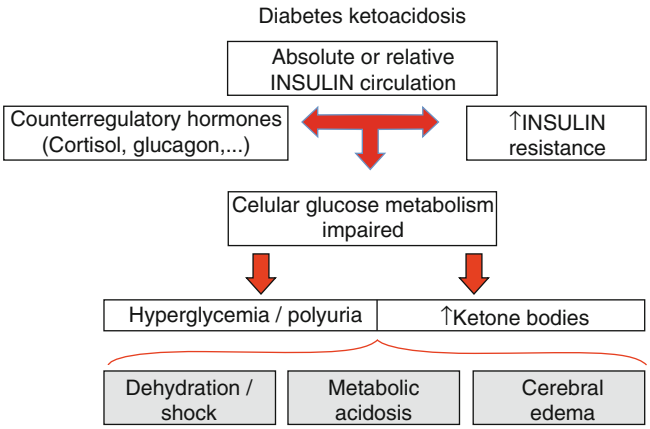

Fig. 7.1 Schematic sequence in diabetic ketoacidosis evolution. The low (or absence) circulating insulin associated with elevated counter-regulatory hormones which increases insulin resistance promotes derangement in the cell glucose metabolism causing: hyperglycemia (polyuria), dehydration (shock), increased ketone bodies (acidosis) and cerebral edema

In DKA, there is relative or absolute insulin deficiency, associated with increased counter-regulatory hormones, changing carbohydrate, protein and lipid metabolism. Hyperglycemia in DKA is usually significant. However, partially treated children with DM and pregnant adolescents may present in DKA with near normal blood glucose levels (so-called euglycemic ketoacidosis) [1–15, 23].

Among the most common precipitating factors of DKA are infections (30–40 % of cases) [1–5, 13, 23]. Insulin resistance is associated with increased levels of stress hormones (epinephrine, glucagon, hydrocortisone and growth hormone) and some cytokines (for example, interleukin-1) that are also increased in infections [1–5, 11]. High doses of glucocorticoids, atypical antipsychotics, diazoxide, and some immunosuppressive drugs have been reported as DKA precipitants in patients without previous diagnosis [2]. Other causes of DKA include pancreatitis and trauma [4, 15]. As a general rule, possible triggering factors should be assessed in all patients with DKA. However, in 2–10 % of cases, it is not possible to identify the precipitating factor [1–5, 9, 10, 15].

Pathophysiology

The absolute or relative insulin deficiency associated with increased counter-regulatory hormones (glucagon, epinephrine, cortisol and growth hormone) promotes the clinical manifestations and laboratory changes in DKA (Fig. 7.1).

Notably, counter-regulatory hormones are usually increased in situations of infection and stress, which often precipitate DKA in diabetic patients, whereas hyperglycemia, dehydration, hyperosmolarity, electrolyte, and acid-basic disorders further perpetuate release of counter-regulatory hormones [1–13].

Ketoacidosis

Insulin is an anabolic hormone, promoting the synthesis and/or storage of carbohydrates, fats, proteins, and nucleic acids. Insulin action allows energy generation through the use of glucose by muscles, adipose tissue, and liver cells. When insulin is absent, there is lipolysis with increased fatty acid mobilization for hepatic gluconeogenesis and release of ketone bodies. Excessive production of ketones exceeds the buffer capacity of organic alkalis, resulting in metabolic acidosis. Consequently, according to acidosis intensity, DKA can be quantified into mild (pH 7.3–7.2), moderate (pH 7.2–7.1) and severe (pH < 7.1) [1–13, 23]. A characteristic of metabolic acidosis in DKA is increased anion gap (normally between 10 and 12), which is obtained by Eq. 7.1.

$$\text{Anion gap} = \text{Na} - \left(\text{HCO}_3 + \text{Cl}\right) \tag{7.1}$$

Due to production of other acids (e.g., ketones and lactic acid) the anion gap in DKA is usually is close to 30–35 [3, 4].

In DKA, ketosis is primarily caused by increases in the ketones, **β**-hydroxybutyrate and acetoacetate. Beta-hydroxybutyrate is the ketone found in higher circulating levels during DKA, with a **β**-hydroxybutyrate:acetoacetate ratio of 3:1 during early disease stages. Ketonemia tests are generally performed qualitatively or semi-quantitatively in relation to acetoacetate. Considering that, during ketoacidosis correction, **β**-hydroxybutyrate is transformed into acetoacetate, such that the ketonemia test can be positive for some time, even with proper treatment. Therefore, persistence of positive ketonemia does not necessarily mean that DKA treatment is ineffective [1–6]. Anion gap could thus be used as an indirect indicator of ketone body levels, since reduction in anion gap value represents reduced ketone body levels, which represent treatment efficiency [1–7, 24].

Hyperglycemia

In case of insulin deficiency (or absence) associated with the action of counter-regulatory hormones, cells cannot capture and metabolize glucose, causing muscle and hepatic glycogenolysis and subsequent hyperglycemia. Blood glucose levels higher than 180 mg/dL exceed the maximum capacity of glucose reabsorption in the proximal tubule, causing glucosuria and a subsequent osmotic diuresis. Osmotic diuresis leads to polyuria with loss of free water and electrolytes, promoting polydipsia. If adequate water ingestion is maintained, dehydration will be mild and blood glucose will stabilize between 300 and 400 mg/dL. In some cases, blood glucose can reach levels of up to 800 mg/dL, especially when there is severe dehydration with decreased renal perfusion and consequently, a reduction in the glomerular filtration rate [1–6, 23]. Although hyperglycemia is the rule in DKA, there may be cases of DKA with normal blood glucose levels (so-called euglycemic DKA). This phenomenon occurs in patients partially treated with insulin and without receiving fluids with carbohydrates and/or in situations with long periods of vomiting and no ingestion of carbohydrates [1–5, 11, 23].

Dehydration

Osmotic diuresis associated with vomiting and insufficient ingestion causes dehydration of several degrees in DKA, although shock is a rare event in most of developed regions [1–4]. As dehydration progresses, there is reduction in the intravascular volume and consequent progressive loss of glomerular filtration rate. Reduction in glomerular filtration rate causes reduction in diuresis and glucose loss, resulting in worsening of hyperglycemia. Blood glucose levels close to 600 mg/dL indicate approximately 25 % reduction in the glomerular filtration rate, whereas glucose of 800 mg/dL suggests a 50 % reduction in glomerular filtration rate, as a consequence of severe dehydration [1–5, 11]. In some less developed regions, hypovolemic and septic shock are frequently observed in children with DKA. In such situations the presence of cerebral edema and the mortality rate has been higher than other developed countries [21, 22].

Hyperosmolarity

Plasma osmolarity can be estimated using Eq. 7.2.

$$\begin{aligned}\text{Plasma osmolarity} = &\left[\left(\text{Na}\right)\times 2\right] + \left(\text{blood glucose} / 18\right) \\ &+ \left(\text{blood urea nitrogen} / 2.8\right)\end{aligned} \tag{7.2}$$

Note that plasma osmolarity is measured as the number of osmoles of solute per liter of solution (Osmol/L), whereas plasma osmolality is measured as the number of osmoles of solute per kilogram of solvent (Osm/kg). Most clinical laboratories measure osmolality using freezing point depression, though in reality the two are very similar (osmolarity is usually slightly less than osmolarity, because the total solution weight used in the calculation of osmolality excludes the

weight of any solutes, whereas the total solution volume used in the calculation of osmolarity includes solute content). As an additional aside, the osmol gap is then defined as the difference between the measured osmolality and the calculated osmolarity (and is usually <10 mOsm/kg). The osmolarity effect of a blood glucose around 180 mg/dL is minimal (approximately 10). However, in case of severe hyperglycemia the osmolarity impact would be higher. Under these circumstances, there is movement of free water from the intracellular to the extracellular space (intracellular dehydration) [1–4, 11, 12, 14, 15, 25].

The maintenance of this hyperosmolar state stimulates cells' (especially neurons) production of substances with intracellular osmotic activity (classically referred to as idiogenic osmoles) to preserve intracellular water. In case of a sudden fall in blood osmolarity (e.g., quick fall of blood glucose or reduction in plasma sodium), this will cause the shift of water into the intracellular space, favoring the development of cerebral edema [1–4, 14, 18, 20, 25]. While advocated by several investigators, this theory has not been definitively demonstrated. In accordance with this hypothesis, hypernatremia has been identified as a protective factor for cerebral edema in patients with DKA [25]. Whereas, the rapid fall in the serum glucose levels has been associated with rapid reduction in the serum osmolality and promoting shift of water toward the intracellular (especially, brain cells, causing cerebral edema) [13, 17, 18, 25–27].

Electrolytic Disorders

Polyuria caused by osmotic diuresis may induce dehydration with several degrees of associated electrolytic changes, most commonly hyper- or hyponatremia, hypokalemia, hypophosphatemia and hypocalcemia.

Sodium

In DKA, the hyperosmolarity caused by hyperglycemia induces a dilutional hyponatremia, estimated by a reduction in the blood sodium level of 1.6 mEq/L for each 100 mg/dL of glucose above the limit of 100 mg/dL. Other factors, such as an increase in serum lipids with low sodium content, action of antidiuretic hormone, urinary sodium loss related to osmotic diuresis, and elimination of ketone bodies, may also enhance hyponatremia [1–4, 18]. Hypernatremia is less frequently observed in children with DKA and is considered a protective factor against cerebral edema, maintaining the plasma osmolarity and compensating for its reduction associated with blood glucose normalization [18, 25]. Therefore, in the light of current knowledge, hyponatremia should be avoided and immediately treated in children with DKA. Moderate hypernatremia (between 150 and 160 mEq/L) could be accepted and considered protective in children with DKA who have more marked hyperglycemia (higher than 600 mg/dL) [4, 5, 23, 25, 26].

Potassium

Many factors influence the serum potassium reduction in DKA. Increased urinary losses of potassium due to the osmotic diuresis and the need to maintain electrochemical neutrality as ketoacid anions are excreted, loss of potassium from the cells due to glycogenolysis and proteolysis, higher aldosterone hormone release triggered by dehydration, and especially, potassium transportation into the intracellular space along with glucose in response to insulin infusion all play a role [1–5]. At DKA diagnosis, the serum potassium may be normal or increased, because acidosis causes potassium to shift from the intracellular environment into the extracellular space. However, it should be stressed that total body potassium is reduced. Therefore, normal or reduced potassium dosage at the beginning of DKA indicates the need of early replacement, since the treatment tends to reduce serum levels of this ion [1–5, 28].

Phosphorus

During DKA, similarly to what occurs with potassium, there is initially hyperphosphatemia secondary to metabolic acidosis. As a result of urinary losses of phosphorus due to polyuria, hypophosphatemia is common, which will cause a reduction in erythrocyte 2,3-DPG levels. Low 2,3-DPG levels can lead to reduction in oxygen supply to tissues due to leftward displacement of the hemoglobin dissociation curve. However, this effect does not usually have clinical repercussions in DKA. Indeed, some prospective studies have not shown any clinical benefit to phosphate replacement [1–5, 28].

Calcium

Hypocalcemia may develop during DKA treatment as a result of the correction of the metabolic acidosis, improvement in the glomerular filtration rate, or the exogenous administration of phosphate [1–5, 28].

Clinical and Laboratory Diagnosis of Diabetic Ketoacidosis

Polyuria, polydipsia, enuresis, weight loss, and polyphagia characterize DM. When it progresses to DKA, common clinical manifestations include nausea, vomiting, progressive anorexia, abdominal pain, fatigue, tachypnea (to compensate for the metabolic acidosis, i.e. Kussmaul respirations), ketotic breath (sweetish odor due to ketosis), and fever (which can be associated with infectious, bacterial or viral process) [1–11]. The signs of dehydration might be mild to severe, with dry skin and mucosa, reduced skin turgor, tachycardia, and reduced perfusion according to the degree of

water depletion. It is estimated that the fluid deficit in extracellular fluid in DKA is between 5 and 10 % of body weight. However, as previously stated, hypotension (hypovolemic shock) is a rare and late finding in children with DKA, often associated with sepsis or cerebral edema [1–5, 18, 20, 25]. Again, as mentioned previously, in some regions where the access to the health care is more difficult as well as with high prevalence of bacterial diseases, DKA is frequently complicated by sepsis, refractory shock, cerebral edema and higher mortality [5, 21].

In case of changes in sensorium (sleepiness, clouding of consciousness), cerebral edema should be immediately considered, since it has high mortality rates. Clinically, DKA cerebral edema could be suspected in any children with decreased the Glasgow Coma Scale at hospital admission or in the next 24–48 h. Additionally, DKA should be suspected in every patient presenting to the Emergency Department with a depressed level of consciousness with or without clinical signs of acidosis. In such cases, capillary blood glucose screening and/or tests for ketonuria should always be performed in the initial assessment [1–5, 16, 18, 20, 22].

Laboratory criteria to define DKA include blood pH (venous or arterial) lower than 7.30 and/or bicarbonate lower than 15 mEq/L, blood glucose higher than 200 mg/dL, and presence of ketonemia and ketonuria [1–5]. It should be stressed that arterial gas analysis is painful, has a higher risk, and the data to be evaluated (pH, bicarbonate and base deficit) are equivalent in both arterial and venous blood. Besides blood glucose, ketonemia and venous gas analysis, serum values of lactate, sodium, potassium, ionized calcium, chloride, phosphorus, urea, creatinine, hematocrit and hemoglobin should be initially monitored, as well as glycosuria and ketonuria [4]. If there is suspicion of infection, further investigation should be performed according to the clinical setting. Unfortunately, leukocytosis with left shift is a frequent finding in patients with DKA, and there is no strong association with the presence of infection. Serum amylase is often high in DKA, which is not usually an indicator of acute pancreatitis. However, a diagnosis of acute pancreatitis should be entertained in the presence of suggestive clinical signs and markedly high amylase levels [1–5, 23].

It should be emphasized that presence of abdominal pain associated with vomiting and often with signs of peritoneal irritation (positive Blumberg's sign) may occur in DKA, mimicking an acute abdomen due to infection, acute appendicitis, pancreatitis, cholecystitis or other causes. Under these situations, before indicating surgical treatment using exploratory laparotomy, the patient should be better investigated and DKA should be corrected, waiting a few hours for resolution of abdominal pain. However, if there are other manifestations of an acute abdomen, such as sepsis or clear evidence of associated abdominal disease, surgical evaluation is indicated [1–5, 23].

Treatment

DKA is a life-threatening situation in which the treatment should be performed by an experienced medical team in the PICU. This situation does not allow improvisations or treatments based on empirical evidence. Therefore, it is recommended that every service has its own protocol adjusted to local operational resources and difficulties. The main goals of DKA treatment are: (a) correct dehydration and electrolytes disorders, (b) reverse ketosis (consequently, correct acidosis), (c) restore blood glucose to the normal levels, (d) avoid complications of the therapy, (e) "prevent" and treat cerebral edema, and (f) identify and treat any precipitating event (e.g., infection). An important principle in the treatment of patients with DKA is individualization of therapy, with careful monitoring of fluids, electrolytes and control of serum glucose as a priority [1, 2, 9, 16]. Below are discussed the main priorities in the treatment of DKA [1–17].

Correction of Dehydration and Electrolytic Disorders

Fluid replacement in DKA follows the same principles of other situations of dehydration or shock – an initial stage of rapid volume expansion (1–4 h) followed by a slower stage of rehydration and replacement of ongoing and accumulative losses (20–22 h) [1–5, 25, 26, 28]. Some retrospective and multi-center studies concluded that in DKA there is a strong association between cerebral edema and administration of large amounts of fluids [17, 18]. However, these studies did not prove cause-and-effect that cerebral edema occurred exclusively due to the excess administration of infused fluids. For example, it may be that the most severe group of patients required greater amounts of fluid and had a higher risk of cerebral edema. At this moment there is no convincing evidence of an cause-and-effect relationship between the rate of fluid or sodium administration to treat DKA and the development of cerebral edema [3, 4]. As such, our practice has followed the current recommendations for volume replacement in patients with dehydration and/or shock: volume expansion in the early stage followed by a judicious fluid maintenance during the late stage [4, 28].

Initial phase – Fluid Expansion (1–4 h)

The volume expansion stage should begin immediately upon presentation with the administration of 0.9 % normal saline solution (NSS), 20 mL/kg infused over 20–60 min, depending on the hydration status and the presence of signs of decreased perfusion, which can be repeated until circulatory stability is obtained [1–5, 28]. In general, DKA usually requires two to three bolus of 20 mL/kg NSS until signs of

dehydration are reverted. This rapid fluid replacement with NSS reestablishes blood volume and improves renal perfusion, which increases glomerular filtration, resulting in glucose-induced osmotic diuresis, with a concomitant reduction in blood glucose and plasma osmolarity [3–5]. Since NSS is isotonic in relation to plasma (Na = 154 mEq/L), it promotes better response in blood volume and lower reduction in plasma osmolality than other IV solutions [3, 4, 25, 26]. Therefore, even in situations of DKA in which initial serum sodium is higher than 150 mEq/L, hypotonic solutions should not be used.

Maintenance phase – Rehydration stage (20–22 h)

As soon as the signs of blood volume depletion (tachycardia, hypoperfusion, hypotension, etc.) are reverted, the maintenance phase of volume repletion is started [3–5, 25–28]. This stage estimates a fluid maintenance volume between 1,800 and 2,000 mL/m^2/day, which could be added with other volume replacement of further losses (e.g., vomiting and diarrhea). In patients with marked hyperglycemia, even receiving adequate treatment, it should be assumed that they would continue to have increased urinary losses. In such case, the fluid maintenance supply could be further increased up to 30–40 %, corresponding to an infusion of up to 2,500–2,800 mL/m^2/day [3–5, 25–29]. In order to avoid fluid overload, periodic assessments should be performed with the aim of reducing the fluid maintenance to the recommended values (~ 2,000 ml/m^2/day). Some authors suggest initial use of NaCl 0.45 % (Na = 75 mEq/L) when serum sodium exceeds 150 mEq/L, or calculated plasma osmolarity is higher than 340 mOsm/L [1–3]. Due to the reasons described above, even in these cases, we prefer to maintain infusion of isotonic NSS. As soon as the blood glucose levels are close to 300 mg/dL, glucose should be added to the fluid maintenance (NSS) [1–12].

It is estimated a potassium deficit of 4–6 mEq/kg in DKA, which is more evident after acidosis correction and due to insulin action (which promotes input of glucose and potassium into the cell) [1–5]. In the presence of diuresis, potassium should be added (40 mEq/L) in the rehydration solution and adjustments should be performed according to laboratory data. In severe cases of hypokalemia (levels lower than 2.5 mEq/L), replacement can be performed using a constant potassium infusion of 0.4–0.6 mEq/kg/h for 6 h. Until recently, there has been a recommendation to administer part of potassium as phosphate, but randomized studies did not show benefits in phosphate replacement, since clinical effects of hypophosphatemia are rare [3]. Phosphate replacement should only be started in patients with respiratory depression and in those with serum level <1.0 mg/dL. In those cases, 1/3 of potassium is administered as potassium phosphate [3, 4].

Correction of metabolic acidosis in patients with DKA occurs with volume replacement associated with insulin action, which reverses the formation of ketoacids [3–5]. Metabolic acidosis, as stated above, is a marker of severity. Differently from what was previously believed, an acidic pH alone is not a determining factor that increases the risk of death or organ failure [9, 30–32]. On the other hand, administration of sodium bicarbonate in DKA has been associated with cerebral edema and death [3, 4, 17, 18, 20]. Use of sodium bicarbonate may cause many side effects, such as hypokalemia, worsening of hyperosmolarity, increased intracellular acidosis due to CO_2 production, paradoxical acidosis in the CNS, leftward shift in hemoglobin dissociation curve with reduction in oxygen supply to tissues, slower reduction of ketonemia and possible association with development of cerebral edema [4, 30–32]. For all of these reasons, routine administration of sodium bicarbonate should be avoided. Some DKA guidelines consider bicarbonate administration when the pH is lower than 6.9 and persists after the first hour of hydration. In such circumstances, 1–2 mEq/kg of sodium bicarbonate would be administered in 1–2 h [1–3]. However, in our experience, we have avoided infusion of sodium bicarbonate in DKA, even in the presence of pH lower than 7.0.

Oral diet should be started when the patient is awake and returns to a normal state of consciousness, without vomiting and with improved acidosis. Parenteral hydration solution should be maintained as along as continuous insulin is necessary [1–12].

Insulin Therapy

Administration of insulin promotes glucose input into the intracellular space, reverses the catabolic state, and suppresses lipolysis and ketogenesis, correcting blood glucose and acidosis [1–5, 11, 15, 23, 24, 33]. A loading dose of regular insulin (0.1 IU/kg) in patients with DKA is unnecessary and has been associated with a higher incidence of cerebral edema [19]. As previously mentioned, adequate replacement of blood volume increases renal perfusion, promoting osmotic diuresis and reducing blood glucose levels [3, 4]. If, in such situations, a loading dose of regular insulin is administered, a marked reduction in blood glucose levels will develop, which decreases the plasma osmolarity and increases the risk of cerebral edema [1–5, 12, 20, 23, 27, 29]. In our experience, we use a dilution of regular insulin at 0.1 IU/mL (250 mL of NSS adding 25 IU of regular insulin), which is infused at a speed of 1 mL/kg/h (0.1 IU/kg/h) using an infusion pump. Due to insulin adherence to plastic, we use the first 30 mL of the solution to wash the catheter [4]. However, several studies have demonstrated that an insulin infusion of 0.05 UI/kg/h is effective, safe, and with minor risk for abrupt reduction in plasma osmolarity [19, 34–36].

In general, glucose infusion should be added to the treatment of DKA when blood glucose reaches 250–300 mg/dL. Glucose is added to the NSS to obtain a 5 % concentration (50 g/L). An infusion of 2,000 mL/m^2/day of a solution with 5 % glucose provides a glucose infusion rate between 2.5 and 3.5 mg/kg/min. Such variation occurs because body weight and surface do not have an absolutely linear correlation. Therefore, besides the calculation of the amount of supplied fluid (mL/m^2/day), glucose infusion rate (mg/kg/min) should be calculated based upon the glucose concentration in the solution, the patient's weight, and the infusion rate.

DKA treatment aims correct acidosis and maintaining blood glucose between 150 and 250 mg/dL during continuous insulin infusion. Use of continuous insulin infusion generally reduces the blood glucose between 40 and 80 mg/dL every hour. In cases in which a reduction in glucose levels is lower than 40 mg/dL/h, insulin infusion should be increased to 0.1–0.2 IU/kg/h. If reduction in blood glucose is higher than 100 mg/dL/h during continuous insulin infusion, administration of intravenous glucose should be increased and may reach up to 5 mg/kg/min [3–5, 24, 33].

Acidosis and ketonemia are the main markers of insulin and glucose insufficiency in the cell metabolism during DKA. Blood glucose correction is faster than acidosis correction. Therefore, in patients who have major reduction in blood glucose, but who maintain positive acidosis and/or ketonemia, continuous insulin infusion should not be reduced. In these cases, it is necessary to increase glucose infusion up to 5 mg/kg/min, being sometimes necessary to infuse solutions containing 10 % glucose [3–5, 24, 33]. Continuous insulin infusion should only be reduced when there is need of glucose infusion higher than 5 mg/kg/min to maintain blood glucose between 150 and 200 mg/dL. Such phenomenon may occur in: (a) patients with recently diagnosed DM who still have some endogenous insulin production and higher insulin sensitivity; and (b) patients with residual long acting insulin levels (for example, users of insulin glargine or detemir). In this situation, we reduce insulin infusion rate to 0.05 U/kg/h and maintain glucose infusion (between 3.5 and 5 mg/kg/min) [3–5, 24, 33].

Therefore, by adding glucose to hydration solution (NSS) and in the presence of continuous insulin infusion, it is common to perform frequent adjustments in the glucose infusion rate, due to higher or lower blood glucose reduction. Changing solutions is often needed, which demands time and cost. To perform rapid and frequent modifications in the fluid content we use the "two bags system" (Fig. 7.2). In this system, two bags with identical electrolytic content (NaCl = 150 mE/L and KCl = 40 mEq/L), being different in relation to the glucose concentration (0 and 10 %), are placed in the shape of a "Y" in a single venous access. This system allows quick adjustments according to blood glucose, and it is possible to infuse solutions with glucose concentrations between 0 and 10 %, so that therapy can be individualized to the needs of the patient [4, 37].

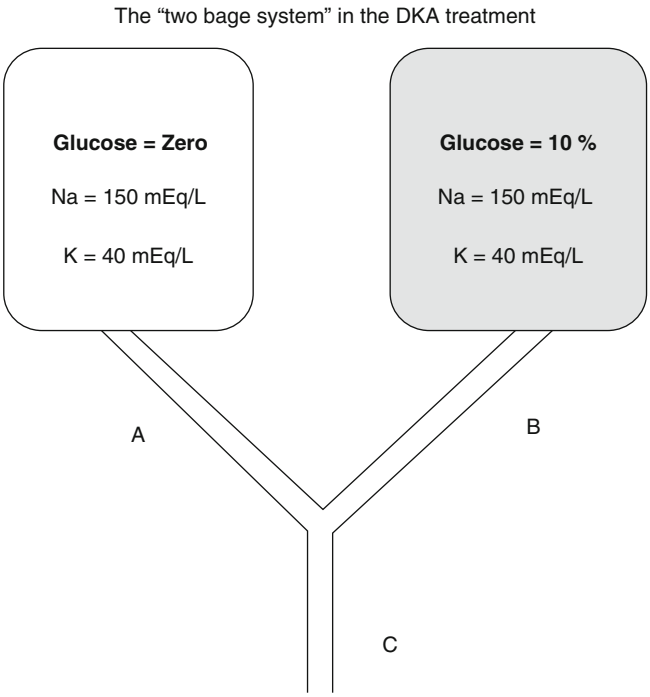

Fig. 7.2 Two bags system permits rapid changes in glucose administration, depending on the proportion of each fluid infusion. "*C*" represents the total rate of fluid infusion (e.g.: 40 ml/h). If blood glucose levels are higher than 250 mg/dl, the total fluid infusion should be restricted to the bag without glucose ("*A*" = 40 ml/h) being the "*B*" side closed. As soon as the blood glucose levels are close to 250 mg/dl, the total fluid infusion should be divided between the two bags ("*A*" and "*B*"; 20 ml/hora each), which correspond to a 5 % glucose infusion

The continuous insulin infusion can be suspended when blood pH is higher than 7.30, serum bicarbonate is ≥18, anion gap is between 8 and 12, and the patient is eating a regular diet. One hour before suspending continuous insulin infusion, a subcutaneous regular insulin bolus of 0.1 IU/kg should be administered. Subsequent doses of insulin should be defined according to the previous insulin regime for each patient. In patients whose DM diagnosis was established based on current DKA status, an initial daily insulin regime between 0.6 and 0.7 IU/kg/day is recommended, divided into long and short acting insulin, which is administered in two or three applications before meals [4]. From the practical perspective, suggestion is to perform transition of intravenous insulin to NPH insulin at times close to the patient's meals, preferentially in the morning. In cases in which the patient fulfils the criteria for suspension of continuous insulin at different times, such as at night, for example, intravenous infusion can be maintained for a few extra hours, with adjustments in glucose infusion rate as needed.

A new option in this transition of regular intravenous insulin into subcutaneous insulin is the use of insulin glargine

(Lantus). Insulin glargine is a slow-release and long-acting insulin, mimicking the effect obtained when using insulin infusion pump therapy. In a study including children with DKA, progression of a group treated with traditional regular intravenous (IV) insulin was compared with another group that was given 0.3 IU/kg of insulin glargine over the first 6 h of treatment associated with regular IV insulin infusion. Addition of that low and stable dose of insulin glargine allowed suspension of continuous IV insulin infusion earlier, reduction in total amount of insulin administered, faster correction of acidosis and earlier ICU discharge [4, 38].

Complications

Electrolyte Disorders

Hypokalemia, hypo- or hypernatremia, hypophosphatemia, etc. and hypoglycemia (mentioned above) are among the main complications in the treatment of DKA. Hyperchloremic acidosis is also a frequent complication, resulting from excess of chloride replacement, present both in sodium chloride and in potassium chloride, used in initial management of patients. In general, it is manifested after some days of DKA and does not require specific treatment, spontaneously progressing in the presence of normal renal function.

Cardiac Arrhythmias

Cardiac arrhythmias are caused by electrolyte disorders (hypo- or hyperkalemia, hypocalcemia, hypomagnesemia), being uncommon event observed in DKA. Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalemia. Tall, peaked, symmetrical T waves and shortening the QT interval are signs of hyperkalemia [3, 4, 28].

Aspiration of Gastric Content

As major changes in the sensorium occur and many patients have recurrent vomiting, there may be pulmonary aspiration of gastric content. This complication should be prevented by careful supervision of patients at an adequate hospital setting and including a nasogastric tube in patients with conscious depression.

Pulmonary Edema

Pulmonary edema is not a common complication. There is an increase in oxygen demand, and there may or may not be radiological changes compatible with pulmonary edema. Many factors can be involved, including low oncotic pressure, increased pulmonary capillary permeability and neurogenic pulmonary edema. Treatment includes supplemental oxygen therapy, use of diuretics and ventilator support when indicated [4, 39–41].

Cerebral Edema

The appropriate administration of intravenous fluid and electrolytes plus insulin therapy has dramatically modified the outcome of DKA, with death being an uncommon event nowadays. Most of the deaths that occur in DKA are related to cerebral edema, which is usually observed within the first 12 h of treatment and often following a period of improvement in hyperglycemia and acidosis [1–5, 17–20, 42–48]. Cerebral edema is practically restricted to the pediatric age group, with a documented prevalence of 1–3.1 % in children with DKA. Cerebral edema is more common in children under 5 years of age and with the first episode of DKA. Cerebral edema is associated with a mortality rate between 18 and 90 %, with significant long-term complications in those who survive [13, 16–19]. Notably, there is evidence that many patients with DKA have some degree of subclinical cerebral edema even before starting treatment [20, 43, 44, 46].

Clinical manifestations of cerebral edema are usually sudden, and there may be fast progression to brain herniation, even when this complication is appropriately recognized and aggressively treated [1–5, 20, 47]. Cerebral edema usually occurs within 4–12 h after beginning treatment and at the moment acidosis, dehydration and hyperglycemia, as well as the patient's general status, are improving. Initial signs and symptoms are headache and reduced level of consciousness, which quickly progress to deterioration of sensorium, dilated pupils, bradycardia and respiratory arrest. In some cases, it can be preceded by a period of change in behavior associated or not with headache and vomiting [1–5, 16–20, 42–47].

As mentioned briefly above, some studies using MRI have demonstrated cerebral edema in more than 50 % of children with DKA [27, 42, 46]. On the other hand, the initial brain images of some children with DKA and neurological deterioration have not demonstrated evidence of substantial edema, with some even appearing normal. Cerebral edema was observed some hours/days later through repeated imaging studies [20, 42, 43]. Therefore, currently, it is accepted that cerebral edema in children with DKA is a continuum process, oscillating from mild to severe manifestation [20, 22, 44].

Rather than a unique mechanism, cerebral edema in DKA is a result and consequence of a multifactorial and complex pathogenesis [16–20, 22, 27, 42, 43]. Diabetes itself may induce cerebral edema as a consequence of inflammatory mediators release, cerebral injury due to hypoxia/ischemia,

severe acidosis, glucose toxicity, ketonemia and uremia [17–20, 29, 42, 43]. In addition, it has been demonstrated that some therapeutic strategies may cause (or aggravate) the cerebral edema associated with DKA, such as (a) quick reduction of the plasma osmolality, which is easily achieved after a rapid blood glucose reduction (e.g., insulin loading dose or bolus) and/or in response to excessive fluids administration (lowering the serum sodium and blood glucose); (b) exogenous bicarbonate administration; (c) hyperventilation (while on mechanical ventilator support); and (d) postponing the fluid infusion that aggravates the hypovolemic status [4, 16, 19, 20, 27–29].

Even in absence of definitive scientific evidence, there are several studies connecting rapid decreases in the effective plasma osmolarity and cerebral edema in children with DKA. Decreasing the plasma osmolarity could worsen a pre-existing injury and even causing additional brain injury via a separate mechanism [20, 27–29, 42]. For these reasons, most authorities recommend a gradual lowering of the blood glucose levels. As such, a loading dose or bolus of insulin is neither necessary nor helpful, and may in fact be harmful as it has been associated with cerebral edema [19]. Several studies even advocate a lower insulin infusion rate (0.05 UI/kg/h), considered safer than the traditional dose (0.1 UI/kg/h) [25, 34, 35]. Intravenous fluids should contain enough amounts of sodium (150 mEq/L) to compensate the natriuresis and to counterbalance the decline in plasma osmolarity (due to the blood glucose reduction) [25, 27, 29, 36]. Excessive fluid administration should be avoided [3, 19, 25, 27–29, 35, 36].

Additionally, it has been demonstrated that children with severe DKA have significantly decreased cerebral blood flow compared with children with diabetes and without DKA [5, 9, 20, 21, 42, 47]. In this regard, cerebral edema in DKA may have a similar pattern that is observed in stroke and other hypoxic/ischemic cerebral injuries [20, 42]. For example, in a rat model of DKA, it was observed that untreated DKA is associated with cytotoxic cerebral edema. However, progression from cytotoxic to vasogenic cerebral edema developed during DKA treatment [42]. In this scenario, a bimodal insult might occur. Initially, acidosis and the compensatory response (hyperventilation and decreased PCO_2) triggers cerebral vasoconstriction, hence reducing the cerebral blood flow. This effect on brain cells is amplified in the presence of dehydration and severe hyperglycemia (direct toxic effect), leading to cytotoxic edema. The second insult occurs during DKA treatment. Aggressive rehydration and cerebral reperfusion (loss of cerebral flow autoregulation and disruption of the blood-brain barrier) worsen cerebral edema through a vasogenic mechanism [20, 22, 27, 29, 42].

Treatment of cerebral edema should follow the usual treatment guidelines for management of cerebral edema. Attention to the maintenance of a stable airway and ventilation are crucial. In addition, mannitol (0.25–0.5 g/kg) should be administered emergently. Alternatively, hypertonic saline (5–10 mL/kg of 3 % hypertonic saline) can be used as well. Plasma sodium levels should be maintained between 150 and 160 mEq/L. There is some controversy regarding the target PCO_2 to be achieved during mechanical ventilator support [48]. Considering the bimodal presentation of cerebral edema, we do not recommend a target PCO_2 lower than 32–35 mmHg. The head should be maintained elevated at 30° and normovolemia carefully monitored.

Therefore, considering the high mortality associated with cerebral edema and DKA, even in the presence of adequate treatment, frequent and judicious monitoring of the patient's consciousness status over the initial hours of treatment is crucial and, in the presence of any acute deterioration, mannitol should be immediately administered [1–5, 20, 46].

Prevention

Despite improvement in diagnostic and therapeutic resources, there has been no reduction in mortality due to DKA over the past two decades [1–5, 18, 20, 26]. Therefore, the main objective of managing patients with insulin-dependent DM should be prevention of DKA episodes through a high index of suspicion and rigorous monitoring of symptoms [1–5]. Prevention of recurrent DKA episodes, especially in adolescents, demands an efficient participation and surveillance by the family and health team. Recurrent DKA episodes should be considered as a failure in long-term treatment. Efficient DKA prevention requires (a) recognition of early signs of diabetes decompensation; (b) identification of events that may precipitate increase in insulin supply; (c) early intervention; and (d) aggressive intervention at the family core of patients with recurrent DKA episodes.

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Hyperglycemia, Dysglycemia and Glycemic Control in Pediatric Critical Care

8

Michael S.D. Agus, Edward Vincent S. Faustino, and Mark R. Rigby

Abstract

Although once considered a benign consequence to the stress of severe illness or injury, a significant body of evidence compiled over the past decade shows that hyperglycemia in critically ill patients is associated with poor outcomes. In both adults and pediatric studies, there is a strong association with hyperglycemia with higher morbidity and mortality, and in some prospective studies, controlling hyperglycemia improves outcomes. These data have resulted in a number of national and international consensus statements and guidelines recommending active glycemic control – though primarily directed at the critically ill or injured adult. Due to the lack of pediatric-specific data, it has been unclear how pediatric intensivists should incorporate glycemic control into their practice. During the past decade data from both retrospective and prospective studies have also shown significant associations between hypoglycemia and dysglycemia (i.e., glycemic variability) and poor outcomes. From the current data, it appears that both hyper- and hypoglycemia occurs in patients who have higher illness severities and require more organ support measures. A number of pediatric-specific protocols have been developed and published which suggest that approaches to identify and manage hyperglycemia in critically ill children can be effectively and safely implemented, and interestingly in many cases hypoglycemic rates are less than that which occurs spontaneously. Although most pediatric practitioners support active glycemic control in certain subsets of patients, it is unclear how widespread standardized, consistent glycemic management has been incorporated into practice. Prospective trials have yielded disparate outcome findings regarding glycemic control in the pediatric ICU. Data from ongoing and completed studies will hopefully yield more definitive data on whether pediatric practitioners should regularly practice glycemic control, and what patient populations might benefit from this practice. This chapter reviews the existing data on hyperglycemia, hypoglycemia and dysglycemia, and will hopefully assist how pediatric practitioners synthesize these data into practice.

Keywords

Hyperglycemia • Hypoglycemia • Dysglycemia • Glycemic variability • Protocol • Insulin Glucose • Clinical trial • Pediatric critical care

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Introduction

A little more than a decade ago active management of glucose in any critical care patient, adult or pediatric, was infrequent and non-standardized. Although likely regularly assessed on most critically ill patients, the impact of blood glucose (BG) level on course or outcome was unclear. Usually considered as part of a protective counter-regulatory fight- or-flight response to acute stress, evidence had been mounting that prolonged exposure to hyperglycemia may be damaging to cells and organs during critical illness and negatively impact recovery. In 2001, a seminal randomized controlled trial from the adult surgical critical care unit in Leuven, Belgium was published demonstrating that in their patient population, maintaining glucose values in a range of "tight glycemic control" (i.e. ~80–110 mg/dL) with infused insulin resulted in improved outcomes compared to patients in whom BGs were controlled in a more "conventional" target range (180–210 mg/dL) [1]. What was most impressive about this report was the range of outcomes that were improved by careful, proactive BG control: shorter lengths of stay, fewer red cell transfusions and bloodstream infections, less renal injury and, importantly, an impressive reduction (i.e. ~40 %) in mortality. The primary adverse effect was an increase in hypoglycemia (from 0.7 to 5.2 %) with unclear clinical impact. In relatively short order, other data from adult ICUs supported the concept of proactive glycemic control using insulin infusions [2–5], which resulted in a number of official recommendations to implement standard approaches in BG management in critically ill patients. Although not specifically stated, recommendations were to practitioners of adult critical care, and it was unclear how these recommendations should be incorporated into pediatric critical care. These included recommendations from the Institute of Healthcare Improvement (IHI) and a combined consensus statement from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) to maintain BG in ICU patients under 110 mg/dL [6]. In 2004, the Society of Critical Care Medicine (SCCM) addressed glycemic control in their Surviving Sepsis Campaign, stating "In patients with severe sepsis, maintain BG <150 mg/dL [using an] insulin infusion and glucose…" [7]. In less than 5 years from the original Leuven report, most adult ICUs had evolved from being indifferent to most patients' BG, to taking a proactive approach in managing BG in a relatively low and tight threshold.

During this time, a number of studies seemed to refute the benefits of tight glycemic control [8–12]. In addition to supporting the concept that there may not be outcome benefits of maintaining BG in the "tight" range (i.e. 80–110 mg/dL), some of these suggested there may be harm, implicating the higher incidences of iatrogenic hypoglycemia and poorer outcomes with tight glycemic control. In fact, two large randomized controlled trials (RCTs) in adult ICUs, the VISIP [9] and Glucotrol [12] studies, which were comparing outcomes in patients with BG targeted to 80–110 mg/dL to more conservative ranges (180–200 and 140–180 mg/dL respectively) were prematurely stopped due to high rates of protocol violations and high rates of hypoglycemia. Neither of these suggested outcome improvements with tight glycemic control. In 2009, a large multi-national RCT consisting of over 6,000 patients from 42 adult medical or surgical ICUs, the NICE-SUGAR trial, compared outcomes in patients in whom glucoses were controlled 81–108 mg/dL versus under 180 mg/dL [10]. Although the difference of the average BG between groups was only ~30 mg/dL, there was a slight, but statistically higher mortality rate in the group undergoing tight glycemic control (27.5 v. 24.9 %, respectively). The tight glycemic control group had higher hypoglycemic rates (6.8 v 0.5 %, respectively), which appears to have influenced the difference in mortality.

Relatively soon after the publication of these last studies, revisions were made to the aforementioned consensus statements. Currently, IHI, ADA/AACE, and the SCCM Surviving Sepsis Campaign suggest active measure to control BG when it rises above 180 mg/dL [13, 14]. Of note, these groups have not suggested against glycemic control, but used recent studies to revise the target goals away from "tight" glycemic control (i.e. ~80–110 mg/dL). In the fall of 2012, the SCCM published the recommendations from a task force and suggested that a "glycemic control end point such that a BG ≥150 mg/dL triggers interventions to maintain BG below that level and absolutely <180 mg/dL" [15]. The rationale being that "there is a slight reduction in mortality with this treatment end point for general [adult] intensive care unit patients and reductions in morbidity for perioperative patients, postoperative cardiac surgery patients, post-traumatic injury patients, and neurologic injury patients". This was the first consensus group that included pediatric intensivists on the panel, reviewed data from pediatric studies, and specifically addressed how pediatric intensivists should incorporate general recommendations (which were mostly based on the adult critical care literature) into their practice. Although it was concluded that "the literature is inadequate to support recommendations regarding glycemic control in pediatric patients", it was recognized that there was associative data on hyperglycemia and poor outcomes in a number of pediatric critical care subpopulations. In addition, there is contrasting data from RCTs regarding direct benefits of glycemic control in critically ill children. In a relatively short time period there has been a substantial philosophical and practical shift adopted by many adult subspecialty critical care practices. Data in pediatric critical care has been slower to come, and due to the paucity of data (which may be conflicting) it has been a challenge for pediatric intensivists to develop a data-based approach to glycemic control.

Incidence and Associations of Hyperglycemia in Pediatric Critical Care

Soon after studies in glycemic control in adult ICUs were published, a number of studies were presented evaluating the incidence of hyperglycemia in pediatric critical care. Rates of hyperglycemia range from as low as 14 % to near 100 % of patients in pediatric ICUs [16–24]. This vast variability is likely due to several factors such as the definition of hyperglycemia and the population studied. There is yet to be a "consensus" on how critical illness hyperglycemia is defined in adult or pediatric critical care. Thresholds to define hyperglycemia in pediatric studies include values from 100 through 200 mg/dL. When given, rationale for these cutoffs included definitions of hyperglycemia and glucose intolerance used to define diabetes and glucose intolerance by the American Diabetes Association (i.e. a non-fasting BG cutoff of 140 mg/dL) and BG levels which surpasses the "renal threshold" and result in glucosuria (i.e. ~200 mg/dL) [25]. Most descriptive studies have been retrospective, and rely on routine, non-standardized glucose testing. In presenting the incidence of hyperglycemia, the denominator given most often is any patient who received a BG evaluation. "Hyperglycemic patients" (i.e. the numerator) are most frequently defined as any patient who had at least one BG greater than their threshold. The lower BG threshold used to define hyperglycemia, the higher the incidence will be, and most likely the more times a patient's BG was checked, the likelihood of a high BG increases. With these caveats, studies by Faustino and Apkon, Wintergurst et al., and Hirshberg et al. all found that one half to almost two-thirds of all patients in a pediatric medical/surgical intensive care (50, 61, and 56 % respectively) had at least one BG reading of >150 mg/dL [19, 20, 23]. Depending on the BG threshold to define hyperglycemia, rates in general PICUs range from about 10–80 % of patients (Fig. 8.1a). To date, there has been no prospective study in which BGs are systematically checked in all PICU patients to define the true incidence of hyperglycemia in pediatric ICUs.

In studies where patients that are more critically ill (i.e. higher illness severity or more organ failure) are evaluated, the incidence of hyperglycemia increases (Fig. 8.1b). Studies have shown that nearly 50–75 % of patients on mechanical ventilation (MV) and 90 % on MV and/or vasopressors [22, 24, 26, 31], 72 % of patients with septic shock [24] and 90 % of patients with meningococcal sepsis had BGs >126–150 mg/dL [18]. When looking in cardiac ICUs, rates of hyperglycemia vary between 57 and 98 %, again depending on BG threshold and patient condition (Fig. 8.1c) [28–30, 32–34]. In other specific high risk PICU subpopulations rates are also high, for example 88 % in traumatic brain injury and 57 % in burn patients [35–38].

Taken together, these studies support an intuitive hypothesis that if patients are "more" critically ill, their likelihood of having a more robust stress response is greater, and thus it is reasonable that their BG would become (more) elevated. From studies of a practice group that initiated a

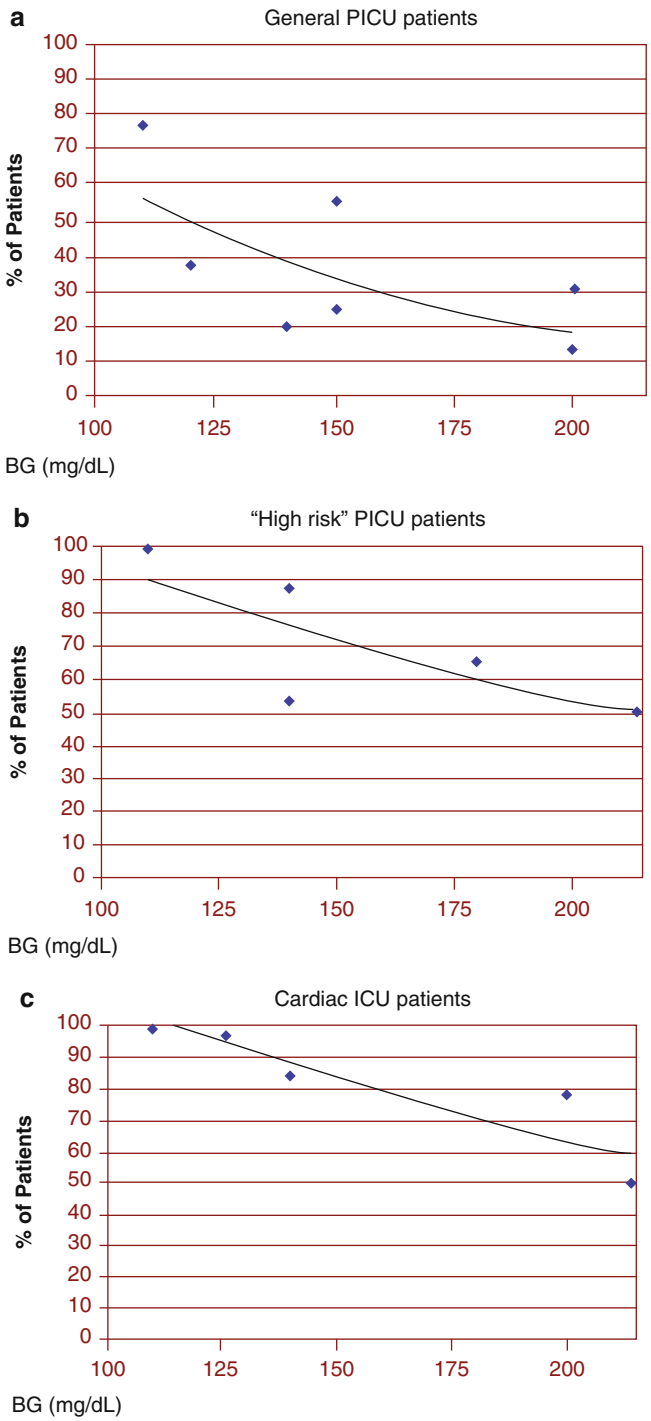

Fig. 8.1 Relationship of hyperglycemia incidence and BG threshold in pediatric critical care. The incidence of hyperglycemia and defining BG was obtained from published studies and plotted. Studies were divided into three categories: (**a**) General pediatric medical/surgical PICU evaluating all admissions, (**b**) Patients with shock or specific organ failure (i.e. requiring mechanical ventilation or vasopressors), (**c**) Patients in cardiac ICUs and/or post-operative from cardiac surgery (Data sources: (**a**) [19–21, 23, 26]; (**b**) [16, 17, 22, 24, 26, 27]; (**c**) [27–30])

standard protocol to screen for hyperglycemia in what were deemed "high risk" patients (defined as those who were receiving mechanical ventilation, vasopressors, or other vital organ support measures) and required to consecutive BG readings of >140 mg/dL to define hyperglycemia, ~50 % of patients who are mechanically ventilated and not receiving vasopressors and ~90 % of patients who are receiving both vasopressor support and are mechanically ventilated develop hyperglycemia [26, 31]. In further evaluation of patients not deemed "high risk" (i.e. no organ failure/support), hyperglycemia was rare (<6 %) [26]. This suggests that in pediatric patients, there is a strong positive relationship with organ failure and hyperglycemia. Taking this into account, the variability of incidence of hyperglycemia in pediatric ICUs is likely strongly influenced by the unit's case mix of acuity and illness severity [31].

In addition to reporting incidences, many retrospective and descriptive studies have documented an association between hyperglycemia and poor outcome. A common theme has been a strong positive association of hyperglycemia and morbidity and mortality. In general, it has been found (similar to adult literature) that there is a positive association between hyperglycemia and ventilator days, ICU length of stay, use of high frequency ventilation, infections, inotrope use and renal insufficiency/failure [16–24, 28, 30, 31, 37, 38]. In general medical/surgical PICU populations, mortality rates are up to five to six times higher in those with hyperglycemia. In septic shock patients with respiratory failure, mortality is 2–3× higher in groups with hyperglycemia than without. In a study by Cochan et al., a BG of >300 mg/dL in children with TBI is predictive of non-survival [36]. Taken together, hyperglycemia exists in a substantial amount of patients in pediatrics ICUs. There are strong correlations of higher instances of hyperglycemia and illness severity, organ failure and poor outcomes, including mortality. It has been such studies which have prompted prospective studies of glycemic control in pediatric critical care, and initiating standard approaches to glycemic control by some pediatric intensivists.

Hypoglycemia in the PICU

The practice of glycemic control in critically ill patients has highlighted physicians' concern for hypoglycemia. Surveys of pediatric intensivists showed that hypoglycemia was considered more dangerous than hyperglycemia [39, 40]. In fact, the fear of hypoglycemia was identified as a barrier to glycemic control in critically ill children [40]. Hypoglycemia is physiologically defined as the concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the adequate delivery of the glucose to a target organ, particularly the brain [41]. Counter-regulatory hormones such as glucagon, epinephrine, growth hormone and cortisol are usually activated in response to hypoglycemia once blood glucose concentration decreases to 60–80 mg/dL [42]. Hypoglycemic symptoms do not occur until blood glucose concentration is approximately 50 mg/dL and cognition does not appear depressed unless blood glucose concentration is approximately 40 mg/dL. Hypoglycemia has variable effects on the developing brain in preclinical models. Compared with adult rats, the brains of newborn rats are more resistant to neuronal injury from insulin-induced hypoglycemia [43]. The cause of hypoglycemia may also be important. During prolonged fast, the body produces ketones that the brain can use as alternative source of energy in the absence of glucose. Insulin inhibits ketogenesis and deprives the brain of both glucose and ketones, potentially resulting in worse outcomes with insulin-induced hypoglycemia [44]. The duration and frequency of the hypoglycemic episodes also affects the impact of hypoglycemia on the brain [10, 45]. Because of the difficulty in using a blood marker, i.e. blood glucose concentration, to diagnose symptomatic neuroglycopenia, pediatric intensivists use different blood glucose thresholds to define hypoglycemia. Values ranging from 40 to 80 mg/dL are typically used in clinical practice [39, 45, 46]. Observational and interventional studies usually report hypoglycemia as <60 mg/dL and severe hypoglycemia as <40 mg/dL [10, 27, 47]. Current convention is the BG value of <40 mg/dL is defined as "severe" hypoglycemia and <60, but greater or equal to 40 mg/dL is "moderate" hypoglycemia.

Hypoglycemia is not uncommon in critically ill children. In children with spontaneous or non-insulin induced hypoglycemia, 7.5–11.7 % of them have at least one blood glucose concentration <60 mg/dL [20, 45, 48]. The prevalence of severe spontaneous hypoglycemia with blood glucose concentration <40 mg/dL is 2.2–3.2 % [45, 48] of all patients in the pediatric intensive care unit but can be as high as 25 % in selected patients undergoing glycemic control with insulin [27].

Even in the absence of inborn errors of metabolism and insulin-secreting tumors that predispose children to hypoglycemia, critically ill children are at risk of hypoglycemia. Hypoglycemia is likely a reflection of the body's overall inability to regulate blood glucose concentration [45, 49]. This may explain why children <1 year old, [20, 48] with higher severity of illness [48] and requiring more therapeutic interventions, [45, 48] who tend to be hyperglycemic, are also likely to have episodes of hypoglycemia. Vriesendorp et al. proposed that critically ill patients have relatively insufficient gluconeogenesis analogous to relative adrenal insufficiency [50]. The gluconeogenic pathways are overstressed because of the underlying illness such that they are unable to produce additional glucose to maintain euglycemia when faced with added stress. Additional stress may include side effects of certain drugs, such as octreotide and beta-blockers, or human error [45, 51]. Abrupt discontinuation of high

glucose containing parenteral nutrition or renal replacement therapy solutions without glucose supplementation may lead to hypoglycemia. Impaired gluconeogenesis may also result from unrecognized renal or hepatic insufficiency.

The outcomes of hypoglycemia in critically ill children depend on the cause, severity and the frequency of the events. Spontaneous hypoglycemia is associated with increased mortality, [45] prolonged hospital stay [20, 23] and increased risk of nosocomial infections [20]. Compared with children with no hypoglycemia, the odds of mortality ranges from 2.7 in those with blood glucose concentration <60 mg/dL to 4.5 in those with blood glucose concentration <40 mg/dL [45]. Children with recurrent hypoglycemia have worse outcomes than those without or with a single episode of hypoglycemia. Depending on the glucose threshold, the odds of mortality in children with recurrent hypoglycemia are 4.8–6.3 compared with 1.2–3.7 odds in those with a single episode of hypoglycemia [45].

Insulin-induced hypoglycemia seems to have better outcomes compared with spontaneous hypoglycemia. In the randomized controlled trial on glycemic control by Vlasselaers et al., 25 % of children in the insulin-treated group developed severe hypoglycemia compared with 1 % in the control group [27]. The odds of mortality are not increased in the presence of severe hypoglycemia, and in fact this group in whom BG were more tightly controlled had less mortality. Insulin-induced hypoglycemia is also not associated with changes in neurocognitive development when children were tested 4 years after the hypoglycemic event [52]. Similar findings are noted in adults. In the NICE-SUGAR trial, the hazard ratio of mortality is significantly lower in patients with insulin-induced hypoglycemia (1.7 vs. 3.8 in adults with spontaneous hypoglycemia) [10]. In adults with acute myocardial infarction, hypoglycemia is a predictor of mortality in patients not treated with insulin but not in those treated with insulin (odds ratio of mortality: 2.3 vs. 0.9) [53].

The difference in outcomes between spontaneous and insulin-induced hypoglycemia suggests that hypoglycemia is merely a marker of the underlying disease [10, 45, 49]. The better outcomes in critically ill patients with insulin-induced hypoglycemia, compared with animal studies, may reflect the shorter duration that these patients are hypoglycemic. While critically ill children may have unrecognized hypoglycemic symptoms, they are unlikely to be hypoglycemic for prolonged periods of time because their blood glucose concentrations are monitored closely [45].

Glycemic Variability

Recent evidence suggests that extreme fluctuations in blood glucose concentrations in critically ill patients are harmful, independent of the actual blood glucose concentrations or the presence of hypoglycemia. It has been postulated that the contrasting results between the Leuven and the NICE-SUGAR trials may be partly explained by differences in glycemic variability [54]. The association between glycemic variability and mortality was initially reported by Egi et al. [55] and Wintergerst et al. in 2006 [23]. Egi et al. reported that in critically ill adults whose blood glucose concentration was strictly controlled with insulin infusion, both the mean and standard deviation of blood glucose concentrations are independently associated with mortality [55]. Subsequent studies have confirmed this association in adults [56]. Wintergerst et al. reported that glycemic variability is also associated with mortality and increased hospital stay in critically ill children [23]. Using a glucose variability index calculated as a time-weighted change in blood glucose concentration, glucose variability had the strongest association with mortality compared with maximal and minimal blood glucose concentrations. Other studies support this association in children. Hirshberg et al. reported that critically ill children with both hyperglycemia and hypoglycemia have higher odds of mortality and nosocomial infection, and longer hospital stays compared with children with isolated hyperglycemia or hypoglycemia [20]. Using the standard deviation of the blood glucose concentrations of each critically ill child, Rake et al. reported that glycemic variability is positively correlated with mortality rates [57].

Similar to hypoglycemia, the increased mortality associated with significant glycemic variability may represent the body's inability to maintain blood glucose allostasis i.e., physiologic adaptation to change [57]. Glycemic variability during the acute phase of illness is likely adaptive that allows the body to respond to stress. However, glycemic variability during the chronic phase of illness may be maladaptive and represent secondary damage to the systems controlling blood glucose concentration. Rake et al. demonstrated that among survivors, glycemic variability decreases during the late phase of critical illness [57]. In contrast, blood glucose concentration was persistently variable among non-survivors. Alternatively, fluctuations in blood glucose may result in increased oxidative stress and endothelial dysfunction leading to worse patient outcomes [54].

Glycemic Control Protocols in the PICU

The efficacy of glycemic control in critically ill children is unclear. The study by Vlasselaers et al. demonstrated a significant mortality benefit in controlling blood glucose concentrations to age-adjusted normal values [27]. In contrast, the study by Agus et al. did not detect any significant benefit with glycemic control in post-operative cardiac patients [47]. The results of trials in adults are also conflicting. The initial

Table 8.1 Comparison of glycemic control protocols in children

	Year published	Protocol type	BG target range (in mg/dL)	Number of patients	Time to reach BG target range (in hours)	Percentage of BG measurements in range	Percentage of patients with BG <40 mg/dL
Thompson et al. [62]	2008	Computer	80–110	48	12	48	20
Preissig et al. [26]	2008	Paper	80–140	74	5.4	N/A	4
Vlasselaers et al. [27]	2009	Paper	50–80 (<1 y/o) 70–100 (1–16 y/o)	349	N/A	N/A	25
Verhoeven et al. [63]	2009	Paper	72–145	50	5	N/A	0
Faraon-Pogecaunu et al. [60]	2010	Paper	90–119	42	10	33	22
Branco et al. [64]	2011	Paper	60–140	44	9.5	73	20
Chima et al. [65]	2012	Paper	100–200	196	N/A	N/A	1
Agus et al. [47]	2012	Computer	80–110	444	6	N/A	3
Hebson et al. [33]	2013	Paper	80–140	44	6.1	N/A	0

Hebson et al. used in the cardiac intensive care unit the protocol initially reported by Preissig et al.
BG blood glucose concentration, *N/A* not available

trial by van den Berghe et al. [1] demonstrated mortality benefit with glycemic control while the NICE-SUGAR trial [10] demonstrated increased mortality in the intervention group. Despite the differences in the results of pediatric and adult trials, glycemic control continues to be practiced in critically ill children [46].

Safe implementation of glycemic control requires the use of protocols. An optimal protocol should include an explicit algorithm that determines insulin dosing and minimizes interpretation by the bedside clinician, frequent monitoring of blood glucose concentration, provision for dextrose supplementation or for stopping insulin if glucose source interrupted, and standardize approach to the management of hypoglycemia [15]. Ideally, a protocol should incorporate patient characteristics and caloric intake to individualize insulin dosing recommendations. Because dosing algorithms are usually complex, computerized protocols are preferred. Computerized protocols have been shown to be more effective in achieving target blood glucose concentrations, [58, 59] associated with less hypoglycemic events, [58, 59] better protocol compliance [60] and higher nurse satisfaction [61] compared with paper-based protocols.

A number of protocols have been developed for controlling blood glucose concentrations in critically ill children (Table 8.1). In most of the protocols, the recommended insulin infusion rate is adjusted based on the rate of change in the blood glucose concentration and the current insulin infusion rate [60]. Computerized protocols tend to have more complex insulin dosing algorithms that are difficult to replicate on paper [47, 62]. Because of uncertainty in the optimal blood glucose target for children, different ranges are used. The performance and the risk of hypoglycemia differ per protocol.

Of the existing protocols there are two main types: those that recommend an incremental response to change in blood glucose within different ranges, and those that change the algorithm's sensitivity to glucose changes. Whichever type of mathematical approach an algorithm employs, the recommendations can be implemented either by written rules for making the incremental adjustments or by equations which continuously calculate incremental adjustments. A benefit of the mathematical algorithm approach is that weight-specific, glucose-concentration specific recommendations can be made for glucose rescue from hypoglycemia.

A critical determinant of the success of any protocol is the quality and frequency of the data that are input into it. Blood glucose concentrations are ideally measured from an arterial source, since there is some arterio-venous decrement due to glucose extraction at the tissue level. Central venous blood may also be a reliable and stable source for measuring glucose. Capillary blood should be reserved for short-term use only due to potential for poor peripheral perfusion in critically ill children. When drawing blood from an intravascular catheter, one should take extreme care to waste adequate amounts of blood, 1–2 mL, prior to collecting the sample that is to be tested. This may be achieved at little cost to the patient by using a closed blood drawing system, several of which are on the market.

Blood glucose should be monitored at a standard interval of 1–2 h during an intravenous insulin infusion. This can be spaced to some extent if insulin dose and carbohydrate supply are not changed in that period. Adult protocols that are based upon every 4 h blood glucose checks may have severe hypoglycemia rates of 10 % or more. There remains much debate as to what devices are acceptable for use to measure blood glucose. The most accurate devices are in the hospital

Table 8.2 Factors leading to hypoglycemia in the ICU during insulin infusion

Risk factors
Transport off ICU
Sick patient or neighbor
Stable trajectory
Final common pathways
Feeds (PN or EN) discontinued, insulin continued
Titrated medication infusions with dextrose-containing fluid as a diluent
Lack of adequate frequency of BG checks
Variable sampling techniques

central laboratory, which measure serum concentrations. Blood gas machines are also particularly reliable; some ICUs have the benchtop machines in the ICU, others use a point-of-care blood gas device. FDA-approved hospital glucose meters have become increasingly reliable in recent years. After taking into account the risk of performing glucose control in the ICU without a glucose measurement device at the bedside, we believe the newest generation (after 2011) are acceptable for use in the PICU.

Continuous glucose monitoring devices have also made significant technological progress in the last 5 years, however, not enough to warrant using them to directly guide insulin dosing. Among FDA approved devices, the most commonly available one is the subcutaneous sensor which is designed for use in ambulatory diabetics. While not FDA approved for this indication, these sensors have been successful in the context of clinical trials to significantly reduce the incidence of hypoglycemia when on an insulin infusion. The most appropriate use is as a hypoglycemia alarm device. Through conducting clinical trials in this field, we have learned that there are identifiable risk factors for hypoglycemia (Table 8.2) which the continuous monitor has helped to address.

Randomized Controlled Trial in Glycemic Control in Pediatric Critical Care

The first pediatric randomized controlled trial of 700 critically ill pediatric patients was completed in a single center in Leuven, Belgium, which established that insulin infusion titrated to a goal of 50–80 mg/dL in infants and 70–100 mg/dL in children, compared with insulin infusion only to prevent BG greater than 215 mg/dL, improved short-term outcomes. The absolute risk of mortality was reduced by 54 % (conventional 5.7 % vs. intervention 2.6 %, $p=0.038$), and insulin therapy also reduced the ICU length of stay and C-reactive protein (the primary outcome variable). The study was notable for its first proof of principle that lower ranges of glycemic control produce clinical benefit in children. It was also remarkable for its low target BG ranges in the intervention groups, which were described as "age-adjusted normoglycaemia" (50–80 mg/dL in <1 year old, 70–100 mg/dL in >1 year old). Although several outcomes in this trial were favorable, there were extremely high rates of severe hypoglycemia (<40 mg/dL): 44 % in those <1 year old and 25 % overall. In light of this, the protocol is unlikely to be replicated outside Leuven, and the findings of clinical benefit cannot be widely applied. Of note, the 4-year follow-up study assessed neurocognitive outcomes in participants in the trial and did not identify any differences in cognitive performance between those enrolled in the tight control versus conventional therapy arm.

The second published randomized clinical trial in the field, called SPECS (Safe Euglycemia in Cardiac Surgery) was conducted in two centers in a relatively homogeneous population of 980 post-operative cardiac surgical patients less than 3 years of age. Subjects were randomized to 80–110 mg/dL versus standard care, which was essentially no insulin. Although subjects in the TGC arm of the trial reached target range more quickly than the standard care arm, stayed in range longer, and had a lower time-weighted blood glucose average, outcomes were identical between the two groups. It is notable that the differences in the glucose profiles across the two groups became indistinguishable after 48 h, raising the question of whether the exposure to glucose control was too brief to affect a difference in outcomes. When analyzing the entire cohort, no differences in outcomes were noted. Post hoc analyses are reported to be underway which may identify subgroups that did derive benefit, but these have not yet been published.

Three other major trials are underway at the time of writing this chapter, which may help us understand more about controlling blood glucose in critically ill children. Control of Hyperglycaemia In Paediatric Intensive Care (CHiP; ISRCTN61735247) is a 1,384-patient study of cardiac, medical and surgical ICU patients, randomizing to either 72–126 or 180–215 mg/dL with primary outcome of ventilator-free days at 30 days. Pediatric ICUs at Indiana and Emory-Children's Center Glycemic Control: The PedIETrol Trial (NCT01116752) is a 1,004-patient trial of 80–140 versus 190–220 mg/dL including cardiac, medical and surgical ICU patients, where the primary outcome is recovery of organ function specified as PELOD score at 6 days. Heart And Lung Failure – Pediatric INsulin Titration trial (HALF-PINT; NCT01565941) is a 30-center multi-center trial of 80–110 vs 150–180 mg/dL with the primary outcome of ICU-free days, or 28-day hospital mortality-adjusted ICU length of stay. As the results are published of these three major trials and possibly others we will be able to generate more definitive recommendations about glycemic control in specific situations.

Conclusion

The past decade has shown rapid change in how hyperglycemia is regarded and managed in all disciplines of critical care. In adult critical care there is a strong body of evidence that, at least in some patients, benefit can come from strict management of hyperglycemia using insulin. Although there are strong associations of poor outcome and hyperglycemia and hypoglycemia in pediatric critical illness, is not yet clear which patient populations, if any, will benefit from routine glycemic control. Data to base best practice will only come through the implementation of carefully planned prospective studies.

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Hypoglycemia

9

Bettina von Dessauer and Derek S. Wheeler

Abstract

Hypoglycemia is increasingly recognized as a significant risk for morbidity and mortality in critically ill and injured children, especially with the recent focus on "tight glucose control" in the pediatric intensive care unit. The lack of adequate energy support in critically ill infants and children with low metabolic reserves is a significant and often underappreciated risk factor, though a variety of other etiologies may be involved. There is no one blood glucose value that defines "hypoglycemia." Rather, hypoglycemia is considered to represent a spectrum of clinical signs and symptoms that occur within a relatively broad range of blood glucose values that resolve when treated with exogenous glucose. Hypoglycemia is clinically important, as glucose is the most important energy fuel of the body, especially for the brain. As such, glucose homeostasis is normally tightly regulated. Treatment of the underlying disease, early enteral nutrition, basic glucose infusion, avoidance of excessive control of transient stress hyperglycemia may be all important factors to maintain glucose homeostasis and the lowest risk of occurrence of hypoglycemia for the individual patient.

Keywords

Hypoglycemia • Children • Energy • Risk • Stress response • Low metabolic reserves Prevention • Prudent control

Introduction

Glucose is the principal source of energy for the body – hence, the concentration of blood glucose is tightly regulated under normal conditions. During the last several years, there has been a growing emphasis on the recognition of stress-related hyperglycemia in critical care settings [1–3]. However, hypoglycemia in the critical care setting may be even more deleterious, especially in critically ill infants and children. Hypoglycemia has been vastly underappreciated as a potentially harmful metabolic disorder, and only recently has greater attention focused upon the risks of hypoglycemia and its harmful effects that occur concomitant with the aggressive treatment of hyperglycemia in critically ill patients using so-called "tight glucose control" [4, 5]. In truth, the incidence of iatrogenic hypoglycemia in the critical care setting has increased with the emphasis on tight glucose control [4–6]. The body composition, metabolic reserves, stress response, and energetic requirements of children differ significantly from adults, making any comparisons difficult at best [7, 8]. Hypoglycemia has a wide spectrum of etiologies and clinical presentations to be considered in the Pediatric Intensive Care Unit (PICU).

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Definition

Hypoglycemia is generally defined as a blood glucose ≤45 mg/dL, regardless of whether signs or symptoms of hypoglycemia are present [9–15]. Of note, the concentration of glucose in serum and plasma is typically 10–15 % higher than the concentration of glucose in whole blood [13]. Hypoglycemia also can be defined as the glucose concentration associated with clinical signs that resolve when dextrose is administered [16]. There is a broader range of blood glucose values to be considered critical in neonates, depending upon the presence of coexistent hypoxemia or hypoperfusion, all of which contribute to a greater risk for permanent brain damage [9, 12]. No clear current evidence exists in the literature about the best safe or "normal" blood glucose value to be maintained in neonates, which can avoid neurologic damage due to hypoglycemia [17]. Blood glucose values less than 70–80 mg/dL, particularly in the context of critical illness, should be viewed with alarm, with the goal of avoiding any further decrease in the blood glucose and loss of homeostasis.

Pathophysiology

Glucose and free fatty acids are the basic energy providers of the human organism. The most important metabolic cell fuel is glucose, especially in the central and peripheral nervous system, brain cells, renal medulla, and red blood cells. The brain cannot use free fatty acids and derives almost all of its energy requirements from glucose metabolism. This is one reason why neonates, with a proportionally larger brain in relation to body weight, have higher glucose requirements (8–10 mg/kg/min in preterm, 4–6 mg/kg/min in term infants compared with 1–2 mg/kg/min in older children [18].

Glucose homeostasis is normally tightly regulated. The concentration of glucose in the body at any one point in time reflects a dynamic balance between glucose input (via both dietary intake and endogenous glucose synthesis – glycogenolysis and gluconeogenesis) and glucose utilization by the tissues (via glycolysis and glycogen synthesis). The liver and muscle tissue both store glucose as glycogen, though only the liver is capable of releasing this storage pool of glucose into the bloodstream (glucose derived from glycogen stores in muscle tissue is used locally). The liver also synthesizes glucose from glycerol (generated via lipolysis), lactate, and amino acids via gluconeogenesis and is therefore especially important in regulating glucose homeostasis. Insulin is the primary hormone that regulates glucose homeostasis by (i) stimulating glucose uptake by muscle and adipose tissue; (ii) promoting glycogen and protein synthesis; and (iii) inhibiting lipolysis and glycogenolysis. The counterregulatory hormones, including growth hormone, cortisol, glucagon, and epinephrine directly oppose these effects and are therefore important in regulating glucose homeostasis as well.

Generally, within 2–3 h of fasting, insulin levels are suppressed and the counterregulatory hormones are released, stimulating glycogenolysis. Hepatic glycogen stores are rapidly depleted – infants, in particular, have a relatively limited supply of glycogen stores and are therefore particularly at risk for hypoglycemia during fasting. Glucose produced via glycogenolysis in the muscles is not released systemically, as muscles lack the enzyme glucose-6-phosphatase. The counterregulatory hormones also stimulate gluconeogenesis. The substrates for gluconeogenesis are derived from the breakdown of fats (lipolysis) and proteins. Glycerol (from lipolysis) is the major source of substrate for gluconeogenesis. Glucose may also be synthesized from recycled substrates, e.g., lactate and alanine. As glucose supplies are further limited, the brain becomes dependent upon ketones as an alternative energy source. With few exceptions then, the vast majority of cases of hypoglycemia in the pediatric age group occur during fasting.

Differential Diagnosis

The differential diagnosis of hypoglycemia in infants and children is broad (Table 9.1) and includes inborn errors of metabolism, toxic ingestions (e.g., ethanol, salicylate, oral hypoglycemic agents), malnutrition, acute illness (e.g., sepsis, congestive heart failure), liver disease, and neoplasia (e.g., Wilm's tumor, nesidioblastosis, islet cell adenoma) [19]. As discussed above, neonates and infants are at risk for hypoglycemia due to relatively limited glycogen and fat stores. These risks are compounded in neonates born prematurely or in those neonates who are small for gestational age, whose capacity for gluconeogenesis is relatively limited due to the delayed maturation of hepatic enzyme systems and limited substrate availability. Other common causes of hypoglycemia during the neonatal period include infants born to diabetic mothers (maternal hyperglycemia leads to hyperinsulinism, as glucose readily crosses the placenta and insulin does not), erythroblastosis fetalis (hyperinsulinism secondary to islet cell hyperplasia), and neonatal sepsis. Critically ill neonates and infants who are receiving the bulk of their nutritional needs via parenteral nutrition may develop hypoglycemia if the infusion of glucose is suddenly interrupted. Less common causes of hypoglycemia in this age group include nesidioblastosis (hyperinsulinism), Beckwith-Wiedemann Syndrome (characterized by macroglossia, omphalocele, macrosomia, and hyperinsulinism secondary to islet cell hyperplasia), and inborn errors of metabolism.

Hyperinsulinism is usually characterized by (i) macrosomia (large for age infant); (ii) severe and persistent *non-ketotic* hypoglycemia; (iii) inappropriately elevated insulin

Table 9.1 Differential diagnosis of hypoglycemia in children

Decreased glucose availability
1. *Decreased glucose intake*
Fasting
Malnutrition
Decreased oral intake (e.g., due to illness)
2. *Impaired absorption via the GI tract*
Diarrhea
Intestinal disaccharidase deficiency
Malabsorbtion syndromes (primary or secondary)
3. *Decreased endogenous glucose production*
Glycogen storage diseases (GSD)
GSD Type I [glucose-6-phosphatase deficiency]
GSD Type III [debranching enzyme deficiency]
GSD Type IV [hepatophosphorylase deficiency]
Glycogen synthetase deficiency
Hereditary fructose intolerance
Fructose 1,6-diphosphatase deficiency
Galactosemia
Glucagon deficiency
Ketotic hypoglycemia
Inborn errors of metabolism (especially fatty acid oxidation defects)
Liver diseases:
Hepatitis
Cirrhosis
Acute fulminant hepatic failure
Reye syndrome
Increased Glucose Utilization
1. Hyperinsulinism
Congenital hyperinsulinism, subtypes diffuse and local
Infants of mothers with gestational diabetes, with altered fetal growth
Islet cell adenoma
Nesidioblastosis
Beckwith-Wiedemann syndrome
Heterozygous mutation in pancreatic ß-cell glucokinase
Exogenous insulin (e.g., diabetic child)
2. Toxic ingestions
Ethanol
Oral hypoglycemic agents
Salicylates
Beta-adrenergic antagonists (*Beta blockers*)
Quinolones
Quinine
3. Münchhausen syndrome (deliberate administration of oral hypoglycemiants or insulin)
4. Critical Illness (multifactorial)
Respiratoy distress
Sepsis/Shock
Trauma/Burns
Surgery

levels (classically, glucose/insulin ratio<4.0); (iv) need for excessive glucose infusion rate (typically well above 8 mg/kg/min) in order to maintain normal blood glucose concentrations; and (v) an increase in blood glucose of greater than 30 mg/dL above baseline 30 min after administration of glucagon. Importantly, infants with hyperinsulinism may be at a greater risk of neurologic injury during episodes of hypoglycemia, as the brain is robbed of both its primary (i.e., glucose) and alternative (i.e., ketones) energy source. For example, Thomas et al. [20] reported a mortality rate of 2.5 % in 165 infants with hyperinsulinism with severe neurologic disability in 52 % of survivors. Treatment options for these infants include diazoxide, octreotide, and subtotal or near-total pancreatectomy [9, 13, 20, 21].

Fatty acid metabolism is essential in order to provide substrates for gluconeogenesis. Several disorders of fatty acid metabolism may therefore present with hypoglycemia. Carnitine is required for the transport of long-chain fatty acids across the mitochondrial membrane – carnitine palmitoyl transferase (CPT) deficiency, as well as short chain, medium chain, and long chain acyl CoA dehydrogenase deficiency all present with nonketotic hypoglycemia and elevated free fatty acids. Glycogen storage disease (GSD) type I (Von Gierke's Disease) is due to a defect of the enzyme glucose-6-phosphatase and is characterized by failure to thrive, hepatomegaly (often massive), profound hypoglycemia, hyperuricemia, lactic acidosis, and hyperlipidemia. Children with GSD type III (Cori's Disease, due to a defect in the debranching enzyme) and GSD type IV (due to a defect in the branching enzyme) typically present with less severe hypoglycemia. Galactosemia (resulting from deficiency in galactose-1-phosphate uridyl transferase) commonly present with jaundice, hypoglycemia, and gram negative sepsis. Hereditary fructose intolerance (resulting from deficiency in fructose-1-phosphate aldolase) produces a clinical syndrome characterized by symptomatic, postprandial hypoglycemia (these children often develop an aversion to sweet foods!). Other inborn errors of metabolism, as well as deficiencies in counterregulatory hormones (e.g., hypopituitarism, Addison's disease, etc.) also produced hypoglycemia, though fortunately most of these disorders are relatively rare.

The most common cause of hypoglycemia in children from 1 to 5 years of age is ketotic hypoglycemia, a disorder that is characterized by recurrent hypoglycemic episodes during intercurrent illness (classically presents as seizure or altered mental status during the morning, i.e., following a prolonged fast) [9, 13, 22, 23]. At the time of hypoglycemia, there is associated ketonuria and ketonemia with low insulin concentrations. These children have hypoalaninemia (presumed to be secondary to a low lean muscle mass), and alanine supplementation has been shown to improve symptomatology [9, 13, 22–24]. Most children outgrow this disorder, and for this reason, some authors feel that ketotic hypoglycemia reflects one extreme of the body's normal response to fasting [13, 25]. Hypoglycemia may also occur in the context of children with diabetes mellitus, especially if

insulin is administered in the face of increased glucose needs or poor oral intake (e.g., acute illness, diarrhea, etc.). Hypoglycemia may also be the presenting feature of Münchhausen Syndrome by proxy (a low C-peptide level with normal or high insulin level suggests the presence of exogenous insulin) [26]. Finally, as discussed above, hypoglycemia can, and often does, occur during management of stress-hyperglycemia with so-called "tight glucose control" [5].

Liver disease (hepatitis, Reye syndrome, cirrhosis, acute liver failure) causes hypoglycemia due to decreased glycogen stores and impaired function of hepatic gluconeogenesis. Large tumors have caused hypoglycemia in small children due to the increased glucose needs of the tumor itself. Finally, several toxic ingestions classically present with hypoglycemia, including salicylates, alcohol, and beta blockers.

Clinical Manifestations

Critically ill children with hypoglycemia may present with a broad spectrum of symptoms and signs, depending on the underlying disease, glucose level, number and duration of the hypoglycemic event. Also the presence of hemodynamic disturbances, hypoxia, ischemia, anemia and the capacity of metabolic adaptations may influence the clinical syndrome. Signs and symptoms are relatively non-specific and generally reflect the effects of low blood glucose on the release of counterregulatory hormones, particularly epinephrine. These signs and symptoms include irritability, inactivity, hypothermia, diaphoresis, tachycardia, tachypnea, and weakness. Neurologic symptoms include mild to severe alteration of consciousness, from lethargy to irritability up to coma and seizures. Apnea and respiratory depression are also seen in the younger child and infant. Severe glucose deficiency leads to brain energy failure, muscle weakness and organ impairment, including heart failure [16]. Seizures are the most common neurologic presentation of hypoglycemia in children [27]. The blood glucose threshold at which seizures occur is highly variable, though a blood glucose level below 40 mg/dL would have a high likelihood of seizures. Early recognition of hypoglycemia requires a high index of suspicion. As a general recommendation, blood glucose should be immediately evaluated in any infant or child presenting with either a seizure or altered mental status. In addition, several studies suggest that blood glucose should be measured in any critically ill or injured pediatric patient. Rapid, bedside glucose measurement should be performed, though glucose should be measured in the laboratory also, as the bedside tests may frequently underestimate the blood glucose value. An extra 3 mL red top should be obtained at this time as well. Therapy should be instituted if the bedside measurement reports a low blood glucose (treatment holds minimal risk and further delays in management may be associated with dire consequences). If the laboratory glucose measurement confirms the bedside measurement, the reserved red top should be sent for further studies (Table 9.2).

Table 9.2 Emergency evaluation of hypoglycemia

1. Obtain rapid bedside blood glucose and treat appropriately
2. Send confirmatory blood glucose sample to the laboratory
3. Draw extra 3 mL red top. If laboratory glucose measurement confirms hypoglycemia, send blood sample for: Insulin Cortisol Growth hormone T4, TSH Free fatty acids Ketones
4. Send first voided urine for urinalysis (hypoglycemia without ketosis suggests hyperinsulinism)

Management

The treatment of choice for symptomatic hypoglycemia is the immediate parenteral administration of glucose (0.5 g/kg of dextrose as either 2–4 mL/kg 10 % dextrose or 1–2 mL/kg 25 % dextrose). Further treatment consists of administration of 6–8 mg/kg/min glucose (which is generally accomplished by infusion of a 10 % dextrose solution at 1.5 times maintenance rate):

$$\text{Glucose infusion rate}\left(\text{mg/kg/min}\right) = \left[\text{mL/h} \times \%\ \text{dextrose}\right] / \left[\text{weight}\left(\text{kg}\right) \times 6\right]$$

Further management is of course dictated by the ensuing diagnostic work-up and serial measurements of blood glucose. Higher dextrose concentrations are occasionally required, though central venous access is recommended if a concentration higher than 12.5 % dextrose is needed to maintain blood glucose concentrations at a safe range.

Hypoglycemia absolutely must be avoided in critically ill infants and children because of a strong association with higher morbidity and mortality. Unfortunately, hypoglycemia is often difficult to diagnose in the critically ill patient based on symptoms, as the patient is often sedated and on mechanical ventilation [28]. Previous malnutrition or progressive nutritional deterioration during critical illness is a frequent feature in PICU and certainly increases the risk of complications from hypoglycemia [29, 30]. "Tight glucose control" has been widely applied in the PICU setting [31–33] with relatively little evidence of either its safety or efficacy. Given their lower glucose reserves, newborns, infants and children may be at even greater risk of hypoglycemia while using "tight glucose control" [34].

Blood glucose should be checked in every critically ill child with sepsis, and if there is evidence of hypoglycemia it should be corrected soon as possible. Glucose supplementation at 1–2 mg/kg/min should be initiated, even if it causes a transient hyperglycemia [35, 36]. Early enteral nutrition is an important factor to stabilize blood glucose levels [37]. Early enteral feeds provide sufficient energy, avoiding glycogenolysis or gluconeogenesis, sparing muscle breakdown and reducing the risk of hypoglycemia due to storage depletion in absence of new enough external supply.

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The Adrenal Glands in Critical Illness and Injury

10

Kusum Menon

Abstract

Proper functioning of the hypothalamic-pituitary-adrenal axis is necessary for normal homeostasis in children, especially under conditions of stress, such as in critical illness. Disturbances of this axis have been classified collectively under the heading of adrenal insufficiency. Although the majority of literature has focused on children with septic shock, more recent evidence suggests that adrenal insufficiency occurs in a much broader group of critically ill children. Its etiology in pediatric critical illness remains unclear but is most likely multi-factorial. Several studies have suggested possible diagnostic criteria for adrenal insufficiency in pediatric critical illness; however, to date none of these biochemical definitions have been validated by a therapeutic trial. Similarly, current management of this condition in critically ill children remains based primarily on an empiric, best practice approach. Future large scale studies are needed to determine the definitive management of this condition.

Keywords

Adrenal insufficiency • Cortisol • Hydrocortisone • Shock • Relative adrenal insufficiency

Introduction

Critically ill children with fluid and/or vasopressor dependent shock are at significant risk for a poor outcome, with ICU mortality approaching up to 30 % in some series [1]. As a result, pediatric intensivists continuously struggle with the clinical question of how to improve the outcomes of these critically ill children. Many clinicians believe that adrenal dysfunction plays an important role in the pathogenesis of fluid and/or vasopressor dependent shock. Adrenal insufficiency is the term used for this condition characterized by inadequate cortisol (either quantity or lack of effectiveness at the receptor level) to meet the physiologic requirements of the patient. Clinically this results in severe hypotension that may be resistant to fluid and/or vasopressor therapy, which may in turn increase mortality [2–4]. The requirement for significant fluid resuscitation and vasopressor support in patients with unrecognized adrenal insufficiency may result in prolonged mechanical ventilation [5] and a subsequent need for ongoing invasive monitoring and vascular access. This in turn has significant implications for both patient morbidity and resource utilization.

Historical Perspective

The association of adrenal disease with fatal outcomes was first reported in 1855 by Addison in 12 patients who died with chronic suprarenal failure [6]. Subsequently, a British dermatologist, Dr. Graham-Little, described acute adrenal hemorrhage leading to circulatory collapse in 1901. This phenomenon was then formally reported in the medical literature by Waterhouse in 1911 [7] followed by a comprehensive review of the subject in 1918 by the Danish pediatrician,

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Friderichsen [8]. Hemorrhage into the adrenal glands was believed to be the main mechanism of adrenal dysfunction in septic shock until the 1980's when evidence began to emerge that the clinical syndrome described by Waterhouse and Friderichsen was not always caused by adrenal hemorrhage. Subsequently, researchers also began to describe non-septic, critically ill patient populations in which this clinical syndrome occurred [9–12]. In the last decade, the focus has shifted from identification of the clinical syndrome associated with adrenal insufficiency to better defining its diagnosis and determining its treatment in critically ill children [12–15].

Normal Adrenal Anatomy and Function

Adrenal Gland

The adrenal gland comprises two retroperitoneal organs located above the kidneys at the level of the 12th thoracic rib. The adrenal gland is divided into two distinct areas, the cortex and the medulla. The cortex is part of the neurohormonal system and is controlled by hormones from the anterior pituitary and hypothalamus. The medulla is considered part of the sympathetic nervous system and is stimulated by preganglionic fibers originating in the thoracic spinal cord.

The cortex comprises the outer layer of the adrenal gland and consists of three zones: the zona glomerulosa, the zona fasciculata and the zona reticularis. The cells of the zona glomerulosa produce mineralocorticoids (e.g., aldosterone), the zona fasciculata produces glucocorticoids (e.g., cortisol) and the zona reticularis is responsible for the production of androgens (e.g., testosterone).

The medulla forms the inner layer of the adrenal gland and is responsible for the production of catecholamines (dopamine, norepinephrine and epinephrine) from tyrosine.

The adrenal gland derives its blood supply from the superior, middle, and inferior adrenal arteries which branch off of the inferior phrenic artery, the abdominal aorta, and the renal artery, respectively. Along with the thyroid gland, the adrenal gland has the largest per gram blood supply of any organ in the body which makes it more vulnerable to changes in cardiac output and blood pressure.

Hypothalamic-Pituitary Adrenal Axis

The hypothalamus produces corticotrophin releasing hormone (CRH), which in turn stimulates adrenocorticotropic hormone (ACTH) to be produced and released from the anterior pituitary. ACTH then stimulates the adrenal cortex to produce cortisol. Under normal circumstances, 30–40 mg per day of cortisol is produced. Cortisol has a half-life of 70–120 min and is metabolized by the liver and excreted by the kidney. Cortisol secretion exhibits a diurnal variation with peak levels occurring early in the morning (at approximately 8 am) and the nadir being reached between midnight and 4 am, or 3–5 h after the onset of sleep. Diurnal variation in secretion is not present at birth but begins anywhere from 2 weeks to 9 months of age [16].

Actions of Cortisol

Cortisol is an important modulator of the body's stress response [17] and plays a significant role in maintaining glucose homeostasis [18] and in the modulation of the body's inflammatory response [17, 18]. Cortisol induces proteolysis and lipolysis in order to generate substrates for gluconeogenesis, decreases peripheral utilization of glucose and increases blood glucose levels [17]. Cortisol exerts its anti-inflammatory effects via inhibition of phospholipase A_2 and its subsequent activation of the arachidonic acid cascade as well as by directly blocking the production of cytokines [17].

Perhaps the most important action of corticosteroids for intensive care physicians is their effect on the cardiovascular system to promote hemodynamic stability. They are thought to exert immediate effects through their non-genomic actions and delayed effects (several hours) through their genomic actions via modification of protein translation. Corticosteroids decrease the re-uptake of norepinephrine by inhibiting the catechol-0-methyltransferase enzyme involved in catecholamine metabolism. This leads to increases in the plasma concentration of norepinephrine by decreasing the lysosomal degradation of adrenergic receptors [19]. Physiologic doses of glucocorticoids may also increase cytosolic calcium availability in myocardial and vascular smooth muscle cells [20]. Steroids inhibit prostacyclin production and the induction of nitric oxide synthase, limiting the pathologic vasodilatation associated with the inflammatory response [21]. In addition, steroids help maintain capillary integrity through preservation of the endothelial glycocalyx [21]. Therefore lack of corticosteroids, i.e. adrenal insufficiency, may lead to significant hemodynamic instability from decreased myocardial contractility, vasodilatation and/or capillary leak syndrome [3, 4].

Normal Response to Stress

The body normally increases its cortisol levels in times of stress by the following mechanisms: increase in ACTH production, decreased extraction of cortisol from the blood, relative resistance to negative feedback by cortisol at the pituitary level, reduced hepatic degradation of cortisol and a shift in adrenal steroid synthesis away from androgens and mineralocorticoids to glucocorticoids. There are also non

ACTH driven pathways for the stimulation of cortisol production through cytokines and vasoactive substances. Finally there is increased demargination of free cortisol from CBG resulting in an increase in the biologically active form [22].

Adrenal Insufficiency

Acute adrenal insufficiency is a clinical condition associated with hypotension that can be resistant to fluid and vasopressor therapy and, if untreated, can result in increased mortality [3, 23]. In addition to severe hypotension, acute adrenal insufficiency may be associated with other non-specific findings such as hypoglycemia, hyponatremia, hyperkalemia and neutropenia making it difficult to diagnose clinically. Adrenal insufficiency occurs when there is inadequate cortisol (either quantity or lack of effectiveness at the receptor level) to meet the physiologic requirements of the patient. It has been traditionally classified as primary, secondary or tertiary adrenal insufficiency by endocrinologists. Others have classified it as either congenital or acquired. In addition, over the last 5 years intensive care physicians have developed the concept of relative or critical illness related corticosteroid insufficiency (CIRCI) [24] versus absolute adrenal insufficiency.

Primary Adrenal Insufficiency

Primary adrenal insufficiency is due to impairment of the hypothalamic-pituitary-adrenal axis at the level of the adrenal gland. In children this is most often due to one of a group of congenital adrenal defects, of which the most common is the CYP21 deficiency. The inability of these infants to produce cortisol and/or aldosterone can lead to shock and vascular collapse in the newborn period. Acquired causes of primary adrenal insufficiency include hemorrhage in the newborn period, infection and autoimmune adrenalitis, the latter two of which are extremely uncommon in children.

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is due to ACTH deficiency which can also be classified as congenital or acquired. Congenital lesions may involve the pituitary alone or occur with other midline defects. It is important to note that pituitary lesions may also result in deficiencies of other hormones including growth hormone and thyrotropin and therefore global pituitary function must be tested in such patients. The most common causes of acquired secondary adrenal insufficiency include craniopharyngiomas, surgical removal of midbrain tumours, cranial radiation and traumatic brain injury [25, 26].

Tertiary Adrenal Insufficiency

Tertiary adrenal insufficiency implies a deficiency in hypothalamic production or secretion of CRH. This may occur following head trauma or cranial radiation but is most commonly caused by prolonged administration of systemic glucocorticoids following by a rapid wean or abrupt cessation. It is important to note that tertiary adrenal insufficiency has been seen following long-term administration of even topical and inhaled glucocorticoids and thus must be considered in such cases [27–29]. The minimum dose required to cause adrenal insufficiency in any given patient is unknown and therefore adrenal insufficiency must be considered in any patient who has been on glucocorticoids in the month prior to their critical illness as well as any patient who has been on the equivalent of 1 mg/kg/day or more of prednisone for more than 1 week within the preceding 6 months [30, 31].

Relative and Absolute Adrenal Insufficiency

Relative adrenal insufficiency is a termed that has been coined by intensive care physicians to describe the condition whereby patients with fluid and/or vasopressor dependant shock respond to corticosteroid therapy, despite what have traditionally felt to be adequate levels of cortisol. Relative adrenal insufficiency or critical illness related corticosteroid insufficiency (CIRCI) is thought to result from inadequate steroid activity at the cellular level, while the plasma cortisol level itself may actually be high, low or normal. Absolute adrenal insufficiency is defined as a cortisol level that would be considered too low under any circumstances. Some authors have defined relative adrenal insufficiency as an increment in cortisol less than 9 μg (micrograms)/dL following ACTH stimulation testing (see below) [14, 32, 33] versus a peak cortisol level less than 18 μg (micrograms)/dL [34]. Similarly, absolute adrenal insufficiency has been defined as a basal cortisol level less than 5 μg (micrograms)/dL [34], while others have defined it as a basal cortisol level less than 7 μg (micrograms)/dL [35]. Currently there is no consensus on the definition of adrenal insufficiency in critical illness; however, most experts would agree that a critically ill patient with a random cortisol level less than 5 μg (micrograms)/dL and/or an increment in cortisol post ACTH stimulation less than 9 μg (microgram)/dL is at risk for the clinical manifestations of adrenal insufficiency.

Adrenal Insufficiency in Critical Illness

Definition of Adrenal Insufficiency

There is considerable controversy in the literature regarding the definition of adrenal insufficiency in critically ill children

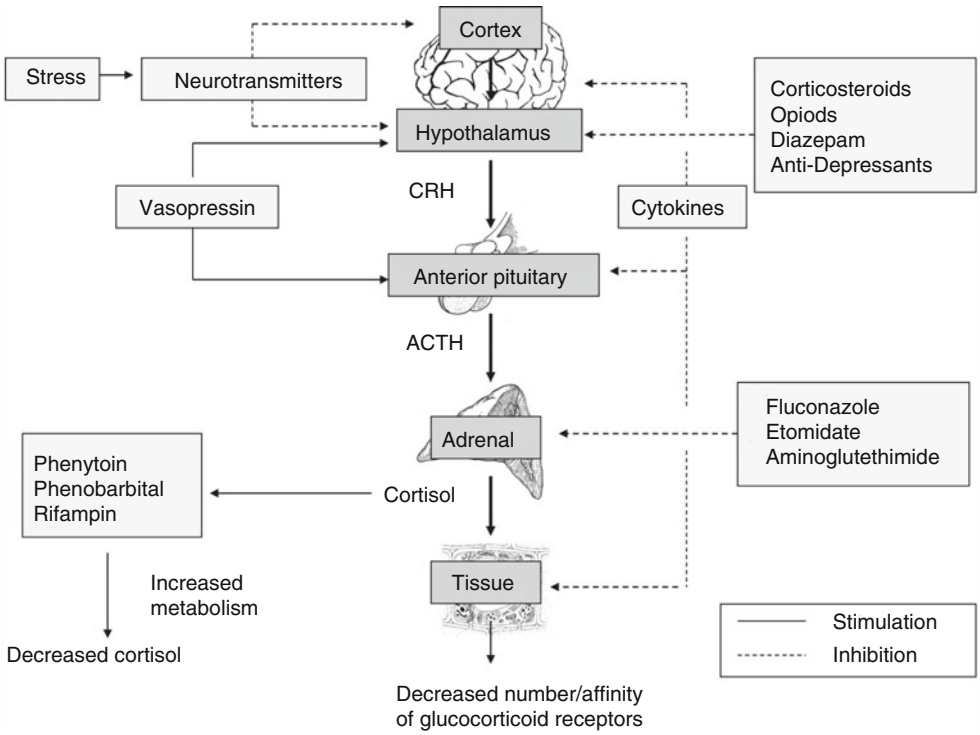

Fig. 10.1 Pathogenesis of adrenal insufficiency in pediatric critical illness

and adults. A Canadian survey of pediatric endocrinologists and pediatric intensivists [12] found that there is no consensus on the definition of adrenal insufficiency in pediatric critical illness. Several studies have assessed the issue of adrenal insufficiency in critically ill children, five of which [12, 14, 32, 36, 37] have linked their definition of adrenal insufficiency (increment <7–9 μg (microgram)/dL, peak <18 μg (microgram)/dL)) to a clinically significant adverse outcome such as hypotension [12, 14, 32, 36] or mortality [37]. An increment of less than 9 μg (microgram)/dL is currently the most commonly accepted definition by critical care physicians and experts in the field [12, 14, 32, 37–40].

Prevalence of Adrenal Insufficiency in Pediatric Critical Illness

The reported prevalence of adrenal insufficiency in pediatric critical illness varies from 14 to 77 % [10, 12, 14, 32, 34, 36, 37, 40, 41]. There are several possible reasons for this observed variation. The first is that these studies were conducted on diverse populations of critically ill children including those with septic shock [32, 34, 36, 37, 41], acute respiratory distress syndrome [40], trauma, post-operative general surgical conditions and other medical illnesses [10, 12]. Even within the septic shock population, however, the prevalence has varied from 9 % [34] to ~30 % [12, 14, 32] to 77 % [37]. This is likely due to the use of different definitions and tests for the diagnosis of adrenal insufficiency with a resulting variation in its reported prevalence.

Possible Mechanisms for Adrenal Insufficiency in Critical Illness

Mechanisms for adrenal insufficiency in critical illness may be broadly classified as primary, secondary or peripheral (Fig. 10.1). Primary adrenal insufficiency is uncommon and may be caused by blockage of corticosteroid synthesis by drugs (etomidate [42], fluconazole [43], exogenous steroids) or cytokines, destruction of the adrenal gland by infection/ischemia/hypoxia/infiltrate [44] and/or reduced secretory reserve [45]. Mechanisms for secondary adrenal insufficiency include inhibition of ACTH/CRF production by cytokines [46, 47], drugs (glucocorticoids, opiates, diazepam, anti-depressants) or destruction of the pituitary/hypothalamus by ischemia/infection/hypoxia/trauma. Peripheral causes of adrenal insufficiency may include increased metabolism of cortisol (rifampin [48], phenytoin, phenobarbital), decrease in the number/affinity of glucocorticoid receptors [49] and decreased demargination of cortisol from CBG and albumin.

Diagnosis of Adrenal Insufficiency in Critical Illness

The simplest and quickest method used for the diagnosis of adrenal insufficiency in critically children is the measurement of random cortisol levels. However, multiple studies have shown that random levels alone [2, 36, 50, 51] are inadequate for the detection of adrenal insufficiency (sensitivity

83 %, specificity 81 %) [41, 52–54]. The most commonly used test in the past has been the high dose short ACTH test in which the patient has a baseline cortisol level drawn followed by an injection of 100–250 μg (micrograms)/1.73 m [2] of ACTH. A cortisol level is then repeated at 30 and 60 min to determine the patient's response to the ACTH stimulus. More recently, investigators have described a low dose ACTH stimulation test using 1 μg (microgram) of ACTH [55–59] based on the rationale that low dose ACTH testing produces levels of ACTH similar to that produced in most stressful situations and thus better mimics physiologic conditions than the high dose test [57]. Furthermore, the total stored pool of endogenous ACTH in the pituitary is 600 μg (micrograms). Therefore the conventional dose of 250 μg (micrograms) of ACTH results in a large, supraphysiologic adrenal stimulus. There is evidence to show that the low dose ACTH stimulation test (1 μg (microgram)) has greater sensitivity in the detection of secondary adrenal insufficiency than the high dose test in non critically ill children with pituitary disease when compared to the gold standard insulin tolerance test (sensitivity 94.7 % vs 12.5 %, specificity 90 % vs 100 %) and the overnight metapyrone test [60] (sensitivity 100 % vs 21 %, specificity 68 % vs 100 %). Given that the mechanism of adrenal function in critically ill patients may involve any or all components of the hypothalamic-pituitary-adrenal axis, it is important to use a diagnostic test that does not exclude patients with secondary adrenal insufficiency (i.e., adrenal insufficiency secondary to pituitary disease). Many of the recent pediatric critical care studies [12, 14, 37, 41] on adrenal insufficiency in critically ill children (in which an ACTH stimulation test was performed), have used a low dose stimulation test and one study showed that the low dose test had a sensitivity of 100 % and a specificity of 84 % when compared to the high dose test [12]. Finally, the 1 μg (microgram) test has been shown to be repeatable and reproducible on a daily basis [59] whereas the repeatability of the high dose test remains unproven.

Measurement of Cortisol Levels

The most commonly used assays for cortisol in clinical practice currently measure total hormone concentration. However, approximately 10 % of cortisol exists in the free, bioactive form in vivo with the remaining 90 % being primarily bound to cortisol-binding globulin (CBG) and albumin. Total protein, including CBG and albumin, decrease in critical illness [61] and a recent adult study suggested that glucocorticoid secretion actually increases in critical illness, but that this increase is not discernable when only the total cortisol is measured [62]. However, a more recent pediatric study found that CBG and albumin levels did not differ in pediatric survivors and non-survivors of septic shock (and were within normal limits in 86 % of these patients) and that therefore total cortisol levels correlated well with bioactive free cortisol levels on admission to the PICU [42]. Zimmerman et al. [63] found that critically ill children had low free cortisol levels ranging from 0.8 to 0.2 μg (micrograms)/dL, but did not exhibit clinical correlates of adrenal insufficiency. Therefore the utility of total versus free cortisol measurements remains undetermined and is further hampered by the limited availability of free cortisol measurements. In order to circumvent this, some investigators have suggested estimating this value using a free cortisol index (FCI) and calculated free cortisol (cFC) [64] while others have suggested that cFC does not provide essential information for identification of patients who would benefit from corticosteroid treatment in septic shock [65]. Furthermore, normative data for these values are not available in children. It is not clear whether the increment in total cortisol level post ACTH stimulation is affected by the serum protein level or not although one study suggested that it is [62]. In the end, clinicians are best advised to remember that serum protein levels may affect total cortisol levels in critically ill children and to consider repeating testing when the protein levels have normalized.

Risk Factors for Adrenal Insufficiency

Our understanding of how to identify critically ill children who may be at risk of adrenal insufficiency remains unclear. Risk factors discussed in the literature include the use of fluconazole [43], etomidate [66] presence of septic shock [67], prior use of inhaled or systemic steroids [27, 68–72], older age and the diagnosis of trauma [12]. Although younger infants do not appear to be at increased risk, prematurity is a definite risk factor for adrenal insufficiency and therefore hypotensive premature infants should be treated with stress doses of hydrocortisone [73–75]. It is important to note that while the majority of pediatric literature to date has focused on patients with septic shock [36, 76–79], emerging evidence suggests that the problem of adrenal insufficiency is not limited to sepsis but may be seen in a variety of other medical and surgical conditions [1, 12, 33]. Illness severity does not appear to be a risk factor [12, 37, 41] and congenital heart surgery patients appear to have a significantly lower risk of developing adrenal insufficiency [12].

Pharmacokinetics of Corticosteroids in Critical Illness

Adrenal insufficiency in critical illness may result from a variety of different causes some of which may result in both glucocorticoid and mineralocorticoid deficiency. As a result, hydrocortisone has been the most commonly recommended steroid for the therapy of acute adrenal insufficiency as it has

Table 10.1 Comparison of corticosteroids

Corticosteroid	Glucocorticoid effect	Mineralocorticoid effect	Equivalent dose (mg)	Duration of action HPA axis (h)
Short acting				
Hydrocortisone	1.0	1.0	20	12
Cortisone	0.8	0.8	25	12
Intermediate acting				
Prednisone	3.5	0.8	6	12–36
Prednisolone	4.0	0.8	5	12–36
Methylprednisolone	5.0	0.5	4	12–36
Long acting				
Dexamethasone	30	0	0.7	>48

equivalent glucocorticoid and mineralocorticoid properties. A comparison of pharmacokinetic properties of different available corticosteroids is shown in Table 10.1.

In the most recent randomized controlled trials [38, 39, 78, 80], four different corticosteroid dosing regimens were used with only one study using a mineralocorticoid (fludrocortisone) in addition to hydrocortisone. Treatment duration and weaning protocols in the studies also differed. The most recent pediatric RCT [78] used a "low dose hydrocortisone" of 5 mg/kg/day till reversal of shock, which contrasts with the up to 50 mg/kg/day of hydrocortisone recommended by the 2007 American College of Critical Care Medicine guidelines for the management of pediatric and neonatal shock [81]. The two studies on pediatric steroids in sepsis currently underway (www.clinicaltrials.gov) utilize different doses of hydrocortisone (25 mg/m [2] q6h versus 2 mg/kg q8h) for differing durations of time (48 h versus 7 days).

Pharmacokinetic studies in healthy adult volunteers or non-critically ill adults with adrenal insufficiency suggest that cortisol levels vary considerably from 26 to 301 μg (micrograms)/dL, peak in 30 min and return to baseline in 3–4 h following 20–40 mg of intravenous hydrocortisone [82, 83]. There is very little information on cortisol levels following hydrocortisone administration in critically ill patients. However, studies have demonstrated that many critically ill children and adults may have cortisol levels well above 200 μg (micrograms)/dL [12, 38, 39]. Therefore therapy with 1–2 mg/kg of hydrocortisone in these patients may not be adequate and/or beneficial. Given that cortisol levels appear to return to baseline in 3–4 h, consideration should be given to administration of hydrocortisone by continuous infusion using a dose of 4–8 mg/kg/day [33]. The considerable variation and lack of consensus in dosing as evidenced by two recent surveys [15, 84] is a major issue in this field and needs to be addressed.

Adverse Effects of Corticosteroids in Critical Illness

There is only one reported study that documented adverse events associated with the use of low dose hydrocortisone (4–5 mg/kg/day) in critically ill children [78]. This randomized controlled trial of only 38 patients did not find a significant difference in the incidence of secondary infections and significant gastrointestinal bleeding between those who did and did not receive hydrocortisone [78]. A retrospective chart review [85] and systematic review [86], however, suggested that hyperglycemia and infection may be associated with the use of stress doses of corticosteroids. In larger trials of critically ill adult populations, the use of stress dose corticosteroids has been associated with statistically significant adverse events including impaired wound healing, hypernatremia [39, 80], hyperglycemia [38, 39], gastrointestinal bleeding [39, 80] and potentially life-threatening infections [39]. In a case control study of 10,285 critically ill adults, a mean dose of 900 mg of hydrocortisone over 3 days was associated with an increased use of diuretics, insulin, protracted weaning from mechanical ventilation and the need for tracheostomy [87]. Given the lack of information in the PICU population, it is difficult for the bedside clinician to make an educated decision regarding the risk versus benefit of administering low dose corticosteroids to a fluid and/or vasopressor dependent pediatric patient in shock.

Management of Adrenal Insufficiency in Pediatric Critical Illness

Based on a limited body of evidence, the 2007 update from the American College of Critical Care Medicine [81] states that "…children are more likely to have absolute adrenal insufficiency (than adults) defined by a basal cortisol <18 μg/dL and a peak ACTH stimulated cortisol concentration <18 μg/dL. The committee only recommends hydrocortisone treatment for patients with absolute adrenal insufficiency. The dose can be titrated to the resolution of shock using between 2 and 50 mg/kg/day as a continuous infusion or intermittent dosing as desired. In a patient with fluid and catecholamine resistant shock, begin hydrocortisone if at risk for absolute adrenal insufficiency. The committee continues to maintain equipoise on the question of adjunctive steroid therapy for pediatric sepsis." The above guidelines present

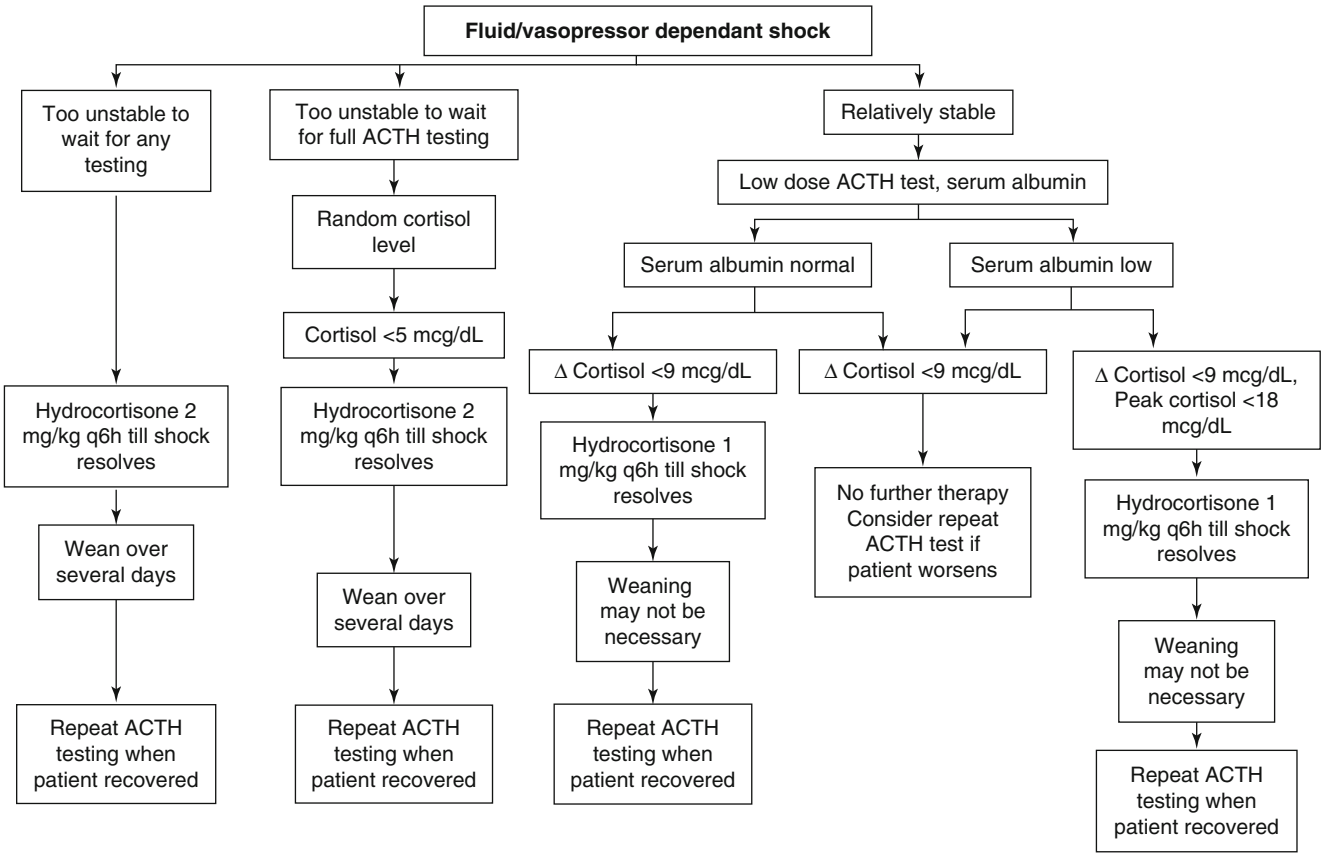

Fig. 10.2 Treatment algorithm for adrenal insufficiency in pediatric critical illness

several problems: results of adrenal testing are seldom available rapidly enough to affect therapeutic decisions, the dose range recommended is very large, the risk factors for the development of adrenal insufficiency are unclear and in the end the committee states that it maintains equipoise on the subject leaving clinicians to make their own individual judgments at the bedside.

There are only four published randomized controlled trials on the use of steroids in shock in pediatric critical illness, [76–78, 88] on a total of 261 patients. One study showed a statistically significant decrease in the duration of shock with hydrocortisone therapy in patients with dengue fever [76] while the other three were insufficiently powered and did not show any change in outcome [77, 78, 88]. Three studies were limited to patients with shock from dengue fever and were conducted over 20 years ago [76, 77, 88], the fourth was conducted as an open-label study [78]. This open label pilot study of 38 septic shock patients in the third world found a non-statistically significant trend toward earlier shock reversal and lower inotrope scores in the hydrocortisone treated group. There are currently two studies of corticosteroids in critically ill children underway (www.clinicaltrials.gov); however, the number of patients is very small (60 and 90 patients respectively) and both trials focus on only patients with septic shock.

Many centers do not have a rapid turn around time for cortisol levels making it difficult to base treatment decisions on the results from ACTH stimulation testing. Ideally, low dose ACTH testing should still be sent prior to the implementation of empiric steroid therapy. An algorithm for the management of critically ill children with suspected adrenal insufficiency is presented in Fig. 10.2. Ultimately, given the many controversies discussed in this Chapter, it is important to remember that the treatment of fluid and vasopressor dependant shock should be based on clinical judgment and should never be delayed or withheld because of lack of availability of or difficulty in interpreting ACTH stimulation testing [24]. While it is important to not delay corticosteroid treatment of unstable patients with shock, it is equally important to rapidly wean steroids once they are no longer needed so as to minimize their potential adverse effects.

Outcomes of Adrenal Insufficiency in Pediatric Critical Illness

Pediatric critical care studies have been insufficiently powered to detect an association between adrenal insufficiency and mortality [12, 76–78] especially given that the overall mortality in pediatric intensive care units is only 3–5 % [89].

However, the presence of adrenal insufficiency in pediatric critical illness has been associated with a greater need for fluid [12] and inotropes [12, 14, 32, 36, 78]. In addition, adrenal insufficiency in post operative congenital heart surgery patients has been associated with a longer duration of mechanical ventilation [90, 91] an increased intensive care length of stay [90], a higher inotrope score [11, 90–92], greater fluid requirements [90] and a reduction in left ventricular shortening fraction [33] suggesting that adrenal insufficiency may significantly impact morbidity and resource utilization. The natural history of critical illness related adrenal insufficiency is unknown as one study suggested that it may be a transient phenomenon in some patients [12] raising questions about the indications for treatment in this condition.

Conclusion

Adrenal insufficiency is a difficult condition to define and diagnose in critically ill patients. Currently there are no large, randomized, controlled trials on which to base definitive management recommendations. In view of this, current practice must be based on the best-available evidence which is largely empiric in nature. Adrenal insufficiency should be suspected in any child, regardless of underlying diagnosis, who presents with fluid-resistant or persistent shock that may be caused at any level of the HPA axis. A pragmatic approach to the management of such a child would be to conduct a low-dose ACTH stimulation test followed by empiric treatment with 1–2 mg/kg hydrocortisone q6h pending results of testing. In a clinically unstable child an increment in cortisol of less than 9 μg (micrograms)/dL following ACTH stimulation would warrant treatment until resolution of shock.

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Thyroid and Growth Hormone Axes Alteration in the Critically Ill Child

11

Ricardo Garcia Branco, Pedro Celiny Ramos Garcia, and Jefferson P. Piva

Abstract

Objective: the aim of this chapter was review the response of the Thyroid and Grown Hormones (GH) in children with severe acute diseases.

Data Source: using the terms Thyroid hormone and grown hormone crossed with sepsis, stress and children the searched the Medline data basis and selected the English, Spanish and Portuguese articles (originals and review articles) published in the last years.

Main results: Stress and critical illness induce changes in circulating hormone levels. Thyroid hormones increase beta adrenergic receptor affinity and responsiveness to catecholamines. During critical illness, children often develop alterations in thyroid hormone concentrations. A low-T3 state develops with preserved serum T4 levels. In prolonged or more severe critical illnesses, serum T4 levels also became reduced (lowT3-T4 state), increasing mortality rate, length of MV and cathecolamine resistance. In the early phase of critical illness, GH level is elevated, with alteration in pulsatility. Low IGF-I levels are a predictive marker of mortality in critical illness. Non-survivors present significantly lower IGF-I levels than survivors, and IGF-I levels correlate inversely with severity of illness.

Conclusion: Thyroid and growth hormone play a major role in the regulatory process related to stress response in acute ill children. The correct diagnosis and early treatment might influence positively the outcome.

Keywords

Stress response • Inflammation • Neuroaxis hormonal response • Sepsis • Cell metabolism

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Introduction

Stress and critical illness induce characteristic changes in circulating hormone levels. These changes are part of the adaptive physiological response to stress that has been tailored through evolution to prioritize vital organ function and stimulate a 'fight or flight' response. A wide neuroendocrine response is involved in this process, with the adrenal, thyroid, and growth hormone axes playing a major role in this regulatory process. In this chapter we will describe the thyroid and growth hormone axes alteration relevant to critical illness.

The Thyroid Axis in Critical Illness

Thyroid hormones have profound effects on major physiologic processes, such as development, growth, and metabolism. In children, thyroid hormones are essential for the growth and maturation of many target tissues, including the brain, heart, lung, and skeleton [1, 2]. Thyroid hormones can also affect hemodynamics through an increase in beta-adrenergic receptor affinity and responsiveness to catecholamines [3]. During critical illness, children often develop alterations in thyroid hormone concentrations despite having no previous history of intrinsic thyroid disease. Initially, a low-T3 state develops, with reduced serum total and free T3 levels, but preserved serum T4 levels. In prolonged or more severe critical illnesses, serum T4 levels also became reduced, producing a lowT3-T4 state. During both low T3 and lowT3-T4 states TSH levels frequently remain normal, and children with this presentation typically do not have features of hypothyroidism. This combination of findings is commonly described as *euthyroid sick syndrome* or *non-thyroidal illness syndrome* [4–7].

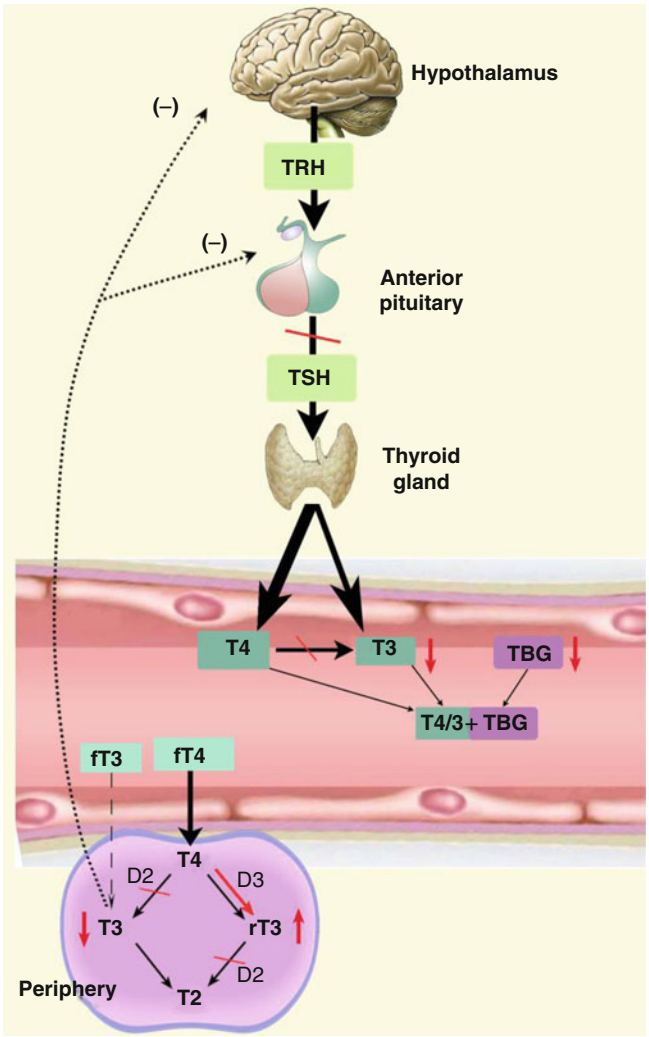

Fig. 11.1 The thyroid axis – simplified diagram of thyroid axis activity. During critical illness (*RED*), reduced conversion of T4 to T3 and increased production of reverse T3 (*rT3*) generate a low T3 state. Thyroxine (*T4*) level can be normal in early/mild disease, but are normally low in severely ill children. This is associated with an acute drop in thyroxine-binding globulin (*TBG*). Although initially preserved, TSH levels decrease in during late critical illness

Thyroid Physiology

Under normal conditions, thyroid stimulating hormone (thyrotropin, TSH) is released in a pulsatile and diurnal fashion from thyrotrophs in the anterior pituitary gland in response to hypothalamic release of thyrotropin releasing hormone (TRH). At the thyroid gland, TSH controls the release to the systemic circulation of thyroxine (T4) and triiodothyronine (T3) that are bound to thyroglobulin [8] and stored in large follicles. Most of thyroidal hormone is normally released in the form of T4 (90 %), with only a small amount released as T3. In the circulation, thyroid hormones are mostly bound to carrier proteins (thyroxine-binding globulin, thyroxine-binding prealbumin, and albumin) with a small amount (0.03 % of total serum T4 and 0.3 % of total serum T3) circulation the free or unbound form. It is the free hormone, however, that determines the biological activity level of the thyroid hormones [1, 4, 7]. In peripheral tissues, free circulating T4 and T3 are taken up by target cells via monocarboxylate transporters (MCT) [9]. In these cells, T4 can be deiodinated via type II iodothyronine deiodinase (D2) into T3, or via type III iodothyronine deiodinase (D3) into reverse T3 (rT3) – a presumably biologically inactive form. Inside the cell, T3 will bind with nuclear thyroid hormone receptors (TR) that can bind to specific nucleotide sequences (thyroid responsive elements) within promoter regions of genes that will regulate the physiological effects of thyroid hormones (Fig. 11.1).

Thyroid hormone production is regulated by feedback inhibition. T3 and T4 inhibit TSH secretion from the pitu-

itary thyrotrope cells and TRH biosynthesis at the hypothalamus [7]. T3 concentrations are also autoregulated by adjustments in peripheral T4 to T3 conversion rate.

Serum concentrations of T3 and TSH tend to be slightly higher in younger children. This fact is related to a physiological slow and progressive decrease in the concentrations of T4, T3, and TSH during infancy and childhood. The serum concentration of reverse T3, however, remains unchanged or increases slightly with age. Serum thyroglobulin levels also fall over the first year of life reaching concentrations typical of adults by about 6 months of age [10].

Another important aspect of thyroid physiology in the infant and child is the markedly higher T4 turnover in this age group relative to that in the adult. In infants, T4 production rates are estimated to be on the order of 5–6 μg/kg per day, decreasing slowly over the first few years of life to about 2–3 μg/kg/day at ages 3–9 years. This is to be contrasted with the production rate of T4 in the adult which is about 1.5 μg/kg/day [11].

Thyroid Hormones During Critical Illness

In the acute phase of illness, T3 and free T3 levels decreased rapidly to extremely low concentrations. The decrease in circulating T3 levels result from a decline in the net conversion of T4 to T3, while T3 clearance remains preserved [7, 12]. The underlying mechanism of reduced T4 to T3 conversion remains controversial, but altered MCT activity (by non-esterified fatty acids/ bilirubin inhibition, or ATP depletion) and diversion of T4 metabolism towards alternative pathways of metabolism may be involved [13, 14].

In contrast to the low T3 levels, rT3 levels increase in the acute phase of illness due to reduced clearance and increased D3 activity [7, 15]. T4 levels usually remain normal (although it can increase temporarily) [16], but in more severely ill patients T4 levels can also decrease rapidly. The reduction in T4 levels in acute critical illness has been associated with a decrease in carrier proteins and circulating inhibitors of T4 binding [17]. In the clinical setting, serum concentration of T4 in early critical illness has inversely correlated with adult intensive care mortality [18]. TSH levels remain normal, but the nocturnal surge of TSH seen in normal physiology does not occur in the acute phase of illness (Fig. 11.1).

In the late phase of critical illness pituitary secretion of TSH is decreased, with a concomitant decline in serum T4 concentrations. There is a dramatic reduction in the normal pulsatile pattern of secretion, and the low TSH pulse amplitude accounts for the low serum thyroid hormone levels [19]. The production and release of thyroid hormones seem to be affected in late critical illness. Fliers et al. studied the expression of the TRH gene in hypothalamic paraventricular nuclei. They showed that when death follows chronic severe illness, the low levels of TRH gene expression correlate with low blood levels of TSH and T3, whereas in the case of death from acute insults, such as lethal trauma due to a road accident, gene expression is normal [20]. Interestingly, increased levels of TSH have also been shown to be a marker of the onset of recovery from severe illness [21].

Thyroid Function in Critically Ill Children

A number of studies have described thyroid dysfunction – euthyroid sick syndrome – in critically ill children. Children with septic shock, in general, present with low free and total T3 and T4 and preserved TSH levels [22–24]. Increased rT3 and decreased T3/rT3 ratio have also been reported. Low levels of both T3 and T4 are associated mortality and severity of illness in these children [17, 22–26]. Interestingly, a lower rT3 and a higher T3/rT3 ratio was associated with mortality in one study involving children with meningococcal sepsis [17]. This paradoxical finding may be explained by a fulminant onset of disease in meningococcal sepsis nonsurvivors, with consequent lack of time and peripheral tissue perfusion for adequate thyroid hormone metabolism and increase in rT3 level. Despite evidence from laboratory studies suggesting beneficial effects of thyroid hormone supplementation in models of sepsis, this therapy has never been adequately evaluated in septic children.

Thyroid hormones have been extensively studied in children undergoing surgical correction of congenital heart disease. Classic euthyroid sick syndrome is observed in most children shortly after cardiac surgery. The severity and duration of drop in serum T3 level in these children correlates with greater therapeutic requirement, prolonged duration of mechanical ventilation, and PICU stay [27]. In these children, in addition to the stress mechanism of euthyroid sick syndrome, thyroid function may also be affected by ultrafiltration [28], selenium deficiency [29], and drugs used for cardiovascular support. The amount of free triiodothyronine filtrated during cardiopulmonary bypass has been shown to influence postoperative recovery [28]. Cardiopulmonary bypass also induces a decreased in serum selenium level. Since the deiodinase that converts T4 to T3 is a selenium-dependent enzyme, selenium deficiency can impair T4 conversion to T3 and further decrease T3 levels in children after cardiac surgery.

A number of drugs used in intensive care can also affect thyroid function in children. Amiodarone, an antiarrhythmic agent frequently used in PICUs, is a competitive inhibitor of the deiodinase enzyme, with a high iodine content, and a similar structure to thyroid hormones [4]. It's use is associated with a high incidence of thyroid dysfunction – mainly hypothyroidism, but hyperthyroidism is also reported [30, 31]. The incidence and severity of side effects seem to be

correlated with age and the dose used, with younger patients exposed to higher doses at increased risk [4]. Iodine in iodinated topical antiseptics can be significantly absorbed in children and neonates. In response to excessive iodine, the thyroid transiently inhibits the organification of iodine, preventing excessive thyroid hormone synthesis (called the Wolff-Chaikoff effect). In some individuals, however, this effects persists after the excess of iodine is removed and transient (2–3 weeks) hypothyroidism develop [32, 33]. Last, dopamine directly inhibits anterior pituitary function through inhibitory dopamine receptors, resulting in diminished TSH release. In newborns, dopamine suppresses prolactin, growth hormone, and thyrotropin secretion consistently, and in children, dopamine suppressed prolactin and thyrotropin secretion, and a rebound release starts 20 min after dopamine withdrawal [4, 34]. Therefore, dopamine infusion can induce or aggravate partial thyroid hormone suppression in critically ill children and its prolonged use should be avoided.

Evaluation of Thyroid Function in the PICU

During critical illness interpretation of thyroid function test in a child is difficult and routine testing should not be performed. Since treatment of euthyroid sick syndrome remains controversial, the goal of thyroid function tests in PICU should mainly be the identification of previously unrecognized thyroid dysfunction that would require therapeutic intervention. Suspicion of thyroid dysfunction should be based on past history or clinical evaluation (such as hypothyroidism in children with trisomy 21 with unstable hemodynamics). In critically ill children with suspected thyroid disease, measurement of TSH alone is inadequate. Low TSH level may represent either hyperthyroidism or euthyroid suck syndrome. Hyperthyroidism should induce high (or high-normal) serum T3 and free T4 levels, while these hormone levels are low (or low-normal) in nonthyroidal illness [14]. Differentiation between true hypothyroidism and euthyroid sick syndrome is complex. True hypothyroidism should manifest with high TSH levels, but this can be masked by a number of PICU confounding factors such as malnutrition, dopamine infusion, or use of corticosteroids. Measurements of rT3 could be helpful in differentiating eythyroid sick syndrome – that present with high rT3 – from secondary hypothyroidism – low TSH and low rT3. However, studies in adults showed that rT3 does not accurately distinguish these two entities [35].

Thyroid Hormone Treatment in PICU

Critically ill children with true hypothyroidism should be treated. Treatment of secondary hypothyroidism due other to intensive care therapies (e.g., dopamine, amiodarone) has not been formally evaluated, but it is a rational approach to treat these children if hypothyroidism symptoms are present or if hypothyroidism may be contributing to the critical illness. Thyroid hormone treatment of euthyroid sick syndrome remains controversial and routine treatment is not recommended.

Sepsis

The current American College of Critical Care Medicine Clinical guidelines for hemodynamic support of neonates and children with septic shock recommend thyroid replacement with T3 in children and neonates with thyroid insufficiency [36]. Since the diagnosis of thyroid insufficiency is difficult during critical illness, T3 therapy in septic shock is reserved for children with known thyroid dysfunction, for children at higher risk of hypothyroidism (e.g., children with Trisomy 21 and children with central nervous system pathology), or as a rescue therapy in refractory septic shock. Although no formal recommendation exists, use of T3 as an intravenous infusion at a dose of 0.05–0.15 μg/kg/h in these conditions it is a rational approach.

Cardiac Surgery

The use of thyroid hormone supplementation in infants undergoing cardiac surgery was reported as a possible therapeutic option by a number of small studies [37–39]. This is in keeping with data from critically ill adults that underwent elective coronary bypass where administration of T3 improved post-operative cardiac function (but did not improve mortality) [40, 41]. In children, this intervention would be of most clinical benefit in children with low cardiac output via an enhancement in left ventricular performance, a significant decrease in systemic vascular resistance, and improved myocardial oxygen consumption. Recently, clinical trials have evaluated the possible benefit of T3 supplementation in children following cardiac surgery [3, 42–44]. These studies were heterogeneous in relation to the population studied and dose used in the T3 treatment. However, all studies showed that T3 supplementation in the post-operative period is safe (at short term) and that it can improve cardiovascular performance of children after cardiac surgery. They also showed that T3 supplementation improves clinical outcome scores, but showed no effect on harder clinical outcomes (e.g., duration of ventilation, PICU stay or mortality). Only one of these studies, however, was adequately powered for a clinical outcome (i.e., time to extubation). This study found that T3 had no effect on the overall time to extubation of the population studied, but did show a significant reduction in the time to extubation of children younger than 5 months of age [3]. Instead of the more studied intravenous infusion (0.05–0.15 μg/kg/h), this study used T3 as an intravenous bolus of 0.4 μg/kg immediately before CPB, 0.4 μg/kg

on the release of the aortic cross-clamp, and 0.2 μg/kg at intervals of 3, 6, and 9 h after cross-clamp release. Despite the encouraging results of these initial trials, further studies are needed to establish T3 supplementation as a routine therapy in critically ill children.

The Growth Hormone Axis in Critical Illness

Growth Hormone Physiology

Somatotropin, or growth hormone (GH), is produced in the pituitary gland and released in a pulsatile fashion. It affects growth and metabolism through stimulation of insulin-like growth factor (IGF)-1 production. GH release is controlled by the hypothalamus through two hormones: GH-releasing hormone (GHRH), which stimulates the production and release of GH, and somatostatin, which inhibits GH release [45]. During the day, GH level varies with exercise, stress, fasting, and sleep.

The pulsatile pattern of GH release is important for its metabolic effects [46, 47]. In healthy individuals, GH levels alternate between high peaks and extremely low troughs. The pulsatile property of GH is not completely understood, but GHRH, somatostatin, and ghrelin are the main factors affecting GH secretion. Ghrelin is a 28-aminoacid peptide that comes from peripheral tissues (such as the stomach) and the hypothalamic arcuate nucleus [48]. It binds to a specific G-protein coupled receptor (GHS-R). Synthetic stimulation of GHS-R leads to potent GH release. GH release is also influenced by other factors such as dopamine and IGFs [4].

IGFs are peptides that resemble the structure of insulin. They have a variety of functions including stimulating mitogenesis, promoting differentiation, inhibiting apoptosis and eliciting insulin-like effects on substrate uptake [49]. GH release stimulates IGF-1 synthesis in peripheral tissues, which then acts as a mediator of body growth [50, 51]. IGFs are associated with binding proteins (IGFBP). In the tissues, the binary complex IGF-IGFBP is predominant, while in the circulation a ternary complex of IGF-IGF with an acid-labile subunit (ALS) is most frequently found [52, 53]. In general, IGFBPs inhibit the effect of IGF and regulate IGF signalling pathways in contrasting ways [54–56].

Growth Hormone During Critical Illness

In the early phase of critical illness, GH level is elevated, with an alteration in pulsatility. The frequency of GH peaks increase, as well as the level of GH between peaks [57]. Despite the high level of GH, circulating IGF-1 level is low, with IGFBP also altered. Interestingly, low IGF-I levels are a predictive marker of mortality in critical illness, with intensive care non-survivors having significantly lower IGF-I levels than survivors, and IGF-I levels correlating inversely with severity of illness [58, 59]. Also, in critically ill children, failure to recover somatotropic function (i.e., failure to increase IGF-1 levels) is strongly associated with mortality [60].

IGFBP-3 and ALS levels are decreased, and these changes are preceded by a fall in serum GH binding protein (GHBP). This pattern of findings can be explained by reduced GHS-R expression and inhibited GH cellular pathways (Fig. 11.2) [61]. Serum concentration of GH-independent IGFBPs (IGFBP-2, IGFBP-4, and IGFBP-6) are, however, elevated

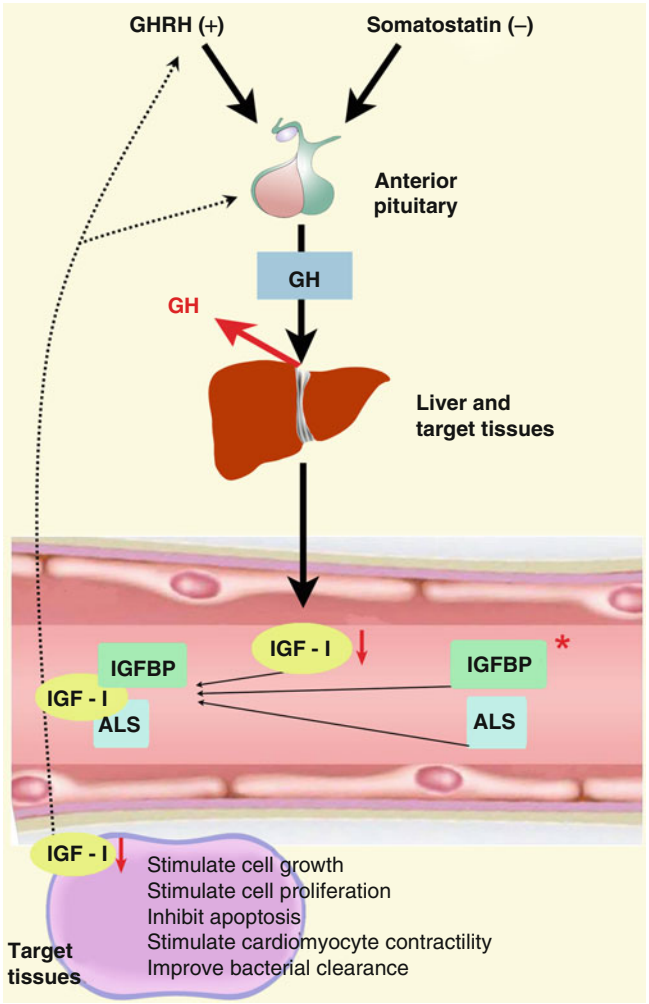

Fig. 11.2 The growth hormone axis – simplified diagram of growth hormone axis activity. During critical illness (*RED*), growth hormone (*GH*) resistance yields high serum GH levels and low circulating insulin like growth factor (*IGF*)-I. IGF binding proteins (*IGFBP*) (*) and acid labile subunit (*ALS*) are in general decreased, but GH-independent IGFBPs (*IGFBP1* and *2*) increase significantly in response to critical illness. These changes are evident in target tissues with reduced GH/IGF induced activity. Low IGF-I also decrease feedback inhibition to the hypothalamus and anterior pituitary, further increasing serum GH levels

[62]. This change suggests redistribution of IGFs from GH-dependent ternary complexes (with IGFBP-3 and IGFBP-5) to binary complexes with these binding proteins, which may facilitate transport to the tissues. Taken together, these changes have been interpreted as the acquired peripheral GH resistance that is found during the initial response to stress. It is believed that these changes could be due to the influence of inflammatory cytokines, such as tumor necrosis factor (TNF), IL-1, and IL-6. Reduced GHS-R expression, post-receptor changes, and the concomitant reduction in IGF-1 level are all believed to be primarily mediated by cytokines. Subsequently an increase in GH occurs, through reduced negative feedback inhibition. The result of these changes is an increment in lipolysis, insulin-antagonism and immune stimulation [63–65].

In the later phase of critical illness, often 7–10 days into the illness, important changes in the somatotropic axis occur. Although GH continues to be released in a high frequency pulsatile fashion during this phase, the intensity of each pulse is smaller [66]. The GH level between pulses is also much lower than in the early phase of illness. Hence, mean GH serum level can be similar to that found when healthy, but it is substantially lower than during acute stress. As pulsatile GH release is reduced, levels of IGF-1, IGFBP-3, and ALS also decrease [63]. During the chronic phase of illness, serum level of GHBP is elevated and in keeping with the recovery of GH responsiveness. The very low serum levels of IGF-1 and ALS are closely related to biochemical markers of impaired anabolism during prolonged critical illness, such as low serum osteocalcin and leptin levels.

During prolonged critical illness, GH resistance is associated with persistent catabolism and muscle wasting. Because of its endogenous ability to induce anabolism, GH therapy has been vastly studied in critically ill patients. Use of GH in the peri-operative period improves nitrogen balance, increases liver protein synthesis, and decreases postoperative fatigue. It has also been shown to increase the rate of protein synthesis in sepsis and trauma patients and the rate of healing in burn patients [65, 67, 68]. However, despite promising results from small trials, GH therapy was associated with increased mortality in a large trial of critically ill adults [69]. In this study, patients treated with GH had nearly double the mortality than control patients (relative risk 1.9- to 2.4). Deaths were related to multiple organ dysfunction syndrome, shock, or uncontrolled infection. Patients receiving GH also had prolonged duration of mechanical ventilation and longer intensive care stay [69]. GH therapy in critically illness was studied with the assumption that high GH levels could overcome GH resistance and increase IGF-1 levels. This study showed that GH therapy increased IGF-1 concentrations, but this increment was mainly present in survivors. Therefore, the increased mortality of patients receiving GH therapy is thought to be secondary to deleterious effects of excessively high GH levels without the benefits of increased IGF-1 levels. Currently the is no evidence to support use of GH therapy in critically ill patients and the Growth Hormone Research Society has released a statement recommending against the use of this therapy in the acute phase of critical illness [70].

Alternative methods for GH axis modulation in critical illness include insulin therapy and use of recombinant IGF-I. Since insulin therapy improves GH resistance in patients with diabetes, we evaluated the efficacy of this therapy in reversing GH resistance in critically ill children [unpublished data]. Despite use of high dose insulin and beneficial effects on metabolic and inflammatory profiles, insulin therapy was not able to increase IGF-1 levels of critically ill children. Studies in adults have shown similar findings [71].

So far only one study has been shown to safely improve IGF-1 levels in critically ill patients [72]. In this study, use of recombinant IGF-1 (rhIGF-1) not only increased IGF-1 levels but also reduced the elevated GH levels and increased levels of the carrier protein IGF binding protein-3 (IGFBP-3). This phase I trial showed that use of rhIGF-1 is safe in critically ill patients, but it did not assess efficacy of this therapy.

Modulation of the GH axis in critical illness is complex and has not been extensively evaluated. GH axis modulation has great potential for improving critical care outcomes, but caution should be exercised when considering further interventions. Lessons from the GH trial need to be learned and more careful approaches should be evaluated in pragmatic trials. Better understanding of the mechanisms involved in GH resistance in critical illness, and the dynamic changes of this axis observed during intensive care may provide insights for future interventions.

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Part III

The Renal System in Critical Illness and Injury

James D. Fortenberry

Applied Renal Physiology in the PICU

12

Ravi S. Samraj and Rajit K. Basu

Abstract

The kidneys are central to numerous homeostatic mechanisms in the body. Responsible for solute and fluid handling, removal of waste products of nutrients, metabolism, detoxification, and excretion of drugs and metabolites, and regulation of vascular tone, the kidneys also elaborate many metabolites that act in local and distant fashion. The kidneys receive a high proportion of cardiac output per minute and have a high rate of oxygen consumption, evidence of the intensity of regulation that occurs in perpetuity. In this chapter, we will discuss renal physiology using the structure as background, function, and response to illness. Both hemodynamics and filtration will be described in detail. Relevant examples of how commonly encountered disease states affect kidney function will be discussed. Finally, the emerging paradigm of crosstalk between the kidneys and other vital organs will be broached. Critical illness carries dramatic consequence on kidney function and understanding the elements of how the kidneys regulate their own mechanics, and what happens when these compensatory mechanisms are overwhelmed, is essential to practitioners in the pediatric intensive care unit.

Keywords

Renal hemodynamics • Filtration • Tubular reabsorption • Tubuloglomerular feedback • Endocrine kidney • Kidney crosstalk

Abbreviations

ACE-I	Angiotensin converting enzyme inh
ADH	Anti-diuretic hormone
AE1	Anion exchanger
ANG-II	Angiotensin 2
ANP	Atrial natriuretic peptide
AQP	Aquaporin
ARB	Angiotensin receptor blockers
AVP	Arginine vasopressin
CA	Carbonic anhydrase
Ca^{2+}	Calcium
Ca^{2+}-ATPase	Calcium ATPase
CD	Collecting duct
Cl^-	Chloride
DCT	Distal convoluted tubule
ENaC	Epithelial sodium channel
GBM	Glomerular basement membrane
GCP	Glomerular capillary perfusion
GFR	Glomerular filtration rate
GLUT	Glucose transporter
H^+-ATPase	Hydrogen ATPase
HCO_3^-	Bicarbonate

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HIF-1	Hypoxia inducible factor
JGA	Juxtaglomerular apparatus
K^+	Potassium
LH	Loop of henle
MCD	Medullary collecting duct
MR	Myogenic reflex
Na^+	Sodium
Na^+-K^+-ATPase	Sodium-potassium ATPase
NaCl	Sodium chloride
NH_3	Ammonia
NHE3	Sodium hydrogen exchanger
NO	Nitric oxide
NPHS1	Nephrin
NPHS2	Podocin
PLCE	Phospholipase C epsilon
PO_4^{3-}	Phosphate
PT	Proximal tubule
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone
RBF	Renal blood flow
RPP	Renal perfusion pressure
RvO_2	Oxygen consumption
RVR	Renal vascular resistance
SGLT	Sodium-glucose transporters
SNGFR	Single nephron GFR
SSAKI	Severe sepsis associated AKI
TAL	Thick ascending limb
TAL	Thick ascending loop of henle
TGR	Tubuloglomerular feedback
TPRC6	Transient receptor potential

Introduction

The kidneys function in myriad ways to maintain homeostasis in the body. The multi-faceted roles played by these organs include, but are not limited to: water and solute balance; removal of waste products of nutrients; metabolism, detoxification, and excretion of drugs and metabolites; production of hormones and paracrine peptide mediators; and regulation of vasomotor tone and blood pressure. Though less than 0.5 % of body mass by volume, the kidneys are highly perfused and receive 20–25 % of the total cardiac output. Due to the work detailed above, oxygen consumption by the kidney (RVO_2) is high. Given the precise machinery required for such balance, the kidneys are also highly sensitive to injury – both from intrinsic and extrinsic disease. The goals of this chapter are to describe renal physiology using the following framework: general structure, function, and pathologic relevance. Kidney vascular structure and blood flow will be detailed, paying particular attention to the regulation of renal hemodynamics. The principle of glomerular filtration rate (GFR) will be described and the key drivers affecting GFR, using a compartmentalized, tubular model of post-glomerular nephron function, will be highlighted. Finally, the emerging role of the endocrine kidney will be described. Proper understanding of renal physiology and the determinants of kidney function are crucial to understanding and guiding therapy for disease states that injure the kidney.

Embryology and Development

While nephrogenesis is complete by 34–36 weeks of gestation (approximately one million nephrons per kidney), tubular maturation continues into postnatal life (reaching adult levels by age 2). The kidneys develop from the urogenital ridge, situated in the posterior part of the abdomen in the developing fetus. Three stages of development lead to the formation of the kidneys: the initial two (pronephros and mesonephros) do not directly contribute to the development of the kidneys though are involved in the signaling pathways for the development of the third stage (metanephros). Signals from the metanephric mesenchyme, around the fifth week of gestation, initiate the dichotomous branching of the ureteric bud, leading to the formation of the renal collecting system and ultimately individual nephron units. Maturation of each nephron requires proper development of the tubular cell phenotype which requires the appropriate mesenchymal-epithelial transition of developing kidney cells. This transition is responsible for the appropriate formation of cell polarity in the tubule, from the tubular lumen (the *apical* surface) to the basolateral membrane (the peritubular capillary network). Altered or reversed cellular conversion (epithelial to mesenchymal transition) is implicated in multiple forms of renal fibrosis [1]. The kidneys are divided into outer cortical and inner medullary regions. Within the medulla, renal pyramids dive into the renal pelvis, the vascular hub of the kidney, with finger-like projections (papillae). Urine formation occurs within the pelvis, is collected by calyces (minor into major), and drained by the ureters (Fig. 12.1). Tubules of individual nephrons originate in the Bowman's capsule, which enclose glomeruli. The glomerular capillary walls are made of endothelia, a glomerular basement membrane (GBM), and an outer layer of epithelial foot processes (podocytes). The tubules project into the renal papillae from the Bowman's capsule and, after forming loops of Henle and distal convoluted tubules, return to the periglomerular space known as the macula densa. The macula densa, a vital connection between the tubular lumen and the vascular tree composed of mesangial cells and juxtaglomerular cells (JGA), highly influences both urine formation and vascular tone (Fig. 12.1).

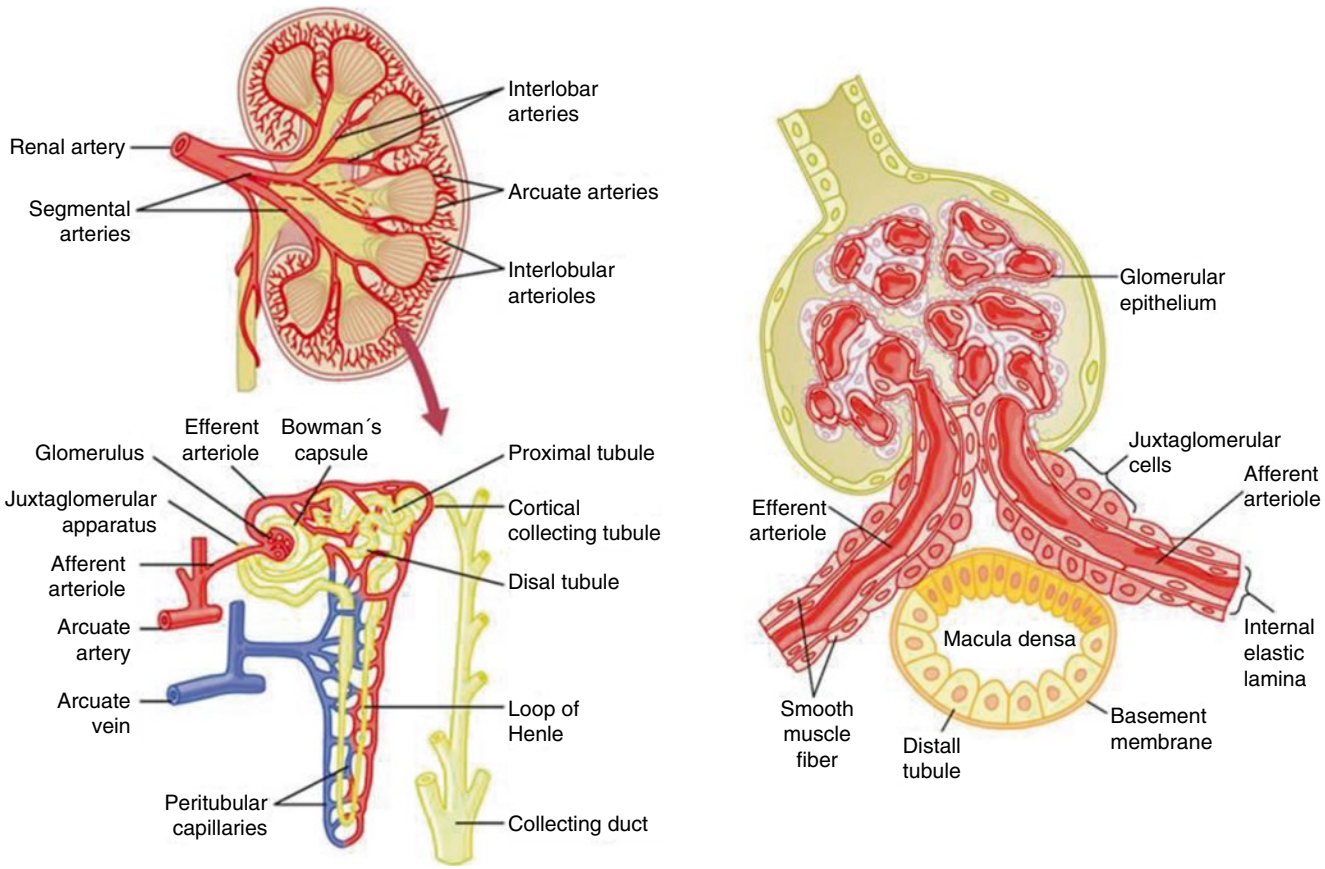

Fig. 12.1 The structure of the nephron and the macula densa (Reprinted from Guyton and Hall [151]. With permission from Elsevier)

Renal Hemodynamics

The kidneys are primarily perfused by renal arteries which arise from the descending aorta, but accessory renal arteries may contribute to the major circulation. The microvasculature of the kidney is supplied by the arcuate artery and interlobular arteries that branch towards the cortex. The afferent arterioles supply the glomeruli while the tubules are supplied by the vasa rectae which arise from the efferent arterioles (Fig. 12.1) [2, 3]. A steep oxygen gradient exists in the kidney from the outer cortex to the inner medulla which underscores the fragility of the glomerular capillary bed, particularly in response to ischemia [4, 5].

Renal Blood Flow

Renal blood flow (RBF) is supplied by the renal arteries arising from the abdominal aorta. The renal arteries separate into anterior and posterior branches, which further divide into four segmental arteries [6], giving rise to the interlobar and arcuate arteries. Finally, the smaller branches of the arcuate arteries give rise to the afferent arterioles which feed individual glomeruli. The decreasing flow gradient of RBF from renal artery to afferent arteriole of the glomeruli is further steepened in the distribution of the vasa recta (the peritubular capillary network for each nephron). Changes in RBF upstream from glomeruli decrease this gradient, amplifying detrimental effects on glomerular perfusion. The afferent arterioles undergo dramatic changes as they enter the glomerulus. Upon entry, the arterioles branch and acquire features of the glomerular capillaries including a fenestrated epithelium, a basement membrane, and epithelial foot processes. The transition from the glomerular capillaries to efferent arterioles is less dramatic and changes are seen progressively. Post glomerular capillary blood drains through the efferent arteriole to the renal vein via a similar pattern, though retrograde, to that of the arterial system. An important difference between arterial and venous circulations is that venous vessels anastomose at various levels. A single efferent arteriole can supply multiple vasa rectae. The venous drainage of the kidney occurs by joining of the deep medullary veins and the arcuate veins with the interlobular veins into the main renal vein.

The blood supply for the kidney is dependent on two capillary resistance beds that operate in series. This unique configuration allows for separate and independent regulation of filtration. Filtration, estimated by the glomerular filtration rate (GFR) is driven by renal perfusion pressure (RPP), directly proportional to renal blood flow (RBF) and renal vascular resistance (RVR). As a function of changing RVR, RBF continuously changes from intra-uterine life [7]; fetal to neonatal changes in vascular supply and tone are significant. The percentage of cardiac output received by the renal bed varies from gestational age to post-birth maturation: 3–7 % for the 10- to 20-week human fetus, 16 % for the term neonate, and 20–30 % in children and adults [8, 9]. At birth, RVR decreases and cardiac output increases, explaining the increase in RBF in the post-fetal circulation. Continual new nephron formation after birth continues to decrease the RVR. Decreases in hormonal vasoconstrictors (drop in angiotensin II) and increases in vasodilators (prostaglandins, kinins, and nitric oxide) further decrease RVR and augment renal blood flow, and thus filtration [10–12]. The RPP is determined by the hydrostatic pressure within the glomerulus, the oncotic pressure, and the tubular oncotic pressure. The perfusion of each glomerulus (glomerular capillary perfusion – GCP) is directly proportional to the overall RPP. Understanding how specific changes in both afferent and efferent arteriolar resistance affect GCP is vital to understanding renal hemodynamics. Selective increases in the afferent arteriolar resistance decrease RBF and therefore GFR. Conversely, decreases in afferent arteriolar tone will increase RBF and also GFR. However, increased efferent arteriolar tone will increase RBF by increasing the GCP which in turn increases GFR. Isolated effects on either end of the arteriolar bed are generally rare. The balance of both 'ends' being affected determines the net effect on glomerular hemodynamics, as we describe next.

Regulation of Afferent and Efferent Arterioles

Blood flow auto-regulation in the kidney is highly developed and tightly regulated, maintaining a constant RPP despite wide variations of arterial pressure. Precise auto-regulation is critical for maintaining solute and fluid homeostasis [13]. As described earlier, the complex channeling of blood flow from the renal artery to the glomerular capillary bed is associated with a decline in flow which leads to a decline in hydrostatic pressure [14]. Additionally, a significant change in pre-glomerular pressure occurs along the afferent arteriole [15, 16] while most of the post glomerular pressure drop occurs in the efferent arteriole.

Numerous endogenous and exogenous mediators of arteriolar tone may be directly responsible for changes in GFR; net effects on GFR depend on their relative contributions to both afferent and efferent glomerular arteriolar tone (Table 12.1). **Angiotensin II** (ANG-II) is a potent vasoconstrictor which has effects on both afferent and efferent arteriolar tone [17]. The effects of ANG-II are mediated by binding at two distinct receptors, AT-1 (vasoconstriction) and AT-2 (vasodilation) [18]. Though controversial, *in vivo* efferent arteriolar sensitivity has been demonstrated to be greater than afferent arteriolar responsivity [19]. Though the measured change on each arteriolar 'portal' may be similar, the smaller diameter of the efferent arterioles results in a greater net change in resistance due to Poiseuille's law [20]. **Endothelin**, a potent vasoconstrictor, through binding to ET_A and ET_B receptors, leads to decreased GFR, from greater vasoconstrictive effects on afferent arteriolar tone (ET_B) than efferent arteriolar tone [21]. **Atrial natriuretic peptide** (ANP) consistently increases GFR by causing afferent arteriolar vasodilation and efferent arteriolar vasoconstriction [22]. ANP also demonstrates effects on the neural auto-regulatory system. **Arginine vasopressin** (AVP) has selective efferent vasoconstrictive effects which may be outside of modulating arteriolar tone [23]. Paracrine acting agents also modulate RPP by modulating RVR. **Nitric oxide** (NO), a potent vasodilator derived from inducible or endogenous nitric oxide synthase, leads to greater vasodilation of the afferent than efferent arteriole. Animal studies suggest that NO attenuates the vasoconstriction due to ANG-II or norepinephrine [24]. Similarly, prostaglandins attenuate the effects of vasoconstrictors [25]. Differential innervation of the afferent and efferent renal arterioles (greater in afferent) implicates norepinephrine and sympathetic activation in the vasoconstrictive auto-regulatory process, decreasing GFR

Table 12.1 Effects on glomerular vascular tone of relevant hormones

Compound	Afferent arteriole	Efferent arteriole	Net GFR effect
Angiotensin II	Constriction +	Constriction +++	Increased
Norepinephrine	Constriction +	Constriction +	Increased
Endothelin-1	Constriction +++	Constriction +	Decreased
Atrial natriuretic peptide	Dilation	Constriction	Increased
Nitric oxide	Dilation +++	Dilation +	Increased
Adenosine triphosphate	Constriction	No effect	Decreased
Ca^{2+} antagonist	Dilation +++	Dilation +	Increased
Angiotensin blocker	Constriction +	Constriction +++	Increased
Dopamine	Dilation +	Dilation +	Increased

Listed above are the predominant effects on afferent and efferent arteriolar tone by the principal governing hormones in the kidney. It should be noted that due to the smaller caliber of the efferent arteriole, constrictive effects will have a larger net effect on glomerular capillary pressure (Poiseuille's law). Data represent consensus views

[19]. Finally, several iatrogenic modulators of arteriolar tone are well established. Calcium antagonists preferentially dilate the afferent arteriole increasing RPP and GFR [26]. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) block the effect of ANG-II and increase RBF but can ultimately decrease RPP due to greater effects on efferent dilation than afferent dilation [27]. Dopamine in animal study increases renal perfusion by afferent arteriolar dilation but has not been demonstrated to be efficacious in improving outcomes in patients with acute kidney injury [28].

Maintenance and Modulation of Renal Hemodynamics in Disease States

Modulation of RPP occurs via three mechanisms largely coordinated by the juxtaglomerular apparatus (JGA): myogenic reflex, tubuloglomerular feedback, and neural regulation. Myogenic reflex (MR) elicits smooth muscle constriction in response to vascular stretch, such as increased hydrostatic intraluminal pressure from changes in RBF [29]. Increases in fluid or solute delivery to the macula densa will lead to afferent arteriolar vasoconstriction – deemed tubuloglomerular feedback (TGR) [30]. Neural regulation depends on the rich innervation of the arteriolar tree, the mesangium, and the macula densa [31]; efferent sympathetic adrenergic stimulation leads to increased afferent arteriolar vasoconstriction. Due to *in vivo* autoregulation through these three mechanisms, GFR does not significantly change despite large changes in systemic blood pressure. Outside the autoregulatory range, however, GFR changes directly with change in RPP.

Critical illness can lead to deleterious consequences on the precise machinery in place responsible for auto-regulation of RBF and GFR. Shock, a primary imbalance of supply-demand of energetics, has profound consequence on renal function. Reversible hypoperfusion of the kidneys is commonly manifest by the state of pre-renal azotemia. Renal hypoperfusion results in the release of various mediators which act together to maintain blood flow to the glomerulus as well as a constant capillary hydrostatic pressure. Prostaglandin I_2 and NO cause vasodilation of the preglomerular capillaries; ANG-II predominantly causes vasoconstriction of the post-glomerular capillaries [32, 33]. The primary defense mechanism against effective volume depletion is via tubular reabsorption of fluid and solute mediated by increased adrenergic activity and the renin-angiotensin aldosterone system (RAAS). Failure of this primary mechanism leads to a reduction in GFR which triggers secondary compensation via renal sympathetic adrenergy, RAAS, and antidiuretic hormone (ADH) [34]. As mentioned earlier, the effects of ANG-II are site specific, but they also vary based on intravascular volume status. In moderate volume depletion, ANG-II causes preferential vasoconstriction of the efferent arterioles and increases filtration fraction. With more severe volume depletion, ANG-II induces constriction of both afferent and efferent arterioles, reducing GCP and filtration fraction. Additionally, renal adrenergic stimulation mediates vasoconstriction of the renal arterioles in conjunction with ANG-II.

In shock secondary to sepsis, renal blood flow is dysregulated in alternate fashion. Anecdotally, GCP was assumed to decrease due to decreased effective RBF (secondary to global capillary leak) with concomitant afferent vasoconstriction. However, ovine models of sepsis demonstrate increased RBF with decreased GCP resulting from decreased efferent arteriolar tone (thereby decreasing RVR). Additionally, the effects of sepsis on RPP likely are dependent on glomerular endothelial apoptosis and inflammation [35]. Production of ANG-II and endothelin, and their concomitant abilities to maintain RPP and GFR, are altered during sepsis [36].

Pharmacologic agents commonly used in the ICU settings can lead to deranged renal hemodynamics. Non-steroidal anti-inflammatory drugs, through inhibition of cyclooxygenases decrease renal blood flow and GFR by impeding afferent arteriolar vasodilation. This can be especially dangerous in states of renal hypoperfusion (e.g., sodium depletion, diuretic use, hypotension, and sodium-avid states, such as cirrhosis, nephrotic syndrome, and congestive heart failure) [37]. Use of medications which alter ANG-II levels can have obvious effects on RPP and GFR; ACE-Is or ARBs can induce acute renal failure in patients with renal artery stenosis (patients who require a given arteriolar tone to maintain RPP) [38].

Finally, while the effects of kidney ischemia on RBF seem obvious, the lack of pulsatile arterial flow in some patients requiring circulatory assist devices has controversial effects on RBF. The available evidence suggests deleterious effects of non-pulsatile blood flow on the preservation of GFR [39, 40].

Filtration

Glomerulus

The Glomerular Tuft and Cellular Elements

As a meshwork of connective tissue and highly sensitive cellular elements responsible for maintaining a patent barrier to filtration and hydrostatic pressure, the glomeruli are the main determinants of kidney function, and fluid homeostasis. Three cell types comprise a functional glomerulus: mesangial cells, endothelial cells, and visceral epithelial cells (podocytes). Aside from the cellular components, extracellular matrix proteins enmesh within the glomerulus and

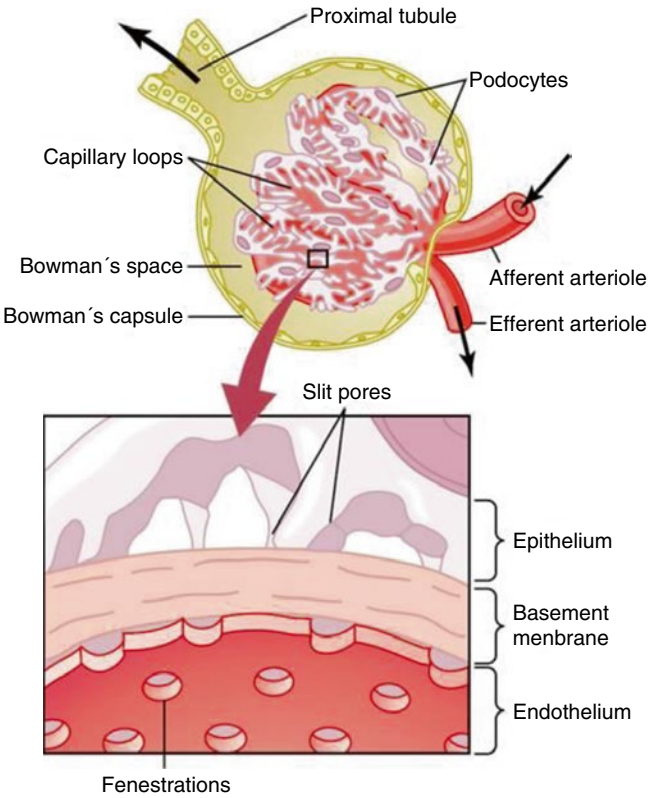

Fig. 12.2 Glomerular structure demonstrates slit-like invaginations in the epithelium, the glomerular basement membrane, and a fenestrated endothelium (Reprinted from Guyton and Hall [152]. With permission from Elsevier)

comprise the glomerular basement membrane. Filtration is regulated by a trilaminar barrier consisting of a fenestrated endothelium, the glomerular basement membrane (GBM), and interdigitating foot processes (Fig. 12.2). The primary determinant of GFR is the balance between glomerular capillary hydrostatic pressure (P_{GC}), the intra-glomerular oncotic pressure (π_{GC}), and the glomerular capillary ultrafiltration coefficient (K_f). Although the hydrostatic and oncotic pressure of Bowman's space factors into the derivation of GFR (or single nephron GFR – SNGFR), the approximate value can be obtained by:

$$SNGFR = K_f \times \left(P_{GC} - \pi_{GC}\right)$$

Interestingly, the glomerular capillary walls do not contain smooth muscle cells and are thus not contractile. They do, however, react to neighboring mesangial cells. **Mesangial cells** contain contractile elements (actin, myosin, α-actinin) that comprise the parenchymal cytoskeleton of glomeruli [41], surround glomerular capillaries, and are contiguous to the fenestrated epithelium. The contact points between the cells and these structures allow for regulation of contraction and relaxation. Thus, in response to external stimuli, mesangial cells can regulate capillary surface area, glomerular capillary blood flow, and influence GFR.

The **endothelial cells** elaborate a protein matrix, the glycocalyx, composed of proteoglycans, anionic amino acids, glycosaminoglycans, and glycoproteins [42]. The GBM lies between the endothelial cell layer and the external layer of the glomerular capillary. Composed of type IV collagen, laminin, and proteoglycans [43], the GBM is a thick latticework that is an intermediate filtration barrier in the glomerulus and provides charge and size selective restriction to glomerular filtration [44–46].

The glomerular visceral epithelial cells (podocytes) are the primary cell determining filtration in the kidney, responsible for ~40 % of the hydraulic resistance of the filtration barrier [47]. Podocytes are polarized epithelial cells derived from the mesenchymal cells and share both epithelial and mesenchymal properties; this allows them to cover capillaries, act as interdigitating bodies (through finger shaped extensions called pedicles), and harbor contractile properties. The podocyte pedicles are anchored to the GBM by means of α3/β1-integrins and α/β-dystroglycans [48, 49]. Foot process contractility allows for adaptation to distensions which occur during glomerular filtration. The foot processes have three important domains: apical (tubular luminal face), basal (glomerular capillary face), and lateral (between processes). The organization and complex series of cytoskeletal elements in the podocyte layer of the glomerular capillary have selective responsivity to external stimuli and to each other. Several cytoskeletal proteins are vital to proper pedicle function: synaptopodin [50, 51], alpha actinin, podocalyxin, and Magi 1, a member of the MAGUK (membrane associated guanylate-kinase family) [52]. Podocalyxin, a major membrane protein of the glomerular epithelium, functions as an anti-adhesin that maintains an open filtration pathway between neighboring foot processes in the glomerular epithelium by charge repulsion [53]. Nephrin is important part of the glomerular filter and inactivation of nephrin gene leads to absence of slit diaphragm [54]. Recently a new component of the filtration barrier has been described, referred to as the sub-podocyte space (SPS). This space covers 60 % of the filtration barrier and increases the glomerular flow resistance by 1.3–26 fold [55]. The three layers of the GBM act as resistances in series; hence the overall permeability of the glomerular tuft is the sum of relative hydraulic permeabilities of the endothelium, GBM, and the podocyte epithelium. The barrier function of the glomerular capillaries is influenced by the size, shape, and charge of the macromolecules. The sieving coefficient, the index of GBM permeability to solute, quantifies the filtrate to plasma concentration ratio at a particular point along a capillary. Local sieving coefficients will vary along the length of the glomerulus because of the changes to P_c and π_c from afferent to efferent end (as hydrostatic pressure decreases from increased filtrated fluid) [56].

Clearance of larger proteins is significantly less than that of smaller molecules indicating the sieving coefficient is inversely related to the radius of macromolecules. Additionally, there is a greater restriction of anionic molecules compared to neutral or cationic molecules illustrating barrier charge selectivity. The charge selectivity of the membrane is secondary to the highly negatively charged endothelial glycocalyx [57]. Finally, for same size and charge density molecules, discrepant protein sieving coefficients suggest barrier shape selectivity [58].

Glomerular Filtration and Tubuloglomerular Feedback

Glomerular filtrate rate (GFR) is the best accepted index of kidney health. Nephron development, and thus GFR steadily increases from birth until 2 years of age (~120 ml/min/m^2) and then declines with advanced age. The GFR is estimated in the adult population by numerous formulae, including the Cockcroft-Gault formulation and the Modification of Diet in Renal Disease Equation [59]. The modified Schwartz formula for calculating estimated GFR in children is:

$$GFR \sim 0.413 * h / S_{Cr}$$

where 'h' = height in centimeters and S_{Cr} = serum creatinine [60]. For the precise estimation of GFR of individual solutes, however, it is necessary to use clearance equations; the clearance of a solute is used as a reference for the function of the kidney glomeruli. Clearance is determined by:

$$C_x = \left(U_x / P_x\right) * V$$

where C_x = clearance of solute X, U_x = urine concentration of X, P_x = plasma concentration of X, and V = urine flow rate. Clearance rate "normals" for age were created using markers such as inulin and creatinine. Because clearance is dependent on size and composition of the host, however, the use of these proxies as estimations of GFR has received tremendous scrutiny. Ideal exogenous markers of clearance can have 5–20 % errors in daily measurements while creatinine [61], the 'accepted' marker of kidney function, varies due to tubular secretion, altered extra-renal elimination, and variable generation rates [62]. This is especially notable in children, given discrepant ratios of age to body mass, muscular development, and total body water percentage which alters the steady states of creatinine. Though promising, use of newer indicators of filtration such as Cystatin C are still in their infancy and have not gained widespread use [63]. As mentioned earlier, TGR plays a critical role in the regulation of glomerular filtration. The macula densa, located between the end of the thick ascending limb of the loop of Henle (TAL) and the distal convolute tubule (DCT), uses the mechanism of TGR to detect changes in tubular solute load to alter afferent arteriolar vascular tone, balancing calcium dependent vasoconstriction to decrease GFR [64] and renin secretion by the granular cells to increase RBF [65, 66].

Glomerular Disease

Glomerular structure and function is affected in various developmental and disease states. Nephritis, often heralded by hematuria and hypertension, and nephrosis, by proteinuria and hypertension, are highly relevant acquired and congenital ICU disease processes. The hypertension in both is a direct result of the renin response of the JGA (TGR) from apparent low GFR and low salt delivery to the TAL and DCT, triggering an exaggerated and deleterious salt and fluid accumulation. Congenital kidney disease often occurs secondary to aberrant glomerular structure. Minimal change glomerulopathy, resulting in loss of charge selectivity, and membranous glomerulopathy, resulting in loss of size selectivity, both manifest with proteinuria [67]. Mutations of the alpha chain of Type IV collagen underlie the development of Alport's hereditary nephritis and thin basement nephropathy. Inherited podocytopathies result from various gene mutations (NPHS1 – nephrin [68], NPHS2 – podocin [69], TPRC6 (transient receptor potential canonical 6) [70], alpha-actinin four gene [71] and PLC-ε (phospholipase C epsilon) [72]. Loss of nephrin phosphorylation deleteriously affects podocyte structure and function. Due to their non-replicative phenotype, damage and loss of mesangial cells over time impairs functional α/β-dystroglycans [48, 49] and can lead to the development of chronic renal disease.

Tubules

The renal tubule balances fluid and solute excretion to maintain homeostasis. Segments of the renal tubule will be discussed in series – describing the mechanism, distribution, and interactions which govern the regulation of solute balance. The two primary functions of the renal tubules are reabsorption and secretion. Reabsorption is defined as the transfer of fluid from the tubular lumen to the pericapillary fluid. This is dependent on the integrity of the apical surface, the GBM, and the basolateral membrane. Secretion functions in the opposite direction and moves fluid into the tubular lumen. As we will describe, specific solutes are moved at different rates in different areas of the tubule. The adequacy of individual nephrons is dependent on a properly functioning counter-current concentration gradient, established by multiple areas of the tubule (Fig. 12.3).

The active transport of solutes in the tubule lumen increases kidney oxygen consumption (RvO_2 second only to the heart) [73]. The primary drivers of solute movement rely on ATP hydrolysis – linked to electrolyte transporters, co-transporters, or exchangers [74]. Arguably the most important of the ATP hydrolytic enzymes is the sodium-potassium ATPase

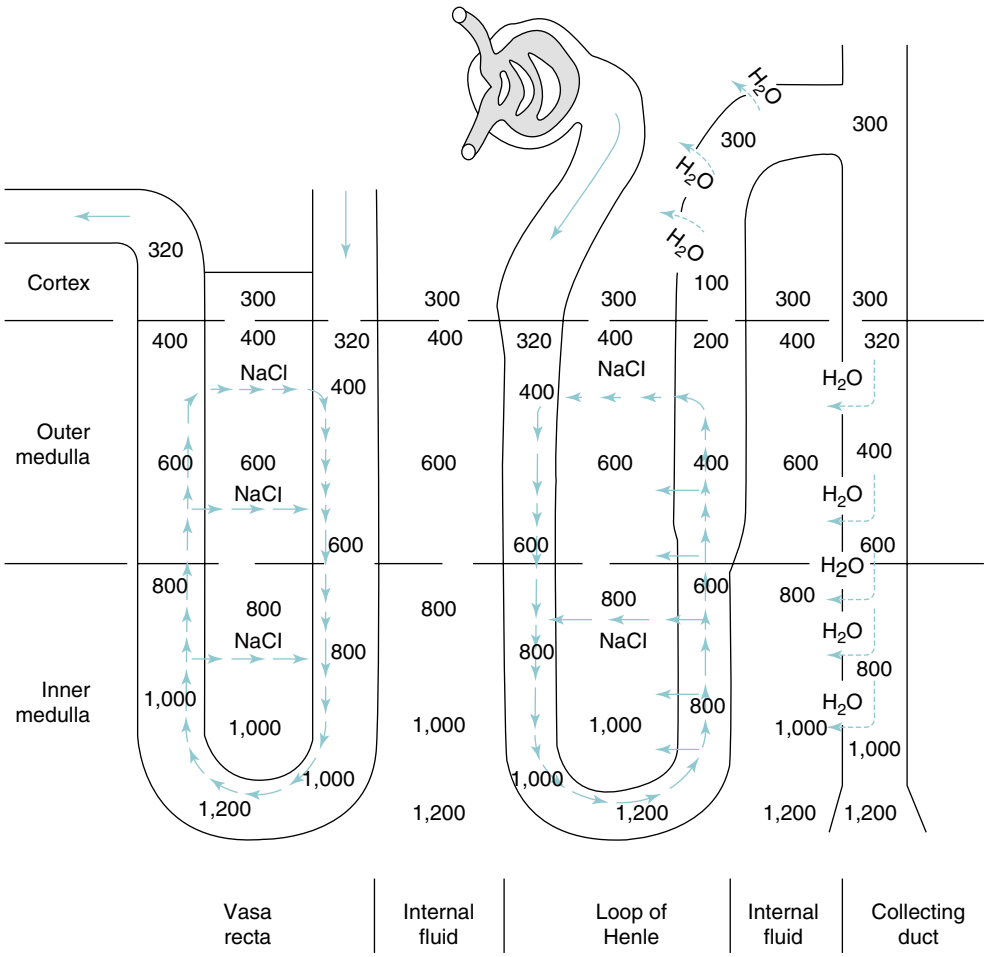

Fig. 12.3 Countercurrent gradient established by the vasa recta and the renal tubules allowing urinary concentration (Reprinted from Weichert [153] With permission from Access Science (www.AccessScience.com), © McGraw-Hill Global Education Holdings, LLC)

(Na^+-K^+-ATPase) – which is primarily responsible for the balance of sodium and water and secondarily propels the function of several other ion channels [75]. The Na^+-K^+-ATPase channel drives both sodium (high extracellular concentration) and potassium (high intracellular concentration) against their concentration gradients at the cost of ATP, establishing the electrochemical gradient of the apical membrane. Creation of this gradient, with assistance from the hydrogen-ATPase (H^+-ATPase) and calcium-ATPase (Ca+2- ATPase), allow the secondary transporters such as Na^+-H^+ exchanger (NHE3) and Na^+-K^+-$2Cl^-$ cotransporter to function. The secondary transporters then permit the tertiary transport systems to function. The exchange of solutes, through reabsorption and secretion, is therefore dependent on a domino-effect of a series of exchange channels. Influenced by electrochemical gradients (dependent on tubular epithelial cell polarity), transport of various solutes occurs transcellularly, paracellularly, or by a combination of the two. Thus, tubular cell polarity is critical for solute transport [76].

The Proximal Tubule

The proximal tubule (PT) reabsorbs 60–65% of the glomerular filtrate. The PT has three segments: S1 (initial short segment), S2 (cortical segment) and S3 (straight medullary section). The PT is lined by a single layer of epithelial cells which separates the luminal fluid from the interstitial fluid. These cells are characterized by high permeability to water due to the presence of microvilli on the luminal surface, invaginations on the interstitial side, abundant mitochondria, and intercellular gap junctions with specialized proteins for passive transport. Due to its workload, the PT is a highly metabolically active segment of the kidney. Accordingly, the PT receives a large amount of cortical blood flow compared to the medulla (Fig. 12.1). The PT has both active transcellular and passive paracellular transport systems. Apart from sodium, the PT is involved in the reabsorption of most major solutes including potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), sulfate, citrate, phosphate (PO_4^{3-}), calcium (Ca^{2+}), glucose, and uric acid. Limited reabsorption capacity exists for some solutes (glucose), known as the tubular transport maximum (Tm). The PT also has important secretory functions. In addition, the PT is responsible for the activity of 1α-hydroxylase, and participates in gluconeogenesis and ammoniagenesis. Oxalate, organic anions and cations, and toxins are secreted in the PT. In spite of the tremendous solute reabsorption, no osmotic gradient develops from the PT due to free permeability to water.

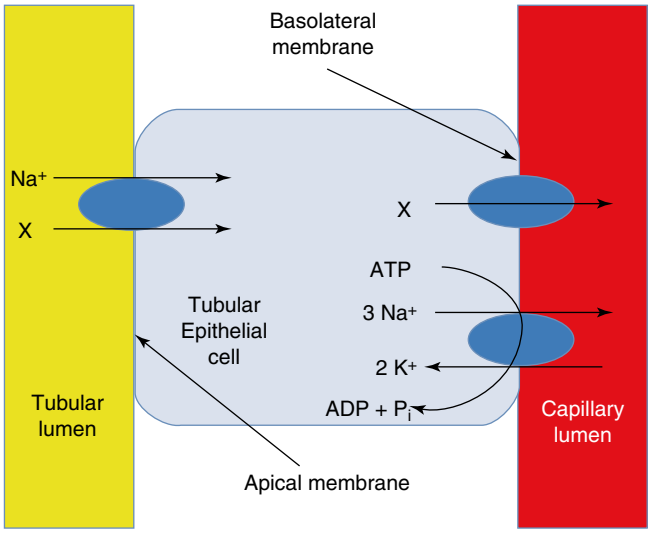

Fig. 12.4 Sodium exchange at the level of the proximal tubule coupled with solute X (e.g., glucose). Through co-transport, along the concentration gradient for sodium, solute X is carried into the tubular epithelial cell cytosol. The Na-K-ATPase maintains the sodium gradient by pushing sodium into the capillary space, against its concentration gradient, at the expense of ATP. The high intracellular concentration of solute X then drives the passive diffusion of the solute across the basolateral membrane using a designated solute transporter (e.g., GLUT)

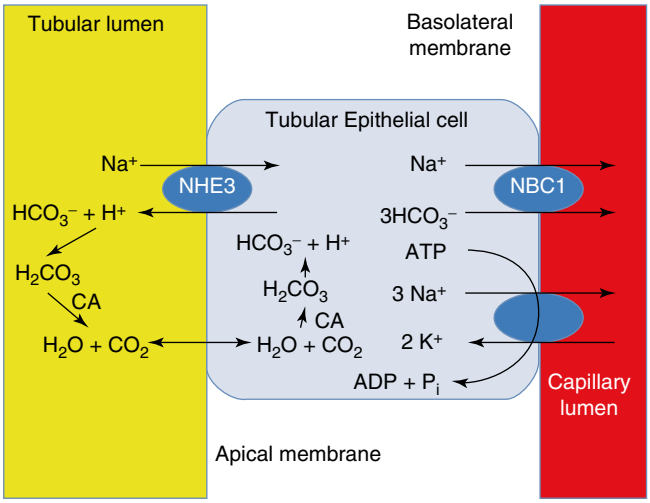

Fig. 12.5 The mechanism of bicarbonate reabsorption and carbon dioxide/hydrogen ion elimination via carbonic anhydrase. Protons (H^+) get secreted by PT cells into the tubular lumen in exchange for sodium (Na^+) via the sodium-hydrogen exchanger (NHE3). The free H^+ then combines with filtered bicarbonate to form carbonic acid (H_2CO_3) which then gets broken down into carbon dioxide (CO_2) and water (H_2O) by carbonic anhydrase (CA). The CO_2 and H_2O freely diffuse into the cell and reform H_2CO_3 which gets metabolized by CA into cytosolic bicarbonate and hydrogen ion. The HCO_3^- then gets reabsorbed into the capillary space by a basolateral Na^+-HCO_3^- cotransporters (NBC1) while H^+ is extruded by the NHE3

Sodium

Proximal tubule solute transport relies heavily on a low intracellular sodium concentration, maintained primarily by the Na^+-K^+-ATPase (Fig. 12.4). A majority of total sodium reabsorption (60–70 %/99 % total) by the body, occurs in the PT [77] [78] and sodium is the only solute that is actively reabsorbed in PT. The primary solutes dependent on low intracellular sodium concentration include HCO_3^-, Cl^-, and glucose.

Bicarbonate

Around 80–90 % of HCO_3^- is reabsorbed in the PT. HCO_3^- reabsorption is linked to hydrogen ion (H^+) secretion. H^+ is secreted by the PT into the tubular lumen via NHE3 and H^+-ATPase [79]. In the tubular lumen, H^+ combines with filtered HCO_3^- in the presence of carbonic anhydrase (CA) to produce carbon dioxide (CO_2) and water by the following reaction:

$$H^+ + HCO_3^- \longleftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

CA in the PT brush border allows CO_2 combination with water, produce H^+ and HCO_3^- in the tubular cell. H^+ enters the tubular lumen in exchange for Na^+ via NHE3 while HCO_3^- is transported out of the cell along with Na^+ via the $Na^+HCO_3^-$ co transporter [80] (Fig. 12.5).

Chloride

Chloride is reabsorbed by both active and passive mechanisms. Passive paracellular transport occurs via tight junctions while active transport occurs via chloride-hydroxyl and chloride-formate ions coupled to NHE3 [81]. The rise in intracellular pH due to H^+ export into the lumen provides a pH gradient for chloride-base exchanger, however electroneutrality is maintained by Na^+ transport coupling with Cl^- [82]. Passive transport is a result of preferential reabsorption of bicarbonate in early PT segments resulting in a higher Cl^- concentration in latter segments where it is reabsorbed passively [83].

Water

Aquaporin water channels (AQP), present on the luminal and basolateral surfaces of the PT, are regulated by ANG-II and lead to water reabsorption via transcellular or paracellular pathways.

Potassium

The proximal tubule reabsorbs 60–70 % of filtered K^+ via paracellular transport dependent on Na^+ and water movement.

Glucose

Almost all filtered glucose is reabsorbed in the PT. Transport from the tubular lumen into the tubular epithelial cell is facilitated by Na^+-glucose co-transporters (SGLT2 proximally and SGLT1 distally) [84]. However glucose from the tubular cells exits by a set of separate transporters (GLUT2 in

proximal segments of PT and GLUT 1 in distal PT segments) [85]. Due to reliance on transporter proteins, the movement of glucose from the tubular lumen is stoichiometrically limited to the finite availability of SGLT2 (or 1). Once the solute exceeds the availability of the transporter protein, the balance of the filtered solute appears in the urine. Clinically, this is manifest as the tubular transport maximum.

Phosphate

The PT is the primary regulator of serum phosphate concentration. Phosphate appears in the urine as either divalent HPO_4^{2-} or monovalent $H_2PO_4^-$. Sodium phosphate cotransporters (NaP_i-IIa and NaP_i-IIc) bind preferentially to divalent HPO_4^{2-} and help in reclaiming the filtered phosphate [86]. $H_2PO_4^-$ in the tubular lumen binds to H^+ and contributes to net acid excretion. Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) are important mediators of phosphate reabsorption through recycling the NaP_i-II cotransporters via endocytosis from the apical membrane into proximal tubule cells [87].

Proteins

Almost all of the filtered amino acids are reabsorbed in the PT via different transporter systems linked to the Na^+ or H^+ gradient [88]. This efficient and near total reabsorption is facilitated by the presence of low affinity/high capacity transporters in the early segments of the PT followed by high affinity/low capacity transporters in the distal segment of PT. Transporter mechanisms are not amino acid specific, rather transport seems to be based on chemical groups (e.g., dibasic separate from neutral amino acid transport). Reabsorption of various proteins and polypeptides is mediated by two multiligand endocytic receptors, megalin and cubilin [89]. Even though albumin is generally not filtered at the glomerulus, a small fraction that gets filtered is reabsorbed through the megalin/cubilin system or via receptor proteins related to the major histocompatibility complex Fc receptors. Peptides and proteins are broken down at the brush border by peptidases before absorption while proteins and larger peptides are endocytosed and transported to lysosomes for degradation. Importantly, the PT is also a site for amino acid metabolism (renal glutamine breakdown to yield ammonia; conversion of citrulline to arginine).

Organic Ions

The proximal tubule is also an important site of secretion of many endogenous anions (bile salts, urate), cations (creatinine, dopamine), and drugs (diuretics, penicillin, probenecid, cimetidine). Cations are secreted using the organic cation transporters (OCT) present in the basolateral membrane while anions use secretory pathways mediated by organic anion transporters (OAT1) [90–92]. A number of endogenous organic cations (choline, epinephrine, and dopamine) are actively secreted by the PT. OCTs share a common electrogenic uniport transport mechanism which is independent of Na^+ and K^+ extracellular concentration. The organic ion transporters play a significant role in excretion of various antibiotics, non-steroidal anti-inflammatory drugs, loop diuretics and cyclosporine [93].

Uric Acid

Specific transporters (URAT1 and OAT10) reabsorb uric acid in exchange for lactate or nicotinate while GLUT9 helps in absorption across the luminal membrane as well as basolateral efflux [94]. Urate, reabsorbed and secreted simultaneously, is exchanged for dicarboxylates (such as lactate, pyruvate, acetoacetate, and numerous intermediaries of the tricarboxylic acid cycle) using OAT4 while OAT1 and OAT3 mediate basolateral membrane urate transport.

Dysfunction in Acute Illness

Due to its central role in solute and water handling, injury or aberration of function of the proximal tubule, particularly to the Na^+-K^+-ATPase can lead to disastrous consequences for the host. Volume depletion leads to increased ANG-II, can lead to higher peritubular oncotic pressure, and enhances fluid movement from the interstitium to the circulation, improving reabsorption of filtered glomerular solute. Norepinephrine signaling can produce similar findings [31, 95]. Dopamine, however, acts as a counter-regulatory hormone in the stressed host – inhibiting transport of solute [96]. Glucocorticoids can upregulate transcription of the ATPase subunits leading to increased activity of the enzyme.

Dysfunction of the proximal tubule can occur commonly in critical illness. The proximal tubule is at high risk of hypoxic-ischemic injury; the straight portion of the PT present in the outer medulla has comparatively less blood supply and is more susceptible to hypoxia and acute tubular necrosis [4]. Global dysfunction of the proximal tubule (Fanconi syndrome) either from drugs (e.g., valproate, gentamicin, methotrexate, cisplatinum) or inherited causes (e.g., cystinosis), leads to impaired transport of multiple solutes resulting in bicarbonaturia, glucosuria, phosphaturia, and aminoaciduria. As mentioned earlier, these solutes then enhance diuresis by exceeding the stoichiometric handling of their specific transporter proteins (i.e., hyperglycemic osmotic diuresis). Additionally, inhibition of CA (e.g., acetazolamide) leads to a relative surplus of tubular bicarbonate over transporters, leading to an osmotic diuresis. Other transporter protein dysfunction can lead to impaired tubular reabsorption of proteins and solutes: dysfunction of megalin and cubulin results in low-molecular-weight proteinuria and albuminuria, aminoaciduria results as a consequence of defects in amino acid transporters (Hartnup's disease and Cystinuria) [97, 98], and phosphatonins, a group of newly discovered phosphate regulators, inhibit phosphate transport and lead to tumor-induced

osteomalacia and X-linked or autosomal dominant hypophosphatemic rickets [99].

The Loops of Henle

By maintaining a hyperosmolar interstitium, the loop of Henle (LH) is the part of the nephron responsible for the kidney's ability to concentrate or dilute urine [100]. Situated uniquely, the LH starts with a thick descending limb extending from the PT, transitions to thin descending and ascending limbs, and ends with the thick ascending limb (TAL) near the macula densa. The counter-current multiplication and the medullary concentration gradient are generated by the U-shape of the LH, differential permeability of the LH segments to water and salt, and the active reabsorption of sodium in the TAL (Fig. 12.3). Raised medullary osmolarity, a result of sodium chloride reabsorption from the water impermeable ascending limb (lack of vasopressin insensitive AQP1) [101]), induces water reabsorption in the thin descending limb raising the osmolarity and sodium chloride concentration in the tubular fluid delivered to the ascending limb. Sodium movement in the thin limbs occurs via passive reabsorption of sodium chloride by paracellular Na^+ transport and transcellular Cl^- transport. As the LH ends in the TAL, Na^+ transport becomes a secondary active process driven by the electrochemical gradient established by the Na^+-K^+-ATPase. The increasing medullary osmolality along the LH results in hypo-osmolar tubular fluid. The permeability of the LH to urea is the other important factor in maintenance of the counter-current concentration gradient. The thin limbs of the LH are relatively permeable to urea, but the distal nephron segments (notably the TAL, DCT, and collecting ducts) are impermeable. Due to vasopressin dependent water reabsorption in the collecting ducts, the urea concentration in the tubular lumen is high. This leads to urea reabsorption in the interstitium, secondary movement of urea into the vasa recta, and explains the tertiary movement of water out of the tubular lumen in the thin descending loop of Henle. The net effect is to further increase the relative sodium concentration in the tubular lumen at the interface between the thin descending limb and the thin ascending limb of the LH, leading to passive diffusion of salt *out* of the thin descending limb prior to the TAL [102].

The vasa recta is important in maintaining the hyperosmolality of the medullary interstitium and functions via two primary mechanisms. First, owing to small cross-sectional area, blood flow flows at low velocity, reducing the solute and osmotic washout from the interstitium. Second, the vasa recta participates in the counter current exchange mechanism – as water moves out, sodium chloride (NaCl) moves in. Conversely, water re-enters and NaCl leaves the ascending limb of vasa recta. Thus, the vasa recta contributes no dilutional effect on the interstitial osmotic gradient. These processes are entirely passive [103]. The net effect of the differential movement of salt and water and the interaction with the vasa recta is that the interstitial osmolality increases from the cortex to the medulla and then decreases at the end of the LH so that the surrounding tissue of the DCT is hypo-osmolar [104].

The LH regulates the movement of other significant solutes. About 15 % of HCO_3^- is reabsorbed in the LH, mainly at the TAL [105]. Microperfusion studies reveal that in the TAL, the luminal HCO_3^- concentration is high and NHE3 channels facilitate bicarbonate movement out of the tubular lumen [106]. Reabsorption of K^+ into the interstitium, facilitated by the ATP-dependent renal outer medullary channel (ROMK) in the TAL, is critical to Na^+ reabsorption. Luminal Cl^- is reabsorbed by TAL chloride channels (CLCNKA, CLCNKB) in the basolateral membrane. Glutamine metabolism in the proximal tubules leads to formation of ammonia (NH_3). Elimination of NH_3 is facilitated by medullary TAL reabsorption and movement of interstitial NH_3 into the lumen of the collecting ducts (whereupon it binds to tubular H^+ in the acidic lumen of the collecting duct and is eliminated) [107]. Finally, under the control of parathyroid hormone, Ca^{2+} reabsorption in the LH occurs at the TAL. Additionally, magnesium reabsorption occurs mainly at the LH (60 % of total reabsorption vs. 15 % at the PT) [108]. The positive luminal voltage of the TAL is the main driving force behind the paracellular reabsorption of both divalent cations [109].

The macula densa lies adjacent to the glomerular hilum and the TAL. Extra-glomerular mesangial cells may serve as a functional link between macula densa and glomerular arterioles [110]. The regulatory function of the macula densa was described earlier: increased sodium and fluid delivery to the TAL signals the JGA to secrete renin, leading to afferent arteriolar vasoconstriction and a decrease in filtration and sodium/fluid delivery to the TAL [111] whereas low solute and fluid delivery triggers RAAS which increases aldosterone and vasopressin secretion leading to NaCl and fluid reabsorption from the PT [112].

Dysfunction in Critical Illness

As the primary regulators of the counter-current gradient, and the urine concentrating ability of the kidney, injury to the LH can have severe consequence to the host. The vasa recta traverses from the cortical region to the inner medulla and back placing it at risk of hypoxic – ischemic injury [4]. Though involved in its homeostasis, aberrations in acid-base balance can have significant consequence for the function of the LH. Metabolic acidosis increases urinary calcium and magnesium excretion while metabolic alkalosis has the opposite effect. Significant acid load can impair the ability of the TAL and CD to buffer the urine with NH_3 by inhibiting NHE3. The effects of diuretics on the LH are notable. Loop diuretics (torsamide, furosemide, bumetanide) are potent inhibitors of the Na^+-K^+-ATPase in the thin ascending limb and can eliminate the counter current mechanism which allows for urine concentration – thereby facilitating a dilute diuresis. Loop diuretics also 'trap' sodium in the tubular

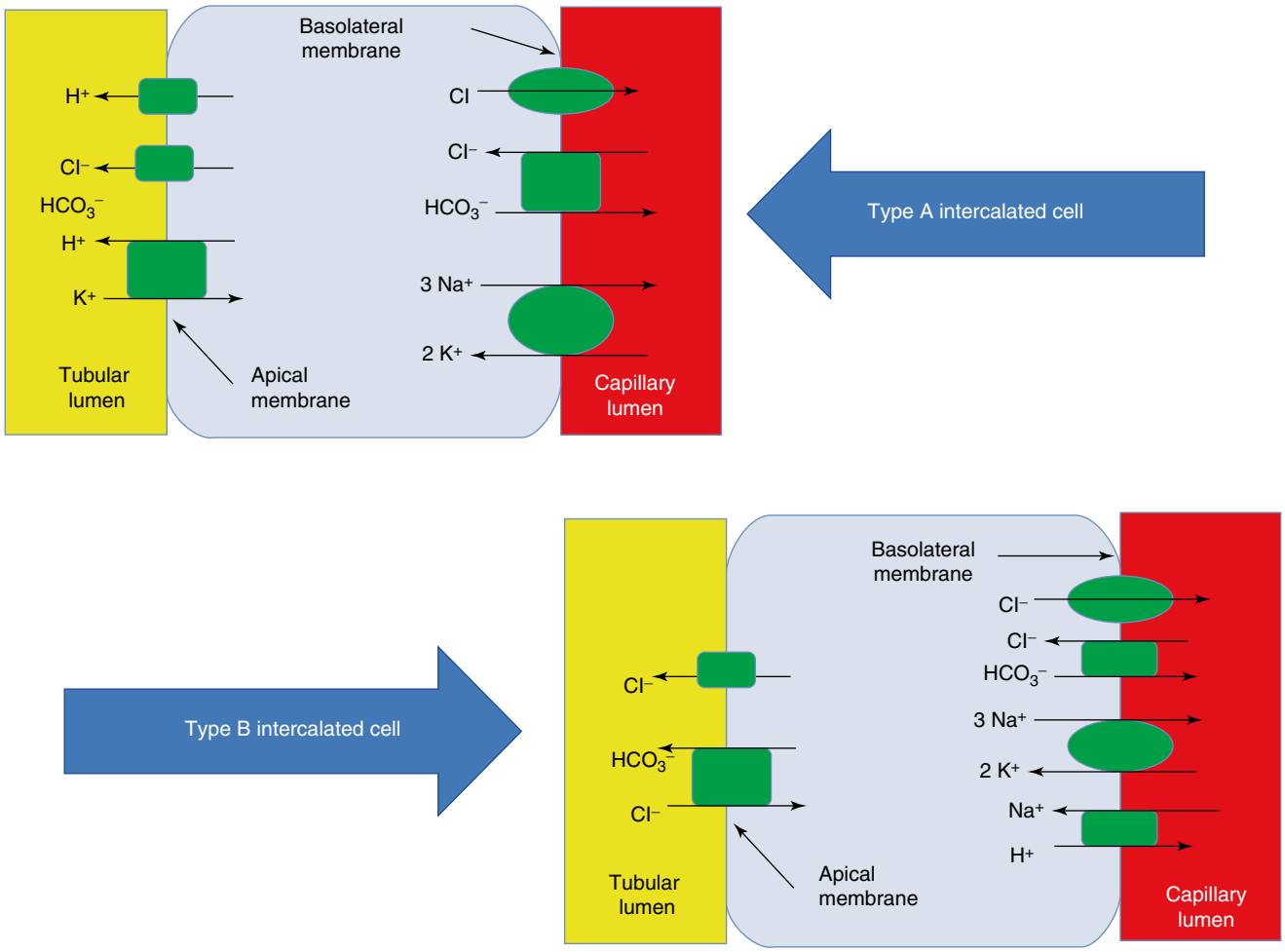

Fig. 12.6 The cortical duct intercalated cells (*A* and *B*) have separate functions. Type A cells are associated with net proton secretion and thus acid balance (as evidenced by the anion exchange (*AE*) channel and the H + -K + ATPase). Meanwhile, Type B cells are responsible for regulating bicarbonate levels in response to pH – thus are critical to base balance

lumen, leading to a natriuresis (manifest as an increased fractional excretion of sodium (FeNa) for patients on these medications). Additionally, inhibition of the Na^+, K^+, and 2-Cl^- co-transport simulates HCO_3^- reabsorption (via rise of the sodium gradient across the apical membrane and increasing the rate of Na-H exchange) [113]. Loop diuretics increase calcium excretion via action on TAL voltage dependent paracellular calcium reabsorption. Congenital diseases of the LH include a group of related disorders leading to hypokalemia and metabolic alkalosis, termed Bartter syndrome, stemming from a genetic disruption of sodium reabsorption in the thick limb of LH (mutations of NKCC2 leads to antenatal Bartter syndrome type 1, loss-of-function ROMK mutations cause antenatal Bartter syndrome type 2, simultaneous mutations of the adjacent *CLCKNA* and *CLCKNB* genes (usually deletions) cause infantile Bartter syndrome type 4B) [114].

The Distal Tubule and Collecting Ducts

The terminal section of the functional nephron is the distal tubule, comprised of four separate segments: the distal convoluted tubule (DCT), connecting segment, collecting duct (CD), and medullary collecting ducts (MCD). The three primary functions of this section of the kidney are balancing sodium-potassium, acidification-alkalinization of the urine, and net water movement.

The DCT extends from beyond the macula densa to the connecting tubule. It reabsorbs 5–10 % of Na^+, is a site of calcium and magnesium reabsorption (via the TRPV5 channel [115]), and is the primary site of urine concentration – reabsorbing 20 % of water delivered to the segment. The DCT has the highest Na^+-K^+-ATPase activity of any segment. The sodium chloride co-transporter (NCC), a thiazide sensitive electro-neutral transporter is involved in the reabsorption of NaCl in this segment and is regulated by aldosterone and Na^+ delivery to the segment [116].

The two primary functions of the CD are cell specific: principal cells direct completion of Na^+, K^+, and water reabsorption while intercalated cells regulate acid-base balance (Fig. 12.6). The principal cells predominate the cortical portion of the collecting tubule and are responsible for

Table 12.2 Hormones that affect sodium and water reabsorption in the collecting duct

Hormone	Sodium reabsorption	Water reabsorption
Aldosterone	Increases	Increases
Vasopressin	Increases	Increases
Insulin	Increases	Increases
Endothelin	Decreases	Decreases
Prostaglandin E_2	Decreases	Decreases
Bradykinin	Decreases	Decreases
Dopamine	Decreases	Decreases

reabsorption of Na^+ and secretion of K^+. The epithelial sodium channel (ENaC), an aldosterone regulated epithelial sodium channel present in the principal cells, is the main pathway of sodium reabsorption. In addition to the distal nephron, ENaC is expressed in the colon and in the lungs in humans. Even though 90 % of the K^+ is reabsorbed in the PT and LH, fine tuning occurs in the distal tubule. Aldosterone sensitive distal tubular segments (the late distal convoluted tubule, the connecting tubule, the cortical collecting duct, and to a lesser extent the medullary collecting duct) are the primary sites of potassium regulation. In contrast to the PT where K^+ reabsorption occurs in parallel to Na^+ reabsorption, K^+ *secretion* occurs in parallel to Na^+ reabsorption in the distal nephron. Distal K^+ secretion is mediated by apical K^+ channels and is dependent on adequate Na^+ delivery to the distal tubule and is augmented by vasopressin. The major driving force for potassium secretion is the lumen negative potential generated by Na^+ absorption by ENaC. Potassium secretion is mediated by principal cell ROMK activity and is affected by dietary K^+ load [117], aldosterone, lumen electronegative potential produced by ENaC, With-no-lysine kinase (WNK1) [118, 119], magnesium [120], and fluid flow. K^+ is secreted in the cortical collecting duct and absorbed in the MCD resulting in marked increase in medullary interstitial K^+. Aldosterone antagonists (e.g., spironolactone) inhibit K^+ secretion. A list of hormones that affect sodium and water reabsorption from the CD is depicted in Table 12.2.

The collecting tubular cells are impermeable to water in the absence of vasopressin except for the terminal MCD, which has moderate water permeability even in the absence of vasopressin [121]. Vasopressin induces AQP2 expression on the luminal surface of principal cells in the cortical and medullary collecting ducts stimulating water reabsorption [122]. Ten different types of aquaporins have been identified, the most clinically understood being AQP2 (mediates water influx into the tubular lumen through the apical membrane) and AQP4 (mediates water efflux through the basolateral membrane). Additionally, in the CD, vasopressin binds to the receptor V2R, triggering subluminal vesicles bearing AQP2 bearing vesicular fusion with the luminal membrane in a cAMP dependent mechanism, thus increasing water permeability [123].

Finally, urea homeostasis is regulated by the CD. The inner medullary collecting duct has high urea permeability, which increases in the presence of vasopressin. There is a progressive rise in the concentration of urea in the connecting tubule and proximal portions of the CD as they are impermeable to urea. When the fluid reaches inner medullary part of the CD, urea rapidly diffuses to the interstitium. Urea is reabsorbed in the medullary collecting duct through the urea transporters UTA1 and UTA3 and trapped due to a low effective blood flow owing to countercurrent exchange system in vasa recta, as described earlier [124]. Equilibration of urea prevents the otherwise inevitable osmotic diuresis.

The intercalated cells predominate in the medullary collecting ducts and are important for final acidification or alkalization of urine. Type A intercalated cells secrete net acid mediated by apical H^+-ATPase (allowing for replenishment of body bicarbonate levels) while Type B intercalated cells secrete net base mediated by the Cl^--HCO_3^- exchanger and AE1 (anion exchanger) [125]. There is some evidence that Type A and Type B cells may represent different functional states of same cell in response to acid base status of the body [126] and may actually demonstrate plasticity dependent on the hormone hensin [127]. Only Type A intercalated cells are present in the medullary collecting ducts, thus only net acid secretion, through active H^+ secretion, can occur in this segment. H^+ secretion is linked to HCO_3^-reabsorption via carbonic anhydrase activity but is also dependent on the availability of NH_3^+ to form NH_4^+. Meanwhile $HCO_3^-$is reclaimed into the interstitial fluid by AE1.

Acid-base balance is maintained by titratable acid secretion such as citrate, phosphate and ammonia. Of these, ammonia is the most clinically relevant buffer. From the medullary interstitium, NH_3 diffuses into the tubular lumen across the tubular epithelial cells where it combines with H^+ to form NH_4^+. The epithelial cells are impermeable to NH_4^+ leading to net acid and ammonia excretion.

Dysfunction in Critical Illness

The fine tuning of solute balance, water homeostasis, and acid-base balance by the distal tubular system of the nephron can be disrupted by critical illness. Renal ischemia leads to cell damage and death by one of the two processes, necrosis or apoptosis. Apoptosis is more commonly seen in distal tubular cells and may be caspase-mediated [128]. Regulation of the ENaC affects the balance of sodium in urine and plasma. Up-regulators of the channel include aldosterone, vasopressin, and alkalosis (all favoring sodium retention) while acidosis, oxidative stress, and natriuretic peptides induce down-regulation of the channel leading to a natriuresis. Exogenous medications such as triamterene and amiloride bind to the extracellular domain of ENaC channel and inhibit its activity [129]. Meanwhile, genetic mutations activating ENaC cause Liddle syndrome [130]

while inactivating mutations cause pseudo-hypoaldosteronism type 1[131]. Magnesium inhibits the ROMK channel which may result in refractory hypokalemia for hypermagnesemic patients [132]. Acidosis favors the production of ammonia and thus increased hydrogen ion elimination while alkalosis reduces ammonia-genesis. Water imbalance syndromes may be secondary to aberrancies in the expression and regulation of AQP and V2R channels. V2R mutations with loss of function leads to nephrogenic diabetes insipidus while decreased or absent synthesis of antidiuretic hormone (ADH) in body results in central diabetes insipidus. On the other hand, syndrome of inappropriate ADH secretion (SIADH) is characterized by excess free water retention and hyponatremia due to excess secretion of ADH in the absence of osmotic or physiologic stimulus for secretion. Osmotic regulation of vasopressin release can be overridden in certain situations (e.g., hypovolemia, severe fatigue, or physical stress). Such non-osmotic stimuli, coupled with continued water intake, explain the hyponatremia that occurs in severe congestive heart failure and cirrhosis. Maximal urine concentrating ability is decreased in states of protein deprivation or malnourishment. Newborn infants have a poorly developed cortico-medullary gradient and limited ability to concentrate urine which predisposes them to dehydration in case of high solute loads. Finally acquired or congenital disorders of the CD can alter solute and water handling in the kidney. Inactivating mutations in the NCC are associated with autosomal recessive Gitelman syndrome, characterized by hypokalemic metabolic alkalosis, hypocalciuria, and hypomagnesemia.

The Endocrine Kidney

The central physiologic "location" of the kidney, make it an ideal warehouse of vital endocrine mediators of renal and extra-renal function. Increasing evidence suggests that crosstalk between the kidney and other organs occurs at baseline and during critical illness [133].

Known Renal Mediators of Extra-Renal Homeostasis

Production of red blood cells is a tightly regulated process, driven by the kidney derived glycoprotein erythropoietin. Renal production of erythropoietin during hypoxia or anemia is triggered by hypoxia inducible factor 1 (HIF-1) and induces a bone marrow response to increase RBC production [134, 135]. Bone mineralization is kidney-dependent. Vitamin D precursors, either from dietary sources or dermal synthesis, are hydroxylated in the liver to yield 25-hydroxyl-cholecalciferol. Hydroxylated and activated Vitamin D is then transported to the renal tubules and hydroxylated by the α-1-hydroxylase enzyme to form 1, 25 hydroxyl cholecalciferol (calcitriol). Calcitriol regulates calcium absorption from intestine and kidneys, regulates bone osteoclast activity and increases reabsorption of phosphate from the intestine. The effects of angiotensin and aldosterone on homeostasis of body volume and blood pressure have been detailed in previous sections and are counter-balanced by the effects of prostaglandins such as D_2, E_2, and I_2 (prostacyclin). The production of these autocoids are triggered and governed in some part by angiotensin. The kidney also plays a role in the immunologic response to injury. Pro-inflammatory chemokine expression after acute ischemic kidney injury has been documented [136, 137]. Additionally, extra-renal effects in the heart, lungs, and brain occur after isolated kidney injury [133, 138–141]. Taken together, evidence suggests that the kidney likely has a larger contribution to whole animal homeostasis in health and illness than previously suspected (Fig. 12.7).

Organ Syndromes in Critical Illness

The endocrine role of the kidney in critical illness is demonstrated by evidence of organ-kidney crosstalk syndrome such as pre-renal azotemia syndromes (hepato-renal and cardiorenal). Hepato-renal syndrome is characterized by concurrent renal dysfunction in the face of hepatic failure and is felt to be secondary to regional renal ischemia from vascular perturbations induced by disruption of the portal venous system and hepatic arterial circulation. Zellweger syndrome, a peroxisomal disorder of β-oxidation and hypomyelination, is manifest by disruption of the cerebro-hepatic-renal axis [142]. Cardiorenal syndrome, concomitant acute kidney injury in the face of cardiogenic circulatory dysfunction, has been documented in pediatrics [143, 144]. Finally, evidence of crosstalk between the lung and the kidney has been widely discussed. More than the effects of fluid overload on pulmonary function, kidney injury disrupts pulmonary function and fluid clearance (potentially by effects on ENaC and AQP [145]) even in the absence of overt failure [139, 146–148]. The role of the kidney in mediating, and not just succumbing to, severe sepsis associated kidney injury (SSAKI) is controversial. Modification of ANG-II, and thus systemic perfusion pressure, is altered during sepsis and the impact of SSAKI on GFR continues to be explored, both clinically and experimentally [149, 150]. The liberation of erythropoietin,

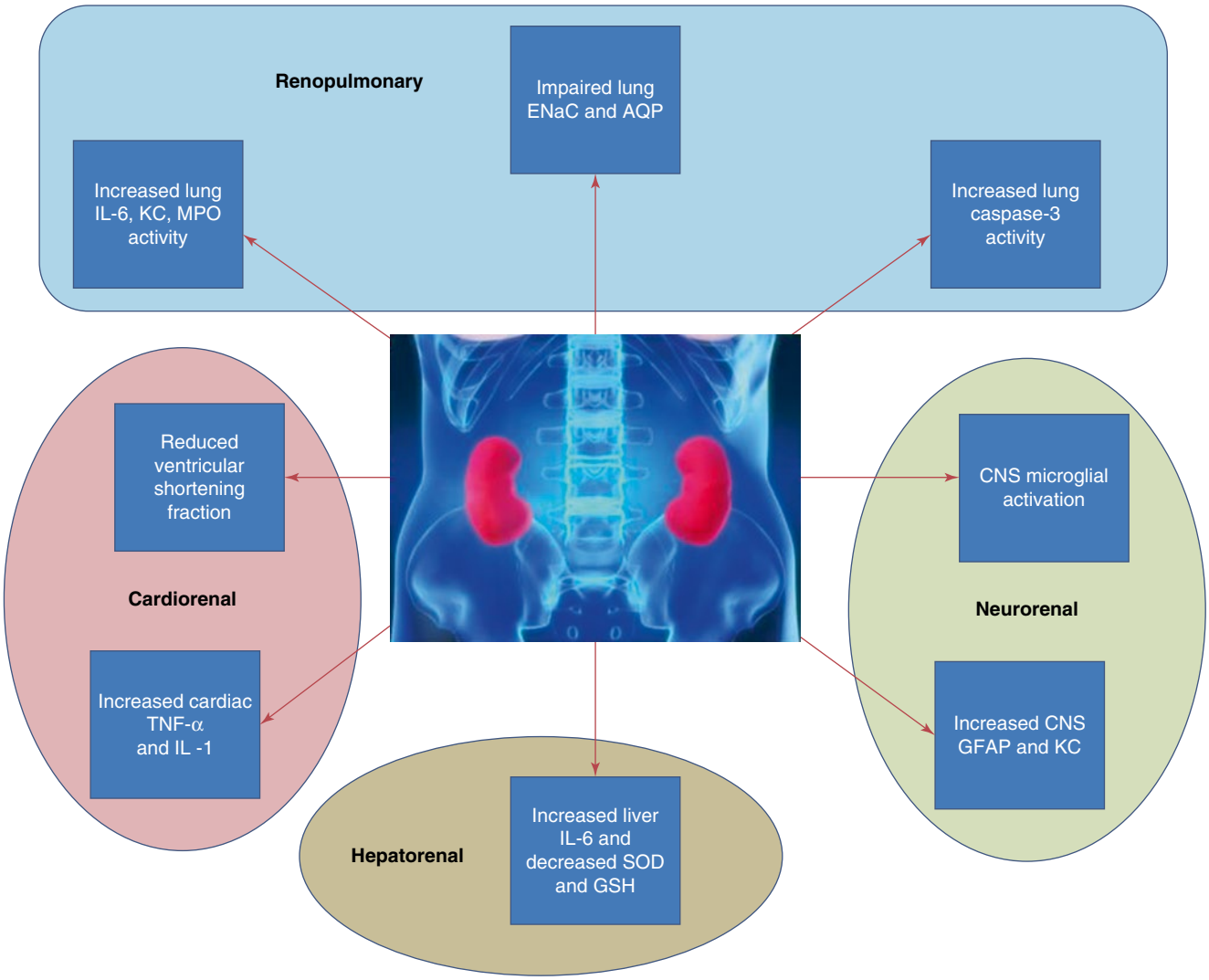

Fig. 12.7 Kidney cross-talk with distant vital organs. Kidney cross-talk with distant vital organs after isolated ischemic kidney injury is supported by: *Renopulmonary* – aberrant IL-6 and KC cytokines, aquaporin (*AQP*) and epithelial sodium channel expression (*ENaC*), myeloperoxidase activity (*MPO*), and increased caspase-3 pro-apopotic activity; *Cardiorenal*– reduced shortening fraction and elevated pro-inflammatory cytokines; *Neurorenal* – increased inflammation (glial fibrillary acidic protein (*GFAP*)) and apoptosis; *Hepatorenal* – increased inflammatory and decreased anti-oxidant markers (*SOD* superoxide dismutase, *GSH* glutathione)

renin-aldosterone, and calcitriol are notably increased in stress states such as shock and hypoxia.

Conclusion

Understanding renal physiology is vital to treating the critically ill pediatric patient. Modulation of solute handling, water balance, and the potential autocrine and endocrine mediators are all intertwined components of "kidney function". Though a full discussion of acute kidney injury is not presented here, the obvious ramifications of the disruption of these processes is evident and carries significant deleterious consequence for the host.

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Electrolyte Disorders in the PICU

13

Gabriel J. Hauser and Aaron F. Kulick

Abstract

Only a small fraction of acutely ill children are hospitalized with an electrolyte disorder as their primary diagnosis. However, many patients encounter secondary homeostatic imbalances that involve one or more of the following: sodium, potassium, calcium, magnesium and phosphorous. Abnormalities in the serum concentrations of these electrolytes could result from an underlying disease process; however, more frequently they are the result of complications, end organ injury or iatrogenic interventions such as fluid and electrolyte therapy, medications, or applications of critical care technology (positive pressure ventilation or renal replacement therapy), and should therefore be anticipated and prevented. Because of the fragile state of many of the pediatric intensive care unit (PICU) patients, electrolyte imbalances may have profound effects on patient outcomes, and in their extreme forms may be life-threatening. Careful, stepwise management is essential, as aggressive correction may at times result in further injury. This chapter outlines the pathophysiology and management of electrolyte disorders in the PICU. The authors have attempted to include a practical diagnostic and therapeutic approach to the most common disorders, but also provide a comprehensive differential diagnosis that would enable the practicing clinician to capture less common etiologies for electrolyte abnormalities in critically ill children.

Keywords

Electrolytes • Sodium • Potassium • Calcium • Magnesium • Phosphorus

Introduction

Only a small fraction of acutely ill children are hospitalized with an electrolyte disorder as their primary diagnosis. However, many patients encounter secondary homeostatic imbalances that involve one or more of the following: sodium, potassium, calcium, magnesium and phosphorous. Abnormalities in the serum concentrations of these electrolytes could result from an underlying disease process; however, more frequently they are the result of complications, end organ injury or iatrogenic interventions such as fluid and electrolyte therapy, medications, or applications of critical care technology (positive pressure ventilation or renal replacement therapy), and should therefore be anticipated and prevented. Because of the fragile state of many of the pediatric intensive care unit (PICU) patients, electrolyte imbalances may have profound effects on patient outcomes, and in their extreme forms may be life-threatening. Careful, stepwise management is essential, as aggressive correction may at times result in further injury.

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Disorders of Sodium Homeostasis

A physiologic serum osmolality of 285–290 mOsm/kg H_2O is essential to human survival. Homeostatic mechanisms that ensure its maintenance through control of water intake (i.e. thirst) and excretion are therefore mandatory. With these mechanisms properly in place, the ability to both dilute and concentrate urine allow for large fluctuations in oral solute and water intake, with minimal changes in serum osmolality and serum sodium concentration. In the critically ill child, self regulation of fluid intake and renal water handling is often impaired, thus disorders of water balance (dysnatremias) are pervasive in the PICU.

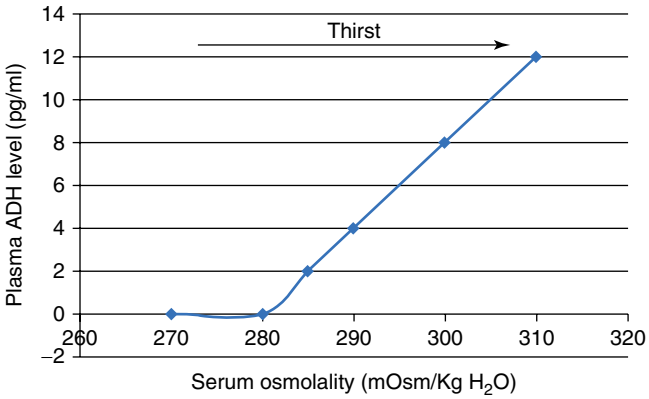

Fig. 13.1 A schematic representation of the effect of rising serum osmolality on plasma ADH levels. ADH levels start to rise at serum osmolality around 280 mOsm/KgH_2O and reach a maximum level at about 310 mOsm/KgH_2O

Hyponatremia

Hyponatremia, defined as a serum sodium <134 mmol/L, or <134 mEq/L, occurs in 3 % of hospitalized patients [1]. The incidence in the PICU, however, may be as high as 30 % [2]. Hyponatremic patients have been shown to have increased mortality [1, 3].

Pathophysiology

While the physiologic control of effective arterial blood volume (EABV) is regulated principally through the renin-angiotensin-aldosterone system (RAAS), control of plasma osmolality is regulated by arginine vasopressin, also known as anti-diuretic hormone (ADH). As serum sodium is the primary constituent of plasma osmolality (see equation below), ADH directly regulates serum sodium level as well.

$$\textit{Predicted Serum Osm} = 2*\left[Na^{+}\right]_{(mmol/L)} + BUN_{(mg/dl)}/2.8 + glucose_{(mg/dl)}/18$$

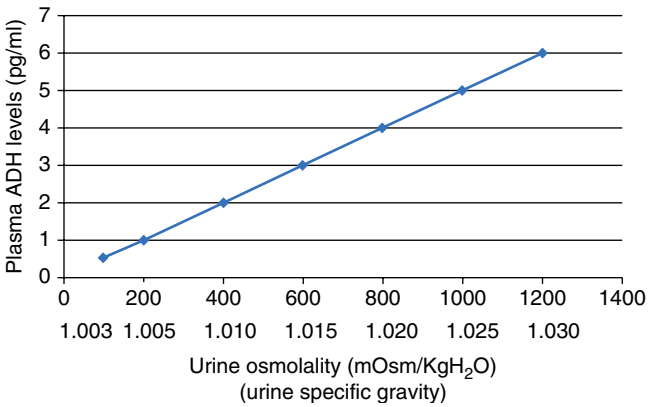

Fig. 13.2 A schematic representation of the effect of rising plasma ADH levels on urine osmolality and urine specific gravity (Urine Osmolality rises 34–40 mOsm/KgH_2O for every 0.001 increase in specific gravity)

When serum osmolality rises such as in the dehydrated hypernatremic patient, hypothalamic osmolar receptors detect this change, thirst is generated, and ADH is secreted by the pituitary gland. Thirst is a powerful corrective motivator for the replacement of a free water deficit but ADH allows the body to minimize free water loss through the urine. ADH secretion begins at a serum osmolality of approximately 280 mOsm/Kg (Serum Na+ of 135 mmol/L). It is near maximal at 310 mOsm/KgH_2O (Serum Na+ of 150 mmol/L, Fig. 13.1). At the level of the kidney, ADH mediates the insertion of collecting duct water channels. These channels act to absorb collecting duct water and may concentrate the urine up to 1,200 mOsm/L. Urinary concentration has a linear relationship with serum ADH levels (Fig. 13.2). As filtered water is reabsorbed into the blood from the tubular lumen, serum osmolality is diluted and corrects downward towards normal.

On the other hand, when serum sodium falls below normal, such as in the hyponatremic patient, ADH secretion is inhibited and collecting duct water is excreted. In the absence of ADH, urine becomes maximally dilute to 50–150 mOsm/KgH_2O which is equivalent to a urinary specific gravity (USG) of approximately ≤1.002–4 (Fig. 13.2). Then, as free water is mobilized and excreted, serum sodium concentrates and corrects upwards toward normal. The human body thus has a wide physiologic range in which water balance and thus serum sodium can be closely regulated through ADH.

The presence of hyponatremia suggests that ADH secretion continues despite the normally inhibitory presence of a hypo-osmotic state. This continued ADH secretion and impaired free water excretion is the underlying pathophysiologic mechanism in most patients with hyponatremia. Occasionally however, ADH may not be the cause of hyponatremia. The determination of ADH vs Non-ADH-mediated hyponatremia is at the foundation of understanding the hyponatremic patient. It is therefore essential to understand the pathophysiology of this hormone.

ADH may be secreted *appropriately* during times of severe volume depletion (depletion of >7 % plasma volume). In this case water retention takes a priority over osmolar regulation. Such is the case in a patient with severe dehydration from diarrhea. If the patient does not have access to water or cannot voice their desire for water (such as an infant, a severely debilitated patient, or an anesthetized patient) then hypernatremia generally ensues due to poorly replaced water loss which is greater than salt loss. If that same patient does have access to water and can respond to thirst, then he or she usually drinks as the hypovolemic state induces intense thirst. In this case, ADH levels are high from *appropriate* hypovolemic ADH release and the ingested water is retained. Because food intake is often minimal until the sickness abates, water is replaced more than salt and ADH-mediated hypovolemic hyponatremia results. The stimulus for ADH secretion may also be independent and not related to osmotic or volume status of the patient. This is considered *inappropriate* and may be seen in the Syndrome of Inappropriate ADH secretion (SIADH), hypothyroidism, and glucocorticoid insufficiency (see below).

In both appropriate and inappropriate ADH secretion, retention of body water through the non-osmotic secretion of ADH is the primary pathophysiologic mechanism. If ADH stimulation were to be inhibited for whatever reason, water would be quickly mobilized and the hyponatremia would correct. A diagnostic approach is outlined using the following steps (Fig. 13.3):

1. Check serum osmolality, BUN, creatinine and potassium, and urine osmolality, USG and urine electrolytes.
2. Determine if the patient has renal failure. If the patient has a GFR <30 mL/min then renal failure-related impaired water excretion is likely the underlying pathophysiology (see below).
3. Hyponatremia is not ADH mediated under two conditions:
   (A) ADH is absent (serum osmolality <280 mOsm/KgH_2O,USG <1.002–4, urine osmolality <100–150 mOsm/KgH_2O)
   (B) ADH is present, but is not the cause of the hyponatremia (Serum sodium >280 mOsm/KgH_2O or GFR <30 mL/min)
4. In the ill hospitalized patient hyponatremia is usually ADH-mediated (the result of ADH excess). If ADH is present serum osmolality should be low (<280 mOsm/KgH_2O) and the urine should be somewhat concentrated (>100–150 mOsm/KgH_2O and USG >1.004–5). You must now determine the reason for ADH secretion. It may be:
   (a) Appropriate from a decreased EABV (i.e. severe dehydration, congestive heart failure)
   (b) Inappropriate from a non-osmotic non-volume related stimulus of ADH release (i.e. SIADH)

Hyponatremia that Is Not Mediated by ADH

Renal Failure: As glomerular filtration and tubular function decline, maximal urinary dilution also declines. In the hyponatremic patient with renal failure, urine osmolality and specific gravity increase and become closer to serum osmolality despite the absence of ADH. Urine therefore becomes closer to isosthenuric (1.008–1.012) as renal failure worsens. It is difficult to clearly define when renal failure-related impaired free water excretion is the primary pathophysiologic mechanism in the hyponatremic state but it is usually seen when GFR falls below 30 ml/min. Renal failure-related hyponatremia cannot be easily categorized using serum and urine osmolality as both may vary but is easily recognized in critically ill patients by an elevated serum BUN and creatinine. These patients are usually volume expanded and are best managed with free water restriction, loop diuretics and dialysis when necessary.

Translocational Hyponatremia: Serum osmolality is primarily a function of serum sodium, blood urea nitrogen (BUN), and glucose as predicted by the equation presented above. Only sodium and glucose, however, induce osmotic water shifts, as BUN is freely permeable across cell membranes and thus is osmotically inactive. When the concentration of an osmotically-active substance (i.e., glucose) rises within the plasma compartment, water moves from the intracellular to the extracellular space and dilutes serum sodium (*translocational hyponatremia*). Earlier evidence suggested that serum sodium decreases by 1.6 mmol/L for every 100 mg/dL increase in plasma glucose above 100 mg/dL [4, 5]. More recent evidence, however, indicates that the correction factor may be closer to 2.4 mmol/L [6]. Translocational hyponatremia may also result when an unmeasured osmole such as mannitol is added to the plasma compartment (Fig. 13.3). This can be detected by the presence of an osmolar gap greater than 10 mOsm/kg H_2O:

$$\text{Osmolar gap} = (\text{measured serum osmolality}) - (\text{predicted serum osmolality})$$

and is often iatrogenic. Substances that may be associated with an osmolar gap but are not osmotically active and which do not result in translocational hyponatremia include ethanol, ethylene glycol, isopropyl alcohol, and methanol.

Pseudohyponatremia: The conventional technique for measuring serum sodium concentration (in mmol/L) is via flame emission spectrophotometry. This technique reports sodium content in a volume containing both the aqueous and non-aqueous phase of serum. The non-aqueous phase consists of serum proteins and lipids which normally account for 7 % of the serum volume. Serum water accounts for the remaining 93 %. Using this technique, an aqueous serum sodium of 142 mmol/L, for example, will be reported as serum sodium of 132 mmol/L (142 mmol × 0.93 serum water

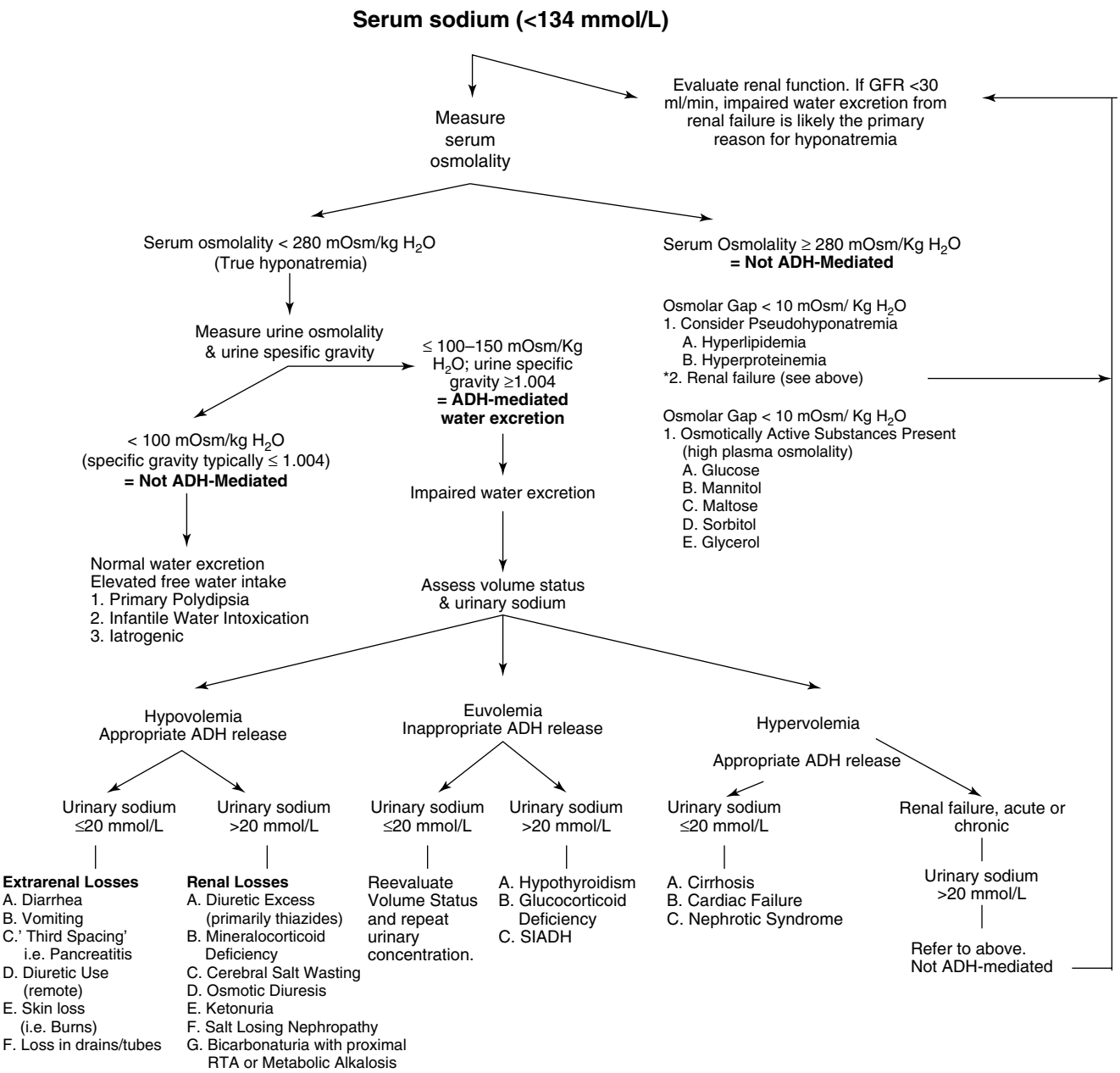

Fig. 13.3 Algorithm for the diagnostic evaluation of hyponatremia. * Note that in renal failure serum osmolality is usually >280 mOsm/KgH_2O but may be <280 mOsm/KgH_2O because of decreased water excretion, these cases will be characterized by high urine osmolality

fraction). During conditions of severe hypertriglyceridemia or hyperproteinemia, the serum water fraction is reduced further and serum sodium may be erroneously reported as true hyponatremia [7]. In this situation, an osmolar gap is not present. It is important to familiarize oneself with the method of determination at your local lab as many health care laboratories now use ion-specific sodium electrodes to measure the sodium concentration in the aqueous phase thus avoiding this problem.

Excess Water Intake: In a few hyponatremia conditions free water excretion is at or near normal and ADH is appropriately suppressed. They are best identified when there is very dilute urine manifested by an osmolality less than 100–150 mOsm/kg H_2O. In this setting, hyponatremia is usually the result of excessive water ingestion (*water intoxication*). While this is uncommon in children, it can occasionally be the result of mistakes in the preparation of infant formula [8] or in fresh water immersion injury (toddlers occasionally swallow substantial amounts of water when wading in a pool). In older children and adolescents with psychiatric disorders, chronic primary polydipsia (psychogenic polydipsia) should be considered.

Hyponatremia that Is Mediated by ADH

Hypovolemic Hyponatremia: Hypovolemic hyponatremia results from loss of both sodium and water. Relative to sodium, however, water is better conserved due to the non-osmotic stimulation of vasopressin release through volume contraction (hormonal response to a reduced EABV). Volume loss may be extra-renal or renal in origin:

1. *Extra-renal Volume Loss*: An extra-renal cause of volume loss is evident when appropriate renal sodium conservation is observed (urinary sodium concentration ≤20 mmol/L). Diarrhea, vomiting, increased ileostomy or surgical drain output, and extravascular volume loss (*third spacing*) all result in relative intravascular volume depletion and renal sodium conservation. It is important to note that when severe vomiting is present, urinary sodium may be elevated, despite significant extra-renal volume depletion. This results from obligate bicarbonaturia which drags sodium with it in order to establish electro-neutrality in the tubular fluid. Occasionally, remote diuretic use may masquerade as an extra-renal cause of hyponatremia if the urine is sampled after the diuretic has already been metabolized. In this situation, urinary sodium will not be high as would be expected with contemporaneous diuretic use but rather will be appropriately low due to volume contraction.
2. *Renal Volume Loss*: A renal cause of volume loss is evident by an inappropriately elevated urinary sodium concentration (>20 mmol/L) despite volume contraction. It may occur as a result of the following conditions – diuretic usage, cerebral salt wasting syndrome, and mineralocorticoid deficiency. Thiazide diuretics cause hyponatremia by impairing urinary dilution and stimulating vasopressin release through intravascular volume depletion. Loop diuretics, however, infrequently cause hyponatremia. These drugs inhibit sodium chloride transport in the loop of Henle, thereby reducing the countercurrent exchange gradient and blunting vasopressin action. Cerebral salt wasting syndrome (CSW) is an important cause of hyponatremia in children with central nervous system diseases [9]. It can lead to rapid decline in serum sodium and acute cerebral edema. This condition has been primarily described in patients with subarachnoid hemorrhage and other forms of central nervous system injury [10, 11]. The primary defect is renal salt wasting (urine sodium >20 mmol/L) and vasopressin release due to intravascular volume depletion. The pathogenesis of the salt wasting has not been fully elucidated but it may result from a direct action of brain natriuretic peptide on the kidney [12]. Serum sodium levels should be closely monitored in all patients with central nervous system injury. The only characteristic which distinguishes CSW from SIADH is the volume status (patients with SIADH are euvolemic). Thus, a very rigorous volume assessment must be performed in the neurosurgical patient with hyponatremia. If volume depletion is detected, CSW is likely and intravenous hydration with isotonic saline, hypertonic saline (3 % saline) or oral salt may be used [9]. Recent reports suggest that fludrocortisone therapy may correct hyponatremia in cases resistant to salt supplementation alone [13]. If no evidence of volume depletion exists, a brief trial of fluid restriction for the treatment of SIADH is reasonable. However, if overt volume depletion subsequently develops or if serum sodium does not improve, CSW becomes more likely and volume expansion with salt supplementation is then indicated. Mineralocorticorticoid deficiency related to Addison's disease in the PICU may be associated with severe hemodynamic failure/septic shock, necrotic purpura, disseminated intravascular coagulation, and massive bilateral adrenal hemorrhage [14–16]. Infection has been noted to directly destroy adrenal tissue and high levels of inflammatory cytokines in patients with sepsis may directly inhibit adrenal cortisol synthesis [17]. In these critically ill children, hyponatremia is frequently multifactorial, but adrenocortical insufficiency contributes to it by causing salt wasting and secondary vasopressin release.

Euvolemic Hyponatremia: In conditions associated with euvolemic hyponatremia, a non-hypovolemic and non-osmotic stimulus induces vasopressin release. There is no evidence of volume depletion or of volume excess. *SIADH* is one of the most common causes of hyponatremia in the inpatient setting and may cause severe hyponatremia (plasma sodium <120 mmol/l) [1]. Vasopressin secretion occurs in the absence of hypovolemic or osmotic stimulus and is diagnosed only after other euvolemic defects of water secretion are ruled out, such as hypothyroidism and glucocorticoid deficiency. *Hypothyroidism* is an uncommon cause of hyponatremia, and is seen in patients with myxedema or severe hypothyroidism. The pathogenesis is unclear but the defect of water balance is reversible with hormone replacement. Similarly, g*lucocorticoid deficiency* causes a dilutional hyponatremia similar to SIADH. Mineralocorticorticoid synthesis is intact and volume depletion is therefore absent. Vasopressin-dependent and independent factors are likely responsible for the hyponatremia [18]. In considering these alternate etiologies, SIADH is therefore a diagnosis of exclusion (Table 13.1). In the PICU, the most common causes of SIADH are intracranial pathology, increased intrathoracic pressure and drugs (Table 13.2).

Hypervolemic Hyponatremia: In hypervolemic hyponatremia, total body sodium and water content are elevated (as often manifested by edema), but water content is elevated to a greater degree. *Decompensated congestive heart failure* causes a reduction in sensed EABV and ADH is secreted as a result. This response is mediated by baroreceptors in the carotid sinus, which sense a reduction in pressure or stretch.

In addition, neurohormonal activation increases proximal tubular water uptake and thereby reduces delivery of free water to the diluting segment. Once heart failure is treated and forward outflow is restored with inotropic medications, loop diuretics and/or afterload reduction, EABV normalizes. As a result, ADH secretion is turned off and hyponatremia may be reversed. *Hepatic failure* such as in patients with severe cirrhosis may also cause hyponatremia. Splanchnic arterial vasodilation and the presence of multiple arteriovenous fistulae in the alimentary tract and skin cause a reduction in EABV which stimulates ADH release. *Nephrotic syndrome* in children may result in extreme urinary albumin loss (especially with minimal change disease) and intravascular volume depletion through a decrease in plasma oncotic pressure. This may provide the stimulus for vasopressin release. Finally, as described previously, r*enal failure* may present with hypoosmotic, hypervolemic hyponatremia that is not ADH-mediated.

Table 13.1 Diagnostic criteria for the Syndrome of Inappropriate Diuretic Hormone Release (SIADH)

Essential diagnostic criteria
1. Decreased extracellular fluid effective osmolality (<275 mOsm/Kg H_2O)
2. Inappropriate urinary concentration (>100 mOsm/kg H_2O)
3. Clinical euvolemia
4. Elevated urinary sodium concentration under conditions of normal salt and water intake
5. Absence of adrenal, thyroid, pituitary, or renal insufficiency Absence of diuretic use
Supplemental criteria
1. Abnormal water-load test (inability to excrete at least 90 % of a 20 ml/kg water load in 4 h and/or failure to dilute urine osmolality to <100 mOsm/Kg H_2O)
2. Plasma vasopressin level inappropriately elevated relative to the plasma osmolality
3. No significant correction of plasma sodium level with volume expansion, but improvement after fluid restriction

Management

Prevention of Acute Hyponatremia

Children with fever, pneumonia, bronchiolitis, and sepsis are susceptible to the development of hyponatremia due to decreased free water clearance and vasopressin excess. Pneumonia, meningitis, and encephalitis are associated with a 20–45 % incidence of hyponatremia [19–23]. In many cases, however, the increased vasopressin levels are the result of hypovolemia, not SIADH [24] and routine fluid restriction in these patients is not recommended. Hypotonic intravenous replacement should be minimized when possible in these individuals [25]. Isotonic replacement (0.9 % saline) can be given (with or without 5 % dextrose) and serum sodium monitored carefully. Desmond Bohn's group from Toronto is credited with first suggesting that administration of hypotonic fluid is the most important factor for hospital-acquired hyponatremia and should be avoided in children with serum sodium levels below 138 mmol/L [26]. Subsequent prospective studies in hospitalized children confirmed that the routine infusion of isotonic solutions (0.9 % saline with or without dextrose) significantly reduces the risk of hyponatremia compared to the infusion of hypotonic solutions, without increasing the risk of hypernatremia [27–30]. Furthermore, these studies showed that the rate of hyponatremia was affected by the tonicity rather than volume of the administered fluid [27, 29, 30]. It is therefore reasonable to conclude that the initial fluid regimen for hospitalized pediatric patients should include an isotonic solution with or without dextrose depending on the patient's risk of hypoglycemia. Sodium administered via other routes (i.e., arterial line fluid) should be taken into consideration, especially in infants. Careful monitoring of serum sodium levels is still required to allow for proper adjustments.

Acute Versus Chronic Hyponatremia

The management strategy for hyponatremia depends on the rapidity of onset and the presence or absence of symptoms. An acute fall in serum sodium (hyponatremia developing

Table 13.2 Common causes of SIADH in children

CNS disorders	Pulmonary disorders	Malignancy	Medications
Meningitis/encephalitis	Pneumonia	Neuroblastoma	Vincristine
Vascular abnormalities	Asthma	lymphoma	Cytoxan (intravenous)
Neoplasms	Tuberculosis	Ewing's sarcoma	Carbamazepine-oxycarbazepine
Psychosis	Pneumothorax		Serotonin reuptake inhibitors
Hydrocephalus	Positive pressure vent		Ifosfamide
Head trauma	Cystic fibrosis		Non-steroidal anti-inflammatory
Pituitary surgery	Pulmonary abscess		Narcotics
Guillain-Barré syndrome	Aspergillosis		Haloperidol
Stroke			
S/P craniotomy			
S/P craniofacial surgery			
S/P spinal fusion surgery			

within 48 h) results in a rise in the gradient between intracellular and extracellular osmolality and water shifts into the intracellular compartment throughout the body. In severe hyponatremia (serum sodium <120 mmol/L), intracellular shift within the brain may result in cerebral edema [31]. Cerebral edema and intracranial hypertension may manifest first as nausea, vomiting, malaise, and headache but then may rapidly progress to lethargy, ataxia, psychosis, seizures, coma, neurogenic pulmonary edema and ultimately cerebral herniation [32, 33]. By 6 years of age, a child's brain reaches adult size but the skull does not reach adult size until 16 years of age. Children under 16 years of age are therefore at increased risk for hyponatremic encephalopathy due to a larger brain to intracranial volume ratio [34, 35]. Menstruating females also appear to be more vulnerable to acute cerebral edema, especially when given hypotonic fluid replacement post-operatively [36, 37].

If the fall in sodium occurs more chronically (over more than 72 h), cerebral edema and neuropsychiatric symptoms are less likely to occur. This is the result of the intracellular adaptation to chronic extracellular hypotonicity. As soon as 3 h after the development of hyponatremia, the brain loses intracellular electrolytes such as potassium and some organic solutes, thereby diminishing the osmotic gradient driving cerebral edema. If the hyponatremia persists for 72–96 h, additional organic osmolytes such as myoinositol, amino acids, and phosphocreatine are lost, thus further completing the process of cellular adaptation [38]. Too rapid a correction of chronic hyponatremia at this stage can produce pontine and extrapontine myelinolysis (PEM), a brain demyelinating disease that can cause substantial neurologic morbidity and mortality [39, 40].

If the patient is asymptomatic, urgent correction of hyponatremia is not mandated and is potentially harmful regardless of the serum sodium level [41–44]. The treatment of hyponatremia without symptoms should be directed towards a thorough diagnostic evaluation and disease-specific therapy (Fig. 13.4). Symptomatic hyponatremia rarely occurs when serum sodium concentration is greater than 125 mmol/L. When neuropsychiatric symptoms of hyponatremia are present, urgent treatment with hypertonic saline is indicated. While the precise correction rate of symptomatic hyponatremia is not known, guidelines may be proposed, which weigh the risk of rapid correction (extrapontine myelinolysis) against the risk of worsening brain edema and further neurologic compromise (Fig. 13.4). For acute hyponatremia (developing over <48 h) with mild neurological symptoms, attempts may be made to correct the serum sodium at a rate of 0.5–1 mmol/L/h with 3 % saline (a solution containing 513 mmol/L of sodium). For acute hyponatremia and severe symptoms, a more vigorous hypertonic saline replacement target is warranted (1–2 mmol/L/h). For chronic hyponatremia (duration >48 h) with mild symptoms, a

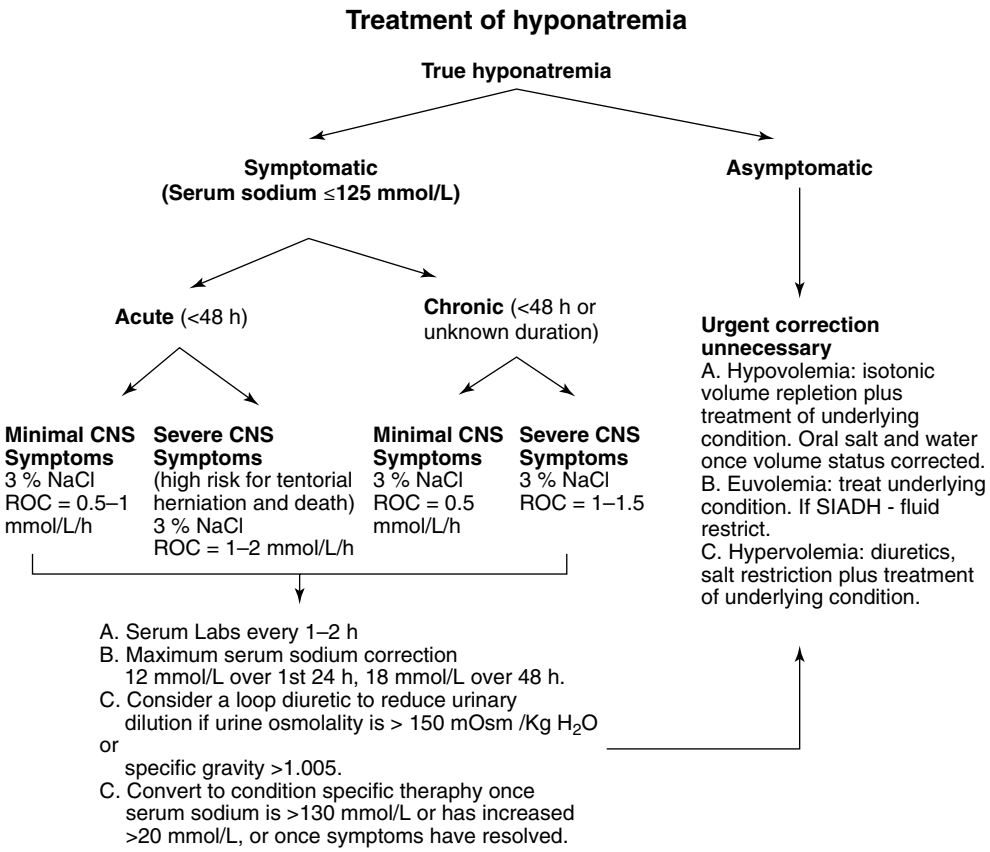

Fig. 13.4 Algorithm for the treatment of hyponatremia. *CNS* Central Nervous System, *ROC* Rate of Correction (of serum sodium concentrations)

lower target serum sodium correction rate of 0.5 mmol/L/h using 3 % saline is reasonable. For chronic hyponatremia with severe symptoms, a correction rate of 1–1.5 mmol/L/h may be used. If the temporal evolution of hyponatremia is unknown, the hyponatremia may be assumed to be chronic in nature.

When adapting the hypertonic saline infusion rate to the target sodium correction rate, it is important to note that an infusion of 1 mL/kg/h of 3 % saline corresponds to a correction rate of approximately 1 mmol sodium/L/h, assuming ongoing isotonic fluid loss. The correction rate will be faster or slower if ongoing loss is not isotonic. For example, because urine is typically the body fluid which represents the greatest volume loss, when urine is more dilute relative to serum sodium [urine sodium $_{(mmol/L)}$ + urine potassium $_{(mmol/L)}$ < serum sodium $_{(mmol/L)}$] serum sodium correction may be expected to be more rapid but less rapid if concentrated [urine sodium $_{(mmol/L)}$ + urine potassium $_{(mmol/L)}$ > serum sodium $_{(mmol/L)}$].

Laboratory monitoring should be performed at 1–2 h intervals during periods of rapid correction, and a loop diuretic may be added if needed to inhibit urinary concentration. Hypertonic saline infusion should be discontinued when symptoms resolve, serum sodium reaches 130 mmol/L, or serum sodium has increased >20 mmol/L [45, 46]. Once symptoms resolve, therapy should become disease-targeted. If correction has exceeded the target sodium level, subcutaneous dDAVP and hypotonic fluid (5 % dextrose in water) may be given to reduce serum sodium concentration to the pre-designated correction goal. This may reduce the risk for central pontine myelinolysis [39].

Treatment of SIADH

The cornerstone of therapy for SIADH lies in fluid restriction (typically to 65 % maintenance) but correction is often slow, and may be impractical in infants who receive most of their nutrition as liquid. Alternatively, agents which inhibit medullary osmolality such as loop diuretics [47] or which directly inhibit the vasopressin effect on the collecting duct such as demeclocycline [48] can be used. The ideal therapeutic agent is a vasopressin-2 (V_2) receptor antagonist, which blocks binding of vasopressin to its site of action in the collecting duct [49, 50]. Intravenous conivaptan and oral tolvaptan are available for use in adult patients. These medications have been shown to be very reliable and effective to date [51] and long-term studies have confirmed their safety [52]. There have been no reports of osmotic demyelination associated with their use. Currently, such agents are in clinical trials and are not yet approved for general clinical use in the pediatric population.

Hypernatremia

The incidence of hypernatremia (serum sodium >145 mmol/L) in the intensive care setting approaches 6 % [53]. In both children and adults, hypernatremia most commonly develops during hospitalization rather than prior to admission [54, 55]. This is frequently due to an inappropriate fluid prescription or lack of identification of the patient's limited access to free water [54]. In the PICU, additional contributing factors include renal concentrating defects, inappropriate dialysis, and a higher incidence of restricted free water access. In children, hypernatremia is associated with a mortality rate of 15 % which is 15-fold higher than that of hospitalized children without hypernatremia [55]. Increased duration of hypernatremia and advanced neurologic impairment seem to be associated with a worse prognosis [55, 56]. Patients with liver failure appear to have an especially high mortality [57, 58]. It is therefore imperative to identify disorders of water metabolism so that hypernatremia may be avoided and rapidly corrected when present.

Pathophysiology

Excessive sodium ingestion, reduced free water intake and decreased water conservation due to either renal, extrarenal, or insensible losses result in hypernatremia. Disorders of water intake and renal water conservation require special mention.

Decreased Water Intake

While thirst is not present until serum osmolality reaches 2–5 mOsm/Kg H_2O greater than the threshold for vasopressin release, it is the single most important defense against significant water depletion and thus against hypernatremia. Even when severe disorders of water conservation exist, such as central diabetes insipidus, patients with intact thirst mechanism may drink enough water daily (up to >12 l) to compensate for water loss. However, when thirst is not intact or access to water is restricted, such as in the intensive care setting or in babies who depend on their caregivers to provide water, thirst cannot drive water intake. Severe hypernatremia may then result. While the pediatric intensivist frequently battles fluid overload, it is also essential to provide critically ill patients with appropriate water repletion to prevent hypernatremia.

Renal Water Loss (A Disorder of Urinary Concentration)

When plasma osmolality rises above 275–280 mOsm/Kg H_2O, vasopressin is released. Vasopressin is stimulated maximally at a plasma osmolality above 290–295 mOsm/Kg H_2O (plasma sodium concentration generally 145–147 mmol/L). With the aid of normal kidney function, vasopressin works at the level of the medullary collecting duct to produce maximal water conservation through the concentration of urine. Optimal urinary concentration (up to 1,200 mOsm/Kg H_2O) requires vasopressin, normal responsiveness to vasopressin at the level of the medullary collecting duct, and sufficient medullary interstitial hypertonicity.

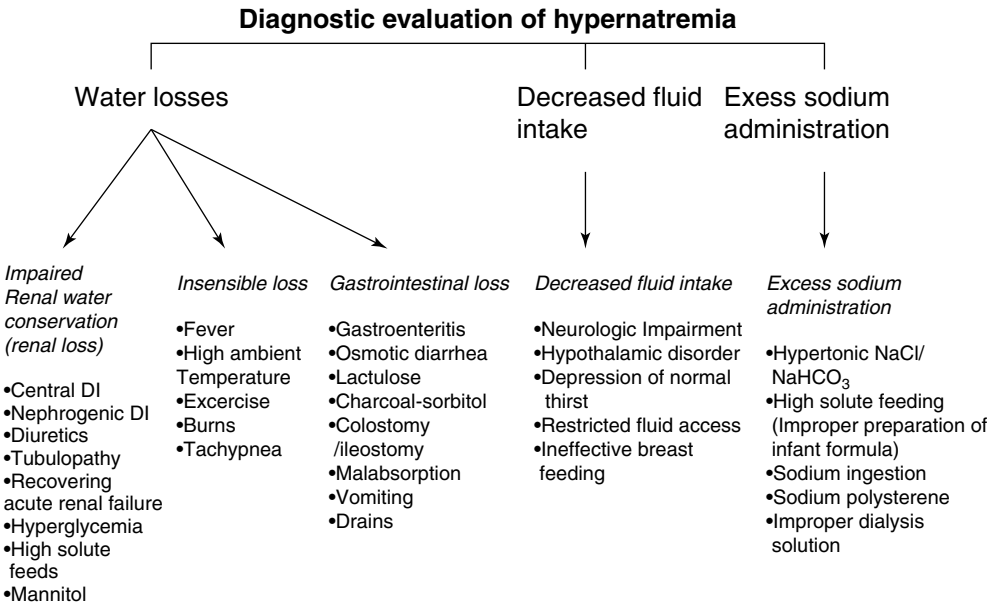

Fig. 13.5 Algorithm for the diagnostic evaluation of hypernatremia

Conditions which diminish vasopressin release (i.e. central diabetes insipidus) result in severe hypernatremia and renal water loss. Nephrogenic diabetes insipidus presents as a decreased responsiveness to vasopressin and thus results in renal water loss and hypernatremia. Water loss, however, is generally less severe compared to central diabetes insipidus. Medullary hypertonicity is the driving force of urinary concentration at the medullary collecting duct. A reduction in medullary hypertonicity equates to a reduction in potential vasopressin effect. Optimal medullary hypertonicity is made possible by the countercurrent exchange mechanism driven by the sodium/chloride exchanger in the loop of Henle. Loop diuretics and renal disease impair this process and thus decrease urinary concentrating ability.

Diagnosis and Management

A thorough history and review of fluid intake and output is critical to the evaluation of hypernatremia. If a patient has an intact thirst mechanism, access to free water should be evaluated. If access is restricted, then reduced free water intake may be instrumental to the development of hypernatremia. If access is unrestricted, ongoing water loss or sodium gain may be too high to be effectively replaced by water intake, especially if the underlying clinical status of a patient has deteriorated. An algorithm to evaluate hypernatremia is outlined in Fig. 13.5. Generally speaking, when hypernatremia is caused by extra-renal water loss, vasopressin release results in effective urinary concentration (urine osmolality greater than 800 mOsm/kg H_2O), while urinary osmolality less than 800 mOsm/Kg H_2O represents a urinary concentration defect. A severe defect in urinary concentration (urine osmolality less than 300 mOsm/Kg H_2O) usually results either from central diabetes insipidus (vasopressin deficiency) or nephrogenic diabetes insipidus (vasopressin resistance) as reviewed below. An intermediate urinary value (urinary osmolality between 300 and 800 mOsm/Kg H_2O) is usually due to partial diabetes insipidus (central or nephrogenic) or osmotic diuresis.

Osmotic water losses are most commonly due to urinary glucose loss, but may be also iatrogenic (i.e., mannitol) or due to high protein intake (urinary urea loss) [59]. It may be diagnosed by measuring the total daily urinary solutes excretion (in mOsm/Kg BW/day), the product of urinary osmolality and urinary volume. Urine osmoles consist primarily of sodium, potassium, chloride, ammonium salts, and urea excretion. On a normal diet, one should dispose of 8–13 mOsm/Kg BW/day. A value ≥14 mOsm/Kg BW/day (1,000 mOsm total for a 70 kg patient) suggests that osmotic water loss is at least partially responsible for the hypernatremia.

Diabetes insipidus is classified into central diabetes insipidus (CDI) and nephrogenic diabetes insipidus (NDI). CDI results from reduced or absent hypothalamic vasopressin release. The most common causes in PICU patients are central nervous system infections, brain tumors, head trauma, intracranial hemorrhage, deceleration injury, pituitary surgery and Guillain-Barré syndrome. Patients diagnosed with neurologic determination of death (brain death) frequently develop CDI. CDI presents as an abrupt polyuria (often >8 mL/kg/h) with high grade free water excretion. When patients have restricted access to water, severe hypernatremia may result. On the other hand, NDI generally has a lower degree of polyuria (generally <6 mL/kg) and results from a varying degree of renal resistance to the action of vasopressin despite its normal release. NDI is most commonly seen in chronic kidney disease but may be evident in other more acute forms of tubular damage such as amphotericin or

foscarnet-induced renal toxicity. Hypokalemia, hypercalcemia, lithium toxicity, pregnancy, partial urinary obstruction and sickle cell disease are other causes of acquired NDI in the ICU. Resolving acute renal failure may also manifest as a renal concentrating defect due to residual tubular damage, the so called "polyuric phase of acute tubular necrosis." In most cases, the distinction between CDI and NDI can be easily established on clinical grounds. Otherwise, the diagnosis can be made using the vasopressin stimulation test. When vasopressin release is maximally stimulated (i.e., serum sodium greater than 145 mmol/L), administration of desmopressin (dDAVP), a V_2 receptor agonist should have a substantial effect on urinary concentration in the setting of CDI but not on NDI. A greater than 50 % increase in urine osmolality is considered consistent with CDI. A less than 10 % increase is compatible with NDI. An increase of 10–50 % may be a result of either partial CDI or partial NDI.

Finally, it should be noted that infants presenting with extreme hypernatremia (serum sodium >160 mmol/L) almost invariably suffer from one of two conditions: improper formula dilution or inadequate breast milk production without formula supplementation. Differentiating these two etiologies can be ascertained by history. In the latter case, a reduction in free water intake, in addition to a rise in milk sodium concentration (which occurs during periods of dwindling milk production), contributes to the infantile hypernatremia [60].

Acute vs Chronic Hypernatremia

Hypernatremia results in cellular dehydration due to osmotic fluid shifts from the intracellular to the extracellular space. When severe hypernatremia occurs acutely, cerebral dehydration may result in a reduction of brain cell volume by as much as 10–15 % [61], which may lead to venous sinus thrombosis [62] or even physical separation of the brain from the meninges causing bridging vein rupture and intracranial hemorrhage [63, 64]. In addition, severe hypernatremia may cause cerebral demyelinating lesions [61, 65]. Children with hypernatremia may present with restlessness and irritability, which may progress to lethargy, confusion, somnolence and coma [66]. Other physical manifestations may include muscular twitching, myoclonus, asterixis, chorea, hyperreflexia, and seizures. Associated hyperglycemia and rhabdomyolysis have also been described [67]. Cellular adaptation to hypernatremia opposes osmotic fluid shifts in a manner which is the mirror image of the adaptation in hyponatremia. Within an hour of the osmotic change, intracellular increases in sodium, potassium and chloride protect the brain from dehydration [38]. Increases in organic osmolytes ("idiogenic osmoles") such as glycerolphosphorylcholine, glutamine and myoinositol complete the adaptation process but take several days to reach full effect [68]. Within a week, the brain regains 98 % of its water content. Chronic hypernatremia is therefore less likely to have neurological sequelae unless severe.

The goal of therapy is to replace the free water deficit, the total volume deficit, and ongoing losses. The rate of correction is dependent on the presence or absence of neurological symptoms and the chronicity of the hypernatremia. If the patient is asymptomatic, the risk of cerebral edema incurred with rapid correction of hypernatremia (especially if hypernatremia is chronic) is not warranted. While there are no definitive studies that define the optimal rate of correction, three studies in children suggest that a correction rate of ≤0.5 mmol/L/h is most prudent [69–71]. In one study [70] no seizures occurred in those corrected at this rate whereas a 20 % incidence of seizures occurred in those corrected more rapidly. In another study multivariable logistic regression analysis performed on data from 97 children with hypernatremic dehydration showed that cerebral edema was primarily associated with a high rate of rehydration, with a cut-off at around 7 ml/kg/h [71] of fluid administration. In severe hypernatremia (>170 mmol/L) serum sodium should not be corrected to below 150 mmol/L in the first 48–72 h [72]. Seizures occurring during the correction of hypernatremia may be a sign of cerebral edema and are not uncommon; they are usually self-limited, may be managed by reducing the rate of serum sodium correction and have not been associated with long term sequelae [73, 74]. Of note, oral hydration may be a safer alternative when hypernatremia is acute, and has been associated with a low incidence of seizures [75]. The type of hypotonic fluid replacement and treatment strategy depend on the underlying pathogenesis of the hypernatremia and the volume status of the patient. In moderate hypernatremia, first priority should be given to the gastrointestinal tract as the route of replacement, and intake and output need to be closely monitored to ensure adequate free water supplementation. Hypernatremia is frequently associated with peripheral insulin resistance leading to hyperglycemia, which may worsen the hyperosmotic state. Glucose levels should therefore be monitored carefully.

Clinical Example: A 12 month infant with a pre-illness weight of 10 kg presents with hypernatremic dehydration (serum sodium 160 mmol/L) and a 2-day history of profuse watery diarrhea. This child can be ***initially*** treated by calculation of the following:

1. *Estimate the total volume deficit*: this child's pre-illness weight was 10 kg, and based on history, physical examination and the current weight of 9 kg, the total volume deficit is likely to be 1 L (10 % body weight [BW]).
2. *Calculate the free water deficit and determine the rate of desired correction*. The formula for water deficit is:

$$H_2O_{def} = (\text{estimated body water fraction}) * (\text{current weight}_{(\text{kg})}) * (\text{plasma sodium} / \text{normal plasma sodium} - 1)$$

Using an estimated body water fraction of 0.6, this child's water deficit was calculated to be 0.77 l (770 mL). Given the absence of neurological symptoms, a reasonable initial sodium correction rate would be 0.5 mmol/L/h. Ignoring ongoing water loss or gain, to reduce serum sodium from 160 to 140 mmol/L at that rate would require a water infusion rate of about 19 mL/h [770/(160–140) * 0.5].

3. *Calculate the remaining volume replacement*. Since 770 mL of the 1 L volume deficit was already determined to be free water, the remaining 230 mL of the volume deficit can be replaced over 24 h with normal saline (9.5 mL/h). This may be considered to be the *isotonic fluid losses*.
4. *Ongoing losses* should be replaced: diarrhea in this child is estimated to be 400 mL/24 h and can be replaced at 16.6 mL/h with 0.3 % saline with 40 mmol/L of potassium chloride added to each 1 L mixture. This replacement fluid was chosen as it best estimates the electrolyte content of the diarrhea. Bicarbonate losses may, however, be significant and some of the sodium chloride should then be replaced with sodium bicarbonate.
5. *Maintenance fluids*: in this child, maintenance requirements can be considered to be 1,000 mL/day, which under normal conditions can be replaced by 5 % dextrose in 0.3 % saline at 40 mL/h.

In summary, the predetermined amount of deficit replacement and maintenance fluid can be added into one bag (calculating the total water and sodium content of these three solutions will end up in 71.5 mL/h of 0.3 % saline). The ongoing losses can be replaced from a second bag.

It is imperative to remember that there is no substitute for frequent monitoring, as these figures/calculations are only estimates and may vary depending on differences in clinical assessment and actual ongoing losses and response to treatment. During periods of rapid correction, serum electrolytes should be measured hourly and hypotonic infusions adjusted accordingly. Likewise, urine must be monitored on a regular basis to evaluate renal response to treatment. A (urine sodium $_{(mmol/L)}$ + urine potassium $_{(mmol/L)}$) that is less than serum sodium indicates poor urine concentrating ability and requires increased water replacement, while the reverse indicates adequate renal response and may require a decrease in water replacement.

While the precise correction rate of symptomatic hypernatremia is not known, the clinician must weigh the risk of rapid correction (worsening cerebral edema) against the risk of further hypernatremia-associated neurologic deterioration. If symptoms are present, the free water deficit may be corrected quickly (up to a 2 mmol/L/h decrease in serum sodium in acute hypernatremia and 1 mmol/L in chronic hypernatremia) with hypotonic fluids. During rapid correction, neurologic examinations should be performed hourly and the rate of free water correction reduced if neurologic symptoms improve. The goal during rapid correction is to replace half of the water deficit during the first 12–24 h with the remainder of the deficit replaced thereafter. Serum sodium levels are targeted at 147–149 mmol/L.

If CDI is present, supplemental intranasal, subcutaneous, or intravenous dDAVP is very effective. After treatment is initiated, the cause of the underlying vasopressin deficiency should be fully evaluated typically including brain imaging studies such as MRI. If NDI is present, the mainstay of therapy is careful replacement of ongoing water loss. In protracted cases, thiazide diuretics may be used as they have a paradoxical antidiuretic effect [76].

Hypervolemic hypernatremia is frequently encountered in patients who have multiorgan system failure including acute renal failure, heart failure, and liver failure. These patients have often received generous saline hydration during their initial resuscitation resulting in both sodium and water overload (sodium overload > water overload). Ongoing gastrointestinal and urinary free water loss may worsen hypernatremia. A combination of a loop diuretic and replacement fluid containing glucose only is the mainstay of treatment for this hypervolemic state. Sodium should be removed from all oral and intravenous fluids including intravenous medications. Occasionally, hypervolemic hypernatremia cannot be corrected despite appropriate diuretic management, and dialysis may be indicated. This most commonly occurs in severe renal failure and occasionally in salt poisoning. Continuous venovenous hemofiltration is the preferred mode of dialysis as it allows slow, well-controlled correction of serum sodium. Hemodialysis or peritoneal dialysis may also be used when continuous renal replacement therapy is not available.

Disorders of Potassium Homeostasis

Potassium is the most important intracellular ion and disorders of potassium metabolism are frequent in critically ill children. Intracellular potassium concentration is 150–160 mmol/L (or mEq/L), while normal extra-cellular fluid (ECF) concentration is 3.5–5 mmol/L. As is the case with other primarily intracellular ions, ECF levels do not accurately represent potassium body stores. A non-linear relationship exists between serum potassium and whole body potassium (Fig. 13.6). This relationship suggests that lower serum potassium levels are insensitive to potassium repletion, while higher serum potassium levels are very sensitive to potassium repletion. This phenomenon is the result of replenishment of serum potassium from intracellular potassium during deficiency states. Arterial plasma potassium concentrations are about 0.5 mEq/L lower than venous serum levels [78]. This may result from difference in pH, sampling

Fig. 13.6 Relationship between serum potassium and whole body potassium deficit or excess. The response to a given dose of potassium repletion varies depending on the whole body potassium (Modified from Marino [77]. With permission from Wolter Kluwers Health)

technique (risk of hemolysis) and presence of heparin in the arterial sample.

Potassium regulates enzymatic reactions such as glycogenesis and reactions involving mitochondrial oxidative metabolism. It has a central role in muscle and nerve excitation. It is also critical for the control of osmotic gradients across the cell membrane and for acid-base balance. Despite the small proportion of ECF potassium, even slight abnormalities in serum levels may cause significant pathology. Potassium homeostasis is regulated by aldosterone, which controls potassium secretion by the colon, sweat gland and salivary glands, as well as the rate of the distal sodium-potassium exchange process, which results in potassium excretion. Serum potassium itself regulates aldosterone secretion.

Potassium and hydrogen ions compete for their exchange with sodium in cells. A rise in potassium ion concentration in the extracellular fluid will increase its movement into the cells at the expense of hydrogen ions, resulting in metabolic acidosis, while a rise in hydrogen ions will result in hyperkalemia. This effect is usually transient and seems to occur with "mineral" acid load but not with organic acidemias (i.e. lactic acidosis) and ketoacidosis [79]. Likewise, a drop in hydrogen ion in ECF during alkalosis will result in increased intracellular shifting of potassium and result in hypokalemia, although the magnitude of this effect is usually very mild. For unclear reasons, respiratory acidosis and alkalosis have only a mild effect on extracellular potassium concentration [80].

Hypokalemia

Pathophysiology

Hypokalemia is one of the most common electrolyte disorders encountered in critically ill children. Common causes of hypokalemia in critically ill children are presented in Table 13.3. Additional causes that are rarely seen in the PICU can be found in Reference [81]. The most common cause of hypokalemia in the PICU is the use of diuretics such as furosemide, bumetanide, ethacrynic acid, thiazides and acetazolamide. Combination of two diuretics that act at different sites of the nephrons (e.g. a loop diuretic and a thiazide) increases the likelihood that hypokalemia will develop [82]. Alkalosis (respiratory or metabolic) is also a common cause for hypokalemia. Hypokalemia, in turn, contributes to bicarbonate reabsorption and alkalosis and since aggressive diuresis often results in hypochloremia and intravascular volume depletion, both of which accentuate metabolic alkalosis, these three conditions can potentiate each other. Since hypothermia also causes hypokalemia [83], potassium repletion in hypothermic patients should be approached with caution as levels may rise acutely during rewarming.

Pseudohypokalemia can be seen in myeloproliferative disorders and is related to the uptake of potassium by the white blood cells [84]. Beta receptor agonists cause a shift of potassium ions into the cell, and hypokalemia has been reported after dopamine and dobutamine infusions [85].

Table 13.3 Important causes of hypokalemia in critically Ill children

Hypokalemia without potassium deficit	**Hypokalemia with potassium deficit**
Pseudohypokalemia	Inadequate intake
Myeloproliferative disorder	Renal losses
Same as pseudohyponatremia	Metabolic alkalosis
Alkalosis	Diabetic ketoacidosis
Hypothermia	Diuretics
Beta adrenergic agonists (including inhaled bronchodilators)	Hyperaldosteronism
Insulin	Excessive adrenal corticosteroids
	Antibiotics
	Amphothericin B
	Gentamicin
	Carbenicillin
	Ticarcillin
	Aminophylline
	Tubular disorders (including proximal and distal RTA)
	Hypomagnesemia
Potassium deficit without hypokalemia	Osmotic diuresis
Acidosis	Cisplatin
Uremia	Gastrointestinal losses
Congestive heart failure	Vomiting, NG suction, diarrhea
	Ureteral sigmoidostomy
	Obstructed ileal loop
	Excessive sweating
	Hypernatremia

Table 13.4 Hypokalemia: clinical manifestations

Metabolic alkalosis	**Neuromuscular**
Depressed intestinal parasympathetic response	Mental status changes
Decreased motility	Precipitation/exacerbation of hepatic encephalopathy
Intestinal dilatation/paralytic ileus	Coma
Abdominal cramps, anorexia, nausea, vomiting	Muscle weakness, cramps, paresthesias
Renal	Respiratory muscle weakness
Impaired urine concentrating ability, polydypsia, polyuria	Depressed deep tendon reflexes
Renal tubular damage (hypokalemic nephropathy)	Cranial nerve weakness
Renal cyst formation	Tetany
Phosphaturia	Rhabdomyolysis
Cardiac	**Impaired glucose tolerance**
Worsening congestive heart failure	**Edema**
Dysrhythmias	
ECG changes	
Vasodilatation, orthostatic hypotension	

Patients with severe status asthmaticus are at a particular risk for hypokalemia since inhaled or intravenous beta agonists, theophylline and diuretics, all of which cause hypokalemia, are frequently used in these patients. These drugs may have also served as a predisposing factor to beta agonist-induced dysrrhythmias and sudden death in these patients [86]. High levels of endogenous cathecholamines may also cause hypokalemia after severe trauma [87] or cardiac arrest [88].

Clinical Manifestations (Table 13.4)

Hypokalemia may be life threatening, particularly in the patient with compromised myocardial function. Levels below 3.5 mmol/L predispose patients to ventricular ectopy. ECG changes are seen when the serum level drops below 3 mmol/L. Typical electrocardiographic changes include T-wave flattening or inversion, ST segment depression and a U wave (Fig. 13.7). Arrhythmias may include sinus bradycardia, heart block, a-v dissociation, atrial flutter, paroxysmal atrial tachycardia, ventricular tachycardia and ventricular fibrillation. Despite potassium being primarily an intracellular ion, the development of ventricular tachycardia has been shown to correlate with depressed serum potassium levels and not with intracellular potassium levels, measured in erythrocytes [89]. Bradyarrhythmias are frequently related to vagal hyperresponsiveness and respond well to atropine [90]. Mental status changes can be influenced by serum potassium level and range from lethargy, confusion, delirium, irritability up to (rarely) coma.

Management

Potassium infusions may be dangerous, especially in patients with compromised renal function. Enteral replacement has similar efficacy and safety profiles as intravenous replacement in PICU patients [91] and is the preferred mode of administration when possible. In patients with severe hypokalemia associated with life-threatening complications, KCl at a dose of 0.5–1 mmol/kg body weight (BW) may be infused intravenously over 1–2 h under continuous cardiac monitoring. Additional doses may be added, but serum potassium levels must be measured prior to each dose. The response to potassium administration depends on the degree of potassium depletion and is not linear (Fig. 13.4). Particular caution must be exercised in patients with mild hypokalemia, as the response to potassium repletion may reach the "inflection point" and result in over-correction. Many institutions have adopted pharmacy-regulated policies for potassium repletion to avoid the untoward consequences of over-correction.

Hyperkalemia

Pathophysiology

Common causes of hyperkalemia in critically ill children are presented in Table 13.5. Additional causes that are rarely seen in the pediatric ICU can be found in Reference 92. Patients with normal renal function and insulin secretion can usually tolerate a considerable potassium load. Iatrogenic hyperkalemia is unfortunately not infrequent, due to either miscalculation of the potassium dose or rate of administration, or rapid administration of large volumes of whole blood. Rapid rise in potassium levels during correction of hypokalemia can produce cardiac toxicity even when the final potassium concentration is within normal limits [92]. Shifting of potassium from the intracellular fluid to the ECF can occur as a result of acidosis, amino acid infusion (positively charged amino acids taken up by the cells are exchanged for potassium), and osmotic agents such as mannitol (which pull water out of cells along with potassium). Beta adrenergic receptor antagonists, alpha agonists, digoxin and nifedipine [93] may cause hyperkalemia by inhibiting cellular potassium uptake. Succinylcholine releases potassium from skeletal muscle during depolarization. In normal children, an increase of about 0.5 mmol/L in serum potassium level is expected following succinylcholine dosing. In patients with neuromuscular disorders, burns and extensive crush trauma this increase may be dramatic and cause life-threatening hyperkalemia so that succinylcholine is contraindicated in these conditions. Heparin, prostaglandin inhibitors and angiotensin converting enzyme inhibitors cause hyperkalemia by inhibiting aldosterone production [89]. Pseudohyperkalemia can be the result of a hemolyzed

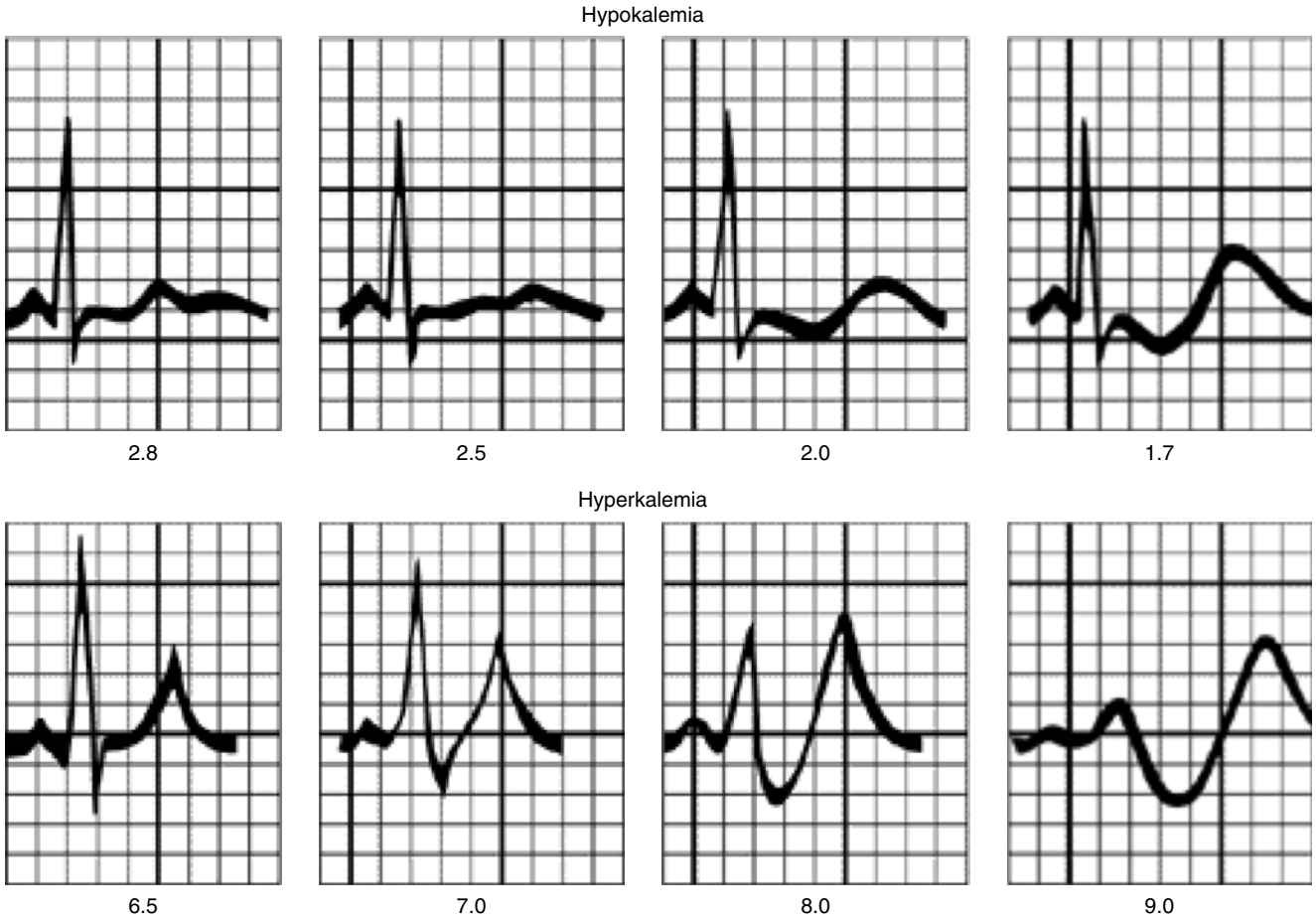

Fig. 13.7 Progression of ECG changes in hypokalemia and hyperkalemia. Serum potassium is in mmol/L. See text for detail (Reprinted from the Merck Manual of Diagnosis and Therapy, edited by Robert Porter. Copyright 2004–2008 by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc, Whitehouse Station, NJ. With permission from Merck Sharp & Dohme Corp)

blood specimen through prolonged tourniquet application (especially with opening and closing of the hand), by rapid withdrawal of blood from small cannulae, by delay in specimen processing, and by measurement of potassium in plasma in the presence of thrombocytosis (in which case potassium is released from platelets during the coagulation phase).

Clinical Manifestations

The primary threat of hyperkalemia is that of ventricular dysrhythmias and cardiac arrest secondary to its effects on cardiac excitability and conduction. Initial ECG changes include peaked T-waves in the precordial leads, followed by decreased R wave amplitude, widened QRS complex, prolonged PR interval, then decreased amplitude and disappearance of P waves (Fig. 13.7). Finally, the QRS blends into the T wave, forming the classic sine wave of hyperkalemia. Since ventricular dysrhythmias and cardiac arrest may occur at any point in this progression, immediate intervention is critical. Unfortunately, hyperkalemia renders the myocardium resistant to excitation by external pacemakers. Neuromuscular effects of hyperkalemia include muscle weakness with decreased deep tendon reflexes, positive Trousseau sign, and muscle cramps. The ascending paralysis may involve the respiratory muscles, and the resultant hypoxia may accelerate the cardiac effects.

Management

Treatment of hyperkalemia depends on the serum level, the hemodynamic status of the patient, the underlying cause and the presence or absence of renal failure. In patients with high potassium levels and ECG changes, treatment is based on three mechanisms: rapid counteraction of the effect of potassium, shifting potassium into the cell, and removal of excess potassium.

1. Immediate resuscitation
   (a) Intravenous $CaCl_2$ infusion, 20 mg/Kg BW over 1–5 min. This is *the fastest* (although transient) means to counteract the effect of potassium. $CaCl_2$ acts within minutes and lasts about 30 min.

Table 13.5 Important causes of hyperkalemia in critically Ill children

Hyperkalemia without potassium excess	**Hyperkalemia with potassium excess**
Pseudohyperkalemia	Increased intake
Hemolyzed sample	Potassium-containing antibiotics
Prolonged tourniquet application	Massive cell necrosis
Thrombocytosis (>1 million/mm3),	Rhabdomyolysis
Leukocytosis (>l00,000/mm3)	Hemolysis
Transcellular shift	Tumor lysis syndrome
Acidosis	Burns
Acute increase in osmolality	Crush injury
Amino acid infusion	Gut or limb ischemia
Drugs	Reabsorption of a large hematoma
Succinylcholine	Decreased excretion
Alpha adrenergic agonists	Renal failure
Beta adrenergic blockers	Renal transplantation
Digitalis intoxication	Sickle cell disease
Nifedipine	Urinary tract obstruction
Vigorous physical exercise	Potassium sparing diuretics (spironolactone)
Cirrhosis	Adrenal insufficiency
Potassium excess without hyperkalemia	Hypoaldosteronism
Alkalosis	Drugs
	Angiotensin converting enzyme inhibitors
	Nonsteroidal anti-inflammatory drugs
	Cyclosporine
	Pentamidine
	Heparin

(b) Intravenous glucose (1 g/Kg BW) and insulin (0.2 U/Kg BW) bolus over 15–20 min and then continued as a slower infusion. This would move potassium into the cells temporarily. Onset of action is in about 30 min and the effect lasts several hours [85]. This is *the most effective* way to lower serum potassium levels [94].

(c) Intravenous sodium bicarbonate 1–2 mmol/Kg BW over 5–10 min, also shifts potassium into cells (acts within 30–60 min for several hours).

(d) NaCl bolus with intravenous furosemide 1 mg/kg BW

(e) Inhaled albuterol (acts within 30 min and lasts for 2 h)

Note: In life-threatening situations, concomitant use of all or some of the above interventions simultaneously may be necessary.

2. Removal of excess potassium

(a) Kayexalate (a cation exchange resin polystyrene sulfonate), 1 g/kg BW P.O, NG or PR (provides more rapid effect) mixed with 30 ml of 50 % sorbitol (to prevent constipation). When given as enema, this mixture should be retained for at least 30 min, and may be repeated as needed. Each treatment usually results in a decrease in serum potassium levels by 0.5–2 mmol/L. Side effects of Kayexalate include increased sodium absorption and hypervolemia, hypocalcemia and hypomagnesemia.

(b) Patients with renal failure may require dialysis to remove excess potassium. Hemodialysis is more effective than peritoneal dialysis, and can lower serum potassium within an hour [95, 96]. Rebound in potassium levels should be expected.

Disorders of Magnesium Homeostasis

The important role of magnesium in numerous metabolic processes has been increasingly recognized. This primarily intracellular ion participates in a number of enzymatic reactions including those mediated by phosphokinases and phosphatases involved in energy metabolism [97]. Magnesium-sensitive ATPases hydrolyse ATP and regulate the flow of potential energy from the mitochondria that is necessary for the function of ion pumps and thus is critical for cell survival. Adenylate cyclase is also a magnesium-dependent enzyme [98], and protein and nucleic acid synthesis, neuromuscular transmission, cardiac excitability, vascular tone and potassium and calcium channels are all regulated by intracellular magnesium.

About 5–15 % of intracellular magnesium and 55–65 % of ECF magnesium are in ionized form [99] that participates in cellular metabolism. About 30 % of the bound magnesium is bound to protein and the rest is in the form of salts (phosphate, oxalate and citrate). Assessment of body magnesium stores is difficult and controversial. One of the challenges to interpretation of magnesium deficiency states is that only 1–2 % of total body magnesium stores are in ECF where its concentration is usually measured in the clinical setting [100]. Furthermore, ionized magnesium serum levels are not readily available and frequently inaccurate while total magnesium serum levels may be misleading, especially in critically ill patients with hypoalbuminemia. In one study, 60 % of PICU patients with ionized hypomagnesemia had normal total serum magnesium levels [101]. Laboratories that do not have whole-blood analyzers with magnesium-selective electrodes measure ultrafilterable magnesium levels as proxy for ionized magnesium levels; however, this measurement has substantial disadvantages compared to ionized magnesium measurement and does not distinguish

between ionized magnesium and magnesium bound to organic and inorganic ions and fatty acids [101]. Opinions in the literature broadly range in their recommendations for measuring magnesium including: a suggestion to measure ionized magnesium serum levels in all ICU patients [101, 102]; that levels should be measured in erythrocytes, to reflect intracellular stores [103]; that erythrocyte levels oscillate and have no clinical value [104]; that there is poor correlation among intracellular magnesium levels in different organs (i.e., muscle and myocardium), and finally, that serum magnesium levels may have no clinical importance and are merely an epiphenomenon [105]. Nevertheless, abnormal total serum magnesium concentrations are the earliest sign of magnesium depletion [106], correlate well with bone magnesium content [107], and are associated with clinical consequences and there exists a general consensus that they should therefore be corrected.

Magnesium body content is balanced by intestinal absorption (primarily in ileum and jejunum), where low magnesium intake results in as high as 80 % absorption and high magnesium intake reduces absorption to as low as 25 %. Magnesium absorption is linked to water absorption and prolonged diarrhea frequently results in hypomagnesemia. Excess lipids in stool from patients with steatorrhea bind magnesium and will also lead to magnesium malabsorption. The kidneys regulate serum magnesium very tightly such that even a slight fall in ECF magnesium concentration leads to abrupt decrease of its renal excretion. Renal magnesium excretion is enhanced by ECF volume expansion, hypermagnesemia, hypercalcemia, phosphate depletion, metabolic acidosis (such as during diabetic ketoacidosis), and a number of drugs (Table 13.6). Most renal magnesium wasting states are associated with hypokalemia, with the exception of cyclosporine-induced renal magnesium wasting that is associated with hyperkalemia or normokalemia. Magnesium wasting quickly resolves upon discontinuation of cyclosporine therapy [113]. Since transplant patients frequently are exposed to drugs listed in Table 13.6, it is not surprising that hypomagnesemia is frequently encountered after organ transplantation. Decreased renal magnesium excretion is seen in ECF volume contraction states, hypomagnesemia and hypocalcemia, metabolic alkalosis, and hypothyroidism.

Table 13.6 Drugs that enhance renal magnesium excretion

Loop diuretics	Pentamidine
Thiazides	Foscarnet
Aminoglycosides [108, 109]	Cisplatin [110]
Cyclosporin [111]	Mannitol
Amphotericin B	Acetazolamide
Tacrolimus [111, 112]	Ticarcillin
Sirolimus (rapamycin) [111]	

Hypomagnesemia

Hypomagnesemia, defined as total serum magnesium level <0.7 mmol/L (or <1.7 mg/dl or <1.5 mEq/L) is very common in critically ill patients. Sixty-one percent of postoperative adult ICU patients were found to have hypomagnesemia and severe hypomagnesemia may be associated with increased mortality rate [114]. Studies suggest that up to 43 % of pediatric ICU patients have hypomagnesemia [115] and 59 % had ionized hypomagnesemia [101]. Some sub-populations of PICU patients have higher rates of hypomagnesemia. Rates may be as high as 72 % after extensive osseous resection (spinal fusion and craniofacial surgery [115] and 61 % after pediatric cardiac surgery [116].

Pathophysiology

Magnesium deficiency is generally due to insufficient intake (in diet, intravenous fluids or parenteral nutrition) or increased losses via the gastrointestinal tract or the kidney. Table 13.7 lists some of the causes for increased magnesium losses. Additional causes include alcoholism, hyperthyroidism, extracellular fluid volume expansion due to SIADH and hyperaldosteronism, burns, excessive sweating, plasma exchange and massive transfusion with citrated blood. Patients with diabetic ketoacidosis may present with hypomagnesemia due to protracted vomiting, urinary loss due to osmotic diuresis, and metabolic acidosis due to shift of magnesium into the intracellular compartment. The most common causes for magnesium deficiency in the PICU are inadequate intake in patients receiving long-term or high-volume intravenous fluids, massive citrate-containing blood transfusion and drug-induced renal excretion (especially loop diuretics and aminoglycosides, (Table 13.6).

Clinical Manifestations

The neurologic manifestations of hypomagnesemia are similar to those of hypocalcemia. Magnesium deprivation in volunteers resulted in positive Trousseau sign, Chvostek sign (sometimes tetany), lethargy, generalized weakness, tremor, ataxia, nystagmus, anorexia, nausea and apathy [118], and rarely, seizures and coma [119]. Hypomagnesemia is frequently accompanied by secondary hypocalcemia and hypokalemia, but these symptoms occur even in the absence of hypocalcemia. All abnormalities can be promptly corrected with replacement of magnesium alone. Psychiatric manifestations include anxiety, delirium and even psychosis [120]. Cardiac effects include prolonged PR and QT intervals [110] and T wave inversion or flattening, although the differentiation from hypocalcemic and hypokalemic effects is frequently difficult. Coronary vasospasm has also been described [121]. Additional effects include lower threshold for ventricular dysrhythmias (ranging from ventricular premature beats to ventricular tachycardia, torsade de pointes

Table 13.7 Causes of increased magnesium losses

Gastrointestinal	Renal
Malabsorption	Renal tubular acidosis
Kwashiorkor	S/p renal transplantation
Chronic diarrhea	Drug-induced (see Table 13.6)
Short bowel syndrome	Post-obstructive diuresis
Selective magnesium malabsorption	Bartter's syndrome
Inflammatory bowel disease	Gitelman's syndrome
Vitamin D deficiency	Interstitial nephropathy
Proton pump inhibitors [117]	Primary renal magnesium wasting
Pancreatic insufficiency	Hypercalciuria
Cystic Fibrosis	Hyperaldosteronism
Acute pancreatitis	Large-volume saline infusions
Continuous nasogastric suctioning	
Protracted vomiting	
Bowel fistula	

and ventricular fibrillation [122, 123], and a lower threshold for digitalis toxicity. It has been suggested that even subclinical magnesium depletion (measured by ionized levels) predisposes patients to digitalis toxicity [124]. Routine magnesium supplementation prolongs QT interval in patients with normal serum magnesium levels [125], and reduces the incidence of postoperative dysrhythmias in adults [126] and children [127] after cardiopulmonary bypass. Magnesium is effective in the terminating and suppressing *torsades de points*, a form of polymorphous ventricular tachycardia because of its ability to shorten the QT interval. Magnesium administration has resulted in attenuation of the electrophysiologic effects of hyperkalemia [128] and may have a role in resistant hyperkalemia-related dysrhythmias.

Hypomagnesemia results in secondary hypocalcemia, probably via combination of suppression of parathyroid hormone release and altered bone solubility with decreased release of calcium to parathyroid hormone stimulation [107]. Hypomagnesemia is also frequently associated with hypokalemia. A refractory potassium repletion state has been described after diuretic use in which hypokalemia cannot be corrected until magnesium is repleted [129]. Similarly, it may be difficult to restore magnesium without concomitant repletion of potassium. Magnesium stimulates Na-K-ATPase activity, allowing the cell to maintain a potassium gradient.

Management

Prevention of hypomagnesemia in critically ill patients is important. Inclusion of magnesium serum levels in routine blood work, and prompt repletion of deficits are recommended. Patients at risk of developing hypomagnesemia, such as those treated with diuretics, those dependent on parenteral nutrition, patients after massive transfusions or cardiopulmonary bypass and patients with diabetic ketoacidosis require close monitoring of magnesium levels. Patients treated with drugs known to cause increased magnesium renal losses such as calcineurin inhibitors, aminoglycosides and cisplatin should also receive close monitoring of magnesium levels. Daily magnesium requirement in total parenteral nutrition ranges from 0.25 to 1.25 g in neonates to 0.5–3 g in adolescents. Asymptomatic patients requiring supplemental magnesium can be given oral magnesium salts; intramuscular injections are painful and less effective and should be discouraged.

Concomitant supplementation of calcium, phosphorus, potassium and vitamin D is important. Patients at high risk for complications from hypomagnesemia or patients who develop neurological or cardiac complications should be treated with intravenous magnesium sulphate, 25–50 mg/kg bolus over 15–60 min, which may be repeated every 6 h. Infusion rate should not exceed 150 mg/min, and drug concentration should not exceed 200 mg/dl. Cardiorespiratory monitoring is necessary during the infusion, since ventricular dysrhythmias, hypotension, flaccid paralysis and respiratory depression have been described, especially in infants.

Hypermagnesemia

Hypermagnesemia is defined as total serum magnesium levels >1.0 mmol/L (or 2.4 mg/dl or 2.0 mEq/L). It is relatively uncommon in PICU patients.

Pathophysiology

The most common etiology is the administration of magnesium-containing medications in the presence of renal failure [130]. Hypermagnesemia may result from decreased clearance of antacids such as magnesium-carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, cathartics such as magnesium citrate, magnesium sulphate and magnesium-hydroxide, and magnesium-containing enemas [131, 132]. High magnesium serum levels were described in a patient treated with magnesium-containing cathartics for theophylline overdose [133]. Hypermagnesemia has also been described in hypothyroidism and adrenal insufficiency [134]. Neonatal hypermagnesemia has been described after maternal treatment with high doses of magnesium sulphate for eclampsia. Extensive soft tissue injury or necrosis can also deliver large amounts of magnesium into the ECF in patients after trauma, shock, sepsis, cardiac arrest or severe burns [135]. With the increasing use of magnesium sulphate for the treatment of severe status asthmaticus [136] and *torsade de pointes*, careful monitoring for signs and symptoms of hypermagnesemia should be carried out. Catecholamine and insulin infusions shift magnesium.

Clinical Manifestations

Hyporeflexia appears at levels >1.64 mmol (4 mg/dl); flaccid quadriplegia has been described with levels >3.29 mmol/L (8 mg/dl, [107]). Magnesium inhibits prejunctional release of acetylcholine due to displacement of membrane-bound calcium at the neuromuscular junction [107]. Severe hypermagnesemia can also lead to respiratory arrest, hypotension (which may be refractory to vasopressors and volume expansion [137]), lethargy, nausea, dilated pupils, urinary retention and constipation. Severe bradycardia with complete heart block and cardiac arrest has been reported [138]. Although most babies exposed *in utero* to high doses of magnesium present only with subtle clinical changes of impaired neuromuscular transmission and neurobehavioral abnormalities [138], cases of hypotonia, respiratory distress and hypotension have been described [139].

Management

Severe intoxication presenting as cardiac dysrhythmias, hypotension and respiratory compromise should be treated with intravenous calcium salt. Calcium gluconate, 25 mg/kg BW i.v. over 5 min can reverse those severe complications via the antagonistic effect of calcium. Patients with adequate renal function should be given i.v. furosemide, 1 mg/kg BW and urine volume replaced with ½ normal saline containing calcium gluconate (to replace intravascular volume and increase magnesium excretion along with the increased calcium excretion). Glucose-insulin combination may shift magnesium into the cells similar to its effect in hyperkalemia. Patients with renal failure should undergo dialysis with magnesium-free dialysate [92].

Disorders of Calcium Homeostasis

Calcium is an essential ion that plays an important role in many cellular processes. Perhaps it's most critical role is the mediation of neuromuscular signals. This is accomplished via regulation of neurotransmitter release in the brain and preganglionic synapses, postganglionic nerve endings, neuromuscular junction and the adrenal medulla and via calcium's central role in the depolarization of nerves, skeletal muscle, smooth muscle (including vascular smooth muscle) and myocardial cells involved in both conduction and contraction. Variations in plasma ionized calcium concentrations correlate directly with clinically significant changes in myocardial contractility [140]. Calcium has a central role in blood coagulation, cellular communications, exocytosis and endocytosis.

About 40 % of circulating calcium is protein bound (90 % of the bound calcium is attached to albumin); about 10 % is chelated by various anions such as sulphate, citrate, phosphate and carbonate; the remaining 50 % is in the biologically active ionized form. Nomograms used for "correction" of ionized calcium levels based on total calcium, pH and albumin level are inaccurate and may be misleading [141]. Alkalosis increases calcium binding to protein, since hydrogen ions normally compete with calcium for protein binding sites. This reduces the available ionized form (by 0.42 mmol/L per 0.1 mmol/L change in pH) and may result in symptomatology while total calcium levels remain unchanged. Ionized calcium assays are now available in most facilities, are frequently included in point-of-care blood gas analyzer cartridges, and are the best means to guide therapy in critically ill children. Normal levels range from 1.1 to 1.3 mmol/L (4.5–5.6 mg/dL). To assure accuracy, samples must be collected anaerobically, preferably with dry heparin in appropriate tubes and assayed immediately [142].

Hypocalcemia

Ionized hypocalcemia is common in critically ill children [143, 144]. In one study, 18 % of 145 PICU patients had ionized hypocalcemia, which was associated with increased mortality [144]. In critically ill adults, hypocalcemia acquired during an ICU stay was associated with increased morbidity and mortality [145, 146].

Pathophysiology

Important causes of hypocalcemia in critically ill children are listed in Table 13.8. A more comprehensive list may be found at [147]. The mechanism underlying ionized hypocalcemia in sepsis and inflammatory conditions is probably multifactorial. Acquired defects along the parathyroid-vitamin D axis have been demonstrated in some studies [145], but not in others [148]. Increases in free fatty acids, inadequate supplementation of vitamin D and liver and renal dysfunction with defective hydroxylation of vitamin D to calcitriol may also play a role. The degree of hypocalcemia correlates with circulating proinflammatory cytokine levels such as tumor necrosis factor alpha and procalcitonin [148]. Hypocalcemia resistant to calcium supplementation should raise suspicion of altered magnesium metabolism. Both hypomagnesemia and hypermagnesemia suppress parathyroid hormone secretion; hypomagnesemia also increases peripheral resistance to parathyroid hormone. Up to 22 % of patients treated with anticonvulsants such as phenobarbital, primidone and phenytoin develop hypocalcemia, probably secondary to interference with normal cholecalciferol metabolism through hepatic microsomal enzyme induction.

Clinical Manifestations

Hypocalcemia may cause hypotension due to decreased myocardial contractility and vascular failure. Ionized calcium levels should be checked in all patients requiring ino-

Table 13.8 Important causes of ionized hypocalcemia in critically Ill children

Hypoparathyroidism	**Associated with inflammation**
After neck surgery or irradiation	Sepsis
Hypo- and hypermagnesemia	Pancreatitis
Autoimmune	Toxic shock syndrome
Invasive (hemosiderosis, infarction, tumor)	**Increased binding of circulating Ca**
DiGeorge's syndrome	Increased protein binding
Drug-induced (*nitroprusside*, *beta blockers*, *cimetidine*, *corticosteroids*, *theophylline*, *protamine*, *indomethacin*)	Hyperproteinemia
Pseudohypoparathyroidism	Alkalosis (respiratory or metabolic)
Maternal hyperparathyroidism	Increased fatty acid levels
Vitamin D deficiency	Stress-induced
Decreased intake or absorption	Diabetic ketoacidosis
Lack of sunlight (with prolonged hospitalization)	Parenteral lipid emulsions
Decreased biotransformation	Drug-induced (i.e., *heparin*, *beta-adrenergic drugs*)
Liver failure	Fat embolism
Renal failure	Increased chelation
Hyperphosphatemia	Citrate in transfused blood
Anticonvulsant therapy	Radiographic contrast media
Increased losses	Hyperphosphatemia
Nephrotic syndrome	Tumor lysis syndrome
Dialysis	Rhabdomyolysis
Loop diuretics	Cow's milk ("late" neonatal hypocalcemia)
	Renal failure

tropic and/or vasopressor support. Patients with underlying heart disease or sepsis may be particularly sensitive to hypocalcemia. ECG changes include prolonged QT interval and occasional T wave inversion. Dysrhythmias (bradycardia and ventricular fibrillation) are uncommon. Neurologic manifestations occur when ionized calcium plasma levels are below 0.63 mmol/L (2.5 mg/dL) and result from over excitation of neuronal membranes because of increased permeability to sodium. Initial signs typically include perioral and peripheral paresthesias. These may be followed by muscle cramps, tremor, twitching, hyperreflexia, Chvostek's or Trousseau's signs, bronchospasm, laryngospasm and stridor, tetany and seizures. The presentation in neonates and infants may be atypical, and seizures, twitching, and apnea may be the presenting signs [149].

Management

In symptomatic patients with seizures or cardiovascular compromise, emergency treatment includes 5–6 mg/kg BW of elemental calcium given either as calcium gluconate (0.6 ml/kg BW of the 10 % solution, maximum 10 ml) or calcium chloride (0.2 ml/kg BW of the 10 % solution, maximum 5 ml) i.v. over 5–10 min. Continuous ECG monitoring is required. Since calcium gluconate requires hepatic metabolism to become ionized, calcium chloride may be preferred in patients with hepatic failure or low blood flow states. In critically ill children, a bolus of 2.7 mg/kg BW elemental calcium as calcium chloride or calcium gluconate resulted in increase in plasma ionized calcium at 30 min by an average of 0.19 and 0.09 mmol/L, respectively [150]. The rise in plasma ionized calcium after calcium chloride (but not calcium gluconate) administration was associated with a significant increase in blood pressure as result of vasoconstriction. This however, may be followed by a decrease in cardiac output as has been demonstrated in children after cardiac surgery [151]. Calcium infusions should therefore be used with caution in this patient population.

Calcium infusion has been associated with bradycardia and asystole. In stable patients, calcium gluconate is preferred, as the likelihood of complications is lower with this preparation. Calcium preparations (e.g., $CaCl_2$) are tissue irritants and should be given intravenously preferably via central venous catheter except in emergent settings. In dire emergency and absence of i.v. access, calcium gluconate may be given intramuscularly in older patients. Asymptomatic patients should be given oral calcium preparations. In hyperphosphatemic patients, phosphate levels should be lowered first, if possible, to avoid tissue precipitation of calcium-phosphate salts. Hypomagnesemia should always be suspected and managed prior to or along with correction of hypocalcemia. In patients receiving digitalis, calcium administration may initiate or exacerbate digitalis toxicity, and hypocalcemia should be corrected slowly, by small increments. Calcium precipitates with bicarbonate, sulphate, citrate and phosphate and should not be infused together with fluids or medications containing these anions.

Hypercalcemia

Pathophysiology

The differential diagnosis of hypercalcemia is broad, but most conditions are not relevant to the acutely ill child. Iatrogenic administration of excess calcium, either in intravenous fluids or in a dialysate solution is the most common cause in the pediatric ICU. Other etiologies include hyperparathyroidism (primary, secondary to a hormone-secreting tumor or tertiary due to renal failure), thyrotoxicosis, prolonged immobilization [152], vitamin D or A intoxication, abrupt glucocorticoid withdrawal, during the diuretic phase of acute tubular necrosis, with use of thiazide diuretics (via increased renal tubular calcium reabsorption and enhancement of parathyroid hormone effect [153] and associated

with the use of citrate-based anti-coagulation in CRRT that requires continuous calcium infusion.

Clinical Manifestations

Patients may remain asymptomatic even with calcium levels that are quite high. Ionized calcium levels >1.85 mmol/L (correspond roughly to total calcium levels of 3.75 mmol/L or 15 mg/dL) place the patient at risk for life-threatening complications and should be treated emergently. Initial signs are usually non-specific and include anorexia, nausea and vomiting, constipation, abdominal pain, arthralgia, bone pain, polyuria and polydipsia. Hypercalcemia can therefore be easily missed in the critically ill child. Neurologic symptoms include personality changes, lethargy, confusion and hallucinations, and on rare occasions seizures and possibly coma [152]. Weakness, hypotonia, diminished deep tendon reflexes and ataxia can also be seen. Cardiovascular effects include hypertension, increased contractility, decreased automaticity and slowed conduction. ECG may show prolonged PR interval, widened QRS complexes and shortened QT interval. Bradycardia and varying degrees of heart block have been described. Triggering of or enhancement of digoxin toxicity may occur. The resultant calciuria may cause nephrolithiasis and nephrocalcinosis leading to nephropathy with hyposthenuria, glycosuria, proteinuria and renal tubular acidosis.

Management

In the symptomatic patients with ionized calcium levels >1.85 mmol/L, the first line of treatment includes aggressive volume expansion with isotonic saline (200 ml/Kg BW/day), to dilute ionized calcium levels and cause calciuresis, combined with furosemide (1 mg/kg BW q 3–6 h) to promote calciuria and protect the patient against volume overload [153]. Specific management is aimed at inhibiting osteoclast-mediated bone resorption and is indicated in patients with persistent symptomatic hypercalcemia after volume expansion and diuresis. Calcitonin is the most rapidly acting drug in that group (within a few hours), although its effect is mild and transient. In addition to inhibition of bone resorption, it enhances renal excretion of calcium. Gallium nitrate (200 mg/M^2 BSA daily for 5 days) is emerging as the drug of choice in patients with cancer-induced hypercalcemia. Biphosphonates such as etidronate (7.5 mg/Kg BW i.v. over 4 h daily for 3–7 days) or pamidronate work by avidly binding to bone and thus inhibiting osteoclastic activity. Effect may be seen after 2 days of treatment. Combination therapy of calcitonin and biphosphonates may provide better results than either therapy alone [154]. Other therapeutic options include mithramycin (25 mcg/Kg BW i.v. over 4 h), which may exert a potent effect within 12 h, but has numerous toxic effects including hepatotoxicity, nephrotoxicity, thrombocytopenia, and tissue injury upon extravasation, making this drug a less attractive option. Patients with hematologic malignancies may also benefit from hydrocortisone therapy, which counteracts vitamin D [155].

Disorders of Phosphorus Homeostasis

Phosphorus is an important intracellular ion, but only 0.1 % of body phosphorus content is present in the ECF, where it is routinely measured. Massive shifts of phosphorus occur frequently between intracellular and extracellular compartments. Phosphorus serum levels are therefore rarely an accurate reflection of total body phosphorus stores [156]. Normal serum levels are 0.9–1.5 mmol/L (2.7–4.7 mg/dl) in adolescents, 1.3–2.3 mmol/L (4–7 mg/dl) in children and 1.6–2.6 mmol/L (5–8 mg/dl) in the first week of life. Phosphorus has important role in cellular metabolism. Phosphoproteins, phospholipids, nucleic acids and nucleotides (i.e., ATP and ADP) contain phosphorus, which is therefore important for all synthetic cellular processes including glycolysis as well as cellular energy production in the mitochondria and of oxygen delivery to the tissues as part of 2,3-diphosphoglycerate.

Hypophosphatemia

Pathophysiology

Causes of hypophosphatemia in pediatric patients are listed in Table 13.9. One study found hypophosphatemia in 61 % of critically ill children, and it was associated with malnutrition, respiratory distress and dopamine infusions [157]. Moderate hypophosphatemia is common but patients are usually asymptomatic. Severe hypophosphatemia (<0.32 mmol/L or 1 mg/dl) may be associated with significant symptomatology. Patients with diabetic ketoacidosis are particularly prone to severe hypophosphatemia as a result of both acidosis-induced shift into the ECF resulting in massive intracellular losses (while masking the true deficiency), followed by intracellular shift during insulin therapy and unveiling of phosphorus deficiency [158]. Increased glycolysis during the anabolic phase of refeeding after starvation [158], with severe thermal burns or with respiratory alkalosis (by the increased intracellular pH) results in trapping of intracellular phosphorus, which is replaced by phosphorus shifted from the ECF. Hyperventilation to a pH of 7.65 will result in a fall in serum phosphorus by 50 % [159]. Metabolic alkalosis causes only minor changes in phosphorus serum levels because bicarbonate is slow to enter the cells to affect intracellular fluid pH.

Clinical Manifestations

Signs and symptoms of severe hypophosphatemia are listed in Table 13.10. Most are the result of impaired

Table 13.9 Causes of hypophosphatemia

Decreased intake	**Intracellular shift**
Malabsorption	Respiratory alkalosis[a]
Inadequate amount in TPN[a]	Insulin (treatment of DKA)[a]
Vitamin D deficiency	Parenteral glucose
Aluminum and magnesium-based P-binding antacids[a]	Salicylate intoxication
Increased renal losses	Gram negative sepsis
Hyperparathyroidism	Hypothermia
Chronic corticosteroid therapy	Refeeding after starvation[a]
Diuretics	Burns[a]
Bicarbonate therapy	Massive fluid resuscitation
Renal tubular disease	Catecholamines, albuterol
Hypomagnesemia	
Diabetic ketoacidosis[a]	
Renal transplantation	
Dopamine infusion	
Acetaminophen overdose	
Chemotherapeutic agents	
Theophylline overdose	

[a]May be severe enough to cause symptomatology

Table 13.10 Clinical manifestation of severe hypophosphatemia

Central nervous system	**Musculoskeletal**
Numbness, tremor, paresthesias	Muscle weakness
Irritability	Rhabdomyolysis
Confusion	Pseudofractures
Seizures	**Hematologic**
Coma	Hemolysis
Guillain-Barre like syndrome	Platelet dysfunction
Respiratory	**Tissue hypoxia** (from 2,3-DPG deficiency)
Respiratory muscle weakness	**Immune dysfunction**
Failure to wean from mechanical ventilation	**Hypercalciuria**
Cardiovascular	**Liver dysfunction**
Decreased cardiac function	
Congestive cardiomyopathy	
Labile blood pressure	

cellular energy metabolism as stated above. Aubier et al. found decreased diaphragmatic contractility in adults with respiratory failure [160] that improved with phosphorus supplementation. Similarly, serum phosphorus levels were found to correlate with maximum inspiratory force and have been implicated in failure to wean from mechanical ventilation [161]. O'connor et al. [162] measured cardiac output by thermodilution and calculated stroke work in seven patients with severe hypophosphatemia before, during and after repletion with an intravenous potassium phosphate solution. Left ventricular stroke work increased significantly and pulmonary-artery wedge pressure fell upon normalization of serum phosphorus. Tissue hypoxia may result from depressed levels of 2,3-diphosphoglycerate and decreased release of oxygen to the tissues.

Management

Moderate, asymptomatic hypophosphatemia may be treated with oral sodium-potassium-phosphate (Neutra-Phos, 30–90 mg/Kg BW/day). The routine addition of potassium-phosphorus salts to the intravenous fluid regimen in diabetic ketoacidosis is widely accepted. In severe phosphorus depletion, intravenous sodium-phosphate or potassium-phosphate (depending on the serum potassium level) at 5–10 mg/Kg BW of phosphorus may be infused over 6 h and repeated if necessary. Complications of aggressive phosphorus repletion include metastatic calcification and nephrocalcinosis (especially in the presence of hypercalcemia), renal failure (especially in oliguric patients), hypocalcemia, and hypotension [158].

Hyperphosphatemia

Pathophysiology

Few conditions lead to hyperphosphatemia. Renal failure is the most common cause, when creatinine clearance falls below 30 ml/min and usually in the presence of excessive phosphorus intake or use of phosphorus-containing medications. Hyperphosphatemia can also be caused by extensive cell lysis such as during tumor lysis syndrome after chemotherapy for leukemia or lymphoma, rhabdomyolysis or massive hemolysis. Additional causes include hypoparathyroidism, excessive phosphorus administration (i.e., for diabetic ketoacidosis) or burns by white phosphorous, and ingestion of toxic doses of phosphorus-containing laxatives. Lethal hyperphosphatemia has been described in infants receiving sodium-phosphate ("Fleet") enemas.

Clinical Manifestations

Hypocalcemia invariably develops and most symptoms are probably attributed to it, including muscle cramps, paresthesias, tetany, seizures, hypotension, prolonged QT interval with ventricular dysrhythmias, cardiac arrest and coma. At least one case report described some of these manifestations in the absence of accompanying hypocalcemia.

Management

Initial management includes intravenous calcium and fluid administration (to increase renal phosphorus loss). In severe refractory cases or in renal failure, dialysis may be indicated. Recent toxic ingestion of phosphorus-containing laxative should be treated with induced emesis followed by aluminum-hydroxide, a phosphorus-binding antacid.

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Acid-Base Disorders in the PICU

14

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Abstract

An appropriate acid-base milieu is essential for normal cellular function of the human organism. Disturbances of the pH balance frequently occur in critically ill or injured children. These pertubations most often serve as a marker of an underlying disorder responsible for their occurrence, but acid-base disturbances may in themselves require monitoring and treatment in the PICU. Proper assessment and treatment of acid-base imbalances therefore requires an understanding of terminology and measurement, insight into buffer systems, and recognition of the compensatory interactions involved in maintaining a homeostatic balance. The terms acidosis and alkalosis refer to the mechanisms which result in a given acid-base disturbance. Primary acid-base disorders are further classified as either metabolic or respiratory. Metabolic contribution to acid-base homeostasis is based on the presence of strong anions and cations. Ion strength is based on the tendency of an ion to dissociate in aqueous solutions and tendency to combine with other ions. The concentration difference between the sum of all strong anions and strong cations is defined as the strong ion difference (SID). The anion gap, determined by presence or absence of unmeasured anions, helps guide understanding of the etiology of metabolic acidosis, one of the most common disturbances in the critically ill child. Hypercapnic acidosis impacts pH balance, but could have potential therapeutic effects in children with acute lung injury. Specific therapies, such as intravenous fluids and cardiopulmonary bypass, intrinsically affect acid-base balance, and their impact should be considered.

Keywords

Acid-base disorder • Children • Critical illness • Buffer • Lactic acidosis • Metabolic acidosis • Respiratory acidosis • Hypercapnic acidosis • Metabolic alkalosis • Respiratory alkalosis • Strong ion difference • Anion gap • pH stat

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Introduction

An appropriate acid-base milieu is essential for normal cellular function of the human organism. Bronsted defined an acid as a substance that can donate H^+ ions and a base as a substance that can accept H^+ ions [1]. There are two classes of acids that are physiologically important – carbonic acid (H_2CO_3) and noncarbonic acids. During the course of a normal day, metabolism of carbohydrates and fats generates approximately 15,000 mmoles of CO_2, which combines with water to generate carbonic acid. The lung then plays an important role in acid-base regulation via removal of CO_2. Noncarbonic acids are derived from the metabolism of proteins (generally limited to approximately 50–100 mEq/day of acid) and are excreted by the kidney. The extracellular pH is tightly regulated between 7.35 and 7.45 under normal conditions by a combination of extracellular and intracellular chemical buffering, as well as by these respiratory and renal regulatory mechanisms. Disturbances of this balance frequently occur in critically ill or injured children. These disorders most often serve as a marker of an underlying disorder responsible for their occurrence, but acid-base disturbances may in themselves require monitoring and treatment in the PICU. Proper assessment and treatment of acid-base imbalances therefore requires an understanding of terminology and measurement, insight into buffer systems, and recognition of the compensatory interactions involved in maintaining a homeostatic balance.

The acidity of a particular solution may be expressed in terms of H^+, i.e., proton, concentration, or in terms of pH. The concentration of H^+ in the serum under normal conditions (0.00004 mEq/L) is relatively low compared to other ions, e.g., sodium ion (140 mEq/L). In order to avoid these cumbersome differences, the pH scale is used by convention to describe acid-base disturbances in the body. The pH of arterial blood is the negative logarithm of the H^+ concentration. Several important points deserve mention. First, pH and $[H^+]$ are inversely related – an increase in $[H^+]$ is defined by a decreasing pH (i.e., more acidic conditions), while a decrease in $[H^+]$ is defined by an increasing pH (i.e. less acidic conditions). Second, the normal arterial pH of 7.35–7.45 corresponds to a $[H^+]$ of 35–45 nEq/L. An *acidemia* refers to an arterial pH <7.35 (H^+ concentration below 35 nEq/L), while an *alkalemia* refers to an arterial pH >7.45 (H^+ concentration above 45 nEq/L). Third, the arterial $[H^+]$ can be estimated from the arterial pH with a reasonable degree of accuracy due to the linear relationship between pH and $[H^+]$ in the physiologic range – within this range, each 0.01 unit change in pH from 7.40 will either increase or decrease the $[H^+]$ by 1 nEq/L [2]. For example, a decrease in pH from 7.40 to 7.20 would require an increase in the $[H^+]$ from 40 to 60 nEq/L. By the same token, when pH changes by 0.3 log units, the $[H^+]$ either doubles or halves [2]. For example, if the pH falls from 7.40 to 7.10, the $[H^+]$ must double from 40 to 80 nEq/L.

The terms *acidosis* and *alkalosis* refer to the mechanisms which result in a given acid-base disturbance. Primary acid-base disorders are further classified as either metabolic or respiratory. For example, when the plasma bicarbonate concentration (HCO_3^-) deviates from the normal range, the resultant alteration in acid-base homeostasis is referred to as a metabolic acidosis or alkalosis. When a deviation in the arterial carbon dioxide tension ($PaCO_2$) is the primary event, the resulting disorder is referred to as a respiratory acidosis or alkalosis. Secondary compensatory mechanisms attempt to restore the extracellular pH back to normal. For example, the secondary respiratory compensation to a primary metabolic acid-base disturbance (i.e., an increase or decrease in minute ventilation to change the arterial $PaCO_2$) occurs within minutes and is usually complete within 12–24 h, though the arterial pH is never restored to a normal pH. Conversely, the secondary metabolic compensation (by the kidney) to a primary respiratory acid-base disturbance occurs more slowly, often requiring 3–5 days for compensation [3, 4]. Most acid-base disturbances are *simple acid-base disorders* in that a primary disruption produces a physiologic compensatory response. However, *mixed acid-base disorders* can also occur in which more than one primary disturbance can occur, particularly in the complex critically ill child.

Acid-Base Physiology

A *buffer* is defined as any substance which can absorb or donate H^+ ions and thereby diminish the effects on the pH of a solution. For example, in the following chemical equation, excess H^+ ions combine with the base, A^- to form the weak acid, HA:

$$H^+ + A^- \leftrightarrow HA$$

The weak acid HA buffers the excess H+ ions such that the effect of the increase in $[H^+]$ on pH is mitigated. The converse is true if there are not enough H^+ ions in solution, i.e., HA dissociates to form excess H^+ ions. Strong acids, e.g., HCl, H_2SO_4 are not effective buffers because, by definition, they dissociate at acidic pH. Conversely, weak acids are not effective buffers either, because by definition, they tightly bind H^+ even at alkalotic pH. Thus, the inherent tendency of a particular acid to dissociate or ionize determines the degree to which it can act as a buffer, denoted by the ionization constant, pK (note that the pK is inversely proportional to the strength of the acid). The most effective buffers have pKs that approximate the physiologic range of pH. The most important buffer pairs in the arterial blood are carbonic acid/

bicarbonate (H_2CO_3/HCO_3^-), phosphate ($H_2PO_4^-/HPO_4^{2-}$), and certain proteins, e.g. hemoglobin. By far the most important buffer system is the H_2CO_3/HCO_3^- system (see below):

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Carbonic anydrase catalyzes the conversion of carbonic acid to CO_2 and H_2O and vice versa. The respiratory system therefore plays an important role in acid-base homeostasis through its effects on $PaCO_2$. The relationship of HCO_3^- and H_2CO_3 to pH is expressed by the Henderson-Hasselbach equation:

$$pH = pK + \log\left(\left[HCO_3^-\right] / \left[H_2CO_3\right]\right)$$

In the clinical setting, pH and $PaCO_2$ are measured, rather than HCO_3^- and H_2CO_3. The Henderson-Hasselbach equation can then be modified:

$$pH = pK' + \log\left(\left[HCO_3^-\right] / \left(0.03 \times PaCO_2\right)\right)$$

The modified Henderson-Hasselback equation can be rewritten without logarithms as the Henderson equation (Kassirer-Bleich modification) [2, 3]:

$$\left[H^+\right] = 24 \times PaCO_2 / \left[HCO_3^-\right]$$

Therefore, using the rules described above for estimating $[H^+]$, any one of the three values in the Henderson equation can be rapidly estimated when the other two are known (see more below).

When chemical buffering is not sufficient to prevent a change in pH, either metabolic or respiratory compensation occurs. Changes in pH, therefore, result entirely from changes in the respiratory response and the subsequent effect on volatile acids ($PaCO_2$), changes in the metabolic response and the subsequent effect on nonvolatile acids (hydrochloric, sulfuric, lactic acids), or changes in nonvolatile weak acid (chemical buffers). These are briefly discussed further below.

Respiratory Compensation: Volatile Acids (CO_2)

CO_2 and water are produced primarily from the combustion of glucose and fatty acids in the oxidative process of cellular respiration. CO_2 is transported through the arterial blood in one of three ways: (i) dissolved in physical solution in the plasma (approximately 5–10 %); (ii) complexed chemically with the terminal amine groups of proteins, e.g. hemoglobin (approximately 5–10 %); (iii) transported as bicarbonate (80–90 %). At the tissue level, CO_2 diffuses across the red blood cell (RBC) membrane and combines with water to form carbonic acid, in a reaction catalyzed by carbonic anhydrase.

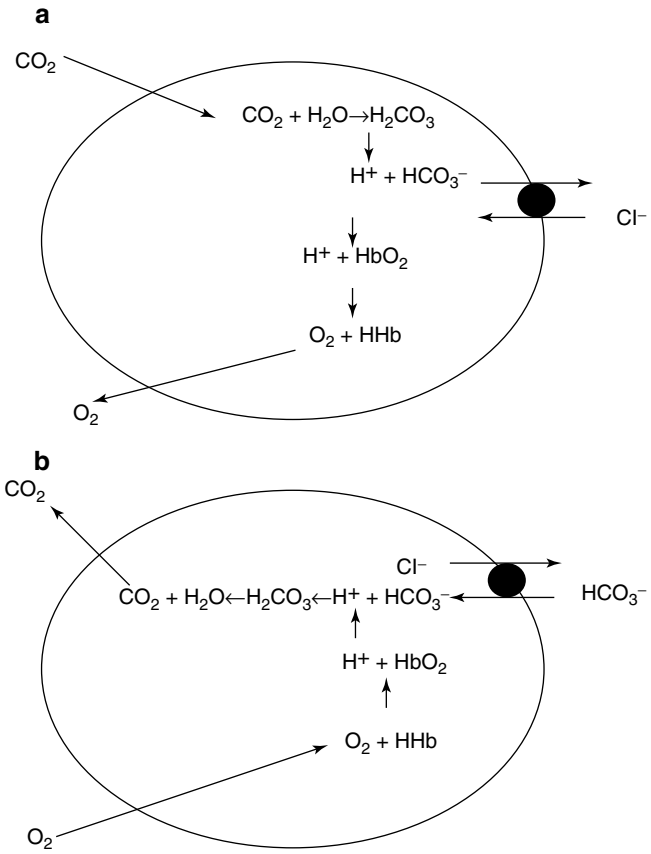

Fig. 14.1 CO_2 exchange at the tissue level (**a**) and alveolar level (**b**). See text for explanation

Carbonic acid then dissociates to bicarbonate (HCO_3^-) and H^+. The H^+ is buffered by hemoglobin (in exchange for O_2, which then is released to the tissues) and HCO_3^- leaves the RBC in exchange for chloride (Fig. 14.1a). CO_2 is then excreted in the lungs by a reversal of this process – bicarbonate re-enters the RBC to combine with protons (H+), forming carbonic acid. Carbonic acid then dissociates to water and CO_2, which diffuses freely into the alveolar space and is removed via the process of ventilation (Fig. 14.1b). Changes in the arterial or cerebrospinal fluid pH stimulate central medullary and carotid body chemoreceptors to regulate minute ventilation for altering CO_2 clearance. The maximum compensatory response (i.e., an increase in minute ventilation) to a severe metabolic acidosis can decrease $PaCO_2$ to a lower limit of 10–12 mmHg, though values less than 10mmHg may be achieved in rare instances (e.g., hyperventilation, or Kussmaul's respirations in diabetic ketoacidosis). Conversely, minute ventilation slows and $PaCO_2$ generally increases to approximately 50 mmHg to compensate for a metabolic alkalosis with plasma bicarbonate concentrations of 35 mEq/L or greater. $PaCO_2$ generally never exceeds 65 mmHg in a compensatory response, even in the face of a profound metabolic alkalosis.

Metabolic Compensation and Nonvolatile Acids/Strong Ion Difference (SID)

Nonvolatile acids are also produced by cellular metabolism, and their resultant effect on acid-base homeostasis is controlled by the kidney. The metabolism of sulfur-containing amino acids, such as cysteine and methionine, to sulfuric acid provides the major source of nonvolatile acids. Additional sources include oxidation of phospholipids to phosphoric acid, nucleoprotein degradation to uric acid, and incomplete combustion of carbohydrates and fatty acids to lactic and keto- acids. Efficient processing by the kidney is necessary to clear the approximately 1 mEq/kg of acids produced on a daily basis. Excretion occurs in tandem with the regeneration of HCO_3^-. In addition, the kidneys filter large amounts of circulating plasma HCO_3^- through almost complete reabsorption with sodium in the proximal tubule. Metabolic compensation for respiratory volatile acid effects occurs here; respiratory acidosis (i.e., high arterial $PaCO_2$) raises the rate of bicarbonate reabsorption, while respiratory alkalosis (i.e., low arterial $PaCO_2$) lowers it. Hypokalemia also increases the rate of bicarbonate reabsorption, probably by raising intracellular H^+ concentration. Volume contraction also increases proximal HCO_3^- reabsorption by resetting glomerulotubular balance upward and increasing the fractional rate of Na^+ and HCO_3^- reabsorption. Thus, correcting hypokalemia may be necessary to correct a metabolic alkalosis, particularly in children with volume contraction.

The actual excretion of nonvolatile acids occurs in the distal tubules with simultaneous regeneration of HCO_3^-. CO_2 is again hydrated to carbonic acid and dissociated into protons by tubular cells. HCO_3^- is reabsorbed and secreted protons titrate urinary buffers. The majority of acid excretion, however, takes place via ammonia (NH_3) secretion to bind protons released by CO_2 hydration.

Metabolic contribution to acid-base homeostasis is based on the presence of strong anions and cations. Ion strength is based on the tendency of an ion to dissociate in aqueous solutions. Strong ions are by nature always free and remain charged because they do not combine with other ions. Strong cations, which include sodium (Na^+), potassium (K^+), calcium (Ca^{++}), and magnesium (Mg^{++}), outnumber strong anions (predominantly chloride, Cl^- and lactate$^-$) in blood plasma. The concentration difference between the sum of all strong anions and strong cations is defined as the strong ion difference (SID). If other *unmeasured* anions are excluded, the apparent SID (SIDa) can be estimated by the following:

$$\text{SIDa} = \left(\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}\right) - \left(\text{Cl}^- + \text{lactate}^-\right)$$

Because of electrical neutrality, plasma cannot be charged, and the SID difference is balanced by negative charges, primarily from CO_2 and from weak acids (A^-, described below). Thus, SID – (CO_2+ A^-) = 0 or SID = CO_2+ A^-. This measure is known as the effective SID (SIDe), where A^-can be estimated by the following formula:

$$\text{A}^- = 2 \times \left(\text{albumin,g/dL}\right) + 0.5 \times \left(\text{phosphorus,g/dL}\right)$$

SID drives water dissociation and with it the generation of H^+ ions; as SID increases, H^+ decreases and pH increases. SID in healthy humans is typically between 40 and 42 mEq/L, but can be significantly decreased with critical illness, resulting in a rapid decline in pH.

Nonvolatile Weak Acid Buffers

In contrast to strong ions, weak nonvolatile acids (or anions) exist as either charged (dissociated) or uncharged forms in vivo. Weak acids can be forced to combine with other ions and thus lose their charge. HCO_3^- is the most important weak acid in the buffer system, as it can readily combine with another weak ion, H^+, to form H_2CO_3, which dissociates into CO_2 and water. Weak acids serve as a buffer to take up protons within the human physiologic plasma pH range.

Quantification of Acid-Base Status

Three different methods are commonly employed to describe and quantify acid-base disorders, each differing only in assessment of the nonvolatile components. These methods quantify changes by assessing (i) HCO_3^- concentration in the context of $PaCO_2$; (ii) standard base excess (BE) supplemented by anion gap determination; or (iii) strong ion gap (SIG) based on the strong ion difference (SID). The first approach has been the most commonly accepted one, but conceptual differences bear discussion. As discussed above, the bicarbonate-carbonic acid pair provides the primary buffer system for extracellular fluid. The relationship between this buffer pair and $PaCO_2$ is defined by the Henderson-Hasselbach equation, in which pH = 6.1 + log [HCO_3^-]/ 0.03 × $PaCO_2$, where 6.1 is the dissociation constant (pK) for this buffer pair. This interaction tells us that an increase in $PaCO_2$ will lead to a decrease in pH and later a compensatory increase in [HCO_3^-]. Compensatory responses by the lungs and kidneys are essential to the physiologic response to primary acid-base disorders. These responses typically form a stereotypical pattern which can be described mathematically based in part on the Henderson-Hasselbach equation (compiled in Table 14.1). This relationship can be complicated by the possibility that an alteration in one element may directly impact another element in addition to its compensatory effect.

Table 14.1 Compensation for primary acid-base disorders

Disorder	Prediction of compensation	HCO_3^- (mEQ/L)	$PACO_2$ (mmHg)	SBE (mEQ/L)
Metabolic acidosis	$PaCO_2 = (1.5\times HCO_3^-)+8$ OR $PaCO_2$ will ↓ 1.25 mmHg PER mEQ/L ↓ $[HCO_3^-]$ OR $PaCO_2 = [HCO_3^-]+15$	<22	$= (1.5\times HCO_3^-)+8$	<–5
Metabolic alkalosis	$PaCO_2$ will ↑ 0.7 mmHg per mmol/L ↑ $[HCO_3^-]$ OR $PaCO_2 = [HCO_3^-]+15$	>26	$= (0.7\times HCO_3^-)+21$ $= 40+(0.6\times SBE)$	>5
Respiratory alkalosis				
Acute	pH will ↑ 0.08 per 10 mmHg ↓ $PaCO_2$ $[HCO_3^-]$ will ↓ 2 mEQ/L per 10 mmHg ↓ $PaCO_2$	$= [(40-PCO_2)/5]+24$	<35	= 0
Chronic	$[HCO_3^-]$ will ↓ 4 mEQ/L per 10 mmHg ↓ $PaCO_2$ pH will ↑ 0.03 per 10 mmHg ↓ $PaCO_2$	$= [(40-PCO_2)/2]+24$	<35	$= 0.4\times (PaCO_2-40)$
Respiratory acidosis				
Acute	$[HCO_3^-]$ will ↑ 1 mEQ/L per 10 mmHg ↑ in $PaCO_2$ pH will ↓ 0.08 per 10 mmHg ↑ in $PaCO_2$	$= [(PCO_2-40)10]+24$	>45	= 0
Chronic	$[HCO_3^-]$ will ↓ 4 mEQ/L per 10 mmHg ↓ in $PaCO_2$ pH will ↓ 0.03 per 10 mmHg ↑ in $PaCO_2$	$= [(PCO_2-40)/3]+24$	>45	$= 0.4\times (PaCO_2-40)$

The use of plasma bicarbonate concentrations does not provide a direct estimate of the total amount of fixed base in blood for clinical use. An alternative expression of buffering capacity in whole blood can be performed by calculation of the base excess (BE):

$$\mathrm{BE} = -1.2\times\left(24-\text{measured bicarbonate concentration}\right)$$

However, the plasma bicarbonate-carbon dioxide system only accounts for approximately 75 % of the buffer action of blood. Buffering is also provided byhemoglobin, phosphates, and plasma proteins, particularly albumin. Use of the Siggaard-Andersen nomogram utilizes pH, $PaCO_2$ and HCO_3^- to calculate a BE that takes into account the remaining buffer systems. Positive base excess signifies metabolic alkalosis, and negative BE implies metabolic acidosis. Standard base excess (SBE) represents the base excess of whole blood together with the surrounding interstitial fluid, comprising total extracellular fluid (ECF).

Calculation of BE and SBE does not allow discrimination between types of metabolic acidosis. The anion gap is more useful for this determination. The anion gap is based on the principle of electroneutrality; that is, the net ionic charge in a given solution is zero. In the case of extracellular fluid, sodium is the primary cation and is balanced primarily by the strong cations, chloride and the weak cation bicarbonate. The difference between these measured ions normally exists due to the presence of unmeasured anions, including sulfates, lactate, and ketoacids, but primarily due to phosphates and negatively charged proteins such as albumin. These are all balanced by sodium ions. The anion gap is the difference between measured cations and anions, represented by the equation:

$$\mathrm{AG} = \left[\mathrm{Na}^+ + \mathrm{K}^+\right] - \left[\mathrm{Cl}^- + \mathrm{HCO_3}^-\right]$$

Potassium is often omitted from the calculation because of its low extracellular concentration.

Under normal conditions, the normal anion gap is equal to 12 ± 4 mEq/L. Calculation of the anion gap is most useful for discerning the cause of metabolic acidosis as described in the section below. Strong ion gap (SIG) refers to the difference between the apparent SID (SIDa) and the effective SID (SIDe):

$$\mathrm{SIG} = \mathrm{SIDa} - \mathrm{SIDe}$$

In contrast to the anion gap, a normal SIG is zero. SIG does not change with changes in pH or in albumin concentration. The AG can be significantly altered by abnormal albumin or phosphate concentrations (see below). Thus, the AG is an estimate of the sum of SIG plus weak acids (A-), where A- can be

Table 14.2 Causes of respiratory acidosis in critically ill children

Acute or chronic lung disease
Upper airway obstruction (e.g., Croup, epiglottitis, foreign body aspiration)
Lower airway obstruction (e.g., Status asthmaticus, bronchiolitis)
Chronic obstructive lung disease (e.g., Cystic fibrosis, bronchopulmonary dysplasia)
Interstitial lung disease
Pneumonia
Pulmonary edema
Neuromuscular respiratory failure
Myasthenia gravis
Guillain-Barre syndrome
Hypokalemic periodic paralysis
Tick paralysis
Poliomyelitis
Muscular dystrophy
Spinal cord injury
Botulism
Chest wall disorders
Kyphoscoliosis
Morbid obesity
Flail chest
Inhibition of respiratory center
CNS depressant drugs
Cardiac arrest
CNS lesions (e.g., tumors)
CNS infection (e.g., meningoencephalitis)
Head trauma
Stroke

estimated as previously described. The SID and SIG concepts are helpful conceptually but AG is more commonly used in clinical practice for assessment and management.

Differential Diagnosis and Basic Management of Acid-Base Disorders

Respiratory Acidosis

A primary respiratory acidosis is defined by an arterial blood pH less than 7.35 due most commonly to a decreased CO_2 clearance (e.g., alveolar hypoventilation) or less commonly to increased CO_2 production. The differential diagnosis of an acute, primary respiratory acidosis is listed in Table 14.2. The acute increase in $PaCO_2$ is buffered by titration of non-bicarbonate intracellular buffers (e.g., hemoglobin, organic phosphates), resulting in an almost negligible rise in arterial HCO_3^- (generally only 0.1 mEq/L for every 1 mmHg increase in $PaCO_2$):

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$

$$H_2CO_3 + Hb^- \leftrightarrow HHb + HCO_3^-$$

The maximal increase in HCO_3^- during acute compensation is 31–32 mEq/L [2, 3]. The arterial pH will decrease by 0.08 units for every 10 mmHg increase in $PaCO_2$. Chronic renal compensation (through proximal reabsorption of filtered HCO_3^- and excretion of H^+ as ammonia) generally occurs within 12–24 h, such that the [HCO_3^-] increases by 0.3 mEq/L for each 1 mmHg increase in $PaCO_2$ to a maximal increase of approximately 45 mEq/L [2–4]. Similarly, pH will decrease by 0.03 units for each 10 mmHg increase in $PaCO_2$. The bone provides additional buffering of chronic respiratory acidosis as calcium phosphates and carbonates (for this reason, osteoporosis is a common finding in children with chronic lung disease). Chronic respiratory acidosis also results in chloride depletion due to increased chloride excretion by the kidney and a shift of chloride ions into the RBC (in exchange for bicarbonate), which usually takes place over 3–5 days [5]. Interestingly, unless adequate chloride supplementation is provided during correction of the chronic respiratory acidosis, arterial bicarbonate may remain elevated, resulting in a post-hypercapnic alkalosis [5].

The clinical implications of respiratory acidosis depend to a great extent upon the acuity of the event as well as the degree of hypoxemia that is present. Even a profound degree of respiratory acidosis is surprisingly well-tolerated – e.g., elevations of $PaCO_2$ as high as 269 mmHg have been observed in some children with acute respiratory failure who ultimately survive [6]. Treatment of respiratory acidosis is directed at the underlying cause (e.g., mechanical ventilatory support for acute respiratory failure; bronchodilators, oxygen, corticosteroids for status asthmaticus; etc.). The role of $NaHCO_3$ in the treatment of acute respiratory acidosis is not well defined. For example, in a recent case series of 17 children with near-fatal status asthmaticus, administration of $NaHCO_3$ was associated with a significant decrease in $PaCO_2$ [7].

Conversely, the administration of $NaHCO_3$ has several theoretical disadvantages. Intracellular pH is probably more important for maintaining homeostasis than arterial pH (which is what is measured). CO_2 freely diffuses across the blood–brain barrier, while HCO_3^- does not. In addition, CO_2 diffuses across cell membranes at a much faster rate than HCO_3^-. Therefore, correction of arterial pH with the administration of $NaHCO_3$ could potentially result in worsening intracellular pH in the brain, cardiomyocytes, and other cells, leading to further cellular damage and dysfunction [8–12]. Additional concerns include (i) displacement of the oxyhemoglobin dissociation curve, (ii) acute intracellular shift of potassium leading to hypokalemia, (iii) calcium binding to serum proteins, leading to decreased ionized calcium, and (iv) sodium and/or water overload. Finally, $NaHCO_3$ administration can theoretically increase $PaCO_2$ transiently, especially in the face of inadequate alveolar ventilation [13–15]. However, in our experience this may be more of a theoretical concern. Given the absence of significant clinical benefit and the potential inherent risks, the routine administration of

Table 14.3 Causes of respiratory alkalosis in critically ill children

Anxiety
Agitation
Pain
Fever
Sepsis
Pneumonia
Hypoxemia
Pulmonary edema
Pulmonary thromboembolism
Central nervous system
Disorders (e.g., Trauma, tumor, infection, stroke)
Acute liver failure
Salicylate poisoning
Hyperthyroidism
Altitude

$NaHCO_3$ in the clinical setting of primary respiratory acidosis is probably not justified [16]. Finally, chronic respiratory acidosis can usually be managed much more conservatively, as metabolic compensation typically leads to adequate systemic pH for cellular function.

Respiratory Alkalosis

A primary respiratory alkalosis is defined as an arterial pH >7.45 in the setting of hypocarbia secondary to hyperventilation. Respiratory alkalosis is one of the more common acid-base disturbances in critically ill children due to a variety of causes (Table 14.3). Most commonly, respiratory alkalosis results acutely via tachypnea secondary to anxiety, pain, agitation, or fever. Hypoxemia may induce a hyperventilatory response in association with parenchymal lung disease, congestive heart failure, pulmonary edema (of any etiology), or pulmonary thromboembolism. Neurogenic causes (increased intracranial pressure secondary to head trauma, infection, tumor, etc.) should also be considered in the differential diagnosis. Respiratory alkalosis may also arise from either deliberate or unintentional overventilation in an infant or child with respiratory failure. Salicylate poisoning causes respiratory alkalosis (in addition to the metabolic acidosis – see below) through stimulation of the respiratory centers in the CNS. Regardless of etiology, the initial fall in $PaCO_2$ is titrated by a mild decrease in arterial HCO_3^- (decrease by approximately 0.2 mEq/L for every 1 mmHg decrease in $PaCO_2$) which occurs within several minutes [2, 3, 17], and the pH will increase by 0.08 units for each 10 mmHg decrease in $PaCO_2$. The compensatory response to a chronic respiratory alkalosis by the kidneys usually occurs within 2–4 days via decreased tubular reabsorption of HCO_3^-, resulting in an increase in pH by 0.03 units for each 10 mmHg decrease in $PaCO_2$. Respiratory alkalosis leads to alterations in serum potassium (decreases), phosphate (decreases acutely, increases chronically), ionized calcium (decreases), and lactic acid (increases) [17]. Clinical manifestations include altered mental status, confusion, and seizures (due to the effects of hypercarbia on cerebral perfusion), tachycardia, arrhythmias, muscle cramping, and muscle spasms. Treatment is again directed towards the underlying cause.

Metabolic Acidosis

A primary metabolic acidosis is defined as an arterial pH <7.35 secondary to a decrease in arterial HCO_3^- (usually <22 mEq/L). Metabolic acidosis is generally caused by loss of HCO_3^- (from gastrointestinal or renal losses), an increase in endogenous acid production (such as lactate or ketoacids), decreased excretion of endogenous acids (as in acute renal failure), or accumulation of exogenous acids from toxins. The lungs respond to an acute metabolic acidosis with increased minute ventilation, leading to a decrease in $PaCO_2$. Maximal compensation occurs at a $PaCO_2$ 10 mmHg. The expected compensatory decrease in $PaCO_2$ may be determined using the Winters equation:

$$PaCO_2 = 1.5 \times \left[HCO_3^-\right] + 8 \pm 2$$

If the observed and calculated (i.e. expected) $PaCO_2$ differ, then a mixed acid-base disorder is present. In most cases of metabolic acidosis, respiratory compensation will be incomplete – even with maximal compensation, pH will never be in the normal range. Furthermore, respiratory compensation is only temporary – after several days, the kidneys will respond to the lower $PaCO_2$ with bicarbonate wasting (decreased tubular reabsorption) [18].

The etiology of metabolic acidosis can be generally characterized by the presence or absence of unmeasured anions – i.e., by the presence or absence of an anion gap (described above). Again, a normal anion gap is 12 ± 4 mEq/L. The anion gap has a few limitations that deserve mention. First and foremost, albumin is the major anion in the blood. Changes in albumin can therefore have a major impact on calculation of the anion gap (e.g., for every 1 g/dL decrease in serum albumin, the anion gap will decrease by approximately 2–3 mEq/L). Hypoalbuminemia is relatively common in critically ill children, and failure to account for this may grossly underestimate the true anion gap [19, 20]. Accordingly, Figge [21, 22] described a correction factor for albumin concentration in adults which has been subsequently validated in a cohort of critically ill children [20]:

$$AG_{corr} = AG + 0.25 \times (40\,g/L \quad \text{observed albumin})$$

Other conditions that may be associated with a falsely *low* anion gap include hyponatremia, profound hyperkalemia,

Table 14.4 Causes of high anion gap metabolic acidosis

M = Methanol
U = Uremia
D = Diabetic KetoAcidosis (DKA)
P = Paraldehyde
I = Iron, Isoniazid, or inborn errors of metabolism
L = Lactic acidosis
E = Ethylene glycol
S = Salicylate

hypercalcemia, hypermagnesemia, and hypophosphatemia. Finally, the arterial pH can affect measurement of the anion gap as well by affecting the anionic charge of serum proteins and by altering the quantity of organic acids – during acidemic states the AG will decrease by 1–3 mEq/L and increase by 3–5 mEq/L during alkalemic states.

Elevated Anion Gap Acidosis

Elevated anion gap acidosis is due to either the retention of endogenous acids (e.g., keto-acids, lactic acid, etc.) or the addition of exogenous acids (e.g., ingestion of ethylene glycol, salicylates) and has a variety of causes that are easily recalled by the classic mnemonic *MUDPILES* (Table 14.4). Lactic acidosis is by far the most common type of a high anion gap acidosis in the PICU and will be discussed in more detail below. Ketoacidosis may develop with starvation (i.e., free fatty acids are metabolized to keto-acids rather than being used for triglyceride formation) but more commonly develops during states of insulin deficiency, e.g., diabetic ketoacidosis (DKA). Starvation is usually associated with a mild metabolic acidosis, while DKA is commonly associated with profound metabolic acidosis. A wide variety of toxins and drugs can also cause an elevated anion gap acidosis, including methanol, ethylene glycol, salicylates (which are also associated with a respiratory alkalosis via direct stimulation of the respiratory centers), iron, isoniazid, and paraldehyde (paraldehyde was once commonly used for the treatment of refractory seizures and is used so infrequently now that this is rarely observed). Methanol and ethylene glycol are rapidly converted to the toxic metabolites, formic acid (via alcohol dehydrogenase) and glycolic acid (via aldehyde dehydrogenase) in the liver, respectively. These two metabolites are responsible for both the toxic effects and the elevated anion gap associated with the ingestion of these two alcohols. An important diagnostic clue to the presence of methanol or ethylene glycol as the etiology for an elevated anion gap is an increase in the osmolal gap:

$$\text{Osmolal gap} = \text{Measured serum osmolality} - \text{Calculated serum osmolality}$$

$$\text{Calculated osmolality} = 2\left[\text{Na}^+\right] + \text{BUN}/2.8 + \text{Glucose}/18$$

The normal osmolal gap is less than 10 mEq/L, though pseudohyponatremia secondary to either hyperlipidemia or hyperproteinemia can falsely elevate the osmolal gap [3]. Inborn errors of metabolism (i.e., endogenous organic acids) also are associated with an elevated anion gap. Finally, uremia (as with renal insufficiency or renal failure) causes an elevated anion gap.

Lactate is a byproduct of anaerobic metabolism. Aerobic metabolism provides 20 times more energy than anaerobic metabolism. For example, glucose is oxidized to pyruvate via glycolysis (also called the Embden-Meyerhof pathway), generating two molecules of ATP in the process (Fig. 14.2; Table 14.5). When oxygen supply is adequate, pyruvate enters the mitochondria and is converted to acetyl coenzyme A (acetyl CoA) by the pyruvate dehydrogenase enzyme complex, after which it is completely oxidized to CO_2 and H_2O via the Kreb's cycle (also known as the tricarboxylic acid or citric acid cycle) (Fig. 14.3) and oxidative phosphorylation (Fig. 14.4), generating a *net* total of 36–38 mol of ATP for every mole of glucose (Table 14.6). Conversely, when oxygen supply is inadequate, pyruvate is reduced by NADH and lactate dehydrogenase to lactate (lactic acid), a relatively inefficient process that generates considerably less ATP. Lactate can be converted back to pyruvate in the presence of oxygen via reduction of NAD^+ to NADH, which in turn enters the Kreb's cycle. Alternatively, lactate can be converted back to glucose via the Cori cycle (which requires 6 mol of ATP) and stored in the liver as glycogen.

The normal arterial lactate concentration is 1.0 ± 0.5 mmol/L, which represents the equilibrium between production and consumption during normal metabolism [23, 24]. The liver, kidneys, gastrointestinal tract, and muscle all have the capacity to remove lactate far in excess of what is normally produced during normal metabolism throughout the day. Therefore, lactate production (i.e., from anaerobic glycolysis) must increase substantially before it accumulates to any significant extent in the arterial blood. Cohen and Woods [25] divided lactic acidosis into two categories. Type A lactic acidosis results from an imbalance between oxygen delivery and oxygen consumption (e.g., shock), while type B lactic acidosis occurs without clinical evidence of tissue hypoxia. Type B lactic acidosis is more often associated with underlying diseases (e.g., diabetes mellitus, liver disease, malignancy, thiamine deficiency, pheochromocytoma), drugs or toxins (e.g., epinephrine, norepinephrine, alcohol, terbutaline, cyanide), or inborn errors of metabolism (e.g., glucose-6-phosphatase deficiency, fructose-1,6-diphosphatase deficiency, pyruvate dehydrogenase deficiency, defects in oxidative phosphorylation) [23, 25, 26]. In addition, hyperlactatemia may occur in critical illness (e.g., sepsis, burns, trauma) even in the absence of tissue hypoxia – in these cases, the increased lactate is secondary to increased glycolytic flux, down-regulation of pyruvate dehydrogenase, etc. [23, 24, 27]. In

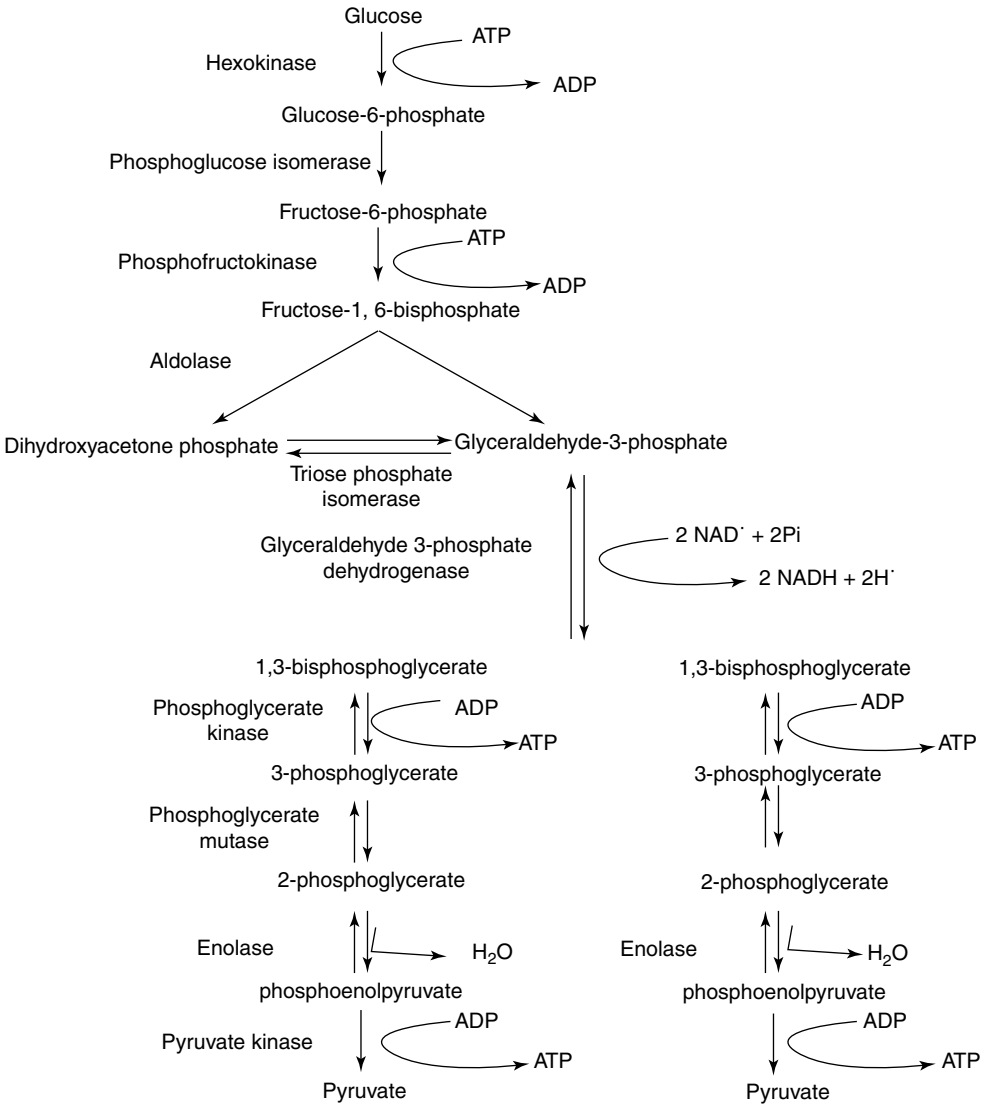

Fig. 14.2 Glycolysis (Embden-Meyerhof pathway): Glucose + 2 Pi + 2 ADP + 2 NAD^+ → 2 Pyruvate + 2 ATP + 2 NADH + 2H^+ + 2 H_2O

Table 14.5 Consumption and Generation of ATP in glycolysis

Reaction	ATP change per mole glucose
Glucose → glucose-6-phosphate	−1
Fructose 6-phosphate → fructose 1,6-bisphosphate	−1
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	+2
2 Phosphoenolpyruvate → 2 Pyruvate	+2
	Net +2

these cases, clinical exam, absence of other indicators of tissue hypoxia (i.e., low mixed venous saturation, worsening base deficit, organ dysfunction, etc.) is helpful in differentiating between increased production versus poor clearance. Alternatively, an elevated lactate/pyruvate ratio (defined as a lactate to pyruvate ratio greater than 18) is a useful indicator of lactate accumulation secondary to tissue hypoxia [28–30].

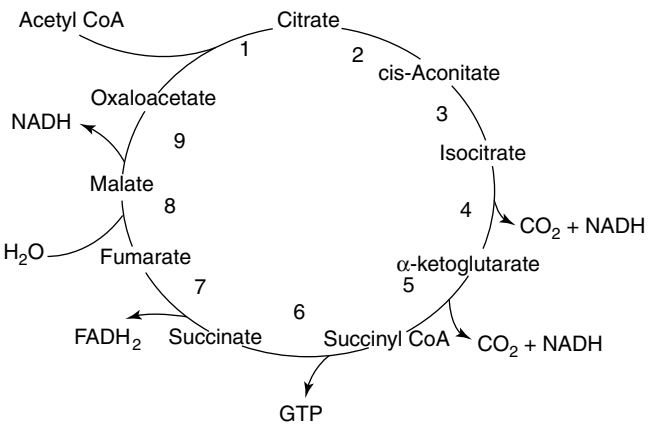

Fig. 14.3 Tricarboxylic acid (Kreb's) cycle: Pyruvate + CoA + NAD^+ → Acetyl CoA + CO_2 + NADH (via Pyruvate dehydrogenase complex) Acetyl CoA + 3 NAD^+ + FAD + GDP + Pi + 2 H_2O → 2 CO_2 + 3 NADH + $FADH_2$ + GTP + 2H^+ + CoA. *1* Citrate synthetase, *2* Aconitase, *3* Aconitase, *4* Isocitrate dehydrogenase, *5* α-ketoglutarate dehydrogenase complex, *6* Succinyl CoA synthetase, *7* Succinate dehydrogenase, *8* Fumarase, *9* Malate dehydrogenase

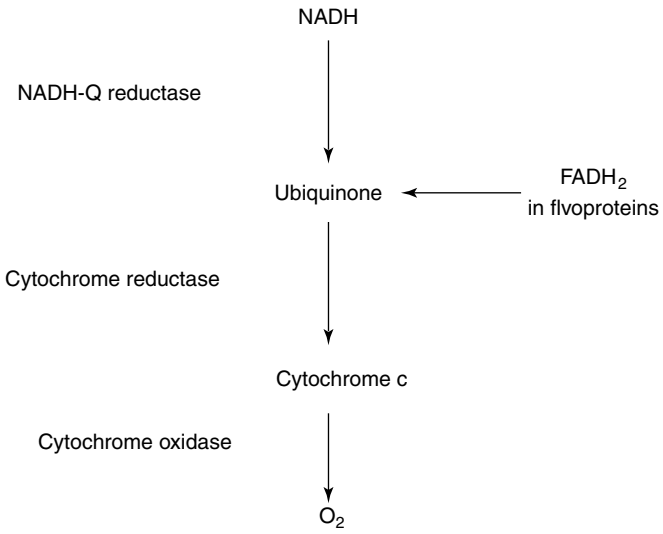

Fig. 14.4 Oxidative phosphorylation, the process by which ATP is formed as electrons are transferred from NADH or FADH $_2$ to O_2 by a series of electron carriers localized to the inner mitochondrial membrane. The oxidation of NADH yields three molecules of ATP, whereas oxidation of $FADH_2$ yields two molecules of ATP through the generation of a proton gradient across the inner mitochondrial membrane. Oxidation and ATP synthesis are coupled by transmembrane proton fluxes. As electrons are transferred from $FADH_2$ or NADH to O_2, H+ is pumped out of the mitochondrial matrix. ATP is synthesized when H+ flows back into the mitochondrial matrix

Table 14.6 Consumption and generation of ATP in aerobic glycolysis (complete oxidation of glucose to O_2 and H_2O)

Reaction	ATP change per mole glucose
Glucose → glucose-6-phosphate →	−1
Fructose 6-phosphate → fructose 1,6-bisphosphate	−1
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	+2
2 Phosphoenolpyruvate → 2 Pyruvate	+2
2 Glyceraldehyde 3-phosphate → 2 1,3-bisphosphoglycerate (yields 2 NADH → oxidation via respiratory chain 2–3 ATP:1 NADH[a])	+4 to +6
2 Pyruvate → 2 Acetyl CoA (yields NADH → oxidation via respiratory chain 3 ATP:1 NADH)	+6
2 Succinyl CoA → 2 Succinate	+2 (as GTP)
6 NADH from Kreb's cycle (oxidation via respiratory chain 3 ATP:1 NADH)	+18
2 $FADH_2$ from Kreb's cycle (oxidation via respiratory chain 2 ATP: 1 $FADH_2$)	+4
	Net +36 to +38

[a]NADH is formed by glycolysis (glycolytic enzymes are located in the cytosol). The inner mitochondrial membrane is impermeable to NAD^+ and NADH. One of two mechanisms is used to transport the electrons from cytoplasmic NADH across the inner mitochondrial membrane:
1 Glycerol phosphate shuttle: this shuttle mechanism transports the electrons from NADH rather than the NADH itself across the inner mitochondrial membrane in a process that generates $FADH_2$
2 Malate-aspartate shuttle: this shuttle mechanism transports the electrons from NADH rather than the NADH itself across the inner mitochondrial membrane in a process that regenerates NADH (dominant mechanism in the heart and liver)

Several studies have examined the correlation between lactic acidosis and subsequent outcome in both children and adults with critical illness from myriad causes [reviewed in [23, 24, 26, 31–34]]. For example, Vincent et al. [35] showed that the initial lactate level, as well as the change in lactate over time during resuscitation was predictive of outcome in adults with shock. These results have been replicated in other studies performed in adults with both hemorrhagic shock [36–39] and sepsis [40–44]. Similarly, the initial lactate level, as well as the change in lactate over time predict outcome in children with septic shock [30, 45–47] and low cardiac output syndrome following cardiopulmonary bypass [48–54]. In summary then, hyperlactatemia appears to be a useful indicator of poor tissue perfusion, though serial lactates are perhaps more useful than any one number. In addition, physicians at the bedside need to be cognizant of other causes of lactic acidosis (i.e. type B disorders – for example, sepsis) and exercise caution when interpreting serum lactate concentrations.

Acute metabolic acidosis can be tolerated in most healthy individuals, e.g. pH values as low as 7.15 may be generated in the exercising adult [55]. However, severe metabolic acidosis (usually pH <7.20) produces a variety of adverse hemodynamic consequences, including decreased cardiac output (via decreased cardiac contractility), decreased systemic vascular resistance (producing hypotension), increased susceptibility to ventricular arrhythmias, increased pulmonary vascular resistance, and decreased responsiveness to both endogenous and exogenous catecholamines [reviewed in [23, 24, 26]]. However, while generally accepted by most clinicians, the negative inotropic effects of acute metabolic acidosis have not been consistently demonstrated. Furthermore, there is evidence to suggest that acidosis may have protective effects in critical illness [reviewed in [26, 56, 57]]. Treatment of metabolic acidosis is therefore determined primarily by its etiology, and in general, the focus of treating an increased anion gap acidosis should be on treating the underlying cause of the increased acid accumulation. Sodium bicarbonate is rarely helpful and may be harmful in children with DKA and is therefore contraindicated in this population [58, 59]. There are several theoretical concerns to treating lactic acidosis with sodium bicarbonate as well (see discussion above). Importantly, acidosis shifts the oxyhemoglobin dissociation curve to the right (*the Bohr effect*), thereby improving oxygen delivery at the tissue level. Bicarbonate administration, by shifting the oxyhemoglobin dissociation curve back to the left could theoretically worsen oxygen delivery to hypoxic tissues. Alternative compounds for treating metabolic acidosis (e.g., Carbicarb, THAM, dichloroacetate) are available but have failed to show any significant improvements in either hemodynamics or outcome [review in [26, 56, 57]]. There are few randomized, controlled trials to suggest either a benefit or harmful effect of sodium bicarbonate in treating metabolic

Table 14.7 Causes of normal anion gap (hyperchloremic) metabolic acidosis

Gastrointestinal bicarbonate loss
Diarrhea
External pancreatic or small-bowel drainage
Ureterosigmoidostomy, jejunal loop, ileal loop
Drugs
Calcium chloride (acidifying agent)
Magnesium sulfate (diarrhea)
Cholestyramine (bile acid diarrhea)
Renal loss
Hypokalemia
Proximal RTA (type 2)
Distal (classic) RTA (type 1)
Hyperkalemia
Generalized distal nephron dysfunction (type 2 RTA)
(A) Mineralocorticoid deficiency
(B) Mineralcorticoid resistance
(C) ↓NA + delivery to distal nephron
(D) Tubulointerstitial disease
(E) Ammonium excretion defect
Drug-induced hyperkalemia (with renal insufficiency)
Potassium-sparing diuretics (Amiloride, Triamterene, Spironolactone)
Trimethoprim
Pentamidine
Angiotensin-converting enzyme inhibitors and AT-II receptor blockers
Nonsteroidal anti-inflammatory drugs
Cyclosporine
Other
Acid loads (ammonium chloride, hyperalimentation)
Loss of potential bicarbonate: ketosis with ketone excretion
Expansion acidosis (rapid saline administration)
Hippurate
Cation exchange resins

RTA renal tubular acidosis, *AT-II* angiotensin-II receptor blockers

acidosis in either children or adults with shock. Therefore, given the theoretical disadvantages of sodium bicarbonate administration and until more convincing evidence is available to support the argument either way, we would advocate the use of small, titrated doses of sodium bicarbonate to achieve a pH >7.15–7.20 in children with shock, while attempts to improve oxygen delivery (and minimize oxygen consumption) are continued [24].

Non-anion Gap Acidosis

A metabolic acidosis in the presence of a normal anion gap suggests that loss of HCO_3^- (usually via the kidneys or gastrointestinal tract) or rapid dilution of the extracellular fluid (ECF) has occurred. In either case, the concentration of chloride will be increased proportionately, resulting in hyperchloremia. Causes of a normal anion gap, hyperchloremic metabolic acidosis are listed in Table 14.7. One of the most common causes of a hyperchloremic metabolic acidosis in children is diarrhea (diarrheal fluid contains a high concentration of HCO_3^- relative to plasma). Large amounts of potassium are lost in diarrheal fluid as well, frequently resulting in hypokalemia. The small bowel and pancreatic fluids are also high in HCO_3^- and low in Cl^- such that tube or fistula drainage (e.g., ureteral diversion procedures using colon or small bowel) from these sites can also precipitate a hyperchloremic metabolic acidosis.

Renal tubular acidosis (RTA) is also characterized by a hyperchloremic metabolic acidosis, resulting from failure of bicarbonate reabsorption/regeneration (i.e. decreased H^+ secretion) in the distal tubule (type 1, or distal RTA), bicarbonate wasting in the proximal tubule (type 2, or proximal RTA), or aldosterone deficiency with decreased clearance of potassium (type 4, distal or hyperkalemic RTA). Certain diuretics can also induce the hyperchloremic acidotic state by inhibiting proximal sodium bicarbonate absorption (acetazolamide) or distal reabsorption (spironolactone). Another potentially significant disturbance in the critically ill children is dilutional acidosis. With large volume ECF expansion, as during resuscitation of shock with non-HCO_3^- -containing fluids such as 0.9 % normal saline, glomerulotubular balance is downregulated. The fractional rate of sodium reabsorption by the proximal tubule is thus decreased and with it, the reabsorption of bicarbonate, inducing hyperchloremic metabolic acidosis. Children with sepsis and trauma in particular may receive rapid volume resuscitation of significant multiples of their plasma volume. Normal saline contains equivalent amounts of sodium and chloride (154 mEq/L), and large volumes of normal saline can induce a hyperchloremic metabolic acidosis [60–64]. Approaches are discussed further later in this chapter.

Calculation of the urinary anion gap can also be helpful in differentiating renal from GI causes of hyperchloremic metabolic acidosis. The urinary anion gap is defined as:

$$\text{Urinary anion gap} = \left[Na^+ + K^+\right] - \left[Cl^-\right]$$

The urinary anion gap is normally negative, as *unmeasured* ammonium is excreted by the kidney to balance Cl^- excretion, which is typically greater than urinary Na^+ and K^+ excretion. In the setting of hyperchloremic metabolic acidosis, a GI-induced bicarbonate loss will lead to normal renal compensation by increasing chloride excretion and balancing this with an increase in ammonium excretion, resulting in a greater negative urinary anion gap. A positive urinary anion gap reflects an impairment in ammonium excretion and suggests the presence of a RTA. The urine pH can then further differentiate between a proximal RTA (low urine pH) and a distal RTA (high urine pH). Patients with a hyperchloremic metabolic acidosis generally have wasting of endogenous bicarbonate buffer and generally benefit from sodium bicarbonate therapy.

Metabolic Alkalosis

A primary metabolic alkalosis is defined as an arterial pH >7.45 secondary to either loss of H^+ from the body or a net gain of HCO_3^-. Metabolic alkalosis is maintained when the kidneys fail to compensate by excreting excess HCO_3^- due to volume contraction, low glomerular filtration, or associated depletion of chloride or potassium. It is typically accompanied by an elevated $PaCO_2$ due to compensatory alveolar hypoventilation. The appropriate compensatory increase in $PaCO_2$ may be calculated by:

$$PaCO_2 = 0.7\Delta\left[HCO_3^-\right].$$

The maximal compensatory increase in measured $PaCO_2$ is approximately 65 mmHg. Conditions of bicarbonate loss can either be temporary and corrected by chloride replacement (so-called *chloride responsive*) or those in which hormonal mechanisms produce ongoing acid and chloride losses that are not effectively corrected by chloride (so-called *chloride resistant*) [2–4, 64]. Chloride responsive causes are characterized by a urine chloride concentration less than 10 mmol/L and include gastrointestinal losses from vomiting or excessive nasogastric suction, renal losses from diuretic use (loop diuretics), and as compensation for chronic hypercarbia. These states are exacerbated by volume contraction and/or hypokalemia, which augment distal H^+ secretion. In these cases, the metabolic alkalosis is corrected by chloride administration. Chloride resistant causes are characterized by a urine chloride greater than 20mmol/L and are generally less common in critically ill children. The chloride resistant causes are related to mineralocorticoid excess from hyperaldosteronism, either in a primary or secondary state. Notably, diuretic therapy produces both states by inducing chloride and potassium depletion but also by stimulating aldosterone secretion. Finally, exogenous alkali loads are relatively common in the PICU and are related to massive blood transfusions (blood products containing citrate), use of acetate in parenteral nutrition, or with citrated sodium as used in replacement solutions for continuous renal replacement therapies (Table 14.8).

Treatment of metabolic alkalosis is based on etiology. Chloride responsive disorders obviously benefit from replacement of chloride through saline infusion (NaCl), though KCl may also provide dual replacement benefit. In more severe states, dilute (0.1 N) intravenous hydrochloric acid can provide more rapid replacement, or oral ammonium chloride can be helpful (avoid in the presence of liver disease). Discontinuation of diuretics may also be necessary. If

Table 14.8 Causes of metabolic alkalosis

Exogenous HCO_3^- loads
Acute alkali administration
Milk-alkali syndrome
Effective ECFV contraction, normotension, hypokalemia, and secondary hyperreninemic Hyperaldosteronism
Gastrointestinal origin
Vomiting
Gastric aspiration
Congenital chlorodorrhea
Villous adenoma
Combined administration of sodium polystyrene sulfonate (Kayexalate) and aluminum hydroxide
Renal origin
Diuretics
Edematous states
Posthypercapnic state
Hypercalcemia/hypoparathyroidism
Recovery from lactic acidosis or ketoacidosis
Nonreabsorbable anions including penicillin, carbenicillin
MG2+ deficiency
K + depletion
Bartter's syndrome (loss of function mutations in TALH)
Gitelman's syndrome (loss of function mutation in NA + -CL- cotransporter in DCT)
ECFV expansion, hypertension, K ± deficiency, and mineralcorticoid excess
High renin
Renal artery stenosis
Accelerated hypertension
Renin-secreting tumor
Estrogen therapy
Low renin
Primary aldosteronism
Adenoma
Hyperplasia
Carcinoma
Adrenal enzyme defects
11 B-hydroxylase deficiency
17 A-hydroxylase deficiency
Cushings syndrome or disease
Other
Licorice
Carbenoxolone
Chewer's tobacco
Lydia Pincham tablets
Gain of function mutation or renal sodium channel with ECFV expansion, hypertension, K+ deficiency, and hyporeninemic-hypoaldosteronism
Liddle's syndrome

ECFV extracellular fluid volume, *TALH* thick ascending limb of Henle's loop, *DCT* distal convoluted tubule

ongoing diuresis is desired, the carbonic anhydrase inhibitor acetazolamide may be effective. Treatment of chloride resistant states is directed at treating mineralocorticoid excess. Use of agents blocking distal tubular sodium reabsorption, restriction of sodium intake, and potassium supplementation are used to treat primary hyperaldosteronism. Angiotensin-converting enzyme inhibitors are typically effective for secondary aldosteronism as well as discontinuation of exogenous corticosteroids.

Mixed Acid-Base Disorders

A mixed acid-base disorder occurs when there is more than one acid-base disorder occurring at the same time. For example, salicylate ingestions classically produce both a respiratory alkalosis (via direct stimulation of the respiratory centers in the brain) and a metabolic acidosis (elevated anion gap). The normal compensation to a primary acid-base disorder is NOT considered a mixed acid-base disorder. Proper analysis and interpretation of acid-base disorders requires a systematic approach [2–4, 65, 66] (Table 14.9).

Table 14.9 Systematic approach to analysis of acid-base disorders

1. *Interpret the arterial pH to determine whether there is an academia or alkalemia present*:
If pH >7.45, an alkalemia is present
If pH <7.35, an acidemia is present
2. *Determine whether the primary disturbance is respiratory or metabolic in origin*
Respiratory acidosis: ↓ pH, ↑ $PaCO_2$
Respiratory alkalosis: ↑ pH, ↓ $PaCO_2$
Metabolic acidosis: ↓ pH, ↑ $[HCO_3^-]$
Metabolic alkalosis: ↑ pH, ↓ $[HCO_3^-]$
3. *Calculate the anion gap (AG)* ($AG = [NA^+] - [HCO_3^- + CL^-]$). *Correct for hypoalbuminemia if indicated*!
Generally, AG >10 mEQ/L suggests the presence of a metabolic acidosis, while AG >20 mEQ/L is always associated with a metabolic acidosis
4. *Using the formulas listed in Table 14.1, determine whether the degree of compensation is appropriate. If it is not, then a mixed acid-base disorder is likely.*
5. *Calculate the delta AG: delta GAP = (calculated anion GAP – normal AG), i.e. (AG_{CALC} – 12). in other words, for every 1 mEQ/L increase in the calculated AG, there should be a 1 mEQ/L decrease in* $[HCO_3^-]$*:*
If the $[HCO_3^-]$ is lower than predicted by this relationship, a normal AG (hyperchloremia)
Metabolic acidosis is also present
If the $[HCO_3^-]$ is higher than predicted by this relationship, a metabolic alkalosis is also present
6. *Measure urine pH and urine electrolytes if a metabolic alkalosis is present*

Special Acid-Base Situations

Cardiopulmonary Bypass and Hypothermia: pH Stat and Alpha Stat Concepts

Hypothermia is a key element in creating optimal surgical conditions and end organ protection, particularly in the brain, during cardiopulmonary bypass (CPB). Two approaches to management of acid-base status during hypothermia (either iatrogenic, as with cardiopulmonary bypass or accidental) have been described – pH-stat versus alpha-stat. Alpha-stat and pH-stat are two divergent blood gas management strategies utilized during cardiopulmonary bypass (CPB) and are a topic of debate among cardiac anesthesiologists. The primary difference centers on the anesthesiologist's response to $PaCO_2$ and the change in its solubility during hypothermia and CPB. The differences between the two approaches is quite complex and deserve some explanation here.

The law of mass action states that the velocity of a reaction is proportional to the product of the concentrations of the reactants. For example, water dissociates into H^+ and OH^-:

$$H_2O \leftrightarrow H^+ + OH^-$$

Recall that the inherent tendency of a particular acid to dissociate or ionize is determined by the ionization constant, pK. Note that the pK is inversely proportional to the strength of the acid to dissociate – in other words, a strong acid (HA) would exist mostly as H^+ and A^- (the pK of this acid would be relatively high). Similarly then, the relative concentration of H+ is determined by the dissociation constant of water (pKw), which decreases as temperature decreases (i.e., water is less likely to dissociate), such that as the H^+ ions and OH^-decrease – the pH then increases [67]. Stated in another way, electroneutrality occurs at a neutral pH when $[H^+] = [OH^-]$. As temperature decreases, the pH at which water is *neutral* increases 0.017 units for each °C decrease in temperature – at 37 °C, the pH of neutral water (i.e. when $[H^+] = [OH^-]$) is 6.8, while at 25 °C, the pH of neutral water is 7.40. Since human plasma is mostly water, the same principles apply. Human blood has $[OH^-]$: $[H^+]$ ratio of 16: 1, resulting in a pH of 7.4 at 37°C (normal body temperature). This relationship remains constant despite changes in

temperature, so that the pH of blood also increases 0.017 units for each °C decrease in temperature [68].

The function of proteins is critically dependent upon their tertiary and quarternary structures, which in turn depend to a great extent upon the ionic charges of the individual amino acid constituents. Thus, intracellular proteins need a buffer to maintain a constant ionization state despite changes in pH [69]. Reeves [70] suggested that the imidazole moiety of histidine could serve this role, as it undergoes a pK change with a temperature that parallels that of pKw (the so-called *alpha-stat hypothesis*). The portion of the histidine imidazole group that loses a proton (H^+) in its dissociation to maintain electrical neutrality (thereby acting as a buffer) is designated alpha-imidazole. Thus, while changes in temperature will affect the pH of water, the ionization state of proteins remains the same relative to this pH – this allows proteins to maintain their structure, and thus function, regardless of the temperature. The *alpha-stat hypothesis* contends that the alpha imidazole histidine ionization state is a primary determinant of the charge state and the pH-dependent functions of most of the body's proteins. With alpha stat management (as observed in poikilotherms whose tissues must function over a wide range of temperatures), changing temperature does not alter histidine ionization and, hence, pH of neutrality, protein charge state, structure, and function are better preserved.

Other factors are important as well. During hypothermia, the solubility of CO_2 in blood increases such that for a given concentration of carbon dioxide in blood, the $PaCO_2$ decreases as total CO2 remains constant. Keeping CO_2 constant is essential because it guarantees that the OH^-/H^+ ratio, alpha-imidazole, and protein charge state remains stable, thereby maintaining biologic neutrality as tissues cool. With regards to CPB, *alpha-stat management* means to measure the arterial blood gases at 37 °C (i.e., the arterial blood is warmed prior to 37 °C prior to analysis) and any necessary adjustments to maintain arterial pH 7.4 and $PaCO_2$ 40 mmHg at 37 °C are then made, regardless of the core body temperature. In theory, the primary advantages to alpha-stat management are preserving the Gibbs-Donnan equilibrium and maintaining a normal cerebral blood flow/metabolism relationship [71–76].

The other commonly used approach to pH management is known as *pH stat management*. Here, arterial pH is maintained constant over varying temperatures – in other words, management is directed towards maintaining pH 7.4 and $PaCO_2$ 40 mmHg, irrespective of core body temperature. Generally, in order to maintain $PaCO_2$ 40 mmHg, CO_2 must be added to the sweep gas as the patient is cooled, owing to the increased solubility of CO_2 with decreasing temperature. Extracellular and intracellular OH^-:H^+ ratios are altered and total CO_2 stores become elevated. This type of pH management is observed in hibernating animals – these animals hypoventilate to generate a respiratory acidosis. Importantly, the goal during hibernation is to minimize oxygen consumption and energy expenditure while preserving blood flow to the vital organs (especially the brain). Many experts argue then that the pH-stat management is more appropriate to the human undergoing CPB [71–76].

The debate surrounding alpha-stat versus pH-stat blood gas management revolves around CO_2 and hypothermia and their effect on cerebral blood flow, cerebral oxygen consumption, intracellular pH, and extracellular pH in the setting of CPB and deep hypothermic circulatory arrest (DHCA). The discrepancy in $PaCO_2$ and pH between the two strategies is significant and approaches 80 mmHg and 0.24 respectively [71–76] (Table 14.10). The main concern of the debate is to minimize poor neurodevelopmental and neuropsychometric outcomes [72, 77, 78]. Studies evaluating both methods present conflicting data and have not resolved the debate as to the ideal acid-base strategy. A prospective, randomized study comparing alpha stat and pH stat in two similar groups demonstrated shorter duration of intubation, ICU stay, and post-operative seizures in pH stat managed patients, however without any statistical significance [79]. The study also looked at 1 year follow up in 111 of 182 patients enrolled and found no difference in neurologic evaluation, EEG, or psychomotor or mental development indices [80].

Table 14.10 Alpha-stat vs pH-stat management

	Measured and reported at 37 °C				Actual (at in vivo temperature)			
Core body temperature	pH alpha-stat	pH pH-stat	$PaCO_2$ alpha-stat	$PaCO_2$ pH-stat	pH alpha-Stat	pH pH-stat	$PaCO_2$ alpha-stat	$PaCO_2$ pH-stat
37 °C	7.40	7.40	40	40	7.40	7.40	40	40
33 °C	7.40	7.34	40	47	7.44	7.40	35	40
30 °C	7.40	7.30	40	54	7.50	7.40	29	40
27 °C	7.40	7.26	40	62	7.55	7.40	26	40
23 °C	7.40	7.21	40	74	7.60	7.40	22	40
20 °C	7.40	7.18	40	84	7.65	7.40	19	40

Hypercapnic Acidosis and Permissive Hypercapnia in Ventilatory Management

Lung protective ventilator strategies utilizing low tidal volumes and permissive hypercapnia are currently standard practice in managing patients with acute respiratory distress syndrome (ARDS). Hypercapnic acidosis (HCA) is regarded as an acceptable side effect of permissive hypercapnia. HCA has a myriad of effects on many physiological processes, mostly demonstrated in animal models. Animal models have suggested that acidosis attenuates hypoxic pulmonary vasoconstriction, maintain nitric oxide, reduction in oxidative stress, attenuates pulmonary endothelial wound repair, and overall dampening the inflammatory response [81]. The recognition of these effects is important as it will affect the decision whether or not to allow the development of HCA on a case by case basis. The resultant effect of HCA on physiological functions depends on a myriad of factors including the level of hypercapnia and patients prior medical illnesses.

Experimental studies have demonstrated therapeutic benefits of HCA in a number of lung injury models [82–90]. However, it is unclear if it is the respiratory acidosis per se rather than the elevated carbon dioxide milieu that is responsible for this beneficial effect. HCA can enhance oxygenation through several mechanisms. Respiratory acidosis resulting in a decreased pH causes a shift of the oxyhemoglobin dissociation curve to the right during acute respiratory acidosis, which causes the release of oxygen to the tissues (the Bohr effect). Additionally HCA causes microvascular vasodilatation, promoting oxygen delivery and tissue perfusion [91, 92]. However, pCO_2 levels of greater than 100 mmHg will result in vasoconstriction. Additional potential benefits include enhancement of lung ventilation-perfusion (V/Q) matching by potentiating hypoxic pulmonary vasoconstriction and increases in CO_2-mediated augmentation of cardiac output and peripheral oxygen delivery. Alternatively, the impact could be harmful by increasing intrapulmonary shunting and worsening pulmonary vasoconstriction [93]. Avoidance of HCA is recommended in patients with intracranial processes or with significant cardiac disease. Hypercapnia increases cerebral blood flow which can have significant deleterious effects in head injury. In children with cardiac disease, the direct effect of myocardial depression may or may not be outweighed the positive effects on coronary blood flow, afterload reduction, and improved cardiac output.

Choice of Intravenous Fluid Composition and Acid-Base Balance

Increasing literature has questioned the use of normal saline solutions (0.9 % NaCl) as the standard fluid for resuscitation, maintenance in intensive care units, or intraoperative surgery [94]. Numerous studies have shown the generation of hyperchloremic metabolic acidosis induced by routine use of 0.9 % NaCl for maintenance and resuscitation in postoperative patients and trauma models [60–64, 94, 95]. Adult studies have demonstrated, however, that the alternative use of lactated Ringers solutions instead of normal saline could also demonstrate acidosis secondary to lactemia. The use of a calcium-free balanced crystalloid (Plasmalyte) for replacement of fluid losses on the day of major surgery, however, was associated with less postoperative morbidity than use of 0.9 % NaCl [96]. Use of 0.9 % NaCl was associated with hyperchloremia, reduced bicarbonate levels, acidosis, and increased base deficit in patients compared to patients receiving Plasmalyte [97]. Patients with diabetic ketoacidosis (DKA) could also potentially have worsening acidosis from 0.9 % NaCl. Resuscitation of DKA patients with Plasmalyte resulted in lower serum chloride and higher bicarbonate levels than patients receiving 0.9 % NaCl, due to decreased generation of hyperchloremic metabolic acidosis [98]. Current evidence is insufficient, particularly in children, to recommend a specific change in practice to completely avoid use of 0.9 % NaCl. However, in patients in whom metabolic acidosis is a concern prior to fluid resuscitation, alternative fluid choices to 0.9 % NaCl could be considered to decrease iatrogenic worsening of acidosis. Use of Ringer's lactate (Na^+ 130 Eq/L, Cl^- 109 mEq/L, K^+ 4 mEq/L, and lactate 28mEq/L) has been recommended by some authors over normal saline for preferential use during resuscitation. The lactate is generally metabolized by the liver and does not usually contribute to lactic acidosis.

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Acute Kidney Injury

15

Rajit K. Basu

Abstract

Acute kidney injury (AKI) is a significant problem for critically ill children. The kidney is responsible for numerous homeostatic controls in the body and disruption of kidney function carries significant and severe consequence for the host. Unfortunately, poor understanding of the multifactorial nature of the causes of AKI and the inability to accurately diagnose real-time injury impedes the derivation of any universally accepted "therapy" for kidney injury. The list of causes of AKI in pediatrics is long, but most etiologies share commonalities in how they induce injury. Recent consensus definitions of AKI have allowed for more stratified and tiered injury levels, improving epidemiologic study of the impact of AKI. Biomarker research continues to pursue the optimal marker, or collection of markers, for prediction of AKI, diagnosis of established AKI, and the ability to predict progression or recovery from AKI. Unfortunately, complete recovery from AKI in the critically ill patient is likely more an assumption than the reality. Many patients transition to chronic kidney disease (CKD) months to years after "recovering" from AKI. As nephrologists and intensivists understand that more patients are dying *from* AKI and not just *with* AKI, attention has been focused on efforts to prevent AKI in the at-risk patient and supportive care for those afflicted with injury. This chapter will discuss the pathophysiology, diagnosis, epidemiology, and management of AKI in pediatrics and the horizon for the optimal care of children at-risk and recovering from this lethal disease process.

Keywords

Acute kidney injury • AKI biomarkers • AKI pathophysiology • KDIGO • AKI epidemiology AKI management • Renal angina

Introduction

Acute kidney injury (AKI) is increasingly recognized as a cause of increased morbidity in critically ill children and adults [1]. Damage to the kidney, a central mediator of homeostasis in the body, affects patient survival. AKI is now known to be an independent risk factor for mortality – as a result, there is an ongoing tremendous research effort pursuing the optimization of diagnosis, management, and outcome [2]. The list of putative causes of AKI in pediatrics is long [3]. However, the true etiology is likely multifactorial, related to a combination of several factors: ischemia and reperfusion injury, disruption of renal vasomotor homeostasis, hypoxic and oxidative stress, and cytokine driven effects. As the kidney is responsible for numerous real-time homeostatic control mechanisms, including water balance, electrolyte handling, erythropoiesis, vascular tone, acid-base status, and regulation of normal glucose metabolism, AKI can have significant deleterious effects on the host. In this chapter, the pathophysiology, epidemiology, and management of AKI

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will be discussed. Special attention will be given to the emerging paradigm of risk-stratification and its potential impact on AKI diagnosis and prognosis. Prevention will be emphasized in the management section; consistently effective therapy for established AKI is lacking. Though renal replacement therapy (RRT) is discussed in depth elsewhere, the salient controversies surrounding RRT for AKI will be discussed. Crosstalk between the kidney and extra-renal organs after AKI will be detailed, emphasizing that AKI is more than simply an "on-off" switch and is associated with more negative global impact on the host than previously believed. Finally, the horizon for pediatric AKI will be discussed – both the management of at-risk children and of children "recovering" from this widespread disease.

Pathophysiology of AKI

The pathophysiology of AKI is multifactorial. Though often secondary to systemic disease or surgery, AKI is triggered by a common set of pathways, characterized independently and concurrent with other disease.

Glomerular Perfusion

Impaired perfusion to the renal bed is a common etiology of AKI. Reversible hypoperfusion leads to the classically described anomaly "pre-renal azotemia" whereas persistent hypoperfusion leads to ischemic injury. The difference between the two processes is akin to the difference between compensated and decompensated shock or heart failure (Table 15.1). As described in previous chapters, the critical index of kidney function (glomerular filtration rate – GFR) is driven by renal perfusion pressure (RPP). Receiving 25 % of the total cardiac output at any given time, the renal blood flow (RBF) determines the RPP as a function of renal vascular resistance (RVR). The approximate relationship between renal blood flow and systemic pressure is a reflection of Ohm's law (current = flow × resistance) [4]:

$$\text{RPP} \sim \text{RBF} \quad \text{RVR}$$

The process of autoregulation in the kidney allows for maintenance of RPP through variation in afferent and efferent arteriolar tone. These modulations afford control of the glomerular capillary perfusion pressure (P_{GC}). The net effect of tubuloglomerular feedback and myogenic reflex on vascular tone around the glomerulus affects filtration. When perfusion pressure falls (states of reduced cardiac output or preload depletion), mediation from the juxtaglomerular apparatus (through renin-angiotensin-aldosterone) act to preserve vascular volume and vascular tone. Prostaglandin and nitric oxide secretion via kidney-dependent mechanisms counteract the vasoconstrictor effect on the glomerulus to preserve P_{GC} [5]. As hypotension persists, GFR is maintained through this balance under the influence of vasopressin, which leads to enhanced urea reabsorption, leading to the characteristic high blood urea nitrogen levels. In specific disease states such as cardiac pump failure, atrial stretch may lead to increased levels of atrial natriuretic peptide-prohormone, which may actually attenuate the regulatory hormones of the kidney (renin, angiotensin, inhibition of the Na^+-K^+-ATPase) through renal conversion to urodilatin [6, 7].

Table 15.1 Pre-renal azotemia versus acute kidney injury

Measured parameter	Pre-renal AKI	Established AKI
Urine sediment	Normal	Epithelial casts
Urine specific gravity	>1.020	<1.020
Urine sodium (mmol/L)	<10	>20
Fractional excretion of sodium	<1 %	>1 %
Fractional excretion of urea	<35 %	>35 %
Urine osmolality (mOsm/kg H_20)	>500	~300
Urine-plasma creatinine ratio	>40	<10
Plasma urea-creatinine ratio	High	Normal

Filtrative Impairment

The transition from persistent hypovolemia and regulated GFR to ischemic injury is manifest by a rapid and progressive fall in GFR. Early in ischemia, there is heightened sensitivity of the vascular endothelium to vasoconstrictors and vasodilators. If impaired RBF persists, however, this sensitivity (the counter-regulatory effect of the kidney to preserve GFR through P_{GC}) is overwhelmed, the window of kidney autoregulation is exceeded, and ischemic kidney injury occurs. Tubular injury is generally manifest by a decreased effective GFR (amount of filtrate in final urine) and characterized by a sloughing of the apical brush border of tubular epithelium. Histopathology of ischemic animal kidneys demonstrate obstruction of the tubular lumen by necrotic debris and resultant rise in the hydrostatic pressure of the Bowman's capsule [8]. Ischemic injury leads to disruption of cytoskeletal protein regulation and integrity of tight junctions at the apical cell surface of the tubular brush border [9]. Interestingly, a drop in the GFR from ischemic injury may result from polarity shifting and inhibition of the Na^+-K^+-ATPase – rendering sodium dependent solute movement impaired [10, 11]. Distal segments of the nephron are generally more resistant to hypoxic injury secondary to greater glycolytic activity than proximal

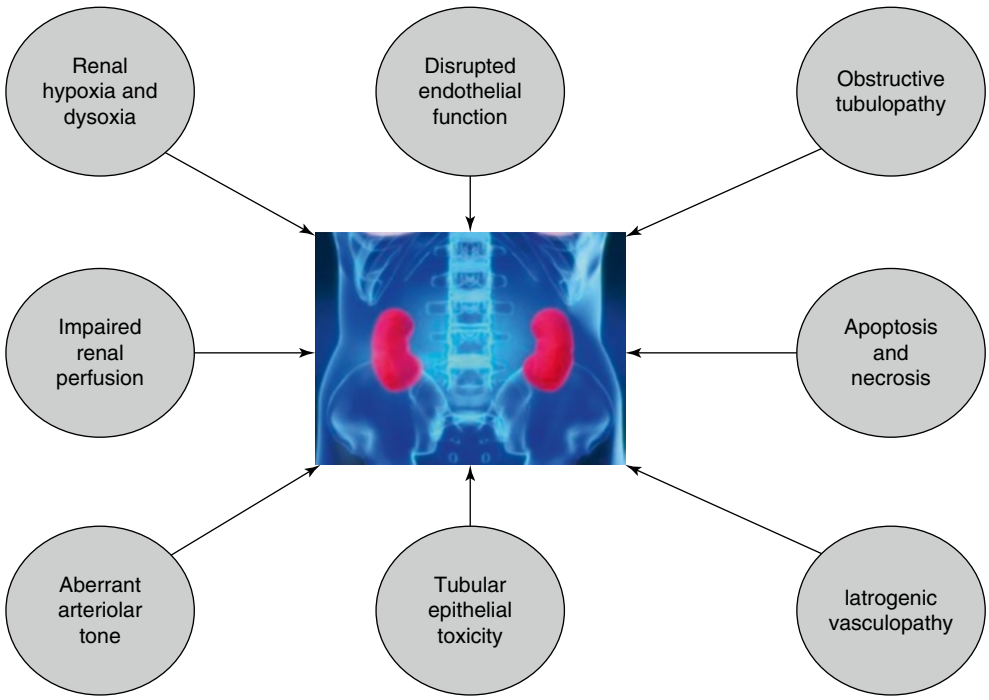

Fig. 15.1 Cellular mechanisms of AKI. Shown above are the contributing mechanisms leading to acute kidney injury

segments. Finally, elaboration of chemokine signals can lead to recruitment of neutrophils and monocytes to areas of damaged tubular endothelium, propagating further cellular injury [12]. Back-leakage, secondary to disrupted cell-cell adhesions leads to accumulation of fluid, urea, and solute in the renal interstitium. This change in the relative distribution of fluid and solute leads to further impingement and obstruction of the tubular lumen (Fig. 15.1).

Disrupted Endothelial Function

Vascular control of glomerular function is disrupted in ischemic injury through disrupted endothelial cell function. The endothelial cell is responsible for liberation of angiotensin-II (ANG-II), endothelin (ET-1), and prostaglandins (PGEs) which modulate afferent and efferent arteriolar tone. In ischemic injury, different segments of the nephron display heterogeneous sensitivity to these vasoactive metabolites and inflammatory mediators. Persistently impeded medullary blood flow leads to endothelial cellular injury, cell swelling, and pronounced decreases in renal blood flow velocity (from physical obstruction) and highly aberrant modulation of vascular tone. Additionally, adhesion molecules on endothelial cell surfaces (selectins, intracellular adhesion molecules (ICAMs)) are upregulated and can 'trap' cellular response elements in the vascular space [13, 14]. Additionally, response to autocrine mediators of endothelial cell function and integrity such as nitric oxide is impaired after ischemic models of AKI [15].

Apoptosis and Necrosis

Cellular viability is a major determinant of kidney function in injury states. In the kidney, disruption of adenosine triphosphate (ATP) balance can lead to either a pro-inflammatory necrotic state or a programmed systematic cellular quiescence (apoptosis) [16]. Experimental and human studies indicate that tubular epithelial cells suffer three potential outcomes resultant from AKI. Cells can take mild injury and recover, can undergo necrosis (secondary to more severe injury and in more susceptible portions of the nephron), or can succumb to apoptosis. Recovery and regeneration of tubular and endothelial cells has been found to be dependent on the early response genes c-fos and Egr-1 [17] and growth factors (insulin-like, hepatocyte, and epidermal) [18]. Necrosis occurs secondary to severe injury (likely in the more susceptible portions of the nephron such as the proximal tubule) and is manifest by a relatively chaotic progression of cellular swelling, fragmentation, and elucidation of a pro-inflammatory phenotype. In clinical AKI, histopathologic evidence indicates that apoptosis is more commonly responsible as the mechanism of cell death than necrosis [19]. Animal and human models of AKI now mirror this finding [20–23]. Tubular cell apoptosis is likely characterized by cellular phagocytosis, obstruction of the tubular lumen by sloughed cells, and an inflammatory response liberating chemotactic signals – all of which contribute to AKI. Endothelial cell apoptosis may lead to disruption of the cytoskeletal matrix and cell-cell junction integrity [24]. Though controversial, the pathogenesis of AKI from cellular injury

likely occurs along a spectrum dependent upon the extent and duration of injury, and is resultant from failure of nephron regeneration, necrosis, and apoptosis.

Iatrogenic Toxicity

Drug induced toxicity is a major cause of AKI in critical illness; nephrotoxins affect kidney function by: altering hemodynamics, acting as direct tubular epithelial and endothelial cell toxins, inducing vasculopathy, and occluding the tubular lumens directly. Modulation of hemodynamics occurs through changing the afferent and efferent arteriolar tone. This primarily occurs through disrupting the balance of angiotensin II and vasodilating agents (nitric oxide and prostaglandins). Non-steroidal anti-inflammatory agents, widely used for treatment of pain, are cyclooxygenase inhibitors that decrease the production of renal effective prostaglandins and decrease the autoregulatory dilatory property required to maintain effective P_{GC} in states of relatively low RPP. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin-II receptor blockers (ARB) are less common in pediatrics, but can decrease effective RBF and RPP. Calcineurin inhibitors, commonly used in pediatric transplant recipients, alter the balance of prostaglandin E_2 (dilating) and thromboxane A_2 (constricting), decrease the activity of nitric oxide synthase, and increase the systemic vascular resistance through effects on sympathetic activation – all of which lead to prolonged vasoconstriction and impaired RBF [25]. Radiocontrast agents also induce AKI through a biphasic hemodynamic change to renal blood flow that has been associated with medullary ischemia [26]. Finally, the association of amphotericin B with AKI appears to be mediated in part by effects on vascular smooth muscle permeability; the drug leads to high intracellular calcium leading to premature and persistent depolarization of voltage gated channels that govern smooth muscle contraction with resultant renal vasoconstriction [27].

Tubular epithelial and endothelial cell toxicity involves the iatrogenic production and action of reactive oxygen species (ROS). Oxidative stress to the kidney is generally countered by the action of anti-oxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase. Persistent stress, however, can overwhelm the ability of these enzymes and lead to liberation of damaging ROS such as superoxide, hydrogen peroxide, and hypochlorous acid. Exposed to these ROS, tubular and endothelial cells experience destabilized cytoskeletons, nucleic acid alkylation or oxidation, DNA strand breakage, damaged plasma and intracellular membranes, and impaired ATP synthesis. Inflammatory responses are triggered by ROS that can lead to increased TNF-α, chemoattraction of injurious leukocytes, and production of proteases and lysosomal enzymes [28]. It is highly likely, however, that ROS participate in a balancing of destruction and regeneration of nephron structure and function. Evidence, from both within and outside AKI literature, suggests that ROS also aid in repairing injured cells, remove debris through induction of apoptosis/phagocytosis, and aid in reestablishing cellular contacts (i.e., the cell-cell adhesions necessary for normal filtration). Commonly used ROS-dependent nephrotoxic drugs in children with critical illness include antimicrobials (e.g., aminoglycosides, vancomycin, and amphotericin B) and oncologic agents (e.g., carboplatin and cisplatin). Radiocontrast agents are also associated with tubular ROS production [29]. These nephrotoxins also act as direct cell toxins, imparting injury in a manner similar to that for tubular epithelial cell injury.

Iatrogenic vasculopathy in the kidney is manifest as thrombotic microangiopathy (TMA). A number of drugs used in the critically ill patient, including anti-neoplastics, anti-platelet agents, and even more common agents (furosemide, NSAIDs, penicillins) are associated with TMA. Growing evidence from the pediatric bone marrow transplant population suggests a direct association between drugs used in the regimen of allogeneic transplant and the development of TMA (transplant associated TMA – (TA-TMA)) leading to AKI [30].

Obstructive tubulopathies can be a direct mediator of AKI. Several medications (e.g., acyclovir, sulfonamides, methotrexate) are associated with the production of urine-insoluble crystallization in the renal tubules [31].

Predisposition and the "at-risk" Patient: Renal Angina

Predisposing factors to iatrogenic AKI aggravate the effect of drug induced injury. Adult data clearly risk factors such as female sex, older age, decreased baseline GFR, and the presence of other pharmacologic agents that are slowly metabolized. Pediatric vulnerability to iatrogenic AKI is similar, but may be more commonly associated with prior kidney injury (versus the other non-modifiable factors listed). Risk factors that are demonstrated to be associated with a higher incidence of AKI and the need for renal replacement therapy include sepsis [32], mechanical ventilation [33], organ transplantation [34], cardiopulmonary bypass [1], and ICU status [35]. Appreciation of patient susceptibility to nephrotoxins is of critical importance. Chronic disease states and patients with a history of ischemic injury demonstrate an augmented response to the oxidative stress induced by nephrotoxins [36]. Children with hepatic insufficiency, hypoalbuminemia, and obstructive liver disease demonstrate poor clearance of nephrotoxic agents [37]. Patients with volume depletion, true (diarrhea/vomiting) or effective (heart failure, sepsis), have increased renal vulnerability to various agents. Finally,

metabolic/electrolyte disturbances can aggravate the effects of nephrotoxins: hypercalcemia induces vasoconstriction and changes in urine pH which promotes tubular crystal formation [38].

Identifying the 'at-risk' patient for AKI is likely critical to early preventative or ameliorating therapy. While novel biomarkers are being developed for earlier identification of injury, they are not, nor will be, widely available for some time. Because development and derivation of these markers occur in models of animals or patients with known injury, the efficacy of many in a broader population is unknown. Renal angina is a recently proposed state of 'pre-injury' which, if identifiable, may increase the utility of AKI biomarkers at identifying stages of AKI [39]. The term "angina", from the Greek *ankhone* meaning strangling, is synonymous with cardiac insufficiency from myocardial ischemia (i.e., strangling of the coronary arteries). In that context, angina improved and now guides the utilization of troponin testing to diagnosis myocardial infarction (MI). Unfortunately, kidney injury generally has no physical symptom like chest pain for MI by which to guide AKI biomarker testing. However, retrospective analysis suggests that patients who develop AKI may share risk factors on presentation. Further analysis may be able to identify a constellation of risk factors and patient indicators that highlight a state of renal *angina* (or "renal strangling") during which the assessment of biomarkers would gain more predictive precision and offer a starting point for therapeutic maneuvers [39] (discussed later).

Cardinal Pathophysiology: Cardiopulmonary Bypass and Sepsis

Cardiopulmonary Bypass and AKI

The complex nature of AKI pathophysiology is best illustrated by the two most common etiologies for AKI in the pediatric population (in the developed world). Palliative or corrective surgery under cardiopulmonary bypass (CPB) is one of the most common causes of AKI in the pediatric age group in most reported series [40–44]. AKI affects between 2.7 and 28 % of children following CPB [42, 43, 45–49]. The pathophysiology of CPB-induced AKI is multi-factorial and is currently believed to be related to the systemic inflammatory response and renal hypoperfusion secondary to extracorporeal circulation. CPB elicits a complex host response characterized by widespread activation of the contact system [50], the coagulation cascade [51], complement [52], the vascular endothelium, and leukocytes [53], resulting in the release of coagulation factors, pro- and anti-inflammatory mediators, vasoactive substances, proteases, and reactive oxygen and nitrogen species. Renal hypoperfusion during both CPB and deep hypothermic circulatory arrest has been consistently demonstrated [54, 55]. Importantly, several studies have indicated that the degree of ischemia-reperfusion injury increases with duration of CPB time and aortic cross-clamp time [45, 56, 57], though this finding may depend on the underlying congenital condition or surgical type [58]. Oxidative stress contributes to the development of AKI after CPB. Finally, stored red blood cells (RBCs) administered during CPB procedures may be less deformable, have increased adhesiveness to vascular endothelium, and lose their ability to generate nitric oxide. In combination, these factors result in impaired tissue oxygen delivery ('renal hypoxia'), tissue oxygen utilization ('renal dysoxia'), and worsening oxidative stress [59–62].

While it is unclear whether the primary aberration in renal oxygenation is excessive demand or inadequate supply, or both, 'renal dysoxia' can be used to describe renal function which varies with renal oxygen tension (pO_2). Interestingly, urinary pO_2 levels in adults following CPB are predictive of AKI [63]. During CPB in a porcine model, medullary pO_2 levels fall to near undetectable levels [64]. Several genes are upregulated by the kidney in response to hypoxia, most notably erythropoietin. *In vitro* studies using glomerular mesenchymal cells have shown that hypoxic cell culture conditions also upregulate the transcription of vascular endothelial growth factor, Sp1, and hypoxia inducible factor-1, all mediators of inflammation and fibrosis [65, 66]. The progression of renal hypoxia and dysoxia is manifest by the differential expression of genes in response to increasing ischemic time [67]. This, and epidemiologic evidence of risk factors for AKI following CPB, support the conclusion that AKI is not simply an "on-off switch" paradigm. Gradations in injury occur. The implication, therefore, is that there are stages in the progression of AKI which are amenable to intervention and reversible.

Sepsis and AKI

The pathophysiology of severe sepsis associated AKI (SSAKI), the most common cause of AKI in adults [68] and arguably the most common in pediatrics [3, 35], is complex and controversial. Although acute tubular necrosis (ATN) has traditionally been considered the etiology of AKI in sepsis, no conclusive pathologic evidence has verified this [69]. Animal models of SSAKI demonstrate increased, rather than decreased, renal blood flow and a state of hyperdynamic AKI [70]. More detailed analysis of glomerular blood flow reveals that true hemodynamic perturbation of sepsis may be a lowering of P_{GC} from decreased RVR (decreased efferent arteriolar tone) [71, 72]. Acute tubular *apoptosis* rather than acute tubular *necrosis* may be the norm [69]. Additionally, chemotaxis of inflammatory mediators to the kidney in response to systemic injury undoubtedly contributes to the progression of SSAKI. The multifactorial etiology of SSAKI pathophysiology likely explains the poor efficacy of traditional biomarkers based on the functionality of proximal tubular

Table 15.2 List of common causes of AKI in pediatrics

Pre-renal	Intravascular volume depletion
Intrinsic renal	Hypoxic-ischemic injury
	Sepsis/toxin mediated: endogenous and exogenous
	Acute tubular apoptosis
	Acute tubular necrosis (vasomotor nephropathy)
	Multiple Organ Dysfunction Syndrome (MODS) driven
	Interstitial nephritis: drug induced and idiopathic
	Tumor lysis syndrome (uric acid nephropathy)
	Glomerulonephritis
	Vascular thrombosis (thrombotic microangiopathy – TMA)
	Cortical necrosis
	Hemolytic Uremic Syndrome (HUS)
	Cortical dysplasia or hypoplasia
Post renal	Obstructive uropathy – ureteral or urethral obstruction
	Solitary kidney obstruction

filtration [73]. The drivers of sepsis (with or without AKI) include mediators of inflammation, cytokine proliferation, changes in apoptotic signaling, altered hemodynamics (direct and indirect), and direct cellular injury. All of these processes likely occur in the kidney during sepsis and serve to overwhelm the autoregulatory abilities of the kidney to maintain glomerular capillary perfusion pressure, glomerular filtrative function, and tubular reabsorptive function.

Epidemiologic Characteristics of AKI: Incidence, Definition, Classification

Research into the impact of acute kidney injury (AKI) in pediatrics has accelerated over recent years. As opposed to the under-developed world where hemolytic-uremic syndrome and hypovolemia from gastrointestinal illness predominates the causes of AKI, AKI in the resource-rich world develops most commonly in hospitalized children secondary to systemic illness or surgery. From published data, approximately 10 % of critically ill children suffer from varying degrees of AKI [68, 74]. If 'severe' AKI is defined by RRT requirement, the estimated incidence is 1–2 % of all critically ill children [44]. In those children, the mortality rate nears 50 % [33, 40, 75]. For children undergoing cardiopulmonary bypass, the incidence of AKI increases (10–50 %) [76, 77]. An abbreviated list of AKI incidence and etiology is depicted in Table 15.2. Recent data suggests that in the non-critically ill pediatric population, AKI secondary to nephrotoxic medications occurs at an alarming rate [78]. Interestingly, even small increases in serum creatinine are associated with the development of severe AKI and are known to portend worse outcomes in pediatrics [76]. AKI survivors are also at risk for progression to chronic kidney disease (CKD) in adults and pediatrics (discussed later) [79–82].

Incidence and Classification

The increased incidence of AKI in pediatrics (and in adults [83]) is likely secondary to the emergence and use of consensus definitions. Prior to 2002, no consensus definition existed for AKI, and over 30 different definitions had been used by general practitioners, intensivists, and nephrologists. To address this variability, the Acute Dialysis Quality Initiative (ADQI), standardized the definition of AKI in 2004 using the "RIFLE" criteria [84], which were later modified in 2007 using the "AKIN" criteria [85]. Based on glomerular filtration rate (GFR), serum creatinine values, and urine output plotted against time of admission, RIFLE is a mnemonic for three levels of severity – Risk, Injury, and Failure, and two outcomes – Loss and End-stage kidney disease. RIFLE marks progressive degrees of injury in both critically ill and non-critically ill patients. In contrast, the AKIN criteria defines AKI based on time in relation to absolute creatinine increase, percentage increase, or documented oliguria, broadening the window for time of AKI diagnosis and creating an automatic "failure" designation for any patient placed on renal replacement therapy [85]. Within RIFLE and AKIN, the incidence of AKI varies from 18 to 63 % in all hospitalized adults and up to 67 % for critically ill patients in the ICU. The RIFLE criteria were modified in pediatrics (pRIFLE) to incorporate creatinine clearance and have been used to stratify patients with AKI in several retrospective studies [33]. Of note, in adults and children, RIFLE criteria have been extensively studied in the inpatient setting and primarily in the intensive care units. Thus, applicability in the non-acute setting may be different and is under investigation. The reported incidence of AKI in pediatric populations varies from 1 to 82 %, with a recent study finding an incidence of 339/3,396 (~10 %) patients admitted to the pediatric intensive care unit (PICU) [35]. Other reports have confirmed the utility of pRIFLE to stratify pediatric AKI severity with evidence of association for outcomes [35, 86]. Comparison of the RIFLE, pRIFLE, and AKIN staging criteria are shown in Fig. 15.2. The recent Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline lists several recommendations for defining AKI including any patient with an increase in serum creatinine (SCr) by 0.3 mg/dl (26.5 mmol/L) within 48 h of admission, an increase of SCr to 1.5 × baseline, or a decrease in urine volume to <0.5 ml/kg/h for 6 h.

Scheme	Stage	Creatinine Criteria	Urine Output Criteria
RIFLE	**R** - Risk	↑ ≥ 1.5× or ↓GFR ≥ 25 %	< 0.5 ml/kg/h for 6h
	I - Injury	↑ ≥ 2× or ↓GFR ≥ 50 %	< 0.5 ml/kg/h for 12h
	F - Failure	↑ ≥ 3× or [Cr] > 350 mmol/L	< 0.3 ml/kg/h for 24h or anuria for 12h
	L - Loss	Persistent failure > 4 weeks	
	E - End stage	Persistent failure > 3 months	
pRIFLE	**R** - Risk	eCCl ↓ ≥ 25%	< 0.5 ml/kg/h for 8h
	I - Injury	eCCl ↓ ≥ 50%	< 0.5 ml/kg/h for 16h
	F - Failure	eCCl ↓ ≥ 75% or eCCl < 35 ml/min/1.73m^2	< 0.3 ml/kg/h for 24h or anuria for 12h
	L - Loss	Persistent failure > 4 weeks	
	E - End stage	Persistent failure > 3 months	
AKIN	**Stage 1**	↑ ≥ 0.3 mg/dl or ↑ to 150-200 % baseline	< 0.5 ml/kg/h for 6h
	Stage 2	↑ to 200–300 % baseline	< 0.5 ml/kg/h for 12h
	Stage 3	↑ to ≥ 300 % baseline or ≥ 4.0 mg/dl with an acute ↑ of 0.5 mg/dl	< 0.5 ml/kg/h for 24h or anuria for 12h
KDIGO	**Stage 1**	1.5× – 1.9× baseline or ≥ 0.3 mg/dl increase	< 0.5 ml/kg/h for 6-12 hours
	Stage 2	2.0× – 2.9× baseline	< 0.5 ml/kg/hr for ≥ 12 hours
	Stage 3	3.0× times baseline Or Increase to > 4.0 mg/dl Or Initiation of renal replacement therapy OR In patients<18 years: Decrease in GFR < 35 ml/min per 1.72m^2	< 0.3 ml/kg/hr for ≥ 24 hours Or Anuria for ≥ 12 hours

Fig. 15.2 Staging criteria of AKI. *GFR* glomerular filtration rate, *ml/kg/h* milliliters of urine per kilogram per hour, *eCCl* estimated creatinine clearance change

Impact of AKI on Outcomes

AKI increases overall mortality, independent of disease severity. In some reports, adult mortality increases to nearly 80 % [87, 88], specifically in conjunction with sepsis, trauma, burns, transplant, and acute respiratory distress syndrome (ARDS). AKI is an independent risk factor for mortality, with odds ratios as high as 4.8, and independently increases hospital costs, lengths of stay, and ventilator days [89]. AKI also leads to end stage renal disease (ESRD) in a significant proportion of adults [90]. In a study of nearly 4,000 critically ill children, AKI increased mortality and lengthened intensive care stay fourfold [35]. AKI increases mortality with multi-organ failure, hematopoietic stem cell or solid organ transplant, extra-corporeal membrane oxygenation (ECMO), or ARDS anywhere from 10 to 57.1 % [91–93]. AKI carries a high risk of death independent of Pediatric Risk of Mortality II (PRISM II) scores in these patients [33]. AKI carries a notable increased morbidity risk after CPB: including longer duration of mechanical ventilation and hospital length of stay [43, 46]. For these children, a creatinine rise of ≥25 % is a significant risk factor for increased length of stay and ventilation, but even a small initial rise in creatinine leads to an increased risk of subsequently developing AKI [76].

Immediate effects of AKI disrupt the homeostatic balance in the body. The metabolic disturbances include hyperkalemia (from inability of tubular excretion to keep up with extracellular movement of potassium), hyperphosphatemia/hypocalcemia (from reduced kidney phosphate excretion, decreased 1-α-hydroxylation of 25-hydroxy-vitamin D, and acidosis), and uremia. Children are traditionally volume overloaded due to a combination of: (1) salt and water retention from relative hyperreninemia (2) oliguria from impaired glomerular filtration and (3) a failure of the counter-current multiplying system responsible for urine concentration.

Immediate Effects

Fluid overload (FO) is increasingly recognized as a poor prognostic factor in kidney injury. Resuscitation guidelines, including early goal directed therapy (EGDT), have specified central venous pressure (CVPs) targets (~ 8 mmHg) for adult and pediatric sepsis [94]. Retrospective analysis

has identified that higher CVPs (~20 s) and high fluid overload status is associated with increased morbidity and mortality in children started on RRT [34, 75, 95–98]. FO is calculated as:

$$\%FO = [(\text{Fluid input(liters)} - \text{Fluid output (liters)}) / \text{PICU admission weight(kg)}]$$
$$\left[(IN - OUT)/wt\right] * 100$$

Though no prospective study has yet confirmed this finding, it bears mentioning that the contribution of fluid to the impact of AKI is substantial. Fluid is a drug, prescribed, dosed, and delivered like other drugs. Nephrologists and intensivists are beginning to advocate more strongly for more parsimonious and discretionary use of fluid in resuscitative situations [95].

Extra-Renal Effects

AKI is increasingly understood to confer deleterious extra-renal effects [99]. Ischemia in rodent models leads to increased pulmonary vascular permeability, altered sodium-potassium ATPase (Na^+-K^+-ATPase) and aquaporin channels, and altered lung fluid balance [100, 101]. Models of murine AKI increase systemic levels of interleukin-6 (IL-6), IL-8 (KC), and macrophage inflammatory protein 2 (MIP-2) [102, 103]. Additionally, ischemia-reperfusion injury induces aberrations in inducible nitric oxide synthase expression and increased MCP-1 in alveolar fluid [104]. Oxidative balance in the kidney governed by heme-oxygenase 1 (HO-1) and hypoxia inducible factor-1 (HIF-1) may be altered during AKI and this may contribute to distal lung injury [105]. Post-ischemic kidneys also express increased levels of toll-like receptors (TLRs), complement activation proteins, and cytokines, indicating a priming effect on the host immune response [67]. Additionally, ischemic AKI increases glial apoptosis and deranged neurologic activity [106], increase myocardial apoptosis and decrease ventricular shortening fraction [107], alter T-cell trafficking [108], and impaired immune regulation [67]. Finally, models of "two-hit" injury demonstrate deleterious effects of AKI on secondary lung injury [109, 110] and morbidity from sepsis [111, 112]. The deleterious bidirectional interaction of kidney-lung crosstalk in the critically ill patient has been discussed in the literature [113–116]. Absent oliguric fluid overload, the available laboratory data indicates that ischemic kidney injury pay may trigger a state of nephrogenic pulmonary edema [117]. In total, deleterious inter-organ crosstalk arises, at least in part, due to the imbalance of immune, inflammatory, and soluble mediator metabolism associated with severe insults to the kidney [118].

Table 15.3 Normal GFR for age in pediatrics

Age	GFR (mL/min/1.73 m^2) (range)
Preterm (<34 weeks)	
2–8 days	11 (11–15)
4–28 days	20 (15–28)
30–90 days	50 (40–65)
Term (>34 weeks)	
2–8 days	39 (17–60)
4–28 days	47 (26–68)
30–90 days	58 (30–86)
1–6 months	77 (39–114)
6–12 months	103 (49–157)
12–19 months	127 (62–191)
2–12 years	127 (89–165)

Adapted from Heilbron et al. [230]. With permission from Springer Science + Business Media

Diagnosis

Tests of kidney function that allow for early diagnosis of AKI are increasingly recognized as vital to the management of critically ill children. Biomarkers used as surrogates for kidney function can be delineated by source (serum or urine) and AKI attribution (structure or function). Novel biomarkers are being tested for prediction of the development of AKI, the presence of AKI, the duration of AKI, and the association of AKI with morbidity.

The gold standard of kidney function is glomerular filtration. GFR is defined as the sum of filtration rates for all functioning nephrons in a given patient. Based on serum creatinine, GFR varies considerably based on age, body mass, race, and sex, and increases markedly from birth until age 2 (Table 15.3). Unfortunately, GFR cannot actually be measured, but only inferred using the clearance for iatrogenic or endogenous substances using the equation:

$$GFR\,(ml/min) = V * (U_x / P_x)$$

Where V = urinary flow rate, U_x = urinary concentration of substance "x", and P_x = plasma concentration of substance "x". In children, the GFR is further multiplied by (1.73 m^2/BSA) to correct for body surface area (BSA). The filtered load of an ideal substance "x" would therefore equal the GFR, but finding such a substance has proven difficult. The characteristics of the perfect "x" include: endogenous, non-toxic, freely filtered at the glomerulus and not excreted by the tubules, not subject to changes by age, sex, mass, or race, and sensitive to early and small changes in amount filtered. Though exogenous markers like inulin and iothalamate are "gold standards", they are of limited utility due to availability, cost, and ease of testing

[119]. The most common serum tests of GFR use the endogenous substances creatinine, urea, and Cystatin C.

Serum Testing for AKI

Creatinine

Derived from the metabolism of creatine from skeletal muscle, creatinine is filtered freely by the glomerulus and demonstrates a non-linear inverse relationship with GFR. Unfortunately, creatinine has many known limitations: excretion into the urine from the proximal tubule (anywhere from 10 to 40 %), impaired filtration by other drugs (cimetidine, trimethoprim), and variation based on diet, muscle mass, and sex. Importantly, the steady state concentration of creatinine is used for a reference value for age when determining "normal" – and children with acute illness are rarely in steady state. In AKI, the GFR may abruptly change, but the production of and elimination of creatinine lags behind – which alters the perceived clearance of creatinine (eCrCl). New data demonstrates that fluid balance can have a significant impact on the noted incidence of AKI based on changes in creatinine [115]. Additionally, the method of measurement of serum creatinine can influence the read-out level (per isotope mass spectroscopy, the conventional Jaffe alkaline picrate method, or enzymatic creatinine assays) [120].

Urea

A water-soluble byproduct of protein metabolism, urea is used as a marker of solute retention and elimination. Urea has known deleterious effects systemically and on the kidney (oxidative stress and impaired Na^+-K^+-Cl^- cotransport in the loop of Henle). While it also demonstrates non-linear inverse kinetics in relation to GFR, urea is not an ideal marker because of variability based on diet, variance in critical illness states such as trauma, muscle injury, and bleeding, and the fact that filtered urea can be passively reabsorbed by the proximal tubule. Additionally, urea resorption and handling is critical to the maintenance of the counter-current exchange system responsible for urine concentration and the elimination of water (Table 15.4).

Cystatin C

An endogenous cysteine proteinase inhibitor to all nucleated cells, Cystatin C (CysC) is freely filtered by the glomerulus and nearly 100 % resorbed and metabolized by the proximal tubule. Though there are reported variations in CysC levels with age, sex, muscle mass, and diet in adults [121], serum values have correlated well with derived measurements of GFR and CysC level based formulae for GFR have been constructed. In children, the inability of CysC to cross the placenta makes it potentially useful for measurement of neonatal renal function; the maturational changes of CysC are more concordant with age than creatinine [122, 123]. Unfortunately, though data is promising, the utility of serum Cys C measurements is rate limited by lack of widespread test availability.

Table 15.4 Variables which artificially increase measured serum creatinine and urea values

Serum marker	Variable
Creatinine	Younger age
	Male gender
	Large lean muscle mass
	High protein diet
	Strenuous exercise
	Drugs (e.g., cimetidine, trimethoprim)
Blood urea nitrogen	Dehydration
	High protein diet
	Gastrointestinal bleeding
	Drugs (corticosteroids)
	Critical illness

Serum GFR Estimation

In adults, the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations have been utilized for estimating GFR. Additionally, numerous estimating equations exist which estimate GFR based on Cystatin C derivation. Equations have been in place to estimate pediatric kidney function since the advent of the Schwartz formula in the early 1970s. After numerous iterations, the most recent modification of the Schwartz formula is calculated as:

$$\text{eGFR} = \left(0.413 * \text{L}\right) / \text{S}_{\text{Cr}}$$

where "eGFR" = estimated GFR, "L" = length in centimeters (accounting for muscle mass variation), 0.413 = an empirical constant derived from reference standards, and S_{Cr} = serum creatinine [124]. Though not readily applicable at the bedside, a recent CKiD study (a cohort study of kidney disease in children) documented a formula including Cystatin C for GFR:

$$\text{eGFR} = 39.1 * \left[\text{ht} / \text{S}_{\text{Cr}}\right]^{0.516} * \left[1.8 / \text{Cys C}\right]^{0.294} * \left[30 / \text{BUN}\right]^{0.169} * \left[1.099\right]^{\text{gender}} * \left[\text{ht} / 1.4\right]^{0.188}$$

where "ht" = height in meters and "gender" = 1 for male and 0 for female [124].

Urinary Testing for AKI

Output

In laymen's terminology, poor urine output is the surest sign of kidney injury. Quantifications of oliguria have traditionally been used to diagnose AKI and have been incorporated into the recent AKI strata (Fig. 15.2).

Derived Indices

Though more commonly utilized in adult AKI, many different indices of urinary tubular function have been studied for AKI diagnosis in children (Table 15.1). The fractional excretions of sodium and urea (FeNa and FeU) give clinicians an indication of the potential responsivity of the AKI to fluid (aka, "pre-renal" AKI). Since sodium is avidly reabsorbed in the proximal tubules, tubular injury generally results in a higher than expected FeNa. However, this value is often unreliable in critically ill patients as natriuretic agents (e.g., diuretics) increase the distal tubular delivery of sodium. Similarly, FeU has been utilized to diagnose pre-renal AKI.

Electrolytes

Urinary sodium helps differentiate 'pre-renal' states from fulminant AKI. When patients have low urinary sodium (<15 mEq/L), the body is sodium "avid", indicating a functional reabsorption of water and salt to conserve intravascular volume. Damage to the tubules, as seen in true AKI, can result in a high urinary sodium. Interestingly, both FeNa and urinary sodium are best interpreted in oliguric states; euvolemia is often dependent on dietary intake.

Microscopy

An oft overlooked test (or series of tests) that is cheap, non-invasive, and gives helpful information on kidney injury is urine microscopy (the common urinalysis). The specific gravity (U_{SG}: weight of urine volume relative to the same volume of water) and urine osmolality (U_{osm}) bear a direct and linear relationship. Measurements of U_{osm} vary in children. Neonates and infants have an immature concentrating apparatus and will have less ability to conserve water and solute in the face of renal hypoperfusion. In pre-renal states, the normal response of the kidney should be to respond to anti-diuretic hormone (ADH) and increase U_{SG} and U_{osm} to >1.015 and >400–500, respectively. In prolonged injury, with fulminant AKI, the urine becomes isosthenuric (U_{SG} 1.01 and U_{osm} ~ 300). Urinary pH yields insight as to the possibility of renal tubular acidosis (in the face of systemic acidosis), but two separate calculated urine electrolyte-based values give additional information about tubular function. The urine net charge:

$$\sum \text{Charge}_{\text{Urine}} = U_{Na} + U_{K} \quad U_{Cl}$$

should be negative in the face of acidosis, indicating the presence of the unmeasured cation ammonium in the urine. However, if urine acidification is impaired, less ammonia is available to allow hydrogen ion to be excreted (forming ammonium) and net urine charge increases. Unfortunately, the urine net charge is subject to change by unmeasured anions (organic acids, β-lactams). Similarly, the urine osmolal gap (difference between measured and predicted urine osmolality) where Uosm is:

$$U_{osm} = 2 * U_{Na} + U_{K} + U_{urea} / 2.8 + U_{glucose} / 18$$

will increase if ammonia-genesis is impaired [125]. Urine protein will be increased in glomerulonephritides (largely leakage of albumin from glomerulus), from tubular injury (impaired reabsorption of filtered proteins such as immunoglobulins), or from an inability of the tubules to keep up with amount of proteins being filtered at the glomerulus. Urine protein/creatinine ratios >0.2 in children are considered to be proteinuric and interestingly, 3–5 year follow-up of 29 children who apparently "recovered" from AKI demonstrated persistent proteinuria in 9/29 (31 %) [80]. Finally, potassium excretion is regulated by aldosterone activity, urinary flow rate, and sodium delivery to the proximal tubule. The transtubular potassium gradient (TTKG) gives an estimation of appropriate aldosterone response to changes in potassium and should be > ~ 4 in the face of hyperkalemia (effect of aldosterone upregulation) or less than 2 in the face of hypokalemia (effect of aldosterone suppression):

$$\text{TTKG} = \left[U_{K} * S_{osm}\right] / \left[S_{K} * U_{osm}\right]$$

Where S_{osm} = serum osmolarity and S_{K} = serum potassium [126].

Biomarkers for AKI

The diagnosis of AKI has long been based on serum creatinine and urine output. The described limitations of using creatinine and urine output as markers of AKI aside, even the RIFLE and AKIN strata are largely used for epidemiologic analysis and not real-time management. Because of this, the search is on for real-time marker(s) of AKI which would allow for rapid and reliable diagnosis, theoretically providing a therapeutic advantage to intensivists akin to the use of troponins as a biomarker for acute myocardial infarction [127]. Such biomarker(s) ideally would describe AKI status in the framework of usable biomarkers, described by Kaplan and Wong, based on intended function: diagnosis, monitoring, surrogate, and stratification [128]. Many candidate biomarkers of AKI have been identified (Table 15.5) [129, 130]. While many of these biomarkers are not yet available in the

Table 15.5 Candidate biomarkers for acute kidney injury

AKI phase	Serum	Urine
Established	CysC	NGAL
	Carbamino-Hgb	IL-18
	NGAL	GST
		NAG
		α-1-microglobulin
		KIM-1
		NHE3
		MMP-9
Early detection	CysC	NGAL
	Pro-ANP	IL-18
	NGAL	KIM-1
	Neutrophil CD11b	GST
		γ-GT
		π-GST
		α-GST
		AP
		NAG
		LDH
		MMP-9
Prognosis of RRT	CysC	NGAL
	NGAL	CysC
		α-1-microglobulin
		RBP
		β-2-microglobulin
		NAG
		α-GST
		GGT
		LDH
		KIM-1
Prognosis of death	IL-6	NGAL
	IL-8	IL-18
	IL-10	NAG
		KIM-1

CysC Cystatin C, *Carb-Hb* carbamino hemoglobin, *NGAL* neutrophil gelatinase associated lipocalin, *IL* interleukin, *KIM-1* kidney injury molecule-1, *NAG* N-acetyl-β-d-glucosamide, *RRT* renal replacement therapy,*α-GST*a-glutathione-s-transferase,*γ−GT*γ-glutamyltransferase, *LDH* lactate dehydrogenase, *MMP-9* matrix metalloproteinase 9, *AP* alkaline phosphatase, *NHE3* sodium hydrogen exchanger 1, *ANP* atrial natriuretic peptide

clinical setting, CysC and neutrophil gelatinase associated lipocalin (NGAL) are now readily available in several centers. These two and several others have been tested retrospectively to diagnose established AKI, to predict AKI, and to estimate AKI severity.

Identification of Established AKI

Serum levels of CysC identified established AKI in 76 % of adult patients versus only 20 % for serum creatinine [131]. In a number of baseline pediatric studies, serum CysC levels were diagnostically superior to serum creatinine and were independent of gender, body composition, or muscle mass [132]. Median urinary interleukin-18 (IL-18) levels were significantly greater in patients with acute tubular necrosis (644 pg/mg) and delayed graft function after cadaveric transplant (924 pg/mg) than in healthy controls (16 pg/mg) and prompt graft function after cadaveric transplant (171 pg/mg), respectively [133]. SDF-1 or CXCL12 are patented as biomarkers for the diagnosis of kidney injury [134]. Urinary NHE3 (Na^+-H^+ exchanger), the most abundant sodium transporter in the renal tubule, and kidney injury molecule-1 (KIM-1), a transmembrane glycoprotein with low basal expression in the proximal tubule, are increased in the urine of critically ill adults with AKI [135, 136].

Prediction of AKI

NGAL is a bacteriostatic siderophore which was first identified as a consistently up-regulated gene product in experimental models of AKI. Urinary NGAL levels have been tested in a number of pediatric studies. Urinary NGAL (uNGAL) levels of ≥50 μg/L were 100 % sensitive and 98 % predictive in the 20/71 children post CPB who developed AKI [49]. In a prospective cohort study, mean and peak urinary NGAL concentrations rose at least sixfold higher in children with AKI than control patients admitted to the PICU [137]. Serum NGAL levels within 2 h of CPB of ≥150 mg/L were 84 % sensitive and 94 % predictive in children who developed AKI within 3 days [138]. Serum CysC levels increased with 82 % sensitivity and 95 % specificity 1.5 days earlier than serum creatinine in 44 patients who developed AKI [139]. IL-18, liver type fatty acid binding protein (L-FABP), and KIM-1 have all been tested to predict AKI with promising results. In children SSAKI, a microarray database leveraged to uncover potential biomarkers demonstrated admission serum levels of matrix-metalloproteinase 8 (MMP-8) and neutrophil elastase-2 (Ela2) with high sensitivity (100 %) and negative predictive value (100 %) on admission for prediction of persistent AKI (AKIN stage 2 or 3) at 7 days [32].

Prediction of AKI Associated Morbidity

Biomarkers have been tested for association with the outcomes of death or the need for renal replacement therapy. Serum CysC levels were 76 % sensitive and 93 % specific for the need of renal replacement therapy (RRT) 24 h prior to initiation based on creatinine levels [139]. In children requiring RRT, urinary NGAL levels demonstrated sharp increases to >5,000 ng/mg within 2–4 h [77]. Additionally, the urinary NGAL area under the curve-receiver operating characteristic (AUC-ROC) for predicting worsening of AKI was 0.61.

Technologic Adjuncts for AKI Diagnosis

Minute to minute variations in somatic near infrared spectroscopy (NIRS) numbers may be correlative with low perfusion states, including hypovolemic pediatric emergency room patients [140, 141]. Imaging modalities such as BOLD (blood

Table 15.6 Biomarker performance for AKI prediction in non-cardiopulmonary bypass pediatric ICU patients

Author	Year	n	Patients	Sepsis (%)	AKI outcome	Biomarker	Sens	Spec	PPV	NPV	AUC-ROC
Herrero	2007	25	Foley	28	Detection	Serum cystatin-C (0.6 mg/L)	85	63	2.3 (+LR)	NR	0.85
						Serum 2-microglobulin (1.5 mg/L)	85	54	1.8 (+LR)	NR	0.82
Zappitelli	2007	140	MV Foley	22.9	Persistent AKI at 48 h	Urinary NGAL (0.2 ng/mg Creatinine)	78	67	NR	NR	0.63
						Urinary NGAL (0.4 ng/mg Creatinine)	67	78	NR	NR	
Washburn	2008	137	MV	21	Prediction at 24 h	Urinary IL-18 (100 pg/ml)	25	81	22	83	0.54
			Foley			Urinary IL-18 (200 pg/ml)	13	89	20	82	
Wheeler	2008	143	Sepsis	100	Prediction of AKI within 7 days	Serum NGAL (139 ng/ml)	86	39	39	94	0.68
Basu	2011	70	Sepsis	100	Persistent AKI at 7 days	Matrix metallopeptidase-8	100	41	24	100	0.66
						Neutrophil elastase-2	100	49	27	100	0.69

Above are the most prominent pediatric studies examining biomarker performance for AKI in critically ill pediatric patients who were not subjected to cardiopulmonary bypass surgery. *Sens* sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *AUC-ROC* area under curve receiver operator characteristic, *Foley* indwelling foley catheter, *(+LR)* positive likelihood ratio, *(−LR)* negative likelihood ratio, *NR* not reported, *MV* mechanical ventilation, *NGAL* neutrophil gelatinase associated lipocalin

oxygen level dependent) magnetic resonance imaging have been used in adults to determine changes in renal parenchymal oxygenation [142]. BOLD uses deoxyhemoglobin as an endogenous contrast agent to identify areas of reduced oxygen tension within the kidneys – resulting in decreased intensity on T2-weighted MR images. Ultrasound and contrast enhanced ultrasound have been used to identify AKI manifest as changes in echogenicity and blood flow. However the risks of contrast instillation confer limited utility of computed tomography in AKI diagnosis of the critically ill patient [143]. Adult urine pO_2 levels, assumed to mirror changes in renal oxygenation, have been correlated to AKI [63]. At present, imaging diagnostic adjuncts are still in validation studies and offer only anecdotal bedside support for the diagnosis of AKI.

Renal Angina and AKI

Successful and rational clinical application of any biomarker demands high statistical performance across a broad swath of patients, including those along all risk spectra. While several candidate AKI biomarkers demonstrate impressive performance (AUC-ROC of urinary NGAL (0.95) [49], IL-18 (0.75) [144], and KIM-1 (0.83) [145]) for prediction of AKI in children after CPB, these relatively homogeneous patients, free from co-morbidities, carry a known timing of insult ("time-zero") and are ideal patients for initial AKI validation studies. However, extrapolation of data obtained from this cohort to a heterogeneous cohort of critically ill children poses a significant challenge to the critical care nephrology community. In fact, very few studies examine the efficacy of AKI biomarkers to predict AKI in critically ill children *without* a history of CPB (Table 15.6). Before wide-spread implementation of AKI biomarkers can begin, independent performance in the non-CPB pediatric population must be determined, bolstered by refined assessment of AKI risk in a specific group of patients. A recent review of pediatric AKI biomarker study underscores the "need to address issues around cost-effectiveness and outcomes" [146]. To advance the science of AKI diagnosis, biomarker utility must be optimized, avoiding a shotgun and capricious approach to the use of biomarkers.

AKI researchers have termed the effort to maximize AKI biomarker efficiency as a quest for the "renal troponin" equivalent. As described earlier, the treatment for acute myocardial infarction was transformed by the use of troponin I measurements in patients with signs and symptoms of cardiac angina. Unfortunately, AKI lacks an important parallel to coronary ischemia. Simply put, AKI does not hurt. As a surrogate for "pain", the empiric concept of "renal angina" [39] was proposed. Renal angina (ANG), fulfilled by achieving a cut-off level of 8 or above on the renal angina index, identifies and stratifies patients at-risk for AKI, by creating a composite index of risk and signs of injury (Fig. 15.3). The tiered strata of angina were constructed from the available data on the increasing risk of AKI in select pediatric populations: children admitted to the ICU carry increased risk over the general population (4.5–10 %) [35, 44], children receiving bone marrow transplantation (BMT) have 3 × risk (11–21 %)

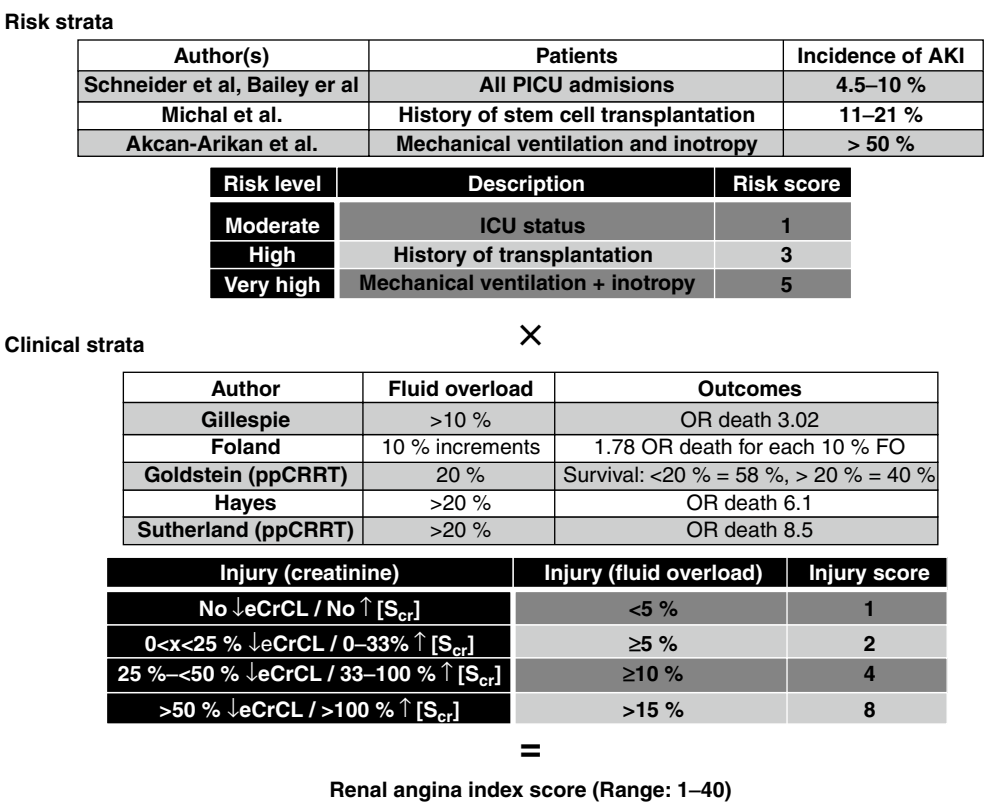

Fig. 15.3 Renal angina index criteria. Plotted above are the criteria used for renal angina risk stratification. *eCCl* estimated creatinine clearance change, *FO* fluid overload. Renal angina index is the composite score of risk and injury level on assessment. Strata for risk and injury (derived from existing pediatric AKI epidemiologic data) create a composite score, ≥8 is considered fulfillment of renal angina. (Possible composite scores: 1, 2, 6, 8, 10, 12, 20, 24, 32, 40). *eCrCl* estimated creatinine clearance by Schwartz formula, [S_{Cr}] serum creatinine. *OR* odds ratio, *%FO* percent fluid overload, *ppCRRT* Prospective Pediatric registry of Patients on Continuous Renal Replacement Therapy, *PICU* pediatric intensive care unit

[34], and those that are intubated and on vasopressor support carry nearly 5× risk versus the general ICU population (51 %) [33]. Incremental escalation in fluid overload at the time of initiation of renal replacement therapy is also associated with worsened risk of mortality in pediatrics and this was incorporated in the construct [95, 96]. Unlike standard AKI risk stratification, which simply quantifies and weights the risk factors for a given patient, in order to fulfill ANG, a patient must have a combination of clinical risk factors and some clinical evidence of acute kidney injury (even if very mild). Fulfillment of ANG serves to direct biomarker assessment, aiming for a *high negative predictive value* (NPV) for AKI of *not fulfilling renal angina*, *thereby identifying those that are* "*responsive to therapy*". Conversely, fulfillment of ANG is a tool to aid the prediction of development of severe AKI, a function not fulfilled by existing severity of illness scoring systems [147]. In the initial derivation and validation study, the RAI demonstrated a NPV of 92–99 % and Area under the curve – receiver operating characteristics of 0.72–0.76 in four separate pediatric patient populations for Day 3 – AKI. Renal angina demonstrated a sensitivity of 75 %, a specificity of 71 %, a negative predictive value of 90 %, and an AUC-ROC of 72 % [148]. This AUC-ROC was on par with other clinical models of AKI used in pediatrics [149]. It should be noted, that renal angina does not purport to serve *as* a biomarker, but as a *guide* to biomarker utilization – to enhance performance by targeting at-risk patients. For example, the AUC-ROCs of MMP-8 and Ela-2 for SSAKI prediction (0.69 and 0.72, respectively) were improved by the incorporation of renal angina risk stratification (0.84 and 0.86, respectively) [150].

Management of AKI

Nowhere is the adage "an ounce of prevention is worth a pound of cure" more appropriate than in the case of AKI. As no single or combination therapy for AKI has proven universally effective, the management of AKI is broken down into three major groups: protection of the kidney from known high risk procedures and interventions, attempted prevention of injury secondary to conditions with recognized association with AKI, and finally supportive treatment aimed at restoring the principle drivers of kidney function, renal perfusion, oxygenation, and tubular integrity.

Prevention Strategies

The two best models studied for AKI prevention include contrast-induced nephropathy (CIN) and CPB-associated AKI. The incidence of CIN in the adult population is documented between 10 and 25 % [151] and is a common complication of diagnostic and therapeutic procedures using iodinated contrast media. Unfortunately, no prospective

study of therapeutic agents combating CIN has been performed in pediatrics. In adults, both low osmolar and high osmolar contrast agents (iohexol and iodixanol) are associated with CIN to similar degrees [152, 153]. Nearly all studies of adult CIN and n-acetylcysteine are single study and demonstrate conflicting results [154, 155]. Sodium bicarbonate was initially reported to markedly reduce the rate of CIN, but meta-analysis of twelve studies of its use for CIN failed to demonstrated an overall benefit in clinical end-points such as use of RRT and mortality [156]. Other strategies such as forced euvolemic diuresis and extracorporeal removal of radiocontrast have been studied in adult CIN [157–159]. Though not all extensively studied or proven to provide unequivocal benefit, the currently recommended strategies for prevention of CIN include: non-iodinated contrast, avoiding non-steroidal anti-inflammatory drugs, providing time between doses of contrast, minimizing contrast volumes, providing ongoing parenteral hydration, and using low-osmolar media [160].

Nephrotoxins are a common cause of potentially preventable AKI. They are also potentially the most preventable cause of AKI. While the list of offending agents are long and the underlying principles behind nephrotoxic-induced injury was described earlier, the incidence of AKI secondary to nephrotoxins is likely underestimated. Recent data suggest that 3 % of all *non*-critically ill children admitted to the hospital are at risk of AKI secondary to nephrotoxins, and in those children, 35 % actually developed AKI, accounting for nearly 900 hospital days (days of AKI suffered by children yearly when incidence data extrapolated over a year) [78]. While the common practices to avoid nephrotoxin associated AKI are accepted (establishing a baseline GFR and adjusting nephrotoxic dose accordingly, avoiding use of multiple concurrent nephrotoxins, seeking alternative, non-toxic drugs), establishment of a novel electronic medical record based surveillance system to track and alert providers to the possibility of nephrotoxin associated AKI decreased the number of average weekly AKI days by 42 % [78].

Cardiopulmonary bypass is one of the most commonly associated causes of AKI in both adults and pediatrics. Consistently effective preventative therapy for CPB associated AKI has not been demonstrated. While sodium bicarbonate demonstrates the most promising preventative adjunct [161], it is not yet clinical standard of care. Published data studying preventative measures for pediatric CPB-AKI are limited. A small, single center study examining the effect of n-acetylcysteine on AKI in neonates after the arterial switch procedure demonstrated a reduced incidence of AKI in the treatment group [162]. Unfortunately, very few other studies to date have demonstrated efficacy of n-acetylcsteine, sodium bicarbonate, or other preventative therapies in pediatric CPB-AKI. The multi-factorial etiology of CPB-AKI delineated earlier has been found to be associated with risk factors such as prolonged bypass time, younger age, and vasopressor support. These findings, however, may be specific to certain lesions and RACHS-1 scores (Risk Adjustment for Congenital Heart Surgery) [58]. Currently, several trials are ongoing to determine the efficacy of pre-operative steroids, peri-operative sodium bicarbonate, fenoldopam, or n-acetylcysteine on post-operative AKI. As discussed in the next section, these preventive measures are parallel to the appropriate post-operative management of patients after bypass – with effort made to limit exogenous toxins, prolonged ischemic injury, inflammation, and oxidative stress.

Therapeutic Strategies

The wide-ranging variability in the medical management of AKI underscores the lack of a singular (or multiple) consistently effective therapies. The principles of management, regardless of disease etiology, are to treat the primary pathophysiologic disturbances that are known to result in AKI. Additionally, a wide array of new targets are being tested for efficacy in combating AKI.

Target: Aberrant Renal Vascular Tone

Renal perfusion pressure, and thus glomerular capillary perfusion, is based on both pressure (the composite of flow and resistance) and volume. The use of renal vasodilators to increase renal perfusion via decreasing renal vascular resistance, has not been associated with improved outcomes. Adult studies of low-dose, or so-called “renal-dose”, dopamine have failed to show benefit and may actually be harmful [163, 164]. A meta-analysis of dopamine use in adults showed that in 24 studies, dopamine did not prevent mortality (relative risk, 0.9 [0.44–1.83]), the onset of acute kidney failure (relative risk, 0.81 [0.55–1.19]), or the need for dialysis (relative risk, 0.83 [0.55–1.24]) [165]. In another meta-analysis of 61 trials, low dose dopamine increased urine output by 24 % but resulted in no significant improvement in serum creatinine levels [166]. Low dose dopamine in children has not been effective at improving outcomes either [3, 167]. Further, low dose dopamine may increase the risk of tachyarrhythmias and ischemic injury to the myocardium by increasing myocardial oxygen consumption. Additionally, its natriuretic effects may worsen the effective hypovolemia seen in AKI.

Fenoldopam, a selective dopamine agonist, increases renal blood flow and may reduce mortality and the need for renal replacement (RRT) in adults. Compared to low dose dopamine, fenoldopam dosed from 0.05 to 0.1 μg/kg/min was shown to improve serum creatinine values in 100 adults matched for severity of illness [168], but showed no difference in 80 patients undergoing cardiac surgery [169]. Fenoldopam of 0.07 ± 0.08 μg/kg/min increased urine output

in critically ill children with progressive oliguria [170], but did not affect overall outcome. Neither low-dose dopamine nor fenoldopam have been tested in a large prospective cohort pediatric study and cannot be recommended for prevention or management of AKI outside of the context of a clinical trial. Renal dose norepinephrine has actually been shown to improve splanchnic blood flow and renal perfusion [171]. In cases of AKI concomitant with liver injury, intravenous prostaglandins (PGE) may increase splanchnic blood flow and ameliorate ischemic AKI [172]. Though selective agonism of the PGE-2 receptor has shown efficacy in the rodent models of AKI, it has not been used extensively in clinical pediatric AKI [173]. Calcium channel blockers have not been demonstrated to be efficacious to increase renal perfusion clinically though they demonstrate success in attenuating ischemic injury in animal models of AKI [174].

Target: Renal Preload

No consensus exists regarding the appropriate *preload*, or balance of fluids, diuresis, and dialysis for patients with AKI. In response to hypoperfusion, many patients may receive total fluid doses to reach central venous pressure and mean arterial pressure targets that result in total body water overload [175, 176]. Intravenous fluids are medicines, prescribed and administered like all other drugs, and warning signs of "overdose" should be heeded before every dose. A study of more than 3,000 adult patients revealed a link between positive fluid balance and mortality in AKI [177]. Additionally, the Fluid and Catheter Treatment Trial (FACCT) in adults demonstrated that in 244 surgical patients, the use of a conservative fluid management strategy resulted in more ventilator-free and ICU-free days in patients with acute lung injury [178]. The Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (ppCRRT) has repeatedly demonstrated an association between increased fluid overload at time of CRRT initiation and mortality [74, 95, 179]. The proper 'dose' of preload is patient specific, therefore contextual clues must be used to determine the adequate amount of fluid appropriate to optimize renal preload.

The type of fluid used in resuscitation does not appear to be related to rates of AKI. In the adult population, studies have compared albumin to saline (SAFE study [180]) and hydroxyethyl starches to saline (SOAP study [181]) for resuscitation. Neither demonstrated clear benefit in colloid over crystalloid infusions. There was no survival difference in over 7,000 patients between recipients of albumin or saline (SAFE). Conflicting correlations between AKI and the use of starches for resuscitation during sepsis have been reported [182]. There have been no published studies relating type of fluid used in pediatric resuscitation and AKI incidence or outcomes. As such, there are no conclusive recommendations regarding which particular type of fluid resuscitation is better for critically ill children with or at risk of developing AKI.

Managing fluid overload may be important in limiting the deleterious effects of AKI. Reducing fluid overload with diuresis can limit the use of renal replacement therapy but has not been proven to improve outcomes from AKI. The use of diuretics in adults with AKI has been associated with an increased risk of death (odds ratio, 1.77 [1.14–2.76]) and has shown no benefit in recovery of kidney function [183, 184]. While robust evidence indicates that hypoxia figures prominently into ischemic kidney injury, the theoretic benefit of loop diuretics limiting energy consumption by inhibiting sodium-potassium ATPases have not been shown to be clinically significant [60, 185, 186]. There is also no evidence of a mortality benefit in using diuretics to convert oliguric AKI into non-oliguric AKI. In a limited adult study of 61 patients after CPB with >50 % increase in serum creatinine, an infusion of 50 ng/kg/min of atrial natriuretic peptide demonstrated hazard ratios of 0.28 [0.1–0.73] and 0.35 [0.14–0.82] for eventual dialysis or death [187]. Data regarding augmentation of urine output in pediatric AKI using diuretics is limited to BMT and post bypass patients [34, 188]. The use of natriuretic peptides has been attempted in patients with AKI and cardiorenal syndrome [189]. Brain natriuretic peptide (nesiritide), described in children with decompensated heart failure, increases diuresis, but its effect on isolated AKI is not known [190]. There have been no prospective studies on the use of diuretics in pediatric AKI.

The use of continuous renal replacement therapy in pediatric AKI is not definitively therapeutic. Other than emergent dialytic therapy for electrolyte disturbance or ingested toxins, controversies abound with regard to the proper timing of initiation, dose, route, and duration of CRRT in AKI. Prospective adult data based on blood urea nitrogen value cutoffs is heterogeneous for timing of initiation and outcome. The mortality for adults started on CRRT is nearly 60 % in some studies [191–193]. As indicated earlier, retrospective study done by the ppCRRT indicates that the degree of FO at time of CRRT initiation is significantly lower in survivors than in non-survivors in critical illness: 16.4 % vs. 34 % [194], in multi organ dysfunction syndrome: (MODS) 7.8 % vs. 15.1 % [96], and in broad all-inclusive study: 12.5 % vs. 23.0 % [95]. The mortality for children started on CRRT is 10–57.1 %. It is important to note that while ppCRRT data suggests that 10–15 % FO is the signal for CRRT or peritoneal dialysis (PD) initiation, this number has yet to be prospectively proven. A large multi-center collaborative study examining the impact of fluid overload on AKI outcome with and without CRRT initiation is required and called for.

Modification of CRRT dose has not changed mortality in AKI. A large recent study with meticulous documentation of actual doses received, demonstrated no improvement in kidney function or mortality outcome in adults receiving high intensity CRRT (35 ml/kg/h) versus low intensity CRRT (20 ml/kg/h) or intermittent hemodialysis [192]. The few

outcomes studies performed in pediatrics investigating the effects of RRT dosage and modality are retrospective. The ppCRRT in 2007 demonstrated no difference in overall outcomes based on modality or dose of CRRT used [195]. While another study showed some improvement in outcome using convective CRRT modes for bone marrow transplant patients, many centers only offer one mode of CRRT delivery and thus study applicability is limited. Peritoneal dialysis (PD) can be efficacious in FO and offers advantages for smaller children including: simplicity, decreased invasiveness, and improved hemodynamic tolerance [196]. PD is generally safe and effective in children post CPB, with some investigators utilizing it as a prophylactic therapy [197]. In summary, little prospectively validated data exists regarding the effect of CRRT on outcomes. While some data suggest that early and aggressive CRRT initiation may be beneficial in children with fluid overload, the questions that need to be objectively addressed are the definitions of "early" and "aggressive."

Target: Direct Cellular Injury

Cellular based therapies are aimed at recovering cellular function after AKI. Tubular cell death from acute tubular necrosis is commonly viewed as a central cog in the AKI machinery and is implicated in the progression of disease. Several novel therapies attempt to reconstitute tubular cell volume and function. A renal assist device (RAD) which contains animal or human renal tubule cells integrates tubular cell function with the filtration of dialysis for a "complete" renal replacement therapy [198]. Selective cytopheretic inhibitory devices are synthetic membranes on extracorporeal devices which bind circulating leukocytes theoretically reducing microvascular damage promoted by activated leukocytes in AKI and SIRS [198]. Mesenchymal stem cells (MSC) home to sites of renal injury and act in paracrine fashion to aid with glomerular growth, post-glomerular circulation, reduce local inflammation, and enhance filtration [199–204]. Serum amyloid A protein (SAA) is an acute phase response protein which promotes tubulogenesis and when programmed into transformed cells accelerates renal recovery in multiple animal models of renal failure [205].

Target: Oxidative and Inflammatory

Common shared pathways of AKI for sepsis, cardiopulmonary bypass, and direct nephrotoxin mediated injury are inflammation and oxidative injury to the glomerulus and renal tubules. Pro-inflammatory signaling pathways are targets of experimental therapy for AKI. The anti-inflammatory effects of the tyrphostins, tyrosine kinase inhibitors, ameliorate acute kidney injury [206]. Heat shock proteins (HSPs) are molecular chaperones that attenuate inflammatory damage in cellular stress. Of note, HSP-70 induction by geranylgeranylacetone (GGA) improves AKI *in vitro* [207] and HSP-90 inhibition by radicolol, which increases HSP-70 expression, also lessens the severity of AKI [208]. Reducing the formation of peroxynitrite in the glomerulus by inducible nitric oxide synthase (iNOS) has been shown to improve experimental AKI [209]. Oxidative balance in the kidney is regulated on multiple levels by the transcription factor, hypoxia-inducible-factor-1 (HIF-1) [210, 211]. Prevention of HIF-1 degradation by selective inhibition of prolyl-hydroxylase enzymes lessens *in vitro* AKI severity [212]. Ethyl pyruvate, a potent anti-oxidant and free radical scavenger, leads to more renoprotection in rodent models of SSAKI [213]. Chloroquine, a commonly available anti-inflammatory drug, inhibits toll-like receptor 9 mediated renal damage during SA-AKI [214]. Peri et al. has described a bifunctional hormone that has alpha-MSH activity for the treatment of acute renal failure [215]. Anti-inflammatory agents such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and IL-10 modulate cytokine responses to sepsis and have both been shown to decrease kidney dysfunction in animal sepsis models [216, 217]. Finally, microthrombosis and disruption of the coagulation cascade, briefly discussed earlier as culpable etiologies of damage in SA-AKI, are targets of therapy. Activated protein C (APC), used in adult sepsis therapy, is an anticoagulant that reduces kidney injury in animal sepsis models [218, 219]. A large scale study of APC in septic adults could not find a significant benefit in mortality and concluded that APC was not recommended as routine therapy unless the patients were extremely sick with a high illness stratification [220]. In pediatrics, clinical use of APC is not supported by prospective data and is certainly not common [221, 222].

Target: Nutrition

Nutrition in adult AKI is important and minding macro and micro nutrient requirements is vital to outcome [92]. Optimizing nutrition in pediatric AKI patients can be challenging and metabolic carts may help determine the amount of nutrition necessary [97]. One major benefit of CRRT is the freedom to liberalize fluid for nutritive purpose; CRRT may reduce fluid concerns when optimal nutrition, using renoprotective and anabolic formulas, is desired. Recent large prospective randomized control trials suggest that tight glucose control increases overall mortality, also showing no difference in the number of adult patients requiring RRT based on glycemic control strategy [223]. A prospective pediatric study demonstrated morbidity improvements in children receiving intensive insulin therapy, but no effects on outcomes with AKI or dialysis were seen [224].

Recovering from AKI

Long term implications of AKI are poorly understood. Adult data demonstrates robust associations with the progression of AKI to CKD, particularly in patients with diabetes mellitus and decreased baseline GFR [225]. This data, however,

does not include the 50–80 % of patients who die after AKI requiring RRT. The available evidence in pediatrics on long-term associations of AKI parallel some findings in adults and echo the statement: "patients are dying *of* AKI, and not just simply *with* AKI" [83]. The long-term prognosis for children who survive the acute phase of kidney injury, and associated diseases, is unclear. Lack of a standardized pediatric AKI definition was previously a barrier to assessing for a potential AKI to CKD link, but epidemiology has become more stratified and emerging biomarkers may afford the possibility of following the transition of AKI to CKD [226].

The longitudinal effects of many primary kidney diseases leading to AKI (nephritis, glomerulonephropathies) and global etiologies of AKI (hemolytic uremic syndrome, tumor lysis syndrome) have been well described in children. There is now growing interest in determining whether acute kidney injury secondary to multifactorial illness (from surgery, sepsis, trauma) or nephrotoxins (through inflammation, apoptosis, or necrosis) leads to a chronic disease phenotype. An initial evaluation of children who survived after AKI demonstrated greater than 50 % with some manifestation of renal insufficiency 3–5 years after their injury [80]. The potential for AKI to progress to chronic kidney disease (CKD) has been discussed in adults and children [79, 81, 226, 227]. In a larger, separate study of 126 patients admitted to a PICU with AKI, 10 % developed CKD after 1–3 years (defined as the presence of albuminuria and/or GFR <60 ml/min/1.73 m^2 [228]. The epidemiologic study of pediatric patients who progress from AKI to CKD is still in its infancy. If the data mirror adult data, where the risk factors for CKD include decreased baseline GFR from a history of TMA, CPB, or sepsis, the effects on global pediatric health are likely to be significant. In adults, the population incidence of AKI is 2,100 per million in the developed world; given the global population – number of yearly AKI patients surpasses two million with 1.5 million "survivors" of AKI – and ultimately 300,000–400,000 cases of CKD per year [225].

Unfortunately, the biologic basis for the AKI-CKD transition is poorly understood at this time. Gene array studies done on murine models of AKI have demonstrated up-regulation of NGAL and KIM-1 weeks after ischemic AKI but the drivers of the transition to a chronic disease phenotype are not known [229]. The progression likely involves a combination of angiogenic, cytoskeletal protein, and matrix deposition factors. Epithelial-mesenchymal transition, a key component of the progression of fibrosis, is known to be involved in chronic kidney disease. Until factors involved in the mechanism of the transition are more completely delineated, intervention in the fragile period between AKI "recovery" and declaration of CKD will be hit or miss.

Conclusion

Acute kidney injury is a disease process which carries significant consequences for the host. It has become clearer that patients are not only just dying with AKI, but from AKI. Proper understanding of the pathophysiology, etiology, and epidemiology of the disease is required in order to have any possibility at "effective" therapy for AKI. Currently, there is no singular effective therapy accepted in clinical practice. The cellular and metabolic contribution to injury is more clearly recognized – which may lead to the discovery of targeted therapies, specifically when patients present with cardinal signs of ongoing injury. Identification of the patient at-risk for AKI is important for real-time diagnosis; biomarker use requires guidance to be effective. While trials are currently examining specific therapies aimed at restoring some of the homeostatic mechanisms which are altered during AKI, the eternal quest of AKI therapeutics follows the lead of the myocardial infarction revolution: early suspicion (risk factors recognized) leads to early diagnosis (clinical signs and biomarkers) which in turns lead to early intervention (specific therapy) and eventual recovery (survival and without progression to CKD).

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Kidney Disorders in the PICU: Thrombotic Microangiopathies and Glomerulonephritis

16

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Abstract

Renal diseases presenting in the Pediatric Intensive Care Unit are diverse. Amongst the most severe lesions are the thrombotic microangiopathies (TMA) and the glomerulonephritides. Both clinical scenarios necessitate nephrology consultation to facilitate diagnosis and timely treatment initiation in order to limit renal mobidity.

TMAs are represented by intravascular platelet aggregation, red blood cell shearing and thrombus formation. The resultant microangiopathic hemolytic anemia and thrombocytopenia are the clinical markers that suggest a risk for the ischemic loss of renal function. The broad differential for TMA includes typical hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), and thrombotic thrombocytopenic purpura (TTP). Though histologically similar, typical HUS, aHUS, and TTP have different causal mechanisms and diverse treatments may be warrented. In contrast to the TMAs, glomerulonephritis is an inflammatory process leading to direct glomerular injury and loss of renal filtering function. The differential for glomerulonephritis can be broad with etiologies ranging from collagen abnormalities (e.g., Alport Syndrome) to antibody-mediated disease (e.g., anti-glomerular basement membrane disease). Acute renal replacement therapy and/or plasmapheresis may be required for successful treatment of disease due to TMA as well as glomerulonephritis.

Keywords

Thrombotic microangiopathy • Microangiopathic hemolytic anemia • Thrombocytopenia • Schistocytes • Glomerulonephritis

Thrombotic Microangiopathies

Thrombotic microangiopathy (TMA) refers to a histologic abnormality that consists of swelling of endothelial cells and disruption of the vascular subendothelial space leading to systemic microvascular thrombosis [1, 2]. Intravascular damage leads to vascular surface abnormalities and disruption in shear forces within the vasculature resulting in microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. The broad differential for causation of TMA includes typical hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), and thrombotic thrombocytopenic

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purpura (TTP). Typical HUS, aHUS, and TTP are unique primary thrombotic microangiopathies with presumably different causal mechanisms characterized by thrombocytopenia, hemolytic anemia and virtually indistinguishable histological appearances. In addition to TTP and HUS, disorders such as malignant hypertension [3], systemic lupus erythematosus [4], and antiphospholipid antibody syndrome may present as a secondary form of TMA. As ultra-rare diseases, TTP and HUS are seen infrequently in the intensive care setting however are often life-threatening. The key to appropriate treatment is a high index of suspicion. The lack of a precise diagnostic pathway and the considerable disease overlap that exists between these entities can lead to delays in treatment and increased morbidity.

In pediatric populations, TTP is defined as microangiopathic hemolytic anemia (MAHA) and thrombocytopenia without significant renal failure [4, 5]. Typical, or enterohemorrhagic HUS is characterized by a gastrointestinal prodrome with affected individuals often demonstrating hemorrhagic colitis associated with a MAHA, acute kidney injury and a pro-thrombotic state [6]. Atypical HUS manifests as a MAHA, renal failure, and thrombocytopenia; however most often without accompanying gastrointestinal prodrome [7].

Thrombotic Thrombocytopenic Purpura (TTP)

Pathophysiology

TTP is defined as a MAHA with thrombocytopenia. In pediatric populations, renal failure is classically absent when making a diagnosis of TTP [4, 5]. On histological examination, small-vessel vasculature affected by TTP demonstrate non-swollen endothelial cells [8], platelet microthrombi within arterioles, and the presence of schistocytes on peripheral blood smear [2]. TTP occurs with an estimated annual incidence of 11.29 cases/million [9] and is more common in females, with a peak incidence occurring in the fourth decade of life [10], with pediatric cases comprising the minority of TTP cases. The mortality rate of patients with TTP exceeds 90 % without therapy [10]. Long-term survival currently approaches 80 % with therapy [5].

The etiology of TTP has been tied to activity of the ADAMTS13 *("A disintegrin and metalloprotease with thrombospondin-1-like repeats")* gene [11, 12]. ADAMTS13 is a plasma enzyme that has a key role in the processing of von Willebrand factor protein (vWF) to its mature form. ADAMTS13 cleaves the large, immature vWF multimers, which are synthesized and secreted by endothelial cells, to render the smaller, mature multimers. When ADAMTS13 is not present, abnormal formation of large, immature vWF multimers can be found in the plasma and on the endothelial cell surface. Immature, large vWF multimers have increased binding capacity and reactivity with circulating platelets. This results in the formation of disseminated platelet thrombi among large vWF multimers in capillary beds, a characteristic finding in TTP (Fig. 16.1). The formation of microthrombi results in thrombocytopenia and anemia due to shear stress and hemolysis from flow disturbance in small vessel beds.

Deficiency in ADAMTS13 can be due to acquired mutation in the gene causing the deficiency and/or to autoantibodies inhibiting ADAMTS13 function [13]. Severe deficiency of ADAMTS13 (<10 % activity) is more often associated with congenital disease whereas idiopathic or secondary TTP is more often associated with slightly low or normal ADAMTS13 activity. Congenital TTP, Upshaw-Schulman Syndrome, is exceedingly rare and is due to a mutation in ADAMTS13 gene resulting in near complete deficiency of the enzyme [14]. The majority of TTP cases are acquired, being idiopathic or secondary to other conditions. It is important to note that the majority of patients with TTP do not have severe deficits in ADAMTS13 activity [12, 15].

Clinical Manifestations and Diagnosis

Diagnostic criteria for TTP include the presence of a MAHA and thrombocytopenia without the presence of another apparent alternative etiology (see Fig. 16.2 for a flow chart demonstrating an algorithm for the diagnosis of TTP) [5]. Given this broad-based criteria, proper diagnosis may be challenging when the clinician further considers that patients presumptively diagnosed with TTP may indeed have alternative disorders underlying the MAHA with thrombocytopenia. Severely deficient ADAMTS13 activity (<10 %) is considered a specific marker for TTP however the significance of deficient values above this level remains unclear. Severe deficiency (<10 % activity) of ADAMTS13 is not essential for initiation of treatment. Common symptoms at presentation among patients with severe ADAMTS13 deficiency include gastrointestinal pain, nausea, vomiting, neurological abnormalities (including coma, stroke, seizure), weakness, bleeding, purpura, and hematuria [4]. In pediatric patients, significant renal failure is not a manifestation of TTP and this finding in the setting of MAHA and thrombocytopenia should prompt concern for an alternative diagnosis atypical or typical HUS.

Laboratory studies obtained during cases of TTP vary greatly. Many patients will have very high levels of lactate dehydrogenase [16]. Anemia typically becomes the most severe during the week following diagnosis. Thrombocytopenia should be evident at the time of initial laboratory study.

It is important to note that the classic pentad [10] of features suggestive of TTP (fever, anemia, renal involvement, neurological symptoms, and thrombocytopenia) occurred in only 5 % of patients surveyed in one longitudinal study. Furthermore, the pentad can be the presenting symptoms in systemic infection or autoimmune disorder, not just TTP. As such, it is clear that the "classic pentad" cannot be used as a

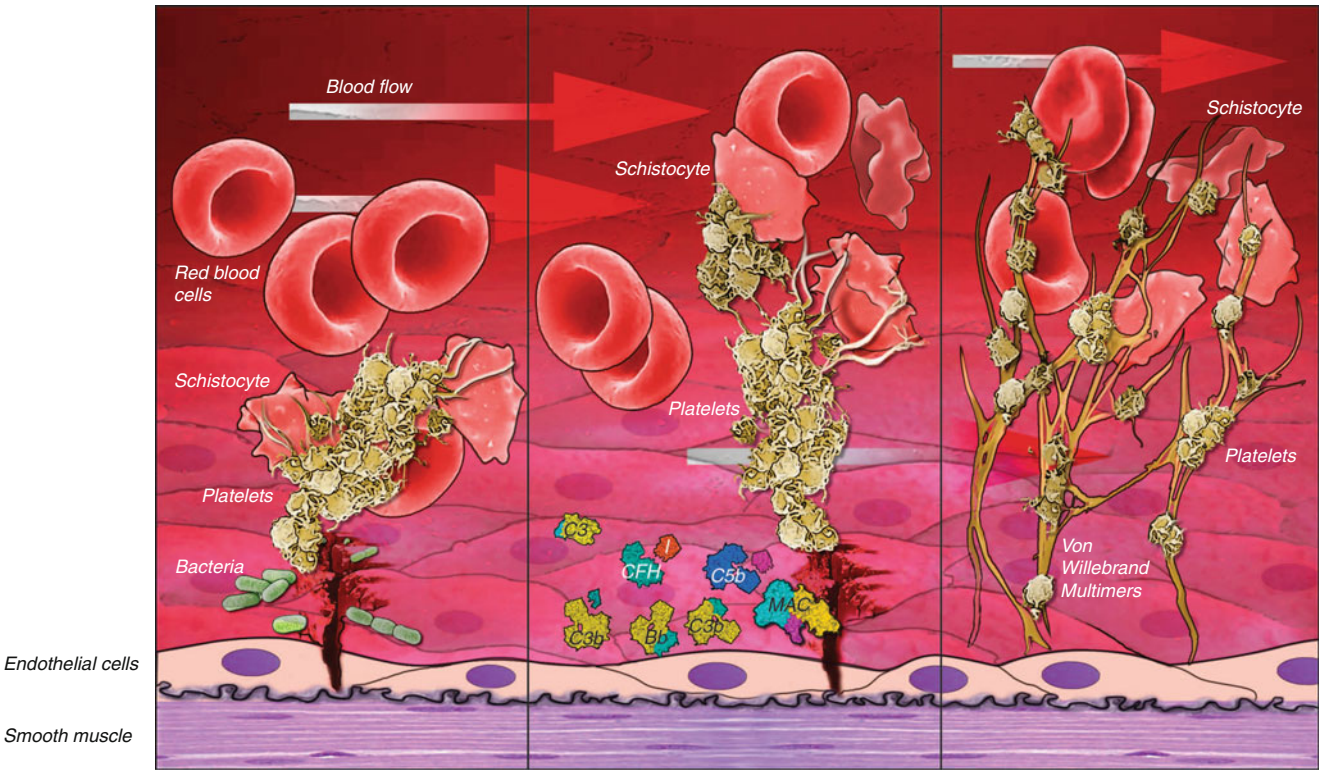

Fig. 16.1 Initiating pathology in thrombotic microangiopathy

clinical diagnostic tool. Because the diagnostic criteria for TTP are broad, multiple other serious disease mimics should be included in the differential diagnosis: disseminated malignancies [17], sepsis [18], SLE [4], malignant hypertension [3]. Severe systemic infection has been found to be one of the most common mimics of TTP and also a potential precipitant to TTP [18]. Alternative diagnoses, as above, should be ruled out to ensure appropriate treatment.

Treatment

Paradigms for pediatric treatment of TTP are largely derived from adult studies. It is important to note that a presumptive diagnosis of TTP requires that treatment other than symptomatic be considered. Plasma exchange (PE), a combination of plasmapheresis and an infusion of fresh frozen plasma (FFP), is the preferred therapy for TTP [5, 19]. This therapy has reduced the mortality rate of chronic recurrent TTP from 90 % to approximately 20 %. PE is thought to work by replacing ADAMTS13 and removing autoantibodies that may inhibit its activity [1]. PE using FFP has been shown more effective than plasma infusion in patients with TTP [5]. Specific to treatment of TTP, PE has a significant rate of major complications (30 %) including bleeding and sepsis due to central venous catheter insertion, anaphylactic reaction from plasma, or cardiac arrest with pulseless cardiac activity. A mortality rate of approximately 2.4 % has been reported [20–22]. With respect to alternative therapies, a recent systematic review of TTP literature suggests that the use of anti-platelet therapy provides no significant additional benefit over PE with the goal of reducing relapse and all-cause mortality and the use of anti-platelet therapy for TTP may invoke additional risk for the patient [19]. Alternatively, there is no evidence demonstrating risk from platelet transfusion during acute TTP [23].

The addition of corticosteroids following initiation of plasma exchange is thought to suppress autoantibodies inhibiting ADAMTS13 activity and should be considered for those patients with severely deficient activity [4]. Existing literature suggests the use of methylprednisolone, 125 mg two to four times daily during severe symptoms (e.g., neurological

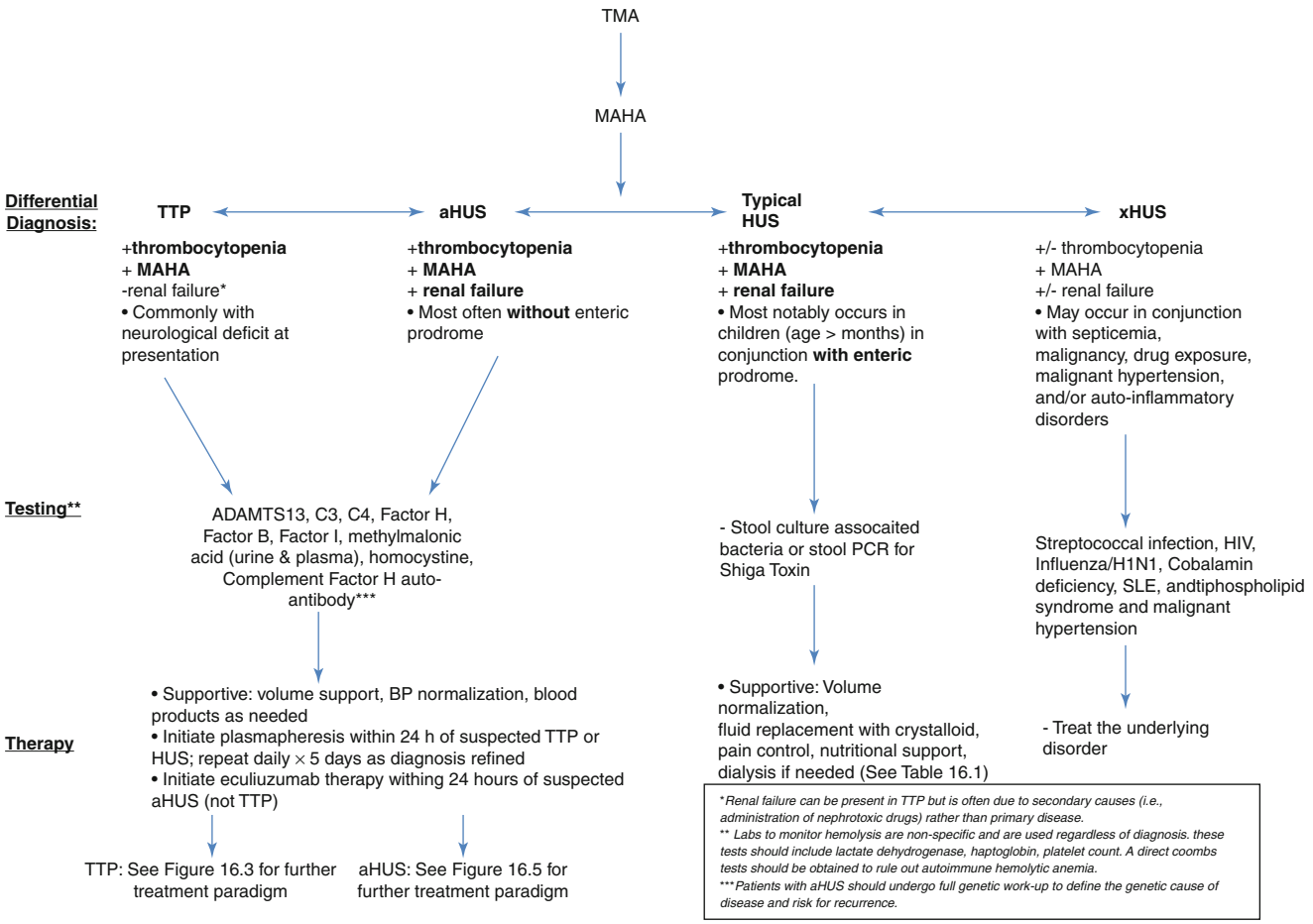

Fig. 16.2 Diagnostic algorithm for thrombotic microangiopathy

impairment) whereas prednisone 1 mg/kg/each day may be used for more stable patients. Once the platelet level has normalized for 2 days, PE may be stopped. Corticosteroid treatment (1 mg/kg/day) should be maintained until the platelet count has been normal for 2 weeks and then tapered while the platelet count is observed [4, 24].

An increase in platelet count is used to judge response to PE and a response should be seen within 2–3 days of PE therapy [4]. A subset of patients with TTP require prolonged plasmapheresis to prevent death and achieve sustained remissions. In these patients, adjunct treatments including other immunosuppressive agents such as vincristine, cyclophosphamide, or cyclosporine have been used with variable results. There appears to be little to no benefit of splenectomy in the era of plasma exchange. No randomized controlled trials testing the effectiveness of any of these interventions has been performed. The use of rituximab, an anti-CD20 monoclonal antibody, has shown promise in a small prospective cohort study of patients with acute refractory and severe relapsing TTP related to anti-ADAMTS13 antibodies [25, 26]. Additional randomized controlled studies are currently underway to investigate potential for this agent in refractory TTP (See Fig. 16.3 for a flow chart depicting the current opinion in the medical literature for a classic treatment algorithm for TTP).

Prognosis

Currently, the most important use for ADAMTS13 is in recognizing risk for relapse. Although ADAMTS deficiency is not a sensitive diagnostic test for TTP, measurement of activity is necessary to define long-term prognosis and follow-up of patients with acquired TTP [15]. Patients with severe deficiency of ADAMTS13 at diagnosis are more likely to relapse, with the majority of relapses occurring by 1 year. Those without ADAMTS13 deficiency rarely relapse. More recent research has reported that the presence of anti-ADAMTS13 antibodies, specifically IgG subclass 4, during recurrence and titer of ADAMTS13 inhibitor during acute disease may also be predictive of recurrent disease [27]. Given that current survival rates in TTP patients are the same for patients with and without severe ADAMTS13 deficiency, effective and prompt treatment of TTP is equally effective for both.

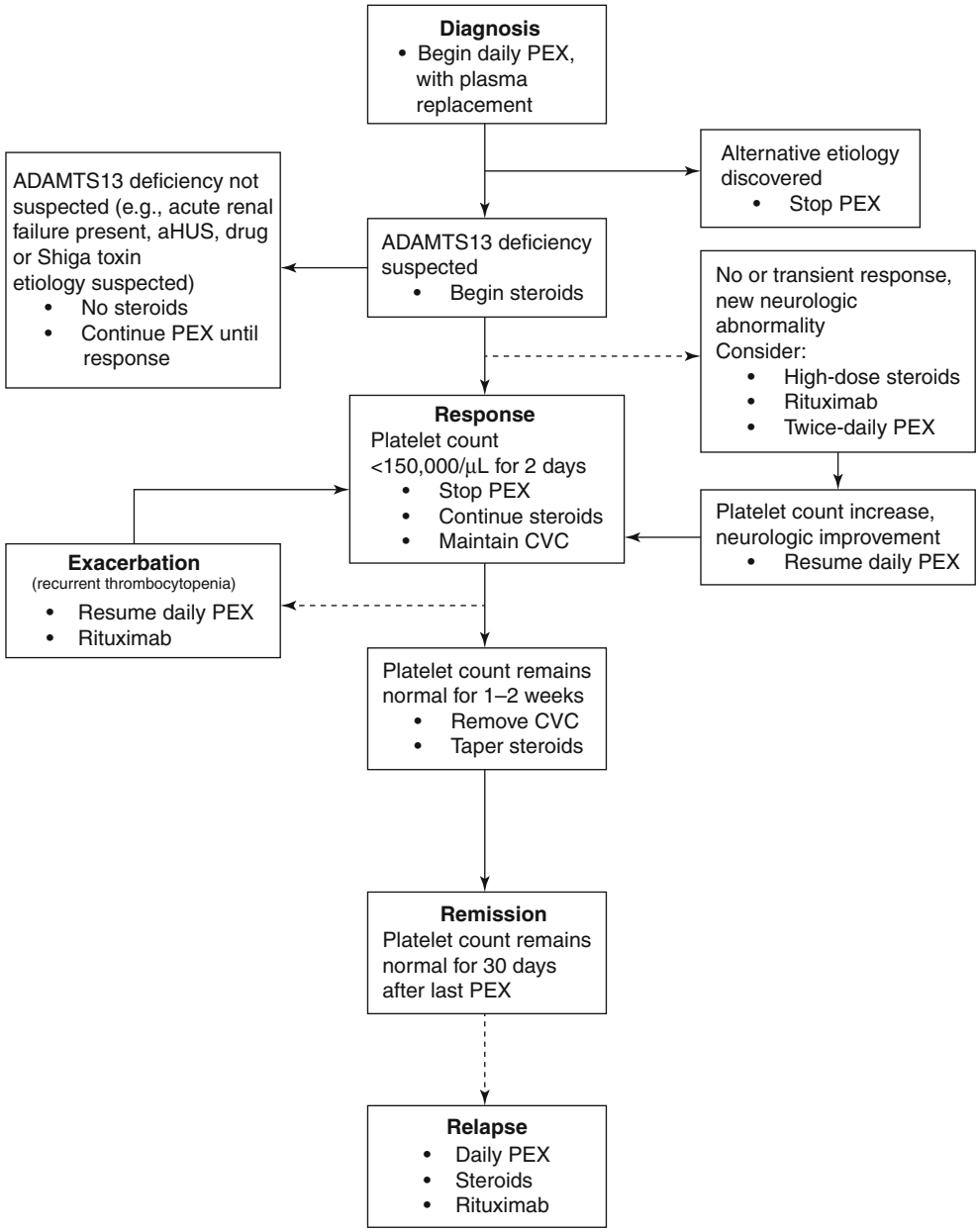

Fig. 16.3 Paradigm for Treatment of TTP Treatment of TTP may require trials of plasmapheresis (PEX), and for a minority of patients, may result in pharmacology using corticosteroids and/or rituximab. Determination of ADAMTS13 deficiency will help the clinician guide therapy but should not hinder the clinician from initiation of plasmapheresis if a diagnosis of TTP is suspected. Abbreviations: *CVC* central venous catheter (Reprinted from George [4]. With permission from American Society of Hematology)

Despite better long-term survival, difficulties in neurocognition for those recovering from prolonged relapses of TTP continue to be reported, including concerns in the domains of memory and concentration. These deficits are likely due to diffuse subcortical microvascular thromboses [28]. Finally, patients with idiopathic TTP in combination with severe ADAMTS13 deficiency have a higher long-term risk for development of additional autoimmune disorders, specifically systemic lupus erythematosus [4].

Thrombocytopenia Associated Multi-organ Failure (TAMOF)

Of note, there is an entity associated with TTP known as thrombocytopenia associated multi-organ failure (TAMOF) [29]. TAMOF occurs primarily secondary to sepsis and is characterized by multi-organ failure with more than two systems failing and platelet count of less than 100,000. TAMOF has a high mortality in children with evidence demonstrating a deficiency of ADAMTS-13 levels in a majority of patients with increased ADAMTS-13 antibodies and/or increasingly large vWF-multimers in a subset of the TAMOF population. Additionally, a prospective, observational trial conducted at a single-center in 2007 (n = 37 patients) suggested that plasma-exchange therapy can successfully replete deficient ADAMTS-13 levels in TAMOF and may be associated with significantly improved survival in pediatric patients as compared to standard therapies without plasma exchange. A smaller prospective, randomized, controlled trial (n = 10 patients) from the same group (and

reported in the same publication) showed that plasma exchange restored ADAMTS-13 activity and organ function compared to standard therapy [30]. A prospective, multi-center, observational trial has recently been completed and will hopefully serve as a springboard for a larger, multi-center, prospective, randomized, controlled trial of plasma exchange in this population.

Typical Hemolytic Uremic Syndrome

Pathophysiology

Typical hemolytic uremic syndrome (HUS) is clinically defined as a systemic spectrum of signs and symptoms including abdominal pain, diarrhea (often bloody), MAHA, thrombocytopenia, and acute kidney injury [31]. Typical HUS is most often associated with enterohemorrhagic *E. coli* (EHEC) [32], with the subtype *E. coli* O157:H7 being the most common. More recently, the broad term "shiga-toxin producing bacteria" (STPB) has been used to encompass pathogens such as EHEC, as well as other shiga-toxin producing pathogens (e.g., *Shigella dysenteriae*) [33] known to cause typical HUS. The vast majority (~80 %) of patients with STPB experience a self-limited course of gastrointestinal symptoms and do not progress to systemic symptoms of HUS [6, 31]. The factors predisposing patients with STPB to systemic symptoms of typical HUS remain unclear.

As stated above, *E. coli* O157:H7 is the major pathogen known to cause typical HUS in the United States, but other EHEC, including 0104:H4, 0121:H19 and 026:H11 are also known to cause typical HUS [32, 34, 35]. Cattle constitute the major natural reservoir for EHEC [36] and sources for transmission of EHEC and other STPB include contaminated beef, raw milk, cheese, water, fruit, vegetables, and juices [35]. The incidence of typical HUS peaks between June and September and is estimated to be 1–2 cases per/100,000 per year, with most pediatric diagnoses occurring in patients under age 5 years [37, 38]. Approximately 90 % of children exposed to STBP develop self-limited bloody diarrhea, with only 15 % of children exposed to STPB experiencing continued bloody diarrhea and typical HUS [6, 31].

The pathophysiology of typical HUS has been largely derived from our understanding of EHEC contributions to the causation of this disease. EHEC is a non-invasive pathogen that causes systemic damage via influx of virulence factors through intestinal injury (Fig. 16.1) [39, 40]. EHEC colonize the terminal ileum following ingestion, and virulence factors are subsequently released to traverse the intestinal epithelium, enter the systemic circulation, and interact with cellular components of the blood [41–43]. There are two notable virulence factors that are a key in the pathogenesis of EHEC-associated typical HUS. First, EHEC maintain a virulence factor that is essential for promoting intestinal colonization, called the locus of enterocyte effacement (LEE) [44]. The LEE encodes a type 3-secretion system (TTSS) that translocates bacterial proteins from EHEC directly into host enterocytes, causing disruption of cellular structure and function [44, 45]. Second, EHEC possess shiga toxin (Stx), a well-known virulence factor consisting of a single enzymatically active *A* subunit linked to five *B* subunits [46, 47]. There are several distinct Stxs (i.e., Stx 1, 2), all of which are pathogenic. As noted previously, Stx is not unique to EHEC and other pathogens must be considered.

Stx demonstrates its effects primarily through cytotoxic means in addition to stimulation of inflammatory and prothrombotic modulators. Mechanistically, Stx binds to the Gb3 (globotriaosylceramide) receptor, which is distributed robustly throughout endothelial cells of the GI tract, pancreas, brain, kidney [48]. After binding of Stx to Gb3, Stx is internalized into endothelial cells by receptor-mediated endocytosis. The inactive Stx *A* subunit is proteolytically cleaved inside the host cell and yields an enzymatically active *A* fragment. Next, the active *A* fragment cleaves a residue within the host cell 60S ribosomal subunit causing inhibition of host protein synthesis, resulting in cell death [49]. In addition to local cell destruction, Stx may stimulate IL-8 production, cause up regulation of endothelial cell adhesion molecule expression, and increase expression of procoagulant properties within the endothelium [50, 51].

The systemic effects of Stx occur via immediate interaction with cell components in the vasculature. Direct platelet interaction with Stx [52, 53], chemokines [54], and lipopolysaccharide [31] result in platelet activation. During typical HUS, activated platelets are deposited on injured endothelium while simultaneously Stx circulates systemically in complexes with platelets and leukocytes, most specifically with neutrophils and monocytes, further activating inflammatory mediators [55, 56]. Leukocytes demonstrate resistance to the cytotoxic effects of Stx normally exhibited on the endothelial surface [57–59], and as such, persistence of leukocytes in complex with Stx allows persistence of Stx to remain in systemic circulation. Stx has been shown to prolong neutrophil lifespan [60], and leukocytosis has been associated with poor outcome [61]. Platelet deposition on endothelial surfaces and in microvasculature leads to microthrombi and thrombocytopenia [62]. Systemic complications, including bloody diarrhea, are a result of platelet deposition and circulating Stx complexes in the microvasculature causing tissue ischemia. Lastly, Stx induces tissue factor expression on endothelial cell surfaces [63], resulting in thrombin generation and further platelet activation. It is important to note that although platelets are consumed during typical HUS, coagulation factors remain within normal limits [31].

Within the vasculature, formation of microthrombi following platelet activation results in abnormal shear stress and disturbances in flow. Disturbances in flow are the cause

of fragmentation and mechanical breakdown of red blood cells, resulting in formation of schistocytes on peripheral smear. Additionally, lysed red blood cell fragments may have cytotoxic and oxidative effects [64] on remaining red blood cells, causing further hemolysis as well as renal tubular injury [65].

Clinical Manifestations and Diagnosis

On histological exam, the appearance of typical HUS is virtually indistinguishable from that of TTP. Thrombotic microangiopathy is a characteristic feature within glomerular capillaries in typical HUS, and as in TTP, platelet thrombi can be found obstructing microvasculature; however, in contrast, there may be swelling and detachment of endothelial cells from the basement membrane in typical HUS [8]. Acute tubular necrosis is a common finding in typical HUS. Cortical necrosis may occur in severe cases of typical HUS.

Diagnosis of typical HUS necessitates an enteric prodrome with MAHA (Hgb <10 in the presence of schistocytes), thrombocytopenia (platelets <150), and acute kidney injury as evidenced by elevation of serum creatinine above the upper limit for age (see Fig. 16.2 for a flow chart demonstrating an algorithm for the diagnosis of typical HUS) [6]. A stool culture positive for Stx-producing *e. coli* aids in diagnosis; however, a negative stool culture does not rule-out typical HUS in the presence of the above signs and symptoms. Thrombocytopenia is the first abnormality often present in patients and is subsequently followed by hemolysis and anemia, due to the presence of thrombi in small vessels [6]. Other symptoms of typical HUS include oligoanuria, neurological dysfunction (ranging from transient ischemic attack to seizures), pancreatitis, and transaminitis. Fever may be present in typical HUS. Metabolic abnormalities are common and include hyperkalemia, hyponatremia, and hyperuricemia. A barium enema may show "thumbprinting," suggestive of colonic wall edema and submucosal inflammation [37].

The enteric prodrome of typical HUS is characterized by a mucoid and/or bloody diarrhea as well as crampy abdominal pain, often mimicking intestinal obstruction or acute peritonitis. It is important to note that more than 90 % of children with typical HUS will experience bloody diarrhea but a subset of patients will not present with bloody diarrhea [6]. Severe hemorrhagic colitis may lead to gangrenous colitis [66], bowel perforation, and sepsis in severe cases [67]. The aforementioned enteric prodrome often lasts 4–7 days prior to the development of typical HUS.

Acute kidney injury is one of the classic components of typical HUS and occurs due to the binding of Stx to the Gb3 receptor on the glomerular basement membrane. Although glomerular damage is a cornerstone of renal damage due to typical HUS, tubular damage often occurs and is more prominent with severe volume depletion [68, 69].

The Gb3 receptor, to which Stx binds, is distributed throughout the central nervous system providing additional space for the pathogen to localize [70]. As such, catastrophic cerebrovascular events, including stroke, may be a rare presenting symptom for typical HUS and these events are the leading cause of death from typical HUS in children [71]. More often, patients will exhibit a range of symptoms from mild irritability to depressed consciousness [72, 73]. Neurological exams should be conducted with regularity in the ICU during acute illness.

Treatment (Table 16.1)

Preventive isolation should be a primary consideration in the treatment of children to prevent secondary spread of disease [74]. The infective inocula of STBP are low, and children may

Table 16.1 Principles of therapy for hemorrhagic colitis and concern for later HUS

At presentation –
1. Bolus with intravenous normal saline or isotonic crystalloid, 20 mL/kg, on presentation, if there is no evidence of cardiopulmonary overload
Repeat boluses of normal saline (20 mL/kg) if there is any question of diminished urine output or continued abdominal pain, and the patient is not showing signs of central volume overload
2. Contact isolation
3. Do not preemptively administer antibiotics in cases of hemorrhagic colitis
Send stool for culture to aid in diagnosis
4. Laboratory tests should include complete blood count, electrolytes, serum urea, creatinine, liver function tests, amylase, and lipase
Blood products may be required if hemoglobin is <6 on presentation
Labs should be repeated daily while patient is acutely ill and hemorrhagic colitis evident
5. Do not administer anti-motility agents, narcotic opioids, or non-steroidal anti-inflammatory drugs
Provide acetaminophen for pain and continue with bolus administration during persistent pain, pending cardiovascular status is stable
6. Following acute presentation of hemorrhagic colitis and satisfactory fluid resuscitation, continue intravenous maintenance fluid in the form of isotonic crystalloid
Hypotonic intravenous fluids are contraindicated
7. Patients are encouraged to eat and drink as able; however, appetite tends to be diminished during acute infection
Central or peripheral venous nutrition should be considered in patients not taking PO and with severe illness
At Discharge –
1. In the setting of hemorrhagic colitis without conclusive HUS, platelet count should be checked at discharge and within 3–5 days to assess for possible onset of HUS after discharge. Risk of typical HUS decreases if the platelet count remains stable following hospital discharge

Adapted from Tarr et al. [6]. With permission from Elsevier

excrete high numbers of organisms early in illness with watery stool; thus, transmission rates decrease as stool solidifies but transmission to others remains possible during a child's hospital stay [75, 76]. Treatment for typical HUS is largely supportive with the intent to normalize blood pressure, restore intravascular volume, mitigate electrolyte abnormalities, and maintain nutrition. Due to the highly inflamed state of the gastrointestinal endothelium, treatment should address gastrointestinal pain via use of acetaminophen with very conservative morphine use to guard against opioid-induced ileus and subsequent pathogen retention [77]. NSAIDs are contraindicated for pain [78]. Patients may require transfusion of packed RBCs for HBG < 6. Platelet transfusions are typically reserved for active bleeding (e.g., epistaxis) or preparing for invasive procedures [67]. Due to ongoing anemia, approximately 70 % of patients with typical HUS require blood transfusions [37].

Key to the treatment of typical HUS and prevention of renal complications is fluid resuscitation and volume expansion; however, the challenge is to restore and maintain perfusion without tipping the patient into fluid overload. Given this, daily patient weights are necessary as is careful clinical observation of cardiorespiratory status to assess for signs of decompensation due to fluid overload during resuscitation. Current treatment using aggressive isotonic volume expansion is based on a protocol designed by Tarr et al. [77]. Crystalloid fluids should be administered in 20 mL/kg boluses [77]. There is little evidence for beneficial effect of loop diuretic during initial fluid resuscitation [79]. Evidence is mixed regarding the proper treatment of hypertension during acute typical HUS with recommendations varying between the use of vasodilatory medications versus antirenin drugs with the thought that the latter as angiotensin converting enzymes inhibitors both reduces the renin drive for hypertension in the setting of glomerular injury but will also assist with proteinuria [6, 37].

Non-renal complications of typical HUS should be considered. As mentioned previously, CNS complications are a leading cause of death in pediatric patients diagnosed with typical HUS. Mental status exams may be further altered in patients due to severe anemia observed in patients with typical HUS. Cranial imaging should be considered if there is suspicion of significant neurological complication [6].

Renal replacement therapy may be required for some patients. Indications for dialysis parallel that of acute kidney injury of any cause: hyperkalemia, oligoanuria, uremia, metabolic acidosis, and/or volume overload. Both hemodialysis and peritoneal dialysis are suitable options [67]. Peritoneal dialysis may be preferable in infants and children with cardiovascular compromise. Continuous renal replacement therapy may also be employed for patients in multiorgan failure due to STBP sepsis, severe fluid overload, and/or cardiovascular instability. There is no proven role for therapeutic plasmapheresis in typical HUS [80, 81].

Antibiotic treatment for the prevention of typical HUS in children with STEC has not been shown to be effective. Specifically, literature has shown use of antibiotics such as fluoroquinolones and sulfa drugs to be more harmful than beneficial [19, 67, 82]. Future directions for typical HUS treatment include the development of Shiga toxin-specific monoclonal antibodies. Monoclonal antibodies to Stx 1 and Stx 2 are based on concept that treatment during early infection will reduce toxin-mediated microvascular and tissue injury. Animal models have been promising to date and early human vaccine trials are underway examining Stx neutralizing antibodies in the prevention of typical HUS-related TMA, organ injury, and death [83, 84].

Prognosis

More than 80–90 % of patients with STBP have a self-limited course; however, those who develop typical HUS may require intensive care. Elevated peripheral neutrophil counts [85, 86], CRP [87], and procalcitonin levels [88] have been associated with development of typical HUS in the setting of STEC infection; however, reliable, early markers of disease development have not been delineated. Long-term sequelae may be present in up to 20 % of children with typical HUS including chronic kidney disease, hypertension, diabetes, and neurological impairment [71, 89]. Acute mortality from typical HUS is between 1 and 4 % [6, 71].

Atypical HUS

Pathophysiology

Atypical HUS (aHUS) is defined as MAHA, thrombocytopenia, and renal failure without an enteric prodrome [37, 90]. aHUS in its classic form is caused by abnormalities in complement regulation, resulting in uncontrolled complement activation and subsequent tissue damage (see Fig. 16.1 for a summary of complement deregulation in aHUS).

The complement system, a part of the innate immune system, is a complex, multi-protein cascade involved in protection against invading microorganisms, removal of debris from plasma and tissues, and enhancement of cell-mediated immune responses. The complement cascade is activated through three distinct pathways (classical, lectin, and alternative pathways) that converge in the generation of the C3 convertases. Because the alternative pathway is initiated spontaneously, the alternative C3 convertase (C3bBb) must be tightly regulated by plasma and membrane-bound factors; mainly complement factor H (CFH), complement factor I (CFI) and membrane cofactor protein (MCP). Lack of control of the alternative C3 convertase leads to the formation of the membrane attack complex (MAC) resulting in recruitment and activation of leukocytes and resultant injury to host cells, particularly endothelial cells. Inactivating mutations in

the CFH, CFI, or MCP genes or activating mutations in the complement factor B (CFB) and C3 genes leads to dysregulation of the alternative C3 convertase and has been established as a risk factor for the occurrence of aHUS. Under homeostatic control, glomerular structures remain relatively unharmed by complement; however, in the setting of mutation, glomerular endothelial cell death results in renal dysfunction. Furthermore, subsequent endothelial injury promotes a prothrombotic state due to exposure of subendothelial collagen, fibrinogen, and vWf. This leads to consumption of platelets and the development of microthombi in tissues further extending injury.

The three most common genetic abnormalities seen in aHUS are in the CFH, CFI and MCP proteins. Complement Factor H (CFH) is a plasma protein predominantly synthesized in the liver that serves to down-regulate alternative complement pathway function by enhancing dissociation of C3 convertase and acting as a cofactor for Complement Factor I (CFI) to compete with Complement Factor B (CFB) for C3b binding and recognition [91, 92]. CFH plays a protective role by downregulating the alternative complement pathway on endothelial surfaces, including the glomerular basement membrane [90]. Most CFH mutations are heterozygous, loss of function mutations resulting in a lower density of functional CFH on cell surfaces [93, 94]. Alternatively, autoantibodies to CFH exist in approximately 10 % of children with aHUS with a resultant effect of decreased CFH binding to promote inactivation of C3b [95, 96].

Like CFH, CFI is a plasma protein that serves to down-regulate complement activation. Normally, CFI cleaves active C3b, rendering it inactive and preventing the downstream formation of the MAC [90]. All reported mutations in CFI resulting in aHUS have been heterozygous and result in either low CFI levels or disruption of cofactor activity [92, 93].

Membrane cofactor protein (MCP) is a widely expressed, cell-surface glycoprotein functioning to regulate complement activation as a cofactor for CFI cleavage of C3b on cell surfaces to prevent formation of C3 convertase [97]. Mutations in MCP have been associated with 10–15 % of aHUS [98].

Atypical HUS may be familial or sporadic. Familial aHUS represents less than 20 % of aHUS cases [90], and has been associated with genetic abnormalities in the alternative complement pathway [98, 99]. Autosomal dominant and autosomal recessive inheritance patterns are both seen [100]. Familial forms of aHUS are more commonly diagnosed in children. It is important to note that the penetrance for clinical manifestation of aHUS in defined mutations is reduced and some genetic mutations are better described as defining a predisposition to aHUS rather than direct mutational causation for disease. Healthy carriers have been reported in multiple family studies. Genetic penetrance appears to be strongest for CFH, CFI, and MCP (approximately 50 % penetrance). Additionally, family studies with known genetic mutations demonstrate that environmental or health-related precipitants may be required to trigger aHUS; specifically, infection, inflammatory disease, pregnancy, and/or use of contraceptive pills have been temporally associated with development of aHUS.

Sporadic aHUS is associated with a variety of disease triggers including organ transplantation, immunomodulatory agents and anti-platelet drugs [76, 101, 102]. The association between renal transplant, calcineurin inhibitor therapy, and the development of sporadic aHUS has also been noted in association with humoral graft rejection [103–105]. Ten to fifteen percent of sporadic cases appear to occur in conjunction with pregnancy or in the post-partum period [37]. Finally, 50 % of sporadic cases appear to be idiopathic [90].

Clinical Manifestations and Diagnosis

An estimated 10 % of all HUS cases are classified as atypical, in that the etiology is not associated with STBP or non-STBP organisms [37, 106]. Acute aHUS episodes are rarely associated with enteric prodrome and classically manifest in severe hemolytic anemia, thrombocytopenia, and acute kidney injury [37]. In contrast to typical HUS, aHUS may be precipitated by illness such as fever, upper respiratory tract infection, and non-bloody diarrhea. There have been reports of 0157:H7 *E. coli* triggering aHUS in pediatric patients with defined mutations [107]. Extra-renal, specifically central nervous system or visceral involvement, occurs in approximately 10–20 % of patients [101, 107]. Patients may have recurrent aHUS episodes, which is in contrast to typical HUS [90]. Among all patients having a genetic mutation predisposing to aHUS, whether familial or sporadic, nearly 70 % of those patients will experience disease in childhood [92, 98].

The diagnosis of aHUS requires that the clinician rule out potential confounding diagnoses, that the patient not meet criteria for typical HUS, and that the patient does not otherwise meet criteria for TTP (see Fig. 16.2 for a flow chart demonstrating an algorithm for the diagnosis of aHUS). aHUS is frequently associated with reduced plasma levels of C3 and normal levels of C4 due to the preferential activation of the alternative complement pathway and depletion of C3 as a result of the conversion of C3 to C3b. Current practice guidelines recommend that patients suspected of aHUS be screened for plasma levels of C3, C4, CFH, CFI and CFB antigen levels, anti-CFH autoantibody levels, and MCP expression on leukocytes [80, 92]. Genetic testing of CFH, CFI, and MCP is recommended in patients thought to have a diagnosis of aHUS and should eventually extend to all known mutations. Referring to the earlier section on TTP and recognition that the presentation of TTP and aHUS may be difficult to delineate, the clinician should also rule out severe ADAMTS13 deficiency as a cause of the presenting symptoms.

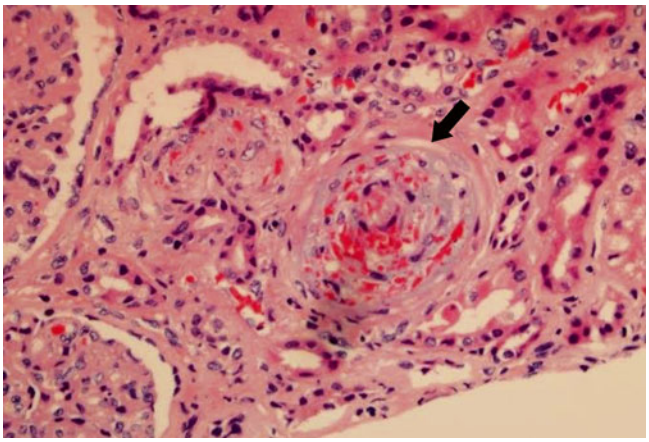

Fig. 16.4 The classic appearance of an arteriole (*arrow*) from a renal biopsy of a patient with TMA showing thickening of the arteriole wall, swelling and detachment of the endothelium and platelet/red blood cell thrombus (PAS 400×)

By histological exam aHUS lesions are generally indistinguishable from typical HUS. Light microscopy will show thickening of arteriolar capillaries, swelling and detachment of glomerular endothelium, widening of sub-endothelial space, as well as platelet thrombi obstructing vessel lumens – similar to typical HUS (Fig. 16.4) [76, 108]. Immunofluorescence staining during acute disease will show deposition of granular C3 deposits within glomeruli and arterioles as a result of local C3 consumption on the vascular endothelium.

Treatment

As with typical HUS, symptomatic management of volume, anemia and renal sequelae (e.g., normalization of blood pressure) should be a primary focus of care for the treating physician. In conjunction with supportive care, plasma therapy has been the historical treatment. Plasma therapy has been the historical treatment for aHUS. In conjunction with symptomatic are, plasma exchange therapy has been the mainstay of acute therapy for aHUS. Anticomplement therapy however is quickly. Although no randomized controlled trials have been completed to date, plasma exchange therapy has been associated with a 25 % decrease in mortality [4]. Plasma exchange therapy should ideally be started within 24 h after diagnosis, recognizing that the diagnosis of aHUS may be difficult [80]. Current recommendations suggest initiating exchange of 1.5 times plasma volumes with fresh frozen plasma or fresh frozen plasma mixed with albumin (approximately 65–70 ml/kg) per session. Exchange should begin as a daily procedure for 5 days followed by 5 days per week for 2 weeks, and finally three times per week for 2 weeks [80]. Plasma exchange appears to be superior in some patients to plasma infusion alone for remission and prevention of recurrences. The most reported explanation for this is that the combination of exchange and infusion allows for the removal of anti-CFH antibodies [92, 95], and dysfunctional CFH molecules [109, 110], while simultaneously providing plasma rich in complement with normal CFH, CFI, and C3. The addition of immunosuppressive agents may be required in combination with plasma exchange for patients found to have anti-CFH antibodies [92, 111]. Patients with CFI and C3 mutations are less likely to have a response to plasma exchange than those with CFH [107, 112]. Resolution of renal sequelae and hematologic normalization, resulting in either complete or partial remission, can occur in up to 60 % of patients undergoing plasma exchange therapy [92, 98]. Patients, particularly those with CFH mutations, may become unresponsive to plasma exchange following long-term therapy (see Fig. 16.5 for a summary of current treatment recommendations for aHUS) [113, 114].

Trial data now exists to support the effectiveness of anti-complement therapy (eculizumab) in inducing a hematologic remission of the MAHA and an improvement in the renal dysfunction associated with aHUS. (NEJM 368:23) Though there will remain some variation across centers, it is clear that anti-complement therapy may be used as an alternative to plasma therapy in those aHUS patients without the autoantibody form of the disease. [Plasma exchange remains the definitive first line therapy for CFH autoantibody induced aHUS.]

Prognosis

Until very recently, prognosis for aHUS has been poor. Prognosis at 1 year following diagnosis is most closely associated with serum creatinine at diagnosis [107]. Without transplant or newly approved pharmacologic regimens, aHUS has been associated with death rates as high as 25 % [106] and progression to ESRD in approximately 50 % of patients [37, 115]. Current literature reports that nearly 60–70 % of all patients with mutations in *CFH*, *CFI*, or *C3* mutations will relapse and suffer end-stage renal disease within the first year of diagnosis, lose renal function during the presenting episode, or die during the presenting episode [92, 105]. Unlike TTP or HUS, the risk for irreversible loss of renal function is high in aHUS. When renal failure occurs, an alternative therapy that is considered is a simultaneous liver-kidney transplant. Given that many of the abnormal or deficient proteins are produced in the liver, the rationale is that liver transplantation will provide the physiologic means to correct the underlying genetic defect and prevent recurrence [116]. Renal transplant alone has been found to have a high disease recurrence rate (50 %) and graft failure rate (80–90 %) in those patients with a history of recurrent disease prior to transplant [117, 118]. Living donor transplants are currently contraindicated due to a high risk of recurrent disease in the recipient following transplant and potential for induction of disease in the donor [119, 120]. Kidney alone transplantation is a reasonable approach in the case of MCP mutations as the transplanted kidney will carry functioning MCP and may be protected from recurrence. Regardless of

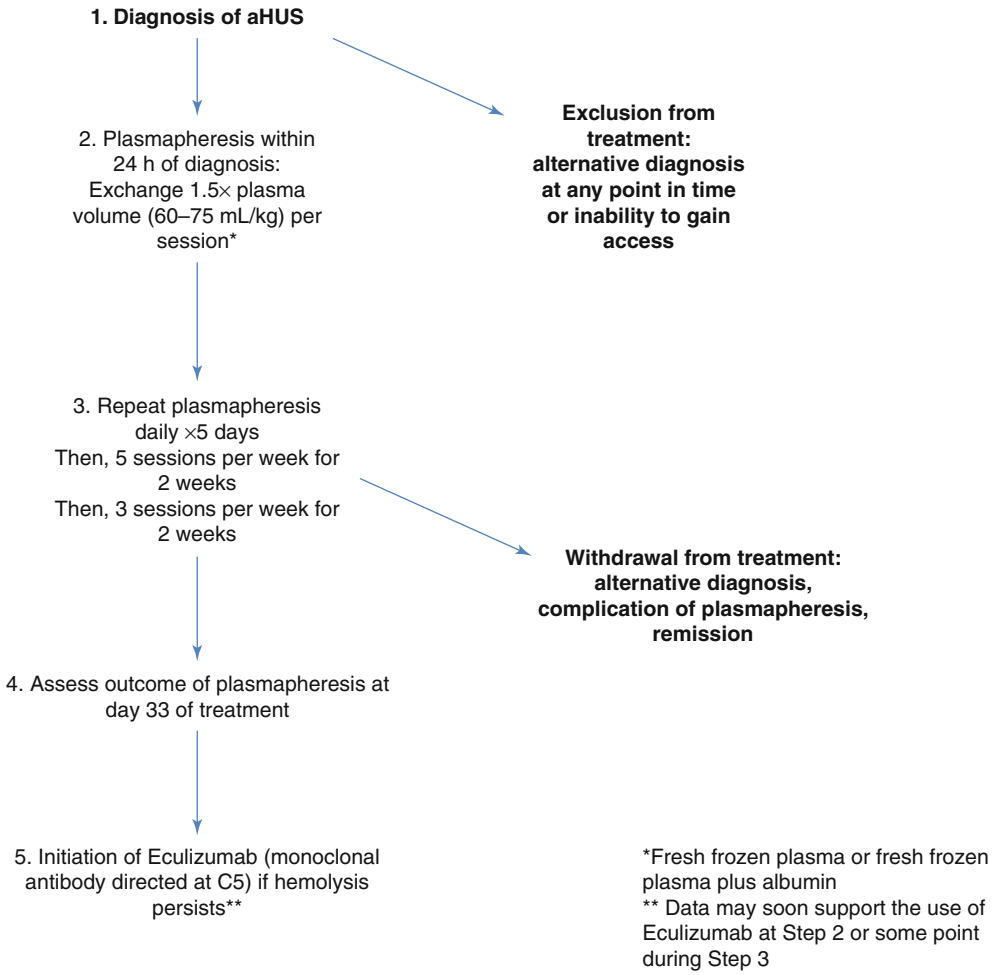

Fig. 16.5 Recommended treatment outline for aHUS (Adapted from Ariceta et al. [80]. With permission from Springer Science + Business Media)

the genetic mutation, the use of eculizumab, the anti-C5 monoclonal antibody alone or in conjunction with plasmapheresis prior to transplant has shown promise in limiting relapse when a kidney only procedure is undertaken [121].

Cardiovascular complications are found in nearly 20 % of patients with *CFH* mutations, most likely due to atheroma formation following chronic complement deregulation [92, 122]. Long-term survival for patients with *CFH* mutations has been 50 % at 10 years and 80–90 % at 10 years for those patients having *CFI* or *C3* mutations [92, 105].

Associated TMA: "xHUS"

Lastly, there remains a subset of thrombotic microangiopathies that do not fit well into the above three classifications. These microangiopathies may be referred to as "xHUS" (see Fig. 16.2 for a flow chart demonstrating an algorithm for the diagnosis of xHUS). This category includes all those diseases that cause HUS as a secondary phenomenon. Secondary aHUS has been described as due to a wide variety of non-complement causes, including infectious agents different from STEC (*Streptococcus pneumoniae*, HIV, and H1N1 influenza A), malignancy, chemotherapy and ionizing radiation, bone marrow or solid organ transplantation, calcineurin inhibitors, sirolimus or anti vascular endothelial growth factor (VEGF) agents, pregnancy, HELLP (Hemolytic anemia, elevated Liver enzymes, and Low Platelets) syndrome, malignant hypertension, systemic lupus erythematous and antiphospholipid antibody syndrome, scleroderma, and disorders of cobalamin metabolism [37, 101, 123–125]. In general the treatment for xHUS is to treat the primary disorder and support the patient with fluid, blood or antihypertensive therapy as necessary. There are no data to support a more specific treatment of the TMA at this time.

Glomerulonephritis

Glomerulonephritis is an inflammatory process, which can lead to damage within the glomerular basement membrane, mesangium, and/or capillary endothelium. Data from adult literature demonstrate that glomerulonephritis, both chronic and acute, accounts for 7 % of estimated acute renal failure

cases requiring hospitalization in an intensive care setting [126]. Cases of glomerulonephritis may manifest in both an acute or acute-on-chronic manner, which typically presents with a spectrum ranging from mild or asymptomatic hematuria with or without proteinuria to acute kidney injury requiring emergent initiation of hemodialysis. Additionally, clinical findings such as edema, joint pain, hypertension, and dark urine may be present. Close attention to clinical course and details such as a rise in serum creatinine, oliguria, hematuria ranging from microscopic to macroscopic, as well as concern for systemic manifestations of glomerular disease (including dyspnea, hemoptysis, arthralgia, or purpura) will aide the critical care physician in both diagnosis and treatment of an acute glomerulonephritis in the critical care setting.

In new cases of acute glomerulonephritis, with the exception of post-streptococcal glomerulonephritis, renal biopsy is required to determine exact histological diagnosis in addition to survey the extent and severity of glomerular disease. Serum studies may be useful in new cases of glomerulonephritis and should include complement levels (both C3 and C4), anti-streptolysin O (ASO) titers, and baseline creatinine. Complement levels are often useful in forming a differential diagnosis for type of glomerulonephritis affecting a patient; for example, C4 depression is associated with lupus nephritis as well as type I membranoproliferative glomerulonephritis whereas C3 depression is more often associated with type II membranoproliferative glomerulonephritis.

In the intensive care unit, care should be given to consider that the majority of glomerulonephritides have the potential to lead to a clinical syndrome called rapidly progressive glomerular nephritis (RPGN), which is a medical emergency. RPGN refers to a clinical syndrome characterized by a rapid loss of renal function, often accompanied by oliguria or anuria, by features of glomerulonephritis, including dysmorphic erythrocyturia and glomerular proteinuria [127]. In particular, immune-mediated glomerulonephritis (e.g., anti-glomerular basement membrane disease, Henoch-Schönlein Purpura) most often lead to RPGN. On renal biopsy, RPGN is most often represented histologically by crescentic lesions within glomeruli. Crescentic glomerulonephritis signifies an aggressive inflammatory response within the glomerulus and portends significant reduction in glomerular function. Typically, more than 50 % of glomeruli should be affected with crescents for a case to be classified as RPGN [128]. Early diagnosis and aggressive treatment are key factors in preservation of renal function.

In all cases of acute and/or acutely worsening chronic glomerulonephritis, initial treatment should focus on correction of fluid and electrolyte abnormalities, stabilization of blood pressure abnormalities, and diagnosis/treatment of underlying infections, which may have precipitated an acute presentation. Following stabilization of a patient with glomerulonephritis in the critical care unit, further treatment may consist of intravenous immunosuppressive agents as well as plasmapheresis.

Alport's Syndrome

Alport's Syndrome (AS) results from inherited mutations in the α3α4α5 network of type IV collagen, which is selectively expressed in the renal glomerular basement membrane, cochlea, eye, lung, and testis [129–131]. AS is a genetically heterogeneous disorder transmitted via autosomal dominant, recessive, and X-linked dominant manners, with all forms resulting from mutations in genes encoding type IV collagen – a major structural component of the basement membrane. Histologically, AS appears most often with a "basket weave" or slit-like appearance on electron microscopy due to abnormal collagen deposition within the basement membrane [132]. Immunofluorescence studies are not required but are supportive of the diagnosis of AS. Approximately 85 % of cases of Alport's syndrome are X-linked involving the *COL4A5* collagen IV gene and about 15 % are autosomal recessive, with autosomal dominant inheritance being more rare [133–135]. Patients with X-linked AS typically present with hematuria by 5–6 years of age [136]. Most evidence suggests that mutations in AS are a result of post-translational defects in one of the three chains assembled within the collagen IV protomer due to missense, deletional or splice site mutations within the COL4A5 gene. Risk of early (i.e., before age 30) progression to ESRD in patients with X-linked AS is most strongly associated with deletions and nonsense mutations in the *COL4A5* gene [137–139].

AS is classically defined as hematuria and proteinuria with progressive renal failure and associated sensorineural deafness [140]. More specifically, mutations within type IV collagen within the glomerular basement membrane manifest as hematuria followed by microalbuminuria and increasing elevations in proteinuria with worsening disease. Additional clinical findings have been known to include lenticonus of the anterior lens capsule, retinopathy, leiomyomatosis, and rare cases of intellectual disability [141]. Both X-linked and autosomal recessive AS lend to onset of symptoms in childhood and adolescence with development of end-stage renal disease (ESRD) typically by age 20–30 whereas autosomal dominant AS progresses relatively slowly with less need for early intervention. Additionally, hearing loss parallels progression of early onset renal disease with approximately 80 % of affected adolescent males evidencing bilateral sensorineural hearing loss, with rate of loss impacted by the type of mutation found within the *COL4A5* gene [137].

Treatment for AS is supportive in efforts to prevent progression to ESRD. Currently, AS therapy utilizes ACE

inhibitors following the onset of proteinuria. Patients who require ICU admission may need dialysis for both the acute admission but also due to ESRD precipitating such an admission; these patients are subsequently considered candidates for transplantation. It is important to note that recipient antibodies can form against normal collagen in the donor kidney, thereby causing anti-glomerular basement membrane nephritis, and may subsequently complicate post-transplant status. Despite this, patients with AS generally have similar outcomes after renal transplantation compared to patients with other forms of ESRD [142].

Anti-glomerular Basement Membrane Disease

Anti-glomerular basement membrane disease (Anti-GBM) is an uncommon cause of rapidly progressive glomerulonephritis but requires prompt diagnosis and treatment because of its association with pulmonary hemorrhage, the combination therein called Goodpasture's syndrome, and its propensity to cause irreversible renal failure if treatment is delayed [143]. Anti-GMB disease, results from the formation of autoantibodies to the NC1 domain of the α3-chain of type IV collagen [144]. This is in contrast to Alport's Syndrome which is a protein level defect caused by missense, splice, or deletional mutations with aberrant production in the resulting α3α4α5 type IV collagen chains found within the kidney, eye, lung, and/or testis. The autoantibodies formed in anti-GBM strike anywhere the α3 chain and its NC1 terminal are found, namely within the pulmonary and renal basement membranes. Autoantibodies in anti-GBM strike specifically against two epitopes hidden within the α3 domain [145–147], which are presumed to become accessible to anti-glomerular basement membrane antibodies upon exposure to environmental factors such as hydrocarbons or tobacco smoke [148, 149].

Clinical indicators suggesting a diagnosis of anti-GBM disease include hemoptysis, dyspnea, pulmonary infiltrates as well as hematuria, RBC casts, and nonnephrotic proteinuria. Disease onset is typically rapid in nature with quick progression to glomerulonephritis and subsequent oligo-anuria. It is important to note that pulmonary hemorrhage can occur without overt renal manifestations. Mechanical ventilation is required in a number of critical care patients due to the severity of pulmonary hemorrhage and alveolar edema. The diagnosis of anti-GBM disease is made on the basis of renal biopsy showing characteristic linear immunofluorescence staining pattern as well as by serum detection of circulating anti-GBM antibodies. Additionally, patients with positive serum antineutrophil cytoplasmic antibodies (ANCAs) and anti-GBM antibodies are termed "double positive" and often present with a higher systemic disease burden [150, 151]. If left untreated, patients with severe anti-GBM disease will not recover renal function and have a high likelihood of death. In the critical care setting, immediate treatment with pulse methylprednisolone, cyclophosphamide, and plasmapheresis often prevents and even reverses renal deterioration in those patients with less severely impaired renal function as well as provides therapeutic benefit for patients with pulmonary hemorrhage [152, 153]. Thus, plasmapheresis and pharmacologic immunosuppression are crucial life-saving therapies for critical care patients with Goodpasture's syndrome.

IgA Nephropathy

IgA nephropathy is the most commonly diagnosed type of glomerulonephritis in the pediatric patient but less frequently results in critical care admission. The classic clinical presentation of IgA nephropathy reveals a patient experiencing isolated macroscopic hematuria during or shortly after the occurrence of an upper respiratory infection; however, no individual viral or bacterial organism has been consistently associated with IgA nephropathy. A renal biopsy is necessary for diagnosis and demonstrates mesangial IgA deposits. Immunofluorescence studies are necessary to demonstrate the presence of IgA in glomeruli for diagnosis of IgA nephropathy. Most patients with IgA nephropathy do not have a familial history of kidney disease. However, familial occurrences of IgA nephropathy have been described in Kentucky [154, 155] and in northern Italy [156] with a locus on chromosome 6 noted in linkage studies [157]. Patients with IgA nephropathy do not demonstrate changes in serum complement levels and serum IgA is often within normal limits [158]. Patients who do present with alterations in renal function will most often demonstrate only mild, temporary reductions in renal function that may occur either at presentation or during an episode of macroscopic hematuria [159, 160]. IgA nephropathy may display a variable clinical course between pediatric patients with some children demonstrating brief, recurrent macroscopic hematuria and fluctuant hypertension in conjunction with upper respiratory illnesses [160, 161] and others may show no overt clinical features with recurrence. Up to 20 % of pediatric patients with IgAN have progressive disease, leading eventually to ESRD [160, 162].

A general consensus exists that initial goals in IgA nephropathy patients demonstrating hypertension and/or proteinuria should be to establish a normal blood pressure for age, gender and height, and to reduce proteinuria via use of ACE inhibitors, without resorting to immunosuppressive drugs – an approach that appears to provide significant reduction in proteinuria and preservation of GFR [163]. Individual treatment of IgA nephropathy aside from the general guidelines above should be directed on biopsy findings. A 20-year follow-up study demonstrated that patients with

mild renal lesions do not progress to ESRD, while 35.6 % of patients with moderate renal lesions and 92.9 % with severe lesions may progress to ESRD [164]. As such, current evidence from randomized-controlled trials suggests a benefit to the use of steroids plus ACE inhibitors (specifically, prednisone and ramipril) in the treatment of moderate IgA nephropathy [165]. Children with IgA nephropathy showing diffuse (>80 %) mesangial proliferation are at high risk for ESRD [166]. A randomized controlled trial for newly diagnosed childhood IgA nephropathy showing diffuse mesangial proliferation utilized combination therapy consisting of prednisolone, azathioprine, heparin-warfarin, and dipyridamole early in the course of IgA nephropathy and demonstrated significant long-term reductions in immunologic renal injury and also prevented the progression of glomerular sclerosis versus control therapy consisting of heparin-warfarin and dipyridamole [167]. Though warfarin and dipyridamole are no longer used, steroids and other forms of anti-cellular immune suppression (cyclophosphamide, mycophenolate and azathioprine) may have a role in progressive disease.

Henoch-Schönlein Purpura

Henoch-Schönlein Purpura (HSP) is a systemic disease characterized by capillary leukocytoclastic vasculitis predominantly affecting the vessels of the skin, joint, gut, and kidney with associated with petechial and purpuric lesions occurring most commonly on the lower extremities and buttocks. Peak age at diagnosis is between 4–6 years of age, and clinical presentation may also include abdominal pain, arthralgia and/or arthritis, and melena. HSP is not well-differentiated histologically from IgA nephropathy and the presence of extra-renal manifestations provides additional clues to distinguishing HSP from IgA nephropathy [168]. Unlike the aforementioned glomerulonephritides, patients with HSP may often have a normal urinalysis at time of diagnosis but urine may later reveal microscopic hematuria with proteinuria in the 1–3 months following diagnosis [169]. Due to the varying degree in change with urinalysis, general recommendations within pediatric nephrology are that patients with a normal urinalysis at diagnosis of HSP should have a urinalysis performed at weekly intervals for 4 weeks and again at months 2 and 3 from onset of symptoms.

Diagnosis of HSP cannot be made solely on renal biopsy as findings on biopsy are largely indistinguishable from that of IgA nephropathy with the exception that HSP more often reveals crescent formation and may demonstrate the presence of IgA deposits within the capillary loop endothelium [170]. Additionally, there is no serological test available for diagnosis of HSP. Clinical presentation, as noted above, is key in making a diagnosis of HSP. For example, case reports have demonstrated development of HSP in children with isolated macroscopic hematuria, previously thought to have IgA nephropathy and it is further important to note that macroscopic hematuria may recur in HSP in conjunction with upper respiratory illness but without classic abdominal pain, joint symptoms, or rash [171, 172].

Limited evidence for the treatment of HSP nephritis is available. Treatment should be guided by the biopsy. Mildly proliferative disease (disease without crescents) may benefit from a course of steroids in order to reduce glomerular inflammation. In cases where crescentic disease is present, patients may benefit from a combination regimen of steroids and an akylating agent (i.e., cyclophosphamide) or steroids and an antimetabolite (i.e., mycophenolate) with or without a maintenance immune suppression.

Systemic Lupus Erythematosis (SLE)

Systemic lupus erythematosis (SLE) is a well-known cause of secondary GN, and renal involvement (lupus nephritis) occurs in up to 80 % of children with SLE. Although nearly every organ system has potential to be affected by SLE, the presence of lupus nephritis is an important predictor for poor outcome. Children most commonly present with lupus after age 5 with a later peak in diagnoses into adolescence and females being more likely to develop SLE than males, and the majority of children with SLE will have renal involvement as adolescents and adults [173, 174]. Depressed levels of serum complement C3 and C4 in the presence of antibodies to double-stranded DNA support a diagnosis of lupus nephritis and should be further corroborated by renal biopsy. Additional clinical tools for diagnosis include urinalysis and microscopy as well as determination of proteinuria. Lupus nephritis is classified into five categories: Class I – minimal mesangial lupus nephritis, Class II – mesangial proliferative lupus nephritis, Class III – focal lupus nephritis, Class IV – diffuse lupus nephritis, Class V – membranous lupus nephritis, and Class VI – advanced sclerosis lupus nephritis [175]. Class IV lupus nephritis is the most common histological category found at time of diagnosis in children [176]. Knowledge of GN severity in SLE is key as lupus nephritis is the major cause of long-term morbidity in SLE and, if not adequately controlled, may lead to ESRD.

No specific therapy is warranted for Class I or II lupus nephritis; however, worsening renal histology and transition to Class III or higher necessitates use of immunosuppressive agents such as intravenous cyclophosphamide or oral MMF in conjunction with either IV or oral glucocorticoids in effort to diminish advancement of disease and prevent relapse [177].

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) has historically been subdivided into three subtypes: MPGN I, II, and III with MPGN III considered secondary most often to infectious or other causes [178]. Type I is the most common variant and is defined by the presence of subendothelial deposits of immune complexes in association with activation of the classical complement pathway [179]. Type II MPGN, also known as dense deposit disease, is characterized by the presence of additional intra-membranous dense deposits and strongly associated with the presence of C3 nephritic factor, an auto-antibody directed against the alternative pathway C3 convertase, resulting in persistent activation of the alternative complement pathway [180]. Type III MPGN is often considered a variant of MPGN type I and also demonstrates subepithelial as well as subepithelial deposits on renal biopsy [132]. More recently, the classification of MPGN has been broadened to that of immune-complex-mediated MPGN and complement-mediated MPGN [181]. In both categories, alterations within the complement cascade are key to the pathogenesis of disease – whether via the classical or alternative pathways – and the deposition of complement and/or immunoglobulin within the glomerular infrastructure initiates an acute inflammatory injury and subsequent cellular response. Dysregulation within complement pathways, persistent infection, as well as malignancy may cause the inciting deposition of immunoglobulin or complement to persist, thus furthering damage within the glomerulus.

Diagnosis of an MPGN is biopsy-based with immunofluorescence distinguishing between immune and complement-mediated MPGN. Additionally, electron microscopy may be of use in determining structural changes due to MPGN, particularly in the case of dense deposit disease (also known as MPGN II), but is not useful to distinguish between complement- and immune-mediated MPGN. Serum complement C3 and C4 levels are of use in diagnosing MPGN. Hypocomplementemia is common, broadly speaking, in MPGN with depression in both C3 and C4 indicative of immune-complex mediated MPGN whereas depression in C3 with normal C4 is suggestive of complement-mediated dysfunction, specifically within the alternative complement pathway [182]. If a diagnosis of MPGN is suspected, evaluation should include search for a possible catalyst in development of MPGN such as autoimmune disease, infection, and abnormalities within the complement pathway (e.g., presence of C3 nephritic factor and factor H mutations).

Treatment for MPGN is not well delineated due to lack of randomized controlled trials and poorly defined samples in early papers published on treatment. Sources of infectious or autoimmune disease should be treated with appropriate medical management to facilitate care of a newly diagnosed MPGN. Patients with MPGN may present with RPGN and acute renal failure and subsequently require renal supportive therapies (specifically, hemodialysis and/or plasmapheresis) in addition to immunosuppressive agents such as cyclophosphamide [183] or mycophenolate mofetil and glucocorticoids for disease management [104, 184, 185]. New pharmacotherapies, including eculizumab, which inhibits C5 activation within the complement pathway, as well as rituximab have been utilized in patients with known abnormalities of the alternative complement pathway [186–188]. Long-term management includes use of ACE inhibitor therapy to abate proteinuria and target hypertension [189, 190]. MPGN has a high recurrence risk despite transplant, particularly in dense deposit disease with up to 80–90 % recurrence [191].

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Kidney Pharmacology

17

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Abstract

Critical illness and impaired renal function alters drug pharmacokinetics and pharmacodynamics, potentially changing drug efficacy and increasing the likelihood of unwanted effects. Drugs that are most affected are those that are mostly excreted through renal elimination (≥30 %) and those that contain active or toxic metabolites that are excreted through renal elimination. To evaluate the effect of kidney failure on the drug disposition, a comparison among different dosing guidelines must be carried out. A loading dose may be required when it is important to rapidly achieve target plasma drug concentrations. To adjust the maintenance dosage, the interval extension method or the decreasing doses method or both can be used. Extra caution is warranted when prescribing drugs with a narrow therapeutic index in children with renal dysfunction. The correct application of pharmacokinetic principles may be useful in handling drug therapy during continuous renal replacement therapy. Drug elimination in children receiving a renal replacement therapy is a composite of non-renal drug elimination, residual kidney function, and the added elimination provided by the extracorporeal therapy. The efficiency to eliminate drugs depends on the physiochemical characteristics of the drug and the mode and intensity of the dialysis procedure. Six possible approaches for drug dosing during continuous renal replacement therapy have been proposed on the basis of the available references. This chapter also introduces the most common diuretics used in children. Continuous infusion of a loop diuretic is more efficient than intermittent high doses and this method diminishes toxicity and resistance.

Keywords

Acute kidney injury • Drug dosing • Continuous renal replacement therapy • Pharmacokinetics Diuretics

Introduction

The essential function of the kidney is the elimination of endogenous and exogenous toxins such as drugs, and the maintenance of homeostasis. Many commonly used drugs or their metabolites are excreted by the kidney, and this has particular significance for children with renal dysfunction. Impaired renal function alters drug pharmacokinetics, potentially changing drug efficacy and increasing the likelihood of unwanted effects, including renal toxicity [1, 2]. There may also be pharmacodynamic changes. Acute kidney injury (AKI) is common in critically ill children [3, 4]. Critically ill patients may also have multi-system organ dysfunction/failure, e.g. hepatic failure that alters the metabolism of the medications. Furthermore, the metabolic immaturity of children has to be taken into account as well as the fact that in the pediatric intensive care unit (PICU), many of the drugs that

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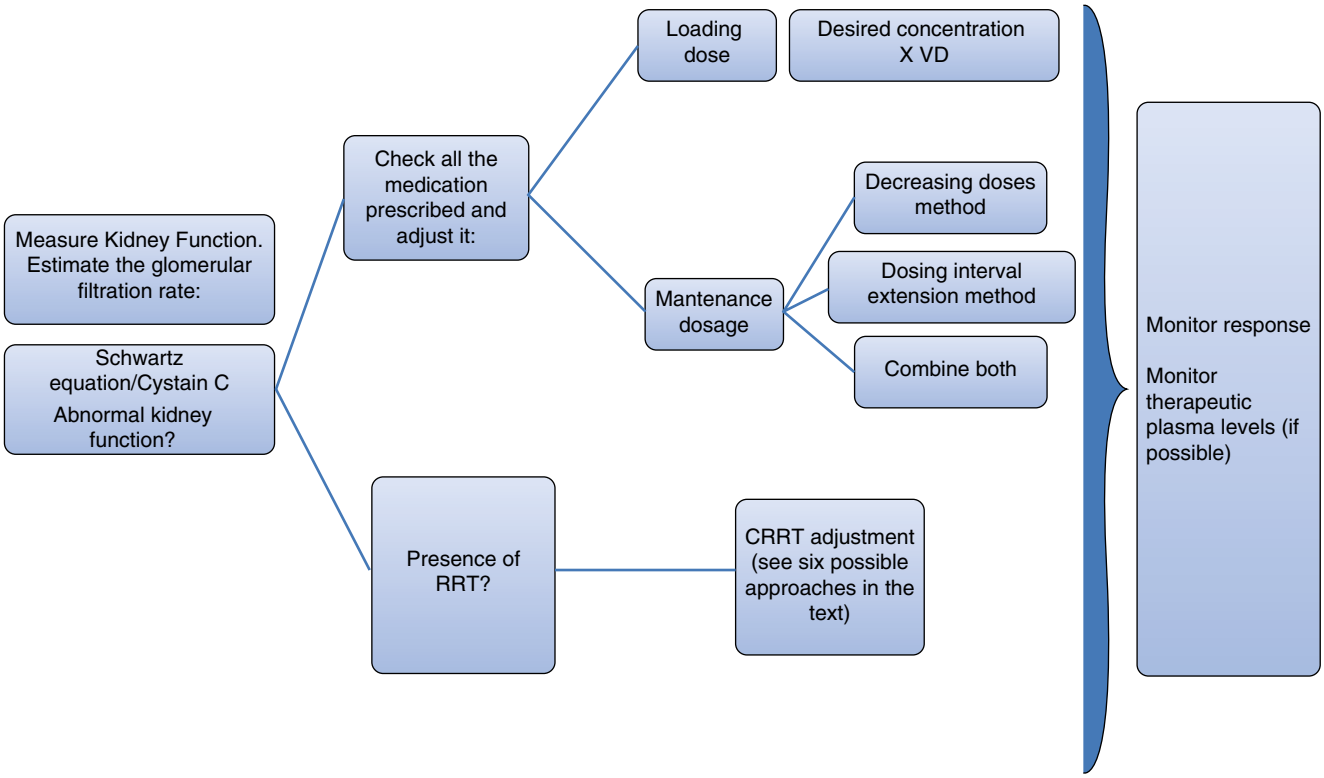

Fig. 17.1 Dosage adjustment for renal failure. *VD* Volume of Distribution, *RRT* Renal Replacement Therapies, *CRRT* Continuous Renal Replacement Therapies

are used do not have well-defined pharmacokinetic and pharmacodynamics parameters in children.

Dosage Adjustment for Renal Dysfunction

Drugs that are most affected by renal dysfunction are either those that are mostly excreted through renal elimination (≥30 %) or those that contain active or toxic metabolites that are excreted through renal elimination [5]. These drugs and drug metabolites will accumulate to higher serum drug concentrations if adjustments are not made to the drug-dosing regimen. Unfortunately, little information is available about drug disposition in children with renal dysfunction. Most of the recommendations are based on available adult literature and extrapolated to pediatric dosage regimens. Several important principles need to be kept in mind when extrapolating adult drug therapy recommendations for children. Age-related differences exist in the renal elimination of certain drugs. For example, the glomerular filtration rate (GFR) differs in children and does not increase to adult levels until the age of 2 years. In addition, the volume of distribution for water-soluble drugs is larger in pediatric patients than in adults, because significant changes in extracellular fluid volume occur in the first few years of life. The quantity and quality of plasma proteins also increase to adult levels during the first year of life. Furthermore, protein-binding characteristics undergo complex changes during human development. Such factors may be the reason for the lower serum protein binding of many drugs in infants [6].

To develop an individualized drug therapy a systematic approach is necessary (Fig. 17.1). The dosing adjustments may be estimated using the following steps [7]:

1. **Estimate the glomerular filtration rate**. An acceptable pediatric equation to calculate GFR is the Schwartz equation. According to the blood creatinine concentration and the height of the patient, this formula estimates the clearance of creatinine (CrCl) in children with a normal body mass index. This equation is easy to calculate and is well correlated with creatinine clearance (mL/min/1.73 m2) [8, 9]. CrCl = [Length (cm) × K]/Serum Cr (mg/dL), where ¨*K*¨ is a constant of proportionality that is age specific (0.33 for low birth weight infants, 0.45 age <1 year, 0.55 age 2–12 years, 0.55 for females between 13 and 21 years or 0.70 for males between 13 and 21 years). The use of serum cystatin C as a measure of GFR in critically ill children is also well documented and some authors have suggested that it may be more accurate than serum creatinine for this purpose [10–12]. Cystatin C is a low molecular weight protein, which has been proposed as a marker of GFR because it is almost completely and freely filtered through the normal glomerular membrane and

then undergoes subsequent tubular reabsorption without tubular secretion (absence of cystatin C in urine from normally functioning kidneys) [11]. The renal handling of cystatin C is combined with a stable production rate, with plasma concentrations not affected by age, sex, muscle mass, or nutritional status [10]. It can shorten the diagnosis time of the renal alteration with regard to the creatinine by 1 or 2 days and, moreover, the withdrawal of urine is unnecessary [13]. Regardless of whether the Schwartz equation or Cystatin C is used, modification of drug doses in renal disease is usually necessary only when the GFR is less than 40 ml/min/1.73 m^2.

2. **Evaluate the effect of kidney failure on the drug disposition for all the medication prescribed for the patient**. A comparison among different references must be carried out. Currently the most often used are: Micromedex [14], Pediatric dosage handbook [15], Physician desk reference [16] and Drug Prescribing in Renal Failure [17]. The most important data is the amount of drug that is eliminated by the kidneys in individuals with normal kidney function. Then, a dose adjustment is applied. Two different methods exist: proportional dose reduction according to **Luzius Dettli** (based on the concept that drug elimination is linearly correlated with GFR) and the half dosage rule according to **Calvin Kunin** (based on the concept that the standard dose is administered initially once, then on-half the standard dose is administered after one individual half-life of the drug). The Kunin rule leads to higher trough concentrations but is probably the preferred method for antibiotic dosing [18].
3. **Adjust dose size**, **dose interval or both**. In patients with impaired renal function, a loading dose should be considered when the half-life of the drug is particularly long [5]. When the extracellular fluid volume is normal, the loading dose administered to a patient with renal dysfunction is the same as the initial dose administered to a patient with normal renal function. Patients with substantial edema or ascites may require a larger loading dose, whereas patients who are dehydrated or debilitated should receive smaller initial drug doses [1, 17]. To adjust the maintenance dosage, the intervals between individual doses can be lengthened, keeping the dose size normal. Extension of the dosing interval is advantageous when drugs with wide therapeutic ranges and long plasma half-lives are prescribed in patients with renal impairment. For example, glycopeptide antibiotics are administered at intervals of several days in anuric patients according to their plasma levels [6]. However, extending the dosing interval may result in wide fluctuations of the plasma drug concentrations from peak to trough levels. If the range between the therapeutic and toxic levels is too narrow, either toxic or subtherapeutic plasma concentrations may result. In this case, the size of the individual doses can be reduced, keeping the interval between doses normal. Decreasing the individual doses reduces the difference between peak and trough plasma concentrations. This effect is important for drugs with narrow therapeutic ranges and short plasma half-lives in patients with renal impairment and is recommended for drugs for which a relatively constant blood level is desired, such as antiarrhythmic drugs. Sometimes, a combination of interval prolongation and dose-size reduction is often effective and convenient, for example, in the case of aminoglycosides [6, 19].
4. **Monitor the response**. These dosing adjustments are estimates based on many assumptions. Close monitoring of clinical efficacy and toxicity is necessary.
5. **Monitor the therapeutic plasma levels**. Substances with narrow therapeutic range or those that bear the risk of severe consequences of under-dosing should be assessed by therapeutic drug monitoring. These include, for example, aminoglycoside and glycopeptides antibiotics, anticonvulsants, cardiac glycosides and anticoagulants. Drug concentrations can be measured directly in blood samples or indirectly by monitoring the drug effect (e.g. anticoagulation).

Renal Replacement Therapy and Medication Dosing

The application of RRT, by leading to extracorporeal clearance, may significantly alter the pharmacokinetic behavior of some drugs [20–22]. At the start of a RRT, all the drugs the patient receives must be checked. It is important to understand how drugs are removed by RRT in order to maximize the potential therapeutic benefit while minimizing the risk of drug toxicity. Several reviews have been written summarizing drug removal during intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) [21–24]. Similar reviews focusing on pediatric patients are scarce [6, 20].

Drug elimination in children receiving a RRT is a composite of non-renal drug elimination (Cl_{NR}), residual kidney elimination (Cl_R) and the added elimination provided by the extracorporeal therapy (Cl_{EC}).

$$\mathbf{Cl_{TOTAL} = Cl_R + Cl_{NR} + Cl_{EC}}$$

The efficiency of a given dialysis modality to eliminate drugs depends on the physiochemical characteristics of the drug and the type and intensity of the dialysis procedure (Table 17.1).

The drug characteristics that affect removal include [20]:

1. **Molecular Weight**: One must take into account the fact that most drugs have a molecular weight under <1,000 Da and pass through the membrane of the filter. Conventional

Table 17.1 Factors influencing drug removal during RRT

Drug characteristics	Hemofilter composition	RRT characteristics
Molecular weight	Membrane type	Dialysis rate
Protein binding	Pore size	Ultrafiltration rate
Charge	Surface area	Predilution/postdilution
Water and lipid solubility	Life time	

dialysis membranes favor diffusive clearance of low molecular weight solutes below 500 Da. The typical high-flux membranes used for CRRT have larger pores (20,000–30,000 Da) and therefore present no significant filtration barrier to drugs not bound to proteins. Vancomycin (1,450 Da) is an example of this phenomenon. Its clearance values with conventional hemodialysis are one-third to one-fifth of those reported with CRRT. The ability of a drug to pass through the membrane is expressed as the sieving coefficient (S_C). The S_C of a drug is the concentration in ultrafiltrate divided by the concentration in plasma. Drug plasma protein binding (PB) is the main determinant of S_C [25].

2. **Protein Binding**: Only the unbound fraction of a drug is available for removal. Drugs that are 80 % or more protein bound are not likely to be significantly removed by either convection or diffusion [24].
3. **Charge**: Anionic proteins retained on the blood side of the filter can exert forces to retain some cationic drug molecules. Anionic drug molecules may experience the opposite effect [7].
4. **Water and lipid solubility**: The distribution of hydrophilic compounds is limited only to the plasma and to the extracellular space and they are usually excreted via the renal route. On the contrary, lipophilic agents may freely cross the plasmatic membrane and so, are widely distributed into the intracellular compartment and must often be metabolized through different pathways before elimination [21].

In addition to drug properties, technical features of the dialysis circuit components and procedure will also affect the extent to which a drug is removed. The filter composition (membrane type, pore size and surface area) influence the clearance of drugs. Another factor that may influence the sieving coefficient for a specific hemofilter is the drug binding to the membrane. This has been shown for several drugs, including aminoglycosides, but this phenomenon is saturable [20]. Also the surface area declines over the filter life time because clotting of individual capillaries occurs [23]. Additionally, for the smallest pediatric patients, the hemofilters available are limited and usually their surface area is too large for their low blood volume.

Drug removal is also dependent on the mode of replacement fluid administration (pre-dilution or post-dilution mode) and on the ultrafiltration and dialysate rates applied [21]. The extracorporeal drug clearance during a continuous therapy is:

$$\mathbf{Cl_{EC} = Cl_{HF} + Cl_{HD}}$$

When the replacement fluid is added in the post dilution mode, drug clearance during haemofiltration will equal the ultrafiltration rate (Q_{UF}):

$$\mathbf{Cl_{HF} = Q_{UF} \times S_C}$$

For readily filterable molecules C_{UF} approximates the concentration of unbound drug in plasma and S can be estimated by the unbound fraction (f_u) of the drug, making

$$\mathbf{Cl_{HF} = Q_{UF} \times f_u}$$

The value of f_u is retrieved from pharmacological tables. Also, the clearance by diffusion depends on the dialysis rate:

$$\mathbf{Cl_{HD} = Q_D \times f_u}$$

where Q_D is the dialysis rate and f_u is the unbound fraction of the drug.

Continuous Renal Replacement Therapy (CRRT) Adjustment

CRRT, particularly continuous venous hemofiltration (CVVH), is the preferred method of RRT in many pediatric intensive care units (PICUs) [3, 26, 27]. According to the literature [22, 28] there are six possible approaches for drug dosing during CVVH. First, drug dosage can be adjusted based upon clinical studies. There are reviews which intend to summarize the most recent findings on each drug [20, 21, 24]. However, it should be noted that among the different studies concerning each single compound, the percentage relevance of CL_{CRRT} was often found to vary significantly [29]. Second, the "total creatine clearance method" can be used. The total creatinine clearance (CL_{TOTAL}) is the sum of extracorporeal (CL_{CRRT}) and estimated endogenous creatinine clearance (CrCl). This CL_{TOTAL} can be used to guide drug dosing using the same recommendations designed for patients with reduced renal function [28]. This method assumes, according to Dettli's fundamental equation [30], that drug clearance is proportional to the glomerular filtration rate, thereby ignoring the contribution of tubular drug handling (tubular secretion and tubular re-absorption) [22, 31]. Third, the drug can be adjusted by reducing the normal dose of the drug (assuming normal renal function) and reducing this dose in proportion to the estimated reduction in the total body drug clearance [22, 25]. For the anuric patient this makes:

$$\mathbf{D = D_N \times Cl_{ANUR} / Cl_N}$$

where D_N is the normal dose, Cl_{ANUR} is drug clearance in anuric patients and Cl_N are retrieved from pharmacological tables. If CRRT contributes significantly to the total body clearance (>25–30 %), a supplemental dose, corresponding to the amount of drug removed by CRRT (Cl_{CRRT}), should be administered, making:

$$\mathbf{D = D_N \times \left(Cl_{ANUR} + Cl_{CRRT} \right) / Cl_N}$$

Fourth, the drug can be adjusted using the maintenance dose multiplication factor "MDMF" method. On the basis of the dose for anuric patients and adjusted by increasing the dose using the maintenance dose multiplication factor (MDMF) [32].

$$\mathbf{Fr_{CVVH} = Cl_{CVVH} / Cl_{total}}$$

$$\mathbf{MDMF = 1 / 1 - Fr_{CVVH}}$$

The calculation of drug clearance by measuring the ultrafiltrate levels is very difficult because many of the drugs cannot be measured in these fluids and because the CRRT dose and the proportion of hemofiltration and dialysis prescribed can change according to the requirements of the patient. Fifth, drug dosages can be adjusted on the basis of drug levels. Particularly for toxic drugs and for drugs with a narrow therapeutic index, (vancomycin, aminoglycosides, tacrolimus) therapeutic drug monitoring is mandatory [28]. Sixth and finally, standard fixed dosages for a 10–30 ml/min GFR can be used. Some statements suggest that for drugs cleared by renal elimination, dosage adjustments might be applied considering the application of CRRT equivalent to a glomerular filtration rate ranging between 10 and 30 ml/min [33]. The very large inter-individual pharmacokinetic variability documented in several studies suggests that standard fixed dosages during CRRT may be an excessive simplification and inappropriate in many cases [21].

Diuretics

Diuretics produce increased urine output by inhibiting the reabsorption of sodium at different segments of the renal tubular system. The increase in urinary sodium produces a greater secretion of water. The increase in urine output decreases the vascular tone. This stimulates the movement of sodium and water from the interstitial space into the vascular and also activates the renin-angiotensin-aldosterone system. Diuretics are prescribed for the mobilization of excess body fluid [34, 35], treatment of cerebral edema [36], and hypertension [37]. A less common indication in children is heart failure [38]. Heart failure leads to the activation of the renin-angiotensin-aldosterone system, which causes increased sodium and water retention by the kidneys. This increases blood volume and contributes to the elevated venous pressures associated with heart failure, which can provoke pulmonary and systemic edema. Diuretics reduce pulmonary and/or systemic congestion and edema, as well as associated clinical symptoms [38]. Long-term treatment with diuretics may also reduce the afterload on the heart by promoting systemic vasodilatation, which can lead to improved ventricular ejection. When treating heart failure with diuretics, care must be taken to not unload too much volume because this may depress cardiac output. Other indications for diuretics are disorders in calcium metabolism, glaucoma and drug overdoses.

Pharmacokinetics of Commonly Used Diuretics

Diuretics are extensively bound to plasma proteins. Their entry into the tubular fluid depends upon proximal tubular secretion. The relation between doses and response is quite variable among subjects. It depends on the renal function and the capacity of the drug reaching the site of action. The response to diuretics follows an S-shape concentration-response curve for loop diuretics and thiazides. There is a minimal concentration to initiate the response, the therapeutic threshold, and a ceiling above which no more response occurs even if the dose is increased. In the case of loop diuretics in children, under certain circumstances, e.g. low renal blood flow and/or decreased kidney function, the dose may have to be increased up to ten times [7]. In these situations a combination of diuretics is given using their synergistic effect [39]. The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.

Categories of Diuretics

A classification of common diuretics is presented in Table 17.2. There are five types of diuretics:

Loop diuretics, Thiazide, Potassium-sparing, Osmotic and Carbonic anhydrase inhibitors.

Specific drugs comprising the five kinds of diuretics are listed in the table. See www.rxlist.com for more details on individual diuretics.

Loop diuretics decrease sodium reabsorption by inhibiting the sodium-potassium-chloride cotransporter in the thick ascending limb of Henle. Loop diuretics are very powerful because this cotransporter normally reabsorbs about 25 % of the sodium load [39]. Therefore, inhibition of this pump can lead to a significant increase in the distal tubular concentration of sodium, reduced hypertonicity of the surrounding interstitium, and less water reabsorption in the collecting

Table 17.2 Classification of diuretics

Diuretics	Mechanism of action	Indications	Side effects
Loop	Blockade of NaK2Cl transporter in the thick ascending loop of Henle	Fluid overload	Hypokalaemia
Furosemide		Heart failure	Metabolic alkalosis
Bumetamide		Hypertension	Hypomagnesemia
Torsemide		Hypercalcemia	Volume depletion (prerenal uremia)
Ethacrynic acid			Ototoxicity (dose-related hearing loss)
Thiazide	Blocks Na/Cl exchanger in the distal convoluted tubule	Antihypertensive combination with loop diuretic for edema	Hypokalaemia, hyponatraemia
Hydrochlorothiazide		Nephrocalcinosis/nephrolitiasis with hypercalciuria	Metabolic alkalosis
Chlorthalidone			Hyperuricaemia
Chlorothiazide			Impaired glucose tolerance
Bendrofluazide, Metolazone			Hypercholesterolemia
Indapamide			Hypertriglyceridemia
Potassium-sparing 2 types:	Blocks channel for Na secretion in collecting duct under aldosterone control	To prevent hypokalemia (caused by loop or thiazides)	Hyperkalemia
Amiloride/triamterene:		Antihypertensive (adjunctive third line therapy for hypertension or first line for conns patients)	Metabolic acidosis
Spironolactone/canrenoate potassium/Eplerenone:	Aldosterone receptor antagonist	Ascites in cirrhosis	Gynecomastia, impotence, reduced libido
		Advanced heart failure	
Osmotic diuretics	Free filtered but not resorbed	Reduce ICP	Volume depletion
Mannitol		Oliguric renal failure	Electrolytes imbalance
		Dialysis disequilibrium syndrome	
		Glaucoma	
Carbonic anhydrase inhibitors	Inhibit the transport of bicarbonate out of the proximal convoluted tubule into the interstitium	Acute mountain sickness	Hypokalemia
Acetazolamide		Glaucoma	Metabolic acidosis
Dorzolamide			

duct. This altered handling of sodium and water leads to both diuresis and natriuresis. Loop diuretics can cause a profound fluid and electrolyte loss. A close monitoring of body fluid volume and serum electrolytes during therapy is necessary. Inhibition of sodium reabsorption causes an increase in the urinary excretion of calcium and magnesium. This produces hypomagnesemia and hypercalciuria and the production of kidney stones with long-term use. Also the collecting duct cells have a transporter that reabsorbs sodium (about 1–2 % of filtered load) in exchange for potassium and hydrogen ion, which are excreted into the urine. Increased sodium delivery with loop diuretics provokes an increase in its activity and more sodium is reabsorbed and more potassium and hydrogen ion are excreted. This process of adaptation diminishes diuretic efficacy and may lead to hypokalemia and metabolic alcalosis. Potassium-sparing diuretics are often used in conjunction with loop diuretics to help prevent hypokaliemia, however oral potassium supplements or even I.V. infusions are sometimes required.

Thiazide diuretics inhibit the sodium-chloride transporter in the distal tubule. As this transporter normally only reabsorbs about 5 % of the filtered sodium, these diuretics are less effective than loop diuretics in producing diuresis and natriuresis. However, they are sometimes used in conjunction with loop diuretics to increase the effect [39]. These diuretics are usually administered once or twice per day. In contrast to the calciuric effect of loop diuretics, thiazides enhance calcium reabsorption and may have a beneficial effect on children with nephrocalcinosis/nephrolitiasis and hypercalciuria. However, thiazide diuretics have a greater propensity than other diuretics to cause hypokalemia. Loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing hypokalemia) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine. The increased hydrogen ion loss can lead to metabolic alkalosis. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics is due to the activation of the renin-angiotensin-aldosterone system that occurs because of reduced blood volume and arterial pressure. Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine [7].

Potassium-sparing Diuretics are called potassium-sparing diuretics because they do not produce hypokalemia, as do the loop and thiazide diuretics. Spironolactone

antagonizes the actions of aldosterone (aldosterone receptor antagonists) at the distal segment of the distal tubule. Spironolactone prevents the binding of aldosterone to the cytosolic receptor resulting in decreased activity of Na/K-ATPase and a decrease in the number of apical sodium channels. By inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine. Spironolactone is effective in primary and secondary hyperaldosteronism. Triamterene and amiloride decrease sodium reabsorption by directly blocking the apical membrane sodium channel in the principal cells of the cortical collecting duct, and therefore have similar effects on potassium and hydrogen ion as the aldosterone antagonists. Because this kind of diuretics has relatively weak effects on the overall sodium balance, they are often combined with thiazide or loop diuretics to capitalize on the K-sparing action [39].

Osmotic Diuretics are freely filtered by the glomeruli, but are incapable of being re-absorbed from the renal tubule, which results in decreasing water and sodium reabsorption via its osmotic effect. Osmotic Diuretics extract and transport water from the intracellular compartments to the extracellular fluid volume. The administration of mannitol is clinically useful to reduce acutely raised intracranial pressure (e.g. after head trauma) [36], treating patients with glaucoma, and for the prevention of dialysis disequilibrium syndrome. It is also used to treat patients with oliguric renal failure and tubular obstruction. Osmotic nephrosis is the nephrotoxicity associated with the use of these agents [40].

Carbonic Anhydrase Inhibitors inhibit the transport of bicarbonate out of the proximal convoluted tubule into the interstitium, which leads to less sodium reabsorption at this site and therefore greater sodium, bicarbonate and water loss in the urine. These are the weakest of the diuretics. Their main use is in the treatment of glaucoma and acute mountain sickness [7]. The effectiveness is limited by the metabolic acidosis that develops because of the bicarbonate loss in the urine.

Diuretic Resistance

Diuretic response may diminish due to adaptation processes. The extracellular volume depletion triggers adaptation processes to protect the intravascular volume. When these adaptation processes interfere with diuretic responsiveness, they contribute to diuretic resistance and the desired reduction in extracellular fluid volume is not achieved. These processes enhance post diuretic sodium retention due to decreased atrial natriuretic peptide, increased renal sympathetic activity, increased antidiuretic hormone, a stimulated renninangiotensin-aldosterone system and a reduced glomerular filtration rate (tubuloglomerular feedback) [7].

Increasing the response intensive diuretic therapy is achieved through high-dose diuretic therapy, combination diuretic therapy or a continuous diuretic infusion [41, 42]. Although a study published in 2011 by Felker et al., showed that the same dose administered intermittently or continuously did not produce any significant difference in the diuresis [43], continuous infusion of a loop diuretic seems to be more efficient than intermittent high doses [44, 45]. Furthermore, the fact that continuous infusion avoids the high and low serum concentrations associated with toxicity and resistance has also been pointed out [44, 45]. In addition, these infusions result in constant diuretic effect and may avoid hemodynamic disturbances associated with rapid changes in extracellular fluid volume. A loading dose of diuretic is recommended at initiation and later a progressive increase until the suitable dose is found.

The diuretic response of loop diuretics may be further augmented by the addition of a distally acting diuretic (thiazide). In severe oliguric scenarios with maximal activity of the renin-angiotensin-aldosterone system such as cardiorrenal syndrome, the combination of all of them: continuous loop diuretic infusion with proximal acting (carbonic anhydrase inhibitor) and distally agent diuretic (thiazide) may result in adequate urine output. However, electrolytic disorders have to be controlled and probably supplement of potassium and sodium can be required, in addition to the use of potassium-sparing agent.

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Renal Replacement Therapy

18

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Abstract

Acute Kidney Injury (AKI) is a common occurrence in the pediatric intensive care unit, with a shift in the last two decades to the majority of etiologies being an outcome of other primary illnesses and the treatments given for these diseases rather than primary intrinsic renal disease. It should be treated with renal supportive measures which include close monitoring, avoiding secondary injury, supportive measures to remove excess total body fluid and/or toxic wastes, and may require dialysis with expectation of renal recovery with adequate support. Renal supportive therapies (RST) should be initiated at the earliest signs of AKI.

Keywords

pRIFLE • Acute kidney injury (AKI) • Renal supportive therapy (RST) • Renal replacement therapy (RRT) • Peritoneal dialysis (PD) • Continuous renal replacement therapy (CRRT) • Hemodialysis (HD)

Introduction

Acute kidney injury (AKI) is a frequent diagnosis in the critically ill child due to ischemic injury causing acute tubular necrosis (ATN) and apoptosis. AKI most commonly results from congenital heart disease surgery, frequent use of nephrotoxic drugs, sepsis, bone marrow transplantation, solid organ transplantation, burns, or malignancies. There is also a low risk of AKI with intrinsic renal disease. When patients meet criteria, renal replacement therapies (RRT) can be used to eliminate volume, acid-base or electrolytes imbalance, including inborn errors of metabolism (IEM), and toxins. AKI is often defined as an acute decrease in solute clearance with a drop in GFR (glomerular filtration rate) from baseline, a drop in urine output to less than 0.5 ml/kg/h or the need for acute dialysis. The development of AKI in an ICU has a guarded prognosis with long-term complications. Prevention & aggressive management are essential to minimize these consequences.

Uniformity in the definition of AKI in children has developed through the pRIFLE (Pediatric-modified Risk, Injury, Failure, Loss, End-stage kidney disease) classification, a

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Table 18.1 The pRIFLE classification for AKI

Class	eCCl	Urine output
Risk	eCCl decrease by 25 %	<0.5/kg/h × 8 h
Injury	eCCl decrease by 50 %	<0.5/kg/h × 16 h
Fail	eCCl decrease by 75 % or <35 ml/min/1.73 m^2	<0.3/kg/h × 24 h or anuric × 12 h
Loss	Failure >4 weeks	
ESRD	Failure >3 months	

eCCL estimated creatinine clearance

Table 18.2 Pathophysiology

Hypovolemia
Hypoxemia
Septicemia – TNF, endotoxin
Hypothermia
Drugs – indomethacin, ACE inhibitors, ARBs, neuromuscular blockers, aminoglycosides, acyclovir, amphotericin, penicillins, radio-contrast material, cisplatin
Pigments – myoglobin, hemoglobin
Renal vascular thrombosis – arterial and venous
Toxins – ethylene glycol, uric acid
Renal & urinary tract abnormalities
Polycystic kidney disease, multicystic dysplastic kidneys, renal agenesis, urinary tract obstruction

Table 18.3 RST for early AKI

Avoid prerenal causes (e.g., volume depletion, hypotension, CHF)
Exclude postrenal causes (using renal ultrasound and measurement of postvoid residual)
Avoid nephrotoxic agents – NSAIDS, ACE inhibitors, ARBs, contrast material, amphotericin B, aminoglycosides
Avoid rhabdomyolysis, myoglobinuria
Urinalysis will show muddy brown casts in ATN; clear sediment in prerenal or postrenal azotemia
Urine electrolytes with or without the use of diuretics (urine osmolality, Na, urine to plasma creatinine ratio, and FE_{Na})
Nephrology consult early
Project the need for dialysis: 85 % of patients with oliguric ATN and 30–40 % of patients with nonoliguric ATN will need dialysis
Avoid excessive fluid resuscitation
"Renal-dose" dopamine – not effective
"Renal-dose" nor epi may be effective
Renal dosing of meds
Protein restriction
Potassium and phosphate restriction
Use enteral rather than parenteral nutrition
Consider preemptive RRT in patients with high risk for AKI – e.g. tumor lysis
Discuss mode of RRT with nephrologist (intermittent vs. continuous)

modification by Akcan-Arikan [1] of the adult RIFLE system (Table 18.1). The RILFE system utilizes the estimated creatinine clearance and urine output to define the prognostic outcome. Eighty-two percent of acute kidney injury occurring in the PICU develops in the first week of admission with AKI being identified as an independent predictor of intensive care stay, hospital length of stay and an increased risk of death separate of the Pediatric Risk of Mortality (PRISM II) score (odds ratio 3.0).

The incidence of AKI in hospitalized children is increasing. A study by Zappitelli et al. showed that children treated with aminoglycosides for 5 or more days had a 33 % incidence of AKI, a longer length of stay, and substantial/added hospital expenditures [2]. In neonates, the incidence of AKI is much higher, with 8–24 % of newborns in the NICU having AKI [3]. The common risk factors for development of AKI in neonates are cardiac surgery, very low birth weight (<1,500 g), newborns with a low Apgar score, presence of a patent ductus arteriosis, or maternal administration of antibiotics and NSAIDs [4]. Decreased renal perfusion caused by hypotension results in renal vasoconstriction from activation of renin-angiotensin and sympathetic nervous systems, producing a reduction in GFR, & renal oxygen delivery which predispose to renal tubular injury. Evaluation of the patient with AKI should focus on identifying the underlying cause(s) and evaluation for renal support therapy (Table 18.2).

For a child at risk for AKI, utilizing serum creatinine as the primary marker of renal dysfunction is inadequate. Even small elevations of creatinine have been found to be a risk factor of mortality in children [5]. An increase in serum creatinine by 0.5 mg/dL or a doubling from its baseline should alert the propensity to AKI. Recent studies evaluating renal biomarkers, NGAL (neutrophil gelantinase-associated lipocalcin), KIM-1 (kidney injury molecule-1), L-FABP (liver-type fatty acid binding protein), and IL-18 (interleukin-18), and cystatin-C, have demonstrated promise for early AKI identification [6, 7]. Screening for pre-renal and post-renal causes should also be initiated. Cumulative fluid overload is strongly associated with poor clinical outcome in critically ill children, therefore monitoring this fluid balance is as important as the vital signs, and is a component used in determining optimal time for renal support therapy [8]. Monitoring electrolytes such as sodium, potassium, bicarbonate, calcium and phosphorus and other waste products such as uric acid and creatine kinase are essential to avoid co-morbidities.

AKI morbidity and mortality may be minimized by early initiation of renal supportive therapies (RST), especially when multi-organ system dysfunction is present. Timing of initiation of RST is of great importance. Renal supportive therapies include not only dialysis modalities but also optimum fluid balance, electrolyte management, maintaining renal perfusion, and optimum nutrition with attention towards protein, potassium, and phosphorus balance (Table 18.3). A trial of diuretics can be initiated for fluid overload if the native kidneys are still functioning, with cautious use of diuresis in oliguric patients and only after careful correction of the

intravascular volume status. Loop diuretics and thiazides can be tried to convert oliguric AKI into non-oliguric AKI, this however was not associated with faster recovery from AKI or improved mortality [9, 10]. A multi-center, retrospective cohort study with use of any diuretic was associated with a 36 % increased risk of death and non-recovery of renal function [11]. In addition the study found a delay in beginning dialysis by 1–2 days in diuretic group. Diuretic trials should be short in duration and if not effective with solute clearance as well as fluid balance must not cause a delay in renal replacement therapies. When early signs of AKI are present, the critical care physician should be managing the patient in close conjunction with the nephrology team to optimize outcome. In situations where this is not available, the patient may need to be transferred to a facility where this multidiscipline approach can be done.

Nutritional Support in AKI

Acute kidney injury most often occurs in conjunction with critical illness, where a hypermetabolic state is present with hyperglycemia, insulin resistance, hypertriglyceridemia, and increased protein catabolism. This can be mitigated by early institution of adequate and appropriate nutrition, enterally if possible. A diet that is high in calcium and protein yet low in potassium and phosphorus is recommended. Infants and children should receive maintenance calories appropriate for age, and additional protein support when on dialytic support with increased nitrogen losses. This nutrition is easily attainable once RRT is initiated to maintain the fluid balance.

Children with a higher cumulative percentage fluid overload have worse outcomes even after controlling for severity of illness. Using the prospective pediatric continuous renal replacement therapy (ppCRRT) registry, Sutherland et al. showed that those who initiated RRT with cumulative percentage fluid overload less than 20 % had better survival than those who had cumulative fluid excess higher than 20 % [12]. Hayes et al. reported similar data related to fluid overload and survival on patients receiving RRT [13]. In a larger study of 113 children with multiple-organ dysfunction syndrome (MODS) started on Continuous RRT (CRRT), median percent fluid overload was significantly lower in survivors compared to nonsurvivors (7.8 % versus 15.1 %), and mortality related to fluid overload was independent of severity of illness [14]. Another study showed that, in 297 patients, % fluid overload was again significantly lower in survivors versus nonsurvivors (12.5 % versus 23.0 %) [9]. A comprehensive review of fluid overload on survival was done by Goldstein [15]. In a prospective, uncontrolled, observational study DiCarlo initiated CRRT for ten children with ARDS after BMT regardless of presence of AKI and demonstrated an 80 % survival rate [16]. Flores et al. utilizing the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry documented a survival rate of 45 % in bone marrow transplant patients on CRRT, and found that patients requiring ventilatory support had a decreased survival with correlation drawn to the mean airway pressure (Paw) at the end of CRRT. The finding of high mean airway pressure (>22 cm of H2O) in non-survivors being related to non-fluid injury, as it was not prevented by early and aggressive fluid management by CRRT therapy [17].

Table 18.4 Indications for RRT

Renal failure
"Hypermetabolic syndrome"
Acidosis
Hyperkalemia
Hypo/hypernatremia
Volume overload – CHF, pulmonary edema
Altered mental status due to fluid overload and cerebral edema
Severe hypertension associated with seizures or heart failure not responsive to medical management
Hyperosmotic nonketotic coma
Tumor lysis syndrome
Inborn errors of metabolism
Toxin ingestion

When initial, conservative management fails, RRT should be considered (Table 18.4). For RRT, highly trained staff and safe technology is mandatory to be able to provide this care for the patient. RRT can be utilized in tandem with extracorporeal circulatory devices. The best mode of dialysis should be individualized for the patient, and early consultation with nephrology can help define this (e.g. high flux hemodialysis for intoxications). Yet in some cases the "best mode" of RRT for a certain diagnosis may be based upon local availability and/or expertise, as well as the individual patient's characteristics (size of patient, hemodynamics, respiratory status, etc). Each form of RRT will be discussed in terms of advantages and disadvantages.

Peritoneal Dialysis

Peritoneal dialysis (PD) is safe and technically simple to perform and hence had been a common mode of therapy historically [18]. The peritoneum represents a large surface area that can be used as the semi-permeable membrane for exchange. Hence it is often preferred in newborns, including low birth weight infants, where vascular access is often limited by the size of available hemodialysis catheters. Acute PD access can be placed easily at bedside by the pediatric nephrologist with immediate commencement of the therapy. Minimal equipment is required for peritoneal dialysis and it can be initiated soon after major abdominal surgery. When applied in a continuous form, this mode is well tolerated by

even hemodynamically unstable patients. PD is less efficient in altering blood solute composition as it is for fluid removal. Mortality and morbidity can be high in newborns that require PD and this is related to the underlying diagnosis. Limiting factors of PD include less efficient solute clearance as compared to other modalities and increased intra-abdominal pressure, which may compromise pulmonary function. High glucose content in the PD solution in theory can cause hyperglycemia with subsequent elevation in the respiratory quotient to >1.0.

Dialysate Solutions

In PD, the glucose concentration of the dialysate solution determines the ultrafiltration (fluid removal). Standard commercial solutions used in North America have a glucose concentration of 1.5 %, 2.5 % or 4.25 %. The higher the glucose concentration in the dialysate, the greater the osmolarity, which results in a greater osmotic pull / ultrafiltration for the child. PD solutions also contain physiologic levels of electrolytes and buffer. The majority of PD solutions used in North America are lactate based, but over the past decade with research in new dialysate compositions, bicarbonate based solutions are now marketed by companies in Europe. A typical PD solution has sodium of 132 meq/L, calcium of 3.5 meq/L, magnesium of 0.5–1.5 meq/L and a lactate (or bicarbonate) of 40 meq/L. Chloride is present at physiologic levels to ensure anion and cation balance. If needed, potassium but not phosphorous can be added to the dialysate to avoid excessive clearance. Frequent passes keeps the PD solution less diluted, i.e. higher osmolarity, and allows for greater ultrafiltration, but less efficient solute clearance. Finally, a greater volume of dialysate per pass will increase the amount of ultrafiltration and solute clearance.

Solute clearance is due to the gradient of the solute across the peritoneum. Classically, the sodium concentration of PD solutions is lower than the normal plasma sodium, allowing for a sodium clearance. Factors that influence solute clearance are the gradient of the solute between the plasma and the dialysate solution, volume of the PD solution per pass (the larger the volume, greater the clearance), the length of dwell time per cycle that the dialysate is in contact with the peritoneum (longer dwell, greater the clearance), and finally the peritoneal surface area over which the gradient exchange occurs.

In cases of a fresh peritoneal access, it is not uncommon to place 250–500 units/L if heparin into the PD solution to minimize risk of fibrin formation and clotting of the newly placed catheter. At this dose, the heparin effect is local with no systemic absorption.

PD Prescription

The basic prescription for PD includes the composition of the dialysate and the volume as well as the cycle components which are the fill, dwell, and drain time intervals, and the number of cycles/passes per day. An example of a typical acute PD prescription is to begin with a volume per pass of 10 ml/kg/pass with a time to fill and dwell of approximately 45 min (total time) and a time to drain of 15 min. If greater solute clearance is needed the volume can be increased, but with cautious increases due to risk of peritoneal leakage at the access insertion site if the volume is advanced too rapidly. In some cases of a larger molecular solute (e.g. phosphorous) a longer dwell time will allow for improved clearance. If more ultrafiltration is needed, the glucose concentration can be increased and or the frequency of the passes increased by decreasing the dwell time.

Complications of PD

Complications of PD can include thermal losses, especially in infants where the peritoneum represents a disproportionately large surface area with respect to the child's size. In manual systems, warming the PD solutions by placing a warming blanket around the bag can be helpful. Serum drugs losses are minimal in PD, yet protein and amino acid losses can be significant resulting in a negative nitrogen balance in the child [19]. Peritonitis can occur and is diagnosed by an elevated WBC count and left shift in the dialysate solution. An antibiotic regimen should be chosen after a discussion with Nephrology. Occasionally a unilateral hydrothorax can occur from leakage of the PD fluid into the pleural space [20]. Other complications include obstruction of dialysis catheter by omental blockage or by bowel constipation. Hypoxemia may occur in patients with significant lung disease from an increase in intra-abdominal pressure affecting the FRC.

CRRT

CRRT is replacing PD in many centers due to the growing experience and technology for this mode of renal support with improved control of solute clearance and ultrafiltration (Table 18.5). CRRT is capable of supporting a patient 1.5 kg or 200 kg, and as a result, CRRT is becoming the preferred method of RST (Table 18.6). Over the past 30 years, the knowledge and technology behind continuous renal replacement therapy (CRRT) has improved including anticoagulation and acid-base balance, and greater control over fluid

Table 18.5 Advantages and disadvantages of CRRT

Advantages	Disadvantages
Hemodynamic stability	Need for intravascular access
Slow fluid & solute removal	Need for anticoagulation but citrate avoids patient anticoagulation
Greater solute clearance (Kt/V)	Need for patient immobilization less concern with an IJ line
Runs continuously	Nutritional clearance
ICU nurses trouble-shoot the machines	Higher cost

Table 18.6 Indications for CRRT

Acute metabolic acidosis (A)
Electrolyte abnormalities (E)
Hyperkalemia
Hypernatremia
Hypo/hypercalcemia
Hypo/hyperphosphatemia
Intoxications (I)
Low molecular weight, not protein-bound
Gentamicin
Lithium
Ethylene glycol
Methanol
Ethanol
Salicylates
Acetaminophen
High molecular weight, protein-bound
Vancomycin
Phenobarbital
Carbamazepine
Theophylline
Fluid overload (O)
Pulmonary edema unresponsive to diuretics
Oliguria
Anuria
Uremia (U)
Uremic sequelae with fluid overload
Pericarditis
Encephalopathy
Myopathy
Neuropathy
Miscellaneous (M)
Coagulopathy, massive transfusion and ARF
Uncontrolled hyperthermia > 39.5 °C
Inborn errors of metabolism
Urea cycle defects
Branched chain amino acidurias
Lactic acidosis
Tumor lysis syndrome
Hyperosmolality

removal and metabolic/solute balance. For this reason it is frequently used in the hemodynamically unstable child, and in sepsis or MODS.

Modes

The terminology of the different forms of CRRT include AV (arterial to venous) or VV (venous to venous) blood flow circuits, minimal use of AV forms are used today with the development of the pump systems:

1. SCUF (Slow Continuous Ultrafiltration) – CRRT is used to remove water without using dialysate or replacement fluid. This can be done through arterio-venous or veno-venous systems.
2. CAVH (Continuous Arterial –Venous Hemofiltration) system is utilizing the patient's own mean arterial pressure from an arterial access to drive the blood through the filter and the solute clearance is by convection with replacement fluid given to maintain normal plasma electrolytes. CAVH is a historical perspective and is a rarely used modality in the care of children
3. CVVH (Continuous Veno-Venous Hemofiltration) is a similar system but the catheter access is venous both from and back to the patient with a pump assisting flow through the hemofilter, again with convective clearance utilizing replacement fluid.
4. CVVHD (Continuous Veno-Venous Hemodialysis) uses dialysate fluid pumped through the hemofilter in a counter current direction from the blood flow and no replacement fluid is used. The access is venous, again with pump assistance through the hemofilter and a venous return.
5. CVVHDF (Continuous Veno-Venous HemoDiafiltration) is a combination system using both counter-current dialysate and replacement fluid in a pump assisted veno-venous access.

In order to utilize CRRT effectively, one must understand the concepts of diffusion, convection, and ultrafiltration [21]. Diffusion is the transfer of solute across a semi-permeable membrane from an area of high concentration to an area of low concentration. Diffusion movement is proportional to the diffusive coefficient of the solute, the surface area of the interface, the concentration gradient, and the individual membrane characteristics (charge, pore size, membrane composition e.g. polysulfone, acylnitrile, etc) Diffusion is effective at clearing small molecular weight solutes, clearance decreases with increasing molecular weight and protein binding. In contrast, convection is the transfer of solute across a semi-permeable membrane in association with water crossing the membrane. Finally, ultrafiltration is the process by which

plasma water and plasma solutes are separated from whole blood by the application of a transmembrane pressure across a semi-permeable membrane. The set-up of the individual CRRT device defines which of these modalities are utilized (see below).

Several devices are available commercially for CRRT. In most cases of the CRRT setup, blood from the patient enters the arterial side of the circuit and flows forward with the use of a pump to generate the hydrostatic pressure through the CRRT hollow fiber (capillary) hemofilter. Ultrafiltration and convective/diffusive solute exchange occurs in the hemofilter and the venous blood is returned to the patient through the venous vascular access. Dialysate used for diffusive solute clearance enters the hemofilter via a side-port and counter-current to the flow of blood in the filter column. CRRT devices use additional pump-assistance for control of the dialysate flow as well as replacement fluid. Most devices allow replacement of fluid at either the pre- or the post-hemofilter location. During the early development of CRRT therapies, intravenous pumps were used to control the rate of ultrafiltration during the treatment. Work by Jenkins et al. demonstrated the inaccuracy of intravenous (IV) pumps with an error rate up to 30 % and could be associated with complications [22]. Current devices have internal ultrafiltration controls that possess an error rate of only 1–2 % of total ultrafiltration affording more accurate control during CRRT therapy. Hemofilters for CRRT are similar in design to hemodialysis membranes, except that the filters have significantly higher hydraulic permeability. Some CRRT devices permit interchangeability of hemofilters that may have varying size and permeability, whereas other systems require the use of specific hemofilter sets.

Vascular Access

Success of CRRT is dependent on the adequacy of vascular access. Therefore, thought must be given to the selection of site for insertion, as well as size and type of vascular access for each patient who is to begin CRRT. Potential sites for placement of the central venous catheter include the internal jugular vein, the subclavian vein, and the femoral vein. Because of lower risk of vascular stenosis and its large size, the internal jugular site is often preferred. The femoral vein is a relatively large vessel in older children and is also often used as an access in CRRT. However, longer catheters may be necessary for the tip of the catheter to reach the common iliac vessel or the inferior vena cava, and may produce a relative increase in resistance to flow, limiting the rate of blood flow to the hemofilter. Finally, the size of the vascular access should be proportional to the size of the patient. Table 18.7 (Catheter and patient size) is a compilation of recommended sizes and lengths of catheters for use in pediatric patients. Because of the small size of infant blood vessels, an alternative strategy in small infants includes placement of two separate central venous cannulas, one to serve as the arterial source of blood to the CRRT circuit and the second as the venous port for returning blood to the patient. The effect of catheter size or location on CRRT performance in the pediatric population was reviewed by Hackbarth et al. using the PCRRT Registry data [23]. Blood flow rates (BFR) achieved in CRRT are highly dependent on the vascular access. The goal is to have a minimum blood flow of at least 5–7 ml/kg/min. Maximum achievable BFR varies depending upon the CRRT system utilized and can reach blood flow rates equal to those of hemodialysis machines.

Table 18.7 Recommended catheters sizes and sites for CRRT

Patient size	Catheter size & location	Site of insertion
Neonate		
<3–5 kg	Two 5-French single lumen	Femoral and internal jugular vein(s)
	Single 7-French double lumen, 10 cm (Medcomp®)	Internal jugular, femoral veins
	Single 7-French double lumen, 13 cm (Cook®)	Femoral vein
	Two 7-French umbilical vein lines	Umbilical veins
Infants/school-age		
5–20 kg	Single 7-French triple lumen, 16 cm (Arrow®)	Internal jugular, subclavian, or femoral veins
	Single 8-French double lumen, 11–16 cm (Arrow®, Kendall®)	Internal jugular, subclavian, or femoral veins
	Single 9-French double lumen, 12–15 cm (Medcomp®)	Internal jugular, subclavian, or femoral veins
20–30 kg	Single 9-French double lumen, 12–15 cm (Medcomp®)	Internal jugular, subclavian, or femoral veins
	Single 10-French double lumen, 12–19.5 cm Mahurkar®)	Internal jugular, subclavian, or femoral veins
Pediatric		
30–70 kg	Single 11.5-French double lumen, 12–20 cm (Medcomp®, Mahurkar®)	Internal jugular, subclavian, or femoral veins
	Single 11.5- or 12-French triple lumen, 12–20 cm (Medcomp®, Mahurkar®, respectively)	Internal jugular, subclavian, or femoral veins

Medcomp, Harleysville, PA; Cook Critical Care, Bloomington, IN; The Kendall Company, Mansfield, MA

Dialysate Solution

Historically, increased plasma lactate concentrations have been reported in patients undergoing CRRT with lactate-based solutions [24]. In patients with acute hepatic dysfunction reductions in mean arterial blood pressure were noted following the development of lactic acidosis [25]. Lactate based solutions are no longer recommended. Multiple clinical trials comparing bicarbonate-based dialysate or replacement fluids to lactate-based have been performed. Studies by Thomas et al. [26] and Zimmerman et al. [27] comparing lactate to bicarbonate based solutions found improved arterial pH and serum bicarbonate concentrations with both dialysate solutions, and an increase in the serum lactate levels during CRRT with lactate-buffered dialysate solutions. A trend towards improved mean arterial pressures was noted to be greater in patients receiving the bicarbonate-buffered dialysate solutions, but this difference did not reach statistical significance. Others have augmented the data of Thomas and Zimmerman to suggest that bicarbonate based dialysate use in CRRT has distinct clinical advantages over lactate-based solutions [28–30]. Because of the improved acid-base status in critically-ill individuals, bicarbonate-based dialysate and replacement solutions are now recommended as the standard of care for CRRT.

Normocarb® (North America, Dialysis Solutions, Inc. Richmond Hills, Ontario), a bicarbonate-based dialysate solution was first made available commercially for use in CRRT in 2000 [31]. Work done by Bunchman et al. has shown that Normocarb® is a safe alternative as a replacement solution for convective solute clearance [32]. Many companies now market FDA approved solutions that can be used both in convective as well as diffusive system setups. Normocarb has now been replaced by 20 or 30 industry produced solutions and one can easily tailor make to the needs of the child the appropriate bicarbonate based solution.

Anticoagulation

Heparin, a large molecular weight glycosaminoglycan, has long been the mainstay of anticoagulation in CRRT. Typically, the CRRT circuit is primed with one to two liters of normal sterile saline containing 2,500–5,000 units/L of heparin, and then, a pre-filter heparin infusion is begun, usually at 5–10 units/kg/h with a goal activated clotting time (ACT) of 180–220 s (see protocol at www.pcrrt.com web site). ACT and activated partial thromboplastin time (aPTT) are used to monitor the adequacy of the heparinization. Commonly the ACT is performed at the bedside, which decreases the turn-around time from the laboratory and achieves more timely control of anticoagulation. In patients with thrombocytopenia, heparin requirements may be minimal to none, whereas thrombocytosis may require higher rates of infusion of heparin in order to achieve the desired ACT [33]. While the goal of heparin administration is to achieve regional anticoagulation of the extracorporeal circuit, heparin is not removed by the CRRT process itself and leads to systemic heparinization of the patient. Consequently, heparin-associated bleeding has been reported to occur in as many as 50 % of patients receiving CRRT. Therefore, in patients who are at risk for bleeding, heparin anticoagulation should be avoided. Heparin use can also result in heparin-induced thrombocytopenia (HIT) in 1–5 % of patients due to development of anti-platelet factor 4/heparin (PF4/H) antibodies [34].

In 1990, Mehta et al. demonstrated the efficacy of citrate anticoagulation for CRRT circuits (Tables 18.8 and 18.9) [35]. As calcium is necessary for the activation of factors XI, IX, X, and Prothrombin, chelation of free calcium by citrate inhibits the activation of the intrinsic pathway of coagulation, thereby resulting in anticoagulation. By infusing citrate in the pre-filter position, one is able to anticoagulate the CRRT system, *regional anticoagulation*, without concern for systemic anticoagulation of the patient. Intravenous calcium infusion must be provided to the patient in order to correct the hypocalcemia induced within the extracorporeal system by citrate infusion. Citrate has been shown to be cleared by

Table 18.8 Adjustment of citrate infusion by circuit ionized calcium

CRRT Circuit iCa + 2 (mmol/L)	Weight >20 kg	Weight <20 kg
	Action	Action
<0.35	↓ Rate by 10 mL/h	↓ Rate by 5 mL/h
0.35–0.40	No change	No change
0.41–0.50	↑ Rate by 10 mL/h	↑ Rate by 5 mL/h
>0.50	↑ Rate by 20 mL/h	↑ Rate by 10 mL/h

Titrate Citrate (ACD-A®) drips in order to maintain CRRT circuit iCa + 2 between 0.35 and 0.40 mmol/L. Notify Nephrology On-Call Staff if ACD-A® Infusion Rate >200 mL/h

Table 18.9 Adjustment of calcium chloride infusion by patient's peripheral ionized calcium

Patient iCa++ (mmol/L)	Weight >20 kg	Weight <20 kg
	Action	Action
>1.30	↓ Rate by 10 mL/h	↓ Rate by 5 mL/h
1.10–1.30	No change	No change
0.90–1.10	↑ Rate by 10 mL/h	↑ Rate by 5 mL/h
<0.90	↑ Rate by 20 mL/h	↑ Rate by 10 mL/h

For either Heparin/No anticoagulation or with Citrate anticoagulation, titrate $CaCl_2$ drip rate in order to maintain the patient's iCa + 2 between 1.10 and 1.30 mmol/L

CRRT and equal to that of urea clearance with no significant difference between CVVH and CVVHD modes [36].

Bunchman et al. have adopted citrate infusion protocols designed for use in pediatric patients [31, 32]. In this protocol, using ACD-A® solution (Baxter Healthcare, Deerfield, IL) is infused at a pre-filter location through a 3-way stopcock placed between the vascular access and inflow tubing. The ACD-A® infusion (in mL/h) is initiated at 1.5 times the blood flow rate (mL/min) of the CRRT circuit. A calcium chloride (8,000 mg calcium chloride/L of normal sterile saline) infusion is begun through either a third lumen of a triple lumen dialysis catheter or through a different central venous line at 0.4 times the ACD-A® infusion rate in mL/h. The circuit ionized calcium (iCa) is checked post-filter with a target iCa of 0.35–0.50 mmol/L. The systemic ionized calcium is checked through a central line or arterial catheter or a pre-ACD-A® site in the "*arterial limb*" of the CRRT circuit, with a target iCa of 1.1–1.3 mmol/L [21, 22]. The ACD-A® and calcium chloride infusions are titrated per guidelines given in Tables 18.8 and 18.9 (see www.pcrrt.com website for protocols).

Complications of citrate anticoagulation include hypocalcemia, metabolic alkalosis, and citrate excess. Hypocalcemia is avoidable by following titration guidelines for infusion of the calcium chloride. Metabolic alkalosis develops due to hepatic conversion of one mole of citrate to three moles of bicarbonate. In the authors' experience, children treated with ACD-A® citrate anticoagulation are at risk of developing some degree of metabolic alkalosis unless the bicarbonate of the replacement or dialysate solution is 25 meq/l or less (e.g. Normocarb HF 25) then metabolic alkalosis does not occur. Failure to develop a metabolic alkalosis while receiving citrate anticoagulation should lead to search for an underlying metabolic acidosis and a mixed acid-base disorder in the patient. The metabolic alkalosis is treated by decreasing the dialysate flow (in CVVHD mode) by approximately 30 %, and by the initiation of replacement fluid with normal sterile saline at 30 % of the total dialysate rate [31]. Finally, citrate excess may be diagnosed by monitoring the ratio of the serum total-to-ionized calcium [37]. A total-to-ionized calcium ratio of > 2.5 represents citrate excess. While the overall prevalence of citrate excess was 12 % in this single-center experience, it affected 33 % of those patients with ARF as a complicating component of hepatic failure.

Apart from less bleeding complications as compared to heparin use, citrate anticoagulation may also offer increased survival of the CRRT circuit. Monchi et al. in a study comparing citrate to heparin anticoagulation protocols in CRRT found that citrate anticoagulated circuits lasted a median of 70 h, compared to a median of 40 h for heparin anticoagulation [38]. The rate of spontaneous circuit failure was 87 % in the heparin arm and 57 % in the citrate arm. In contrast, a multi-center prospective, non-interventional study, mean circuit life was similar between heparin and citrate anticoagulated systems (42.1 ± 27.1 vs. 44.7 ± 35.9 h, respectively) [39].

Special Circumstances

Cancer and Bone Marrow Transplantation

CRRT has been used to prevent life-threatening electrolyte, fluid overload, or acid-base disturbances in patients with underlying malignancies, or following hematopoietic cell transplantation. In tumor lysis syndrome, the destruction of the large tumor load or white blood cell burden by chemotherapeutic agents results in hyperuricemia, hyperkalemia, and hyperphosphatemia with associated hypocalcemia. CRRT is effectively used to normalize serum uric acid, potassium, and phosphorus levels in children at risk for development of tumor lysis syndrome when beginning chemotherapy [40, 41]. Hyperosmolar disorders due to hypernatremia have been associated with a mortality rate of up to 70 % in pediatric patients [42, 43]. Two recent reports describe the slow correction of hyperosmolality using CRRT and hypertonic dialysate or replacement fluid.

Another significant oncologic population at risk for AKI is the hematopoietic cell transplant recipient. Incidence of AKI in these patients, defined as a doubling of the serum creatinine, is 25–50 % of the population [44]. The ppCRRT recently reported on the outcomes of 44 pediatric patients status-post bone marrow transplantation who required CRRT therapy for a variety of reasons (sepsis in 20 %, respiratory difficulty in 14 %, MODS in 11 %, hepatorenal syndrome in 9 %, vaso-occlusive disease in 6 %, and drug toxicity in 4 %) [17]. Overall patient survival to ICU discharge was 40 %, with a trend towards improved survival from 2003 to 2004 in the ppCRRT registry (36 and 44 %, respectively). In this retrospective cohort study, mean airway pressure at the termination of CRRT was significantly greater (26.06 ± 2.02 vs. 8.44 ± 2.69 mmHg) in the non-survivors than the survivors, though the percent of fluid overload did not discriminate between survivors and non-survivors.

Finally, the role of CRRT in the management of bone marrow transplant recipients has been further examined for its effects on those patients who develop acute respiratory distress syndrome (ARDS). In an uncontrolled, non-randomized case series, DiCarlo et al. initiated CRRT concomitantly with endotracheal intubation and mechanical ventilatory support for ARDS in six pediatric bone marrow transplant recipients, three patients following chemotherapy, and one patient with lymphoma/hemophagocytosis [16]. These authors achieved a very high rate of clearance of 50 mL/min/1.73 m^2 by performing hemofiltration with a replacement solution at 1,800 mL/h and dialysis with a counter-current dialysate solution at 1,800 mL/h. Eighty percent of these patients survived to hospital discharge with

recovery of their native renal function. Early and aggressive use of CRRT to normalize fluid balance and potentially high clearance rates may contribute to an improved survival in those hematopoietic cell transplant recipients who develop acute kidney injury, volume overload or ARDS. Alternative approaches for the use of CRRT in such populations are discussed in more detail in the following chapter.

Intoxications and Poisonings

The ability of an extracorporeal therapy to remove an intoxicant is affected by the volume of distribution of the drug. Generally, drugs with volumes of distribution of <1 L/kg (total body water) are amenable to dialytic removal [45, 46]. Drugs with large volumes of distribution are less likely to be effectively removed by dialysis and are more likely to result in rebound elevations of blood levels following a dialytic therapy. Large molecular weight drugs are more difficult to dialyze than low molecular weight drugs, though high-efficiency dialysis filters can overcome this size barrier to some extent. The degree of protein-binding also has a negative effect upon a drug's ability to be dialyzed. However, if protein-binding sites are fully saturated, free drug may be amenable to dialytic clearance.

Numerous medications have been described as being cleared by CRRT. While a complete list is beyond the scope of this section, some intoxicating medications reported include: vancomycin, lithium, ethylene glycol, procainamide, theophylline, methotrexate, phenytoin, carbamazepine, and valproic acid [46–55]. Use of albumin-dialysis has been reported to aid in the removal of highly protein-bound drugs. Askenazi et al. described the use of albumin-dialysis using CVVHD to treat an acute, severe carbamazepine overdose [55]. These authors found a dramatic decrease in the serum half-life of carbamazepine (from 25–60 h to 7–8 h) using albumin-dialysis CVVHD. Phenytoin and valproic acid removal have been reported to be enhanced with albumin-dialysis compared to standard high-efficiency CVVHD [55, 56]. In most intoxications, hemodialysis (HD) is the first line of RRT therapy that can be coupled with CRRT to prevent toxin rebound (see HD section) [46].

Inborn Errors of Metabolism

CRRT has been used effectively to correct metabolic derangements associated with a variety of inborn errors of metabolism. Children with a suspected or confirmed inborn error of metabolism often require an extracorporeal therapy in order to achieve a rapid correction of their metabolic disturbance. For example, in urea cycle disorders, the accumulation of ammonia is a primary abnormality encountered. In these patients, CRRT modalities used following initial control by rapid hemodialysis, have achieved excellent clearance of ammonia and rapid correction of the hyperammonemic coma [57–62]. The extracorporeal clearance of ammonia with CRRT must always be accompanied by the use of alternative pathway medications to aid in the removal of the accumulating nitrogenous substrate. Branched chain amino acidemias, such as maple syrup urine disease (MSUD), methylmalonic acidemia, propionic acidemia, and isovaleric acidemia, have been successfully treated using CRRT [63]. Similar to urea cycle disorders, CRRT provides for on-going removal of accumulated branched chain amino acids and their ketoacid metabolites, which are responsible for the neurologic sequelae of this class of disorders. Work by us has demonstrated the use of HD first then CRRT to follow as the optimal way to normalize the ammonia in these infants [62].

Multiple Organ Dysfunction Syndrome (MODS)

MODS is defined as a clinical condition characterized by simultaneous failure of two or more organ systems [64]. A report by the Prospective Pediatric CRRT Registry Group (ppCRRT) described 181 of a total 294 pediatric patients who had received CRRT for MODS [65]. In this cohort, sepsis (28.7 %) and cardiovascular shock (16.0 %) were the most common causes of MODS. Overall patient survival from MODS requiring CRRT support was 50.8 %. Mean percent fluid overload at the time of ICU admission and the PRISM2 score at the time of initiation of CRRT had a significant impact on patient survival. Survival rates were better for patients having <20 % fluid overload (survival 61 %) at the time of initiation of CRRT than those with >20 % fluid overload (survival 32 %). These data support the concepts that goal-directed fluid therapy and early initiation of CRRT may be more effective in treatment of MODS [66].

Plasmapheresis

The combination of plasmapheresis and CRRT may be occasionally performed in the management of immune-mediated diseases complicated by AKI. In most instances, however, the CRRT treatment is discontinued during the plasmapheresis and resumed after its completion. However, this may decrease fluid ultrafiltration and solute clearance due to the discontinuation of renal replacement therapy. Additionally, the citrate infusion needed for plasmapheresis anticoagulation may result in electrolyte disturbances (e.g., hypocalcemia) and poses a risk for hemodynamic instability [67]. Eding et al. described the use of concurrent plasmapheresis and CRRT [63]. In this instance, the authors placed a 3-way stopcock at both the arterial and venous sides of the double-lumen dialysis catheter. The 3-way stopcocks allowed for parallel flow of the arterial blood through both the centrifugation plasmapheresis circuit and the CRRT circuit and parallel venous blood flow return to the patient. Alternately, in an in-series configuration, a plasmapheresis circuit withdraws the patient's blood from the arterial side of the double-lumen catheter and the venous return line of the plasmapheresis circuit is connected in-series to the arterial

line of the CRRT circuit. The blood from the venous return line of the CRRT circuit is eventually returned to the patient through the venous return side of the double-lumen dialysis catheter. Using this technique, citrate anticoagulation of the plasmapheresis circuit can then undergo high dialytic clearance and thus minimize the risks of hypocalcemia and associated hemodynamic instability in the patient.

Experience using concurrent centrifugation plasmapheresis and CRRT is limited. Ponkivar et al. have reported its use in 21 neonates and infants [68]. These authors found that recovery of renal function occurred in 47.6 % of patients, with an overall patient survival of 42.9 %. Complications of concurrent therapy include hemofilter thrombosis, catheter malfunction, hypotension and bradycardia, and pulmonary edema.

Neonatal CRRT and Outcome

AKI in newborns include pre-renal failure, due to inadequate renal perfusion /neonatal asphyxia, intrinsic renal failure from intrarenal pathology, and post-renal failure, due to obstruction to the flow of urine. The use of CRRT in the neonate requires close attention to the potential for adverse events. Due to their small intravascular blood volume, careful attention must be paid to the volume status and the percent of intravascular blood volume to be contained in the extracorporeal circuit. The target blood flow rate in the neonatal and young infants is 5–10 mL/kg/min. However, this may lead to a slow flow of blood through the extracorporeal CRRT circuit and result in frequent thrombosis of the CRRT filter. Consequently, there may be an increased need of frequent blood priming associated with frequent changing of the CRRT circuit. In order to avoid such problems, some programs have a policy of running the CRRT blood flow at a minimum speed of 50 mL/min in neonates, irrespective of body weight. Calculated extracorporeal blood volume of >10 % of the patient's estimated intravascular blood volume in neonates and infants requires priming the CRRT circuit with whole blood to prevent volume depletion and hypotension. Circuit priming with normal saline or 5 % albumin should be avoided to reduce the risk of hemodilution of the patient's hematocrit.

An overall survival rate in neonates and infants of 38 % (25 % in those children weighing less than 3 kg and 41 % in those weighing between 3 and 10 kg) has been reported [69]. Mean blood flow rate in this series was 9.5 ± 4.2 mL/kg/min with a mean duration of CRRT of 7.6 ± 8.6 days. Survivors weighing more than 3 kg required fewer vasopressor medications than non-survivors, and there was no difference in outcome based upon the use of convective or diffusive clearance [69]. The most common indications for CRRT in this study were: combined volume overload and electrolyte imbalance (54 %), volume overload alone (18 %), metabolic disturbance (14 %), and renal failure (9 %). The clinical conditions in these patients were congenital heart disease (16.5 %), metabolic disorder (16.5 %), multiple organ dysfunction syndrome (15.3 %), sepsis (14.1 %), and liver failure (10.6 %).

ECMO and CRRT

Use of CRRT in patients on ECMO entails both an understanding of the ECMO circuit and the basic principles of CRRT. The merging of CRRT and ECMO requires knowledge of the effect of sharing total circuit blood flow between the membrane oxygenator and the hemofilter. CRRT may be accomplished by use of either a dedicated CRRT machine or the insertion of a post-pump, pre-oxygenator hemofilter. If utilizing a simple hemofilter in-line then the ECMO pump controls flow through the hemofilter and oxygenator. Due to a split of flow between these two devices, to maintain the same patient support, i.e. SvO_2, an upward adjustment of the ECMO circuit flow is required. The difference in ECMO blood flow necessary to maintain the mixed venous oxygen saturation (SvO_2) at the same level prior to and immediately after diverting flow to the hemofilter represent a bedside approximation of the hemofilter flow rate.

The above setup has the disadvantage of poor ultrafiltration control, requiring some form of a resistor, be it a variable clamp or an IV pump to provide some degree of rate control. Use of a CRRT machine in line alleviates this problem, due to its internal control of ultrafiltration, and provides the ability to set independently the blood flow through the hemofilter. Placement of the CRRT system within the ECMO circuit has been done at multiple sites in the past. With the current use of centrifugal ECMO pumps, close attention to prevent risk of air entry from any potential connection within the CRRT system can be done by locating the CRRT access sites distal to the centrifugal pump. Additional anticoagulation for CRRT when on ECMO is not required due to adequate anticoagulation already present from the ECMO therapy.

Outcomes of CRRT on ECMO are more dependent on the underlying disorders requiring treatment with ECMO rather than AKI requiring CRRT. Concomitant CRRT use does not increase the risk of developing anuria and chronic renal failure. Development of chronic renal failure is rare with concurrent ECMO and CRRT. Paden evaluated the outcomes of 154 ECMO/CRRT patients cared for over 10 year at a referral pediatric medical center. Renal recovery occurred in 96 % of surviving patients before discharge. In the absence of primary renal disease, chronic renal failure did not occur after concurrent use of CRRT with ECMO [70]. Another retrospective study of 35 pediatric patients less than 18 years of age receiving CRRT with ECMO therapy found an overall survival of 43 % with 93 % of survivors recovering of their renal function [71]. In a recent study, neonatal survival was

72.6 %, with nonsurvivors experiencing more AKI and therefore received more RRT than survivors. Pediatric survival was 58.4 % and pediatric nonsurvivors similarly experienced more AKI and RRT than survivors [65].

CRRT Complications

Serious metabolic acidosis and hypotension have been reported with priming of the CRRT circuits with stored unbuffered blood [72, 73]. This occurs from a specific bioincompatibility related to use of AN69 hemofilters when stored acidemic blood comes in contact with the membrane with subsequent release of bradykinin. To prevent this complication a by-pass maneuver can be done, where-in the patient's blood is discarded after its first pass through the hemofilter, while simultaneously providing a blood transfusion of packed red blood cells diluted with normal saline in a ratio of 1:1. The procedure requires placement of two 3-way stopcocks on the venous return line of the extracorporeal circuit [72]. The patient's blood containing any bradykinin after contact with the hemofilter membrane is drained into a waste bag connected to the proximal 3-way stopcock. Blood is then transfused to the patient via the distal 3-way stopcock. During the procedure, the CRRT blood pump is set to a flow rate of 10 mL/min, and the packed red blood cell solution is infused at 600–900 mL/h (10–15 mL/min). Buffering of the packed red blood cells with sodium bicarbonate to normalize the pH and the addition of calcium chloride to neutralize the citrate effect will minimize bradykinin release.

Pre-dialysis of the blood primed CRRT circuit for use in neonates has been reported to result in physiologic correction of the metabolic acidosis and hyperkalemia commonly seen in banked blood. The procedure is instituted by recirculation and zero-balance ultrafiltration hemodialysis of the blood prime, prior to connecting the patient to CRRT circuit [74]. Z-BUF, another technique of pre-dialysis of the priming blood, uses recirculation of blood after buffering it with 5 % albumin at a ratio of 60/40 [75]. Dialysate flow rate is recommended at 2 L/h and the procedure is conducted for 30 min in the Z-BUF priming technique. This technique normalizes the blood pH and serum electrolytes, while having virtually no effect on the TNF-α, IL-1β, and IL-6 levels pre- and post-Z-BUF, and achieves the desired reduction of bradykinin in the blood prime.

Technical and Equipment Malfunction

Complications associated with the vascular catheter itself, kinking, partial or complete obstruction or displacement can lead to malfunction or cessation of the CRRT. A device (or machine) can experience failure of the integrity of the tubing set, air may enter into the blood tubing and result air embolism. Newer CRRT devices are equipped with air detectors that clamp the blood return line to the patient if air is detected within the tubing set. Errors of ultrafiltration that were once commonplace with early devices are now uncommon with modern equipment. Finally, the efficiency of clearance of the hemofilter may deteriorate due to the accumulation of blood proteins and blood cells along the intravascular side of the capillary/hollow fiber filters [76].

Bleeding

Anticoagulation associated bleeding is a well known complication seen in CRRT. The source of bleeding is often at the catheter exit site, but can also be internal at the vascular puncture site. If using systemic heparinization, internal bleeding of the gastrointestinal tract and other vital organs can occur.

Infection

The risk of infection associated with central venous access is well identified in the literature and a similar risk is present for dialysis catheters. A high index of suspicion should be present for any unexplained leukocytosis or if any elevation of temperature should occur while on CRRT, due to a natural cooling by the extracorporeal circuit often masking any temperature rise. Appropriate blood cultures from the catheter and CRRT sites should be sent.

Hypotension

Despite the slow nature of CRRT, hypotension often results due to excessive ultrafiltration of the intravascular space. Inattentiveness to ionized calcium levels at the initiation of CRRT in infants or children can contribute to hypotension that is easily correctable by the administration of calcium chloride. Likewise when beginning CRRT the location of any vasopressor near the dialysis catheter will be cleared rapidly and require additional adjustments until the new steady state is reached. Finally, as previously mentioned, clearance of bradykinin from the blood priming should be done to prevent associate hypotension at initiation of CRRT.

Electrolyte Disturbances

Hypokalemia and hypophosphatemia can occur if dialysate or replacement fluid has not been appropriately reconstituted. This is particularly important when using CRRT for intoxications or inborn errors of metabolism. Often these children do not have AKI and thus a potassium restriction and phosphorus restriction during CRRT may result in significant hypokalemia and/or hypophosphatemia. Also, the use of dextrose-containing, citrate anticoagulation will deliver increased amounts of glucose, thereby increasing the risk for the hyperglycemia in the patient. Similarly, hyperglycemia can develop if peritoneal dialysis solutions used as dialysate in CRRT [77, 78].

Table 18.10 Goals for nutritional support in AKI

To prevent protein-energy wasting
To preserve lean body mass and nutritional status
To avoid further metabolic derangements
To avoid complications
To improve wound healing
To support immune function
To minimize inflammation
To improved antioxidant activity and endothelial function
To reduce mortality

(Based on data from Fouque et al. [87])

Hypothermia

Extracorporeal circuits can have a cooling effect upon the patient, and cooling towards room temperature is common. This is especially likely if the CRRT device lacks a blood warming capability. As noted above, extracorporeal cooling of blood may mask development of clinical fever in the critically sick patient.

Nutritional Losses

Malnutrition often accompanies AKI as a result of hypermetabolism and catabolism (Table 18.10). An increased mortality and morbidity, as well as an increased length of hospital stay, as a result of malnutrition has been well established. The term "Protein-Energy Wasting" (PEW) describes the negative metabolic consequences of the acute loss of kidney function on nutritional status, i.e., body protein content wasting and/or depletion of fuel reserves [79]. While on CRRT, patients require as a minimum >1.5 g/kg/day of protein. Maxvold et al. compared amino acid losses and nitrogen balance in critically ill pediatric patients requiring CVVH and CVVHD who were receiving similar dialysate or replacement fluid rates and total parenteral nutrition [80]. They noted that amino acid loss was slightly greater with CVVH than with CVVHD and that these losses accounted for approximately 12 and 11 %, respectively, of the total daily protein intake. Micronutrients also are removed by both diffusive and convective CRRT. A negative net balance of selenium, copper, and thiamine while having a slightly positive net balance of zinc has been shown to occur with hemodialfiltration [81]. Trace element supplementation with selenium, and other micronutrients that are water soluble, may be necessary in situations of prolonged CRRT.

Medication Errors

Adverse drug events and medication errors are usually due to errors in dialysis fluid or anticoagulation. A study by Barletta based on a survey sent to CRRT clinicians (prior to the use of standardized solutions) reported 50 % errors being harmful, either a prolonged hospital stay, near death event or death [82].

CRRT Survival

Large scale survival reports with the use of CRRT in the modern era of pediatric critical care remain limited. In 2001, Goldstein et al. at Texas Children's Hospital retrospectively reported on 21 pediatric patients receiving CVVH therapy, taking into account the patient's severity of illness by using the PRISM2 score [83]. These authors identified the percentage of fluid overload as a significant predictor of mortality after controlling for severity of illness. Shortly after this report, the ppCRRT was established in order to collect multicenter data on CRRT in pediatric patients at 12 pediatric institutions across the United States. In their initial report of 273 pediatric patients, the ppCRRT found an overall survival rate of 58 %, with patients having hepatic failure or a hepatic transplant having the lowest survival rate (37 %) and those with drug intoxication having the highest survival rate (100 %) [84].

Intermittent Hemodialysis

Hemodialysis (HD) is less often used in the PICU situation but has a role in the areas of AKI, in born error or metabolism and in intoxications [85]. HD can be performed for solute clearance only (e.g. urea clearance), or ultrafiltration only or a combination of both. As compared to CRRT (CVVH) or PD, the solute clearance on HD is significantly greater due to a high volume of dialysate turn over (30–50 l/h). HD treatment is often performed within a 2–4 h period of time. Often the goal of fluid removal is achieved easily in that period of time. Due to this need to large ultrafiltration to be achieved in a relatively short period of time, HD is less hemodynamically stable during ultrafiltration removal as compared to CVVH or PD.

Hemodialysis Equipment

Vascular access of acute HD is similar to that of CVVH and has been discussed elsewhere. The machines used in HD have the flexibility of variable blood flow rate and dialysate flow rate. Further, the machines generate their own dialysate utilizing a reverse osmosis (RO) system that blends the RO water with an "acid" and a "base" solution that results in an isotonic physiologic ultrapure dialysate solution. As compared to CVVH and PD the cost of dialysate for HD is significantly cheaper. The machines have the capability of modeling up or down the sodium or bicarbonate if needed in some clinical situations. The machines have the ability to turn up or down the temperature of the dialysate to add to cooling or warming of the child. The extracorporeal volume of the HD circuit is made of up the blood lines and the hemodialysis filter. As a rule this total extracorporeal volume should be less than 10 % of the child's intravascular volume. In some cases, blood priming may be needed to minimize

hemodynamic instability at the initiation of HD. Beware that blood bank blood is acidotic (pH of 6.2), hypocalcemic (ionized calcium of 0.04 mmol/l) and hyperkalemic (as great as 40 meq/bag of blood), therefore this needs to be considered at the time of blood priming. Data to date does not identify the "best membrane" used in AKI therapies.

Anticoagulation

Classically anticoagulation in HD is with heparin with the risk of heparinization of the child during HD therapy. Often, anticoagulation free HD treatments can be performed by using high blood flow rates and short duration treatments.

Hemodialysis Use in Clinical Situations

Due to the large volume of dialysate use per hour HD is superior to other forms of RRT when rapid solute clearance is needed. In situations of high potassium, in born error of metabolism and in intoxications, HD is the first line RRT. In situations of a high osmolar state (elevated BUN, elevated sodium, elevated glucose) HD is the least preferred due to the risk of "dialysis disequilibrium" which is a term that describes seizures due to rapid osmolar shifts in a short period of time primarily noted in times of BUNs greater the 100 mg/dl [86]. Inborn error of metabolism and intoxications are similar in their clinical requirements that RRT is used in the face of no AKI but the need for rapid removal of toxins. In these settings it is imperative that the dialysis solution be normal physiologically in potassium and phosphorous to avoid rapid clearance that could result in cardiac or respiratory compromise. In both of these clinical situations HD is preferred as the first therapy of choice due to the rapid clearance of solute. In situations of in born error of metabolism or in certain "two compartment " drug intoxications (e.g. vancomycin) the serial use of HD followed by CVVH or CVVHD will allow for the initial high clearance then the clearance of the ammonia or intoxicant that will rebound until the clinical situation is resolved.

Outcome in Hemodialysis

Little HD pediatric specific literature exists for the treatment of AKI or inborn error of metabolism but more in intoxications. This form of RRT remains one more form of RRT needed in the critical care arena for the care of complicated patients.

Complications of Hemodialysis

As mentioned early, as compared to CVVH or PD, thermic control is easier to achieve in HD. Excessive solute clearance can be a detriment (e.g. in elevated urea states) but is often seen as a positive in HD. Excessive ultrafiltration can occur in HD, but in the hands of skilled clinician, the ultrafiltration rate is easily controllable avoiding this complication. Mediation clearance will be more efficient in HD that will result in a greater attention to medication dosing when HD is utilized.

Conclusions

Renal replacement therapy has evolved over the past 30 years as an efficient and safe treatment for AKI, intoxications and for inborn error of metabolism in pediatric patients. Whether it is CRRT, PD or HD the choice of the RRT is best decided upon by the local skills and experience of the program.

The mainstay in the PICU has come front and center to be CRRT. For CRRT, over the last decade advances in new dialysate and replacement fluid solutions are available using bicarbonate as the buffer minimizes cardiovascular instability. The nutritional effects of CRRT are numerous, and include the effects of the dialysate or replacement fluids' dextrose content, the dextrose content of citrate anticoagulation, and the diffusive and/or convective clearance of amino acids and trace minerals. Data would suggest that targeting a lower limit of carbohydrate intake while maximizing amino acids to around >2 g/kg/day may improve glycemic control and improve outcome. The effect of CRRT clearance of trace elements is unclear at this time, but protracted CRRT treatments may result in clinically significant disorders. Anticoagulation for maintenance of the CRRT circuit is critical to providing adequate fluid and electrolyte therapy in the pediatric patient with AKI, and citrate anticoagulation appears to have multiple benefits over heparin anticoagulation. Vascular access is critical for proper functioning of a CRRT circuit, and ideally should be the largest catheter possible with a targeted blood flow rates as high as 400 mL/min/1.73 m2. Finally, CRRT is a useful therapy in many special situations, including hyperosmolality, intoxications; hematopoietic cells transplantation, tumor lysis syndrome prevention, extracorporeal hepatic support, and can be coupled with plasmapheresis.

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Part IV

The Hematologic System in Critical Illness and Injury

Jacques Lacroix

Transfusion Medicine

19

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Abstract

Anemia is common in pediatric intensive care units (PICU). Severe anemia can significantly increase the risk of death. Only a red blood cell (RBC) transfusion can rapidly treat a severe anemia. In stable PICU patients, RBC transfusion is probably not required if the hemoglobin concentration is above 7 g/dL, unless the patient has a cyanotic cardiac condition. The trigger or goal that should be used to direct RBC transfusion therapy in unstable critically ill children remains undetermined, although some data suggest that RBC transfusion may help in the early treatment of unstable patients with sepsis if their $ScvO_2$ is below 70 % after mechanical ventilation, fluid challenge, and inotropes/vasopressors perfusions have been initiated. Plasma and platelets are used to prevent or to treat hemorrhage attributable to a coagulopathy, thrombocytopenia or platelet dysfunction. The risks and benefits of plasma and platelet concentrates in PICU patients are discussed. There is almost no evidence at the present time that might permit a strong recommendation with regard to the use of plasma and platelets in PICU. Good knowledge of transfusion reactions is required in order to appropriately estimate the cost/benefit ratio of transfusion. Nowadays, non-infectious serious hazards of transfusion (NISHOT) are more frequent and more challenging for pediatric intensivists than transfusion-transmitted infectious diseases. The decision to prescribe a transfusion must be tailored to individual needs and repeated clinical evaluation of each critically ill child.

Keywords

Anemia • Erythrocyte • Plasma • Platelets • Transfusion

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Transfusion of Red Blood Cells

Anemia in the PICU

Anemia—defined as a hemoglobin (Hb) concentration below the "normal" range for age—has been reported to occur up to 74 % of critically ill children with a pediatric intensive care unit (PICU) stay longer than 2 days. Indeed, anemia is already present at the time of PICU admission in 33 % of children, and an additional 41 % develop anemia during their PICU stay [1]. Patients who become anemic gradually over a long period of time and who are chronically anemic are more tolerant of their anemic state than those who develop anemia acutely. The main symptoms and signs of acute anemia are

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not specific and include pallor, tachycardia, lethargy and weakness. An increased blood lactate level and elevated oxygen (O_2) extraction ratio (>40 %) can also be observed in severe cases [2].

The etiology of anemia may be attributable to: (1) blood loss, (2) decreased bone marrow production, which may in part be secondary to a disturbed bone marrow response to erythropoietin [3], (3) decreased RBC survival [4], and (4) anemia due to underlying diseases such as cancer and congenital hemoglobinopathies. However, blood loss is the most important cause of anemia acquired in the PICU. Blood draws account for 70 % of all blood loss (0.32 mL/kg/day in PICU), and procedures and hemorrhage are other causes of blood loss [1].

In healthy animals undergoing acute hemodilution, evidence of heart dysfunction appears only once the Hb concentration drops below 3.3–4 g/dL [5, 6]. However, animals with 50–80 % coronary artery stenosis can show evidence of ischemic insult to the heart with a Hb concentration as high as 7–10 g/dL [7]. In human beings, Carson et al. [8] studied the outcome after surgery in 1,958 patients who declined transfusion for religious reasons; the odds ratio for death started to increase in those with prior ischemic heart disease when their pre-operative Hb concentration decreased below 10 g/dL. Carson et al. [9] also studied the outcome after surgery in 300 patients without prior ischemic heart disease who declined transfusion for religious reasons. The odds ratio for death started to increase when the post-operative Hb concentration dropped below 4 g/dL. There are some data describing the relationship between anemia in severely ill children and mortality. A prospective cohort study in Kenya of 1,269 hospitalized children with malaria showed that RBC transfusions decreased death rate if anemia was severe (Hb level < 4 g/dL) or if some dyspnea was associated with a Hb level < 5 g/dL [10]. In another study conducted in Kenya, Lackritz et al. [11] followed 2,433 hospitalized children younger than 12 years with chronic or acute anemia among which 20 % received RBC transfusions. Some benefit was observed when a RBC transfusion was given to patients with a Hb level below 4.7 g/dL, and if there were signs and symptoms of respiratory disease. Given these results, guidelines were written suggesting that a RBC transfusion should be given to all children with a Hb level < 5 g/dL hospitalized in this Kenyan hospital. Subsequently, Lackritz et al. [12] undertook a prospective study in 1,223 consecutively hospitalized children. The Hb level was <5 g/dL in 303 patients. Of these patients, 116 (38 %) did not receive a transfusion, mostly because packed RBC units were not available. Each of these 303 children with severe anemia was paired with the next child hospitalized with a Hb level > 5 g/dL; none of the latter children with a Hb level > 5 g/dL received a RBC transfusion. Overall mortality was 30 % in the 303 children with a Hb level < 5 g/dL and 19.5 % in those with a Hb level > 5 g/dL ($p < 0.01$). Among the 303 patients with a Hb < 5 g/dL, mortality in transfused versus non transfused children was respectively 21.4 % and 41.4 % ($p < 0.001$). These studies suggest that there may be some benefit in keeping the Hb concentration of hospitalized children above 5 g/dL, though a higher threshold Hb concentration may be required in critically ill children.

Severe anemia, as described in the studies above, results in tissue hypoxia, which is likely the main mechanism leading to increased morbidity and mortality in these patients. Of note, tissue hypoxia may be due not only to a low Hb concentration (anemic hypoxia), but also to abnormal blood flow (stagnant hypoxia), decreased Hb saturation (hypoxic hypoxia) or to mitochondrial dysfunction (cytotoxic or cytopathic hypoxia) [13]. Stagnant hypoxia can be caused by dysregulated blood flow in the central circulation (cardiac output), the regional circulation (distribution of blood flow between organs), or the microcirculation (distribution of blood flow within organs) [14–16].

Adaptive Mechanisms to Acute Anemia in Critically Ill Patients

While the risks of blood transfusion have been extensively characterized, the risks of anemia are poorly understood, especially in critically ill patients. Shander [7] described the consequences of anemia in the critically ill patient and explained the adaptive mechanisms involved. Anemia significantly decreases the O_2 carrying capacity of blood. In the normal host, the amount of O_2 delivered (DO_2) to tissue exceeds resting O_2 requirements by a factor of two to fourfold [13, 17]. When the Hb concentration falls below 10 g/dL, several adaptive processes ensure a considerable physiologic reserve that maintains DO_2 in spite of major adversity. These adaptive processes include: (1) increased extraction of available O_2, (2) increased cardiac output (elevated heart rate and stroke volume as well as decreased peripheral vascular resistance and blood viscosity) [18], (3) redistribution of blood flow from non-vital organs to the heart and brain, at the expense of the splanchnic vascular bed, and (4) a right shift of the oxyhemoglobin-dissociation curve (leading to decreased O_2 affinity and therefore increased O_2 release) [13, 14, 18, 19]. All these mechanisms facilitate O_2 unloading to tissues. Severe anemia triggers additional adaptive mechanisms, which have limited compensation, such as an increase in cellular O_2 extraction. Indeed, this explains why there exists a critical threshold of DO_2 below which O_2 consumption (VO_2) begins to fall and selective vasoconstriction is observed, which favors blood flow to critical organs, namely the brain and heart, and deprives other organs, in particular those irrigated by the splanchnic vascular bed [13].

Impairment of Adaptive Mechanisms to Anemia

A number of diseases and host characteristics may impair adaptive mechanisms to anemia in critically ill patients. Cardiac compensation is limited when anemia is associated with hypovolemia or cardiac dysfunction. Disease processes such as sepsis and multiple organ dysfunction syndrome (MODS) affect a number of adaptive mechanisms. In sepsis and MODS there is often a high metabolic rate and increased VO_2 that substantially limit the available O_2 reserve and may result in a situation where demand is not met if an additional metabolic stress occurs. In addition, these patients may also have impaired left ventricular function [20, 21], and abnormal regulation of vascular tone [22, 23], restricting DO_2 and redistribution of blood flow, respectively. Moreover, sepsis and MODS may compound the energy crisis observed in many critically ill patients by causing mitochondrial oxidative dysfunction, decreasing tissue O_2 extraction as well as its utilization [14, 18]. Finally, decreased RBC deformability, which can alter microcirculatory function, is also observed with sepsis and MODS.

A number of host characteristics specific to children and infants may also impair their adaptive mechanisms. The energy requirements of young infants are much higher than those of adults [24]. This difference is mostly attributable to growth and implies a greater need for substrates including O_2 and nutrients. In addition to increased metabolic demands, there are also major differences in O_2 delivery between adults and children in the first years of life. Fetal Hb represents a greater proportion of total Hb during the first few months of life, which can cause a left shift of the Hb saturation curve and thus affect O_2 delivery to tissues. Physiologic decrease in Hb concentration is normal in newborns and partially explains the great variability in normal Hb values seen during the first weeks of life. During these weeks, myocardial compliance is decreased, which causes significant impairment in diastolic filling that can limit an increase in stroke volume when needed to maintain O_2 delivery. Moreover, the resting heart rate is relatively elevated in newborns (140 ± 20/min) and in infants (130 ± 20/min), which also limits their ability to increase cardiac output via increasing their heart rate. On the other hand, the health status of children prior to PICU entry is usually better than that of adults, which might explain the comparatively low mortality rates seen in PICUs (about 4 %) [25, 26].

Some cardiovascular consequences of anemia are specific to children [27]. Congenital heart disease is frequently observed in the PICUs. The resulting presentation of heart failure and/or postoperative repair can directly impair DO_2. Children with cyanotic congenital heart disease can have Hb concentrations as high as 20 g/dL, a rare occurrence in adults. Inversely, certain pathologies frequently seen in adult patients, such as coronary artery stenosis caused by atherosclerosis, are very rare in PICU.

Long-Term Adaptive Mechanisms to Anemia

In the healthy human, anemia activates erythropoiesis almost immediately, but a clinically significant increase in the blood Hb level occurs only after a few days. In the critically ill patient, this process may be delayed and the response to usual stimuli may be blunted or absent. Strong stimuli for erythropoietin production, such as tissue hypoxia, acute blood loss and anemia are often present in the critically ill and would be expected to increase erythropoietin production. Yet, paradoxically, erythropoietin plasma levels are often lower than expected in these patients. Several factors may be involved [28]. Certain inflammatory mediators may decrease and even block the production of erythropoietin. More particularly, in the systemic inflammatory response syndrome (SIRS), which is present in >80 % of PICU patients [29], high interleukin-1 (IL-1) and tumor necrosis factor (TNF) levels can substantially attenuate erythropoietin production [7, 30]. Moreover, the response to erythropoietin is not optimal in patients with systemic inflammation, which could explain why the response to erythropoietin is slow and blunted in critically ill patients [31].

Iron metabolism is also affected in critically ill children. In patients without iron deficiency, iron concentration in blood is low despite increased iron storage, and there is less free iron available for erythropoiesis [32]. In addition, a significant proportion of critically ill adults present some iron (9 %), B_{12} (2 %) and/or folate deficiency (2 %) [7] These observations explain (or at least partially explain) why anemia persists in critically ill patients, why their erythropoietin levels are lower than expected, and why their response to erythropoietin is not optimal. As a result, RBC transfusion is frequently the only effective way to rapidly increase the Hb level in critically ill patients whose response to usual medical therapies (iron supplements, recombinant erythropoietin, etc.) is suboptimal.

Management of Anemia in the PICU

Each year, ten million RBC units are transfused in the United States of America [33] and 2.18 million units in the United Kingdom (www.shotuk.org). Forty-nine percent of children in a PICU for more than 2 days receive a transfusion during their PICU stay [1]. It is clear that RBCs are useful: they contain Hb, which transports O_2 to cells, and cells require O_2 to survive. Thus, it might seem reasonable to keep the blood Hb level and hematocrit of critically ill patients in the normal range. However, the safety of RBC transfusion has been increasingly questioned over the last few years, mostly because there is increased awareness among lay people and physicians regarding the risk of contracting infections such as HIV and hepatitis, and to some extent other potential

transfusion-related complications such as bacterial contamination and transfusion-related acute lung injury (TRALI). It is less well recognized that transfusion of packed RBC units may modulate the inflammatory process in recipients (transfusion-related immuno-modulation or TRIM), which may increase the risk of developing nosocomial infections, sepsis and MODS [34]. Thus, it is important to ask what the risk/benefit and the cost/benefit ratios of RBC transfusion are in critically ill children.

Effects of Transfused RBC on Oxygen Delivery

Few studies have examined the role of Hb and RBC transfusions as a means of documenting and potentially alleviating O_2 supply dependence [27]. There is no doubt that RBC transfusion increases global DO_2, but does it increase DO_2 to specific organs and does it improve VO_2? Global DO_2 can be normal in the presence of significant regional ischemia. A number of studies describe the effect of transfused RBCs on the distribution of systemic blood flow to specific organs [14]. For example, Marik and Sibbald [35] showed that RBC transfusion may cause gut ischemia among septic adults, even if it increases global DO_2. RBC transfusion can disturb DO_2 in the microcirculation (cellular DO_2) by many mechanisms, such as increased blood viscosity, lower O_2 release, and shunted microcirculatory flow.

It is generally recommended that the hematocrit level be maintained below 0.45 because blood viscosity increases significantly over this threshold [36]. Messmer et al. [37] have suggested that microcirculatory stasis and impaired DO_2 to tissues may be directly related to changes in Hb concentration. They theorize that normovolemic hemodilution improves microcirculatory flow and DO_2. Other authors have suggested that hematocrit has limited effects on microcirculatory flow [38].

The microcirculatory effects of transfused RBCs may also be attributable to release of inflammatory mediators (cytokines, microparticles, lipids, etc.) in the supernatant of stored RBCs and to increased activation of white blood cells in packed RBCs [39, 40]. These mediators may initiate or enhance an inflammatory reaction, which may result in MODS [41]. They can also mediate vasoconstriction or thrombosis of small vessels, causing local ischemia [42–44]. Leukocyte reduction should decrease the effects attributable to white blood cells (e.g. cytokine release) and platelet-related microparticles [40], but the impact of microparticles released by RBCs remains to be determined [39, 40, 45–47].

Transfused RBCs may also have properties that differ from their in vivo counterparts. There are several age-related changes that occur in stored RBCs. Characteristically, older RBC units have lower levels of 2,3-DPG, which alters Hb affinity for O_2 [48]. Nevertheless, the decrease in 2,3-DPG during storage appears to be of little clinical significance since 2,3-DPG levels increase (in adults at least) to more than 50 % of normal within several hours, and to normal levels within 24 h of transfusion [49].

Hb molecules interact not only with O_2 and CO_2, but also with nitric oxide (NO), which is a key mediator of hypoxic vasodilatation [50]. Free vascular Hb causes vasoconstriction, probably by fixing NO, and can substantially reduce NO bioavailability [51]. Free Hb reacts up to 1,000 times faster than Hb found within RBCs [52]. There is increasing hemolysis over time in stored RBC units: the amount of free Hb increases from 0.5 mg/dL in a 1 day-old RBC units to 250 mg/dL in a 25 day-old unit [53]. However, Hess et al. [54] has shown that prestorage leukoreduction decreases free Hb level by 53 %. The clinical impact of RBC hemolysis remains to be determined in leukoreduced RBC units.

Storage-related changes in intra-erythrocyte Hb might be problematic as well. S-nitrosylated Hb (SNO-Hb) is a protein that can bind, activate, and deploy NO [55]. Intra-erythrocyte SNO-Hb regulates small vessels tone and regional blood flow. SNO-Hb reacts almost immediately to local cellular hypoxia by releasing NO, resulting in local vasodilatation. Conversely, RBCs bind more NO if local cellular VO_2 seems adequate, leading to local vasoconstriction. This function is almost immediately disturbed by storage (<3 h) [15, 16, 56, 57], and most SNO-Hb is lost within 2 days of storage [55]. Decreased NO bioavailability from RBC could explain the increased morbidity and mortality reported in some patients after RBC transfusion [58].

RBC transfusions indeed improve global DO_2, but this does not always result in better regional DO_2 and VO_2 [59–61]. RBC transfusions can impair regional blood flow and cellular VO_2 by many mechanisms: higher viscosity, vasoconstriction (cytokines, NO-Hb, free Hb) and low 2,3-DPG, which may alter O_2 release. As a consequence, transfused RBCs may impair O_2 availability and flow in the microcirculation, which may have adverse effects on tissue oxygenation and cellular respiration [59–61].

Immunologic Effects of Allogeneic RBC Transfusions

Transfusion-related immuno-modulation (TRIM) is another possible concern with regard to RBC transfusion [34]. Both activation and suppression of the immune system have been reported. Blood products such as RBC units, plasma and platelet concentrates contain white blood cells that release inflammatory mediators in concentrations proportional to their number and to storage time. Several pro-inflammatory molecules have been detected in stored non leukocyte-reduced RBC units, including complement activators [62], cytokines [22, 42, 63], O_2 free radicals [64, 65], histamine [66], lyso-phosphatidyl-choline species [67] and other bioreactive substances that modulate the inflammatory process. These white blood cells and inflammatory mediators may

trigger, maintain or accentuate SIRS in the recipients. SIRS is common in critical care units, which may explain why some data suggest that TRIM is one of the insults occurring in the two-hit hypothesis and may be a risk factor for the development of MODS in critically ill patients [68–70].

Transfusions of packed RBC units that are not pre-storage leukocyte-reduced have resulted in clinically important immunosuppression in at least some recipients [71–76]. In particular, before the cyclosporin era, the transfusion of non leukocyte-reduced RBC units was shown to decrease the number of transplanted organ rejection episodes [77–79], and improve renal and cardiac allograft survival [80–82]. This effect may be related to alterations in lymphocyte reactivity observed after blood transfusion. These immunosuppressive properties of non leukocyte-reduced blood products may trigger (in contrast to the situation described above), maintain or accentuate compensatory anti-inflammatory response syndrome (CARS) in the recipients. CARS is also common in critically ill patients [83].

Non leukocyte-reduced RBC units contain about 5×10^9 white blood cells per unit. The risk of TRIM may disappear if the RBC unit is leukocyte-reduced, the latter defined as less than 5×10^6 leukocytes per unit [2]. Pre-storage leukocyte-depletion is superior to reduction done by post-storage filtration at the bedside partially because pre-storage leukocyte-reduction is usually done under more rigorously controlled conditions and also because removal of white blood cells prior to storage reduces the time-dependent accumulation of pro-inflammatory mediators in the supernatant fluid [84–89]. Pre-storage leukocyte reduction is systematically undertaken in many countries (United Kingdom, Canada, etc.); in 2009, 28 out of 33 American blood banks (84.8 %) provided universal leukoreduction [90]. However, pre-storage leukoreduction does not prevent the production of all pro-inflammatory mediators detected in RBC units. For example, stored RBCs shed microvesicles in the supernatant. This process is an integral part of the RBC ageing process, is accelerated in stored RBC units and is not altered by pre-storage leukoreduction. These microvesicles (ectosomes) contain lipids that can amplify an inflammatory reaction [39].

In summary, TRIM may be a risk factor for MODS in critically ill patients [68–70], and may cause some immunosuppression, thereby increasing the risk of acquiring sepsis and nosocomial infections [91–100], which may ultimately result in higher mortality rates [70]. In spite of these concerns, the clinical impact of TRIM is still a matter of considerable debate [34]. Moreover the clinical effects of RBC transfusion on the immunological responses of critically ill children remain to be determined, and it is possible that pre-storage leukocyte reduction decreases or eliminates the risk and/or the severity of TRIM [101–104]. More studies are required to better determine if TRIM is indeed a clinically significant problem, particularly when pre-storage leukocyte-reduced blood products are used.

Length of Storage of RBC Units

RBC units can be stored up to 42 days. The normal average life-span of RBCs is 120 days. RBC ageing is a normal process; it is slowed down in stored RBC units [105]. The storage lesion comprises the time-dependent metabolic, biochemical, and molecular changes that stored blood products undergo over time. Storage lesions changes are observed in all stored RBC units and are not normal processes. They include increased levels in the supernatant of potassium, lactate, PCO_2 as well as many inflammatory mediators (cytokines, lipids, CD40, etc.) associated with diminished levels of sodium, low pH and PaO_2. Storage-associated RBC abnormalities also include low ATP levels, increased hemolysis with the release of free Hb, iron and lipids, a diminished 2,3-DPG concentration, less RBC deformability, increased RBC adhesiveness and aggregation, disturbed intra-erythrocyte Hb-nitric oxide (NO) interaction and regulation of small blood vessels, etc. [106, 107].

Most of these changes appear within 2–3 weeks of storage. Currently, the average length of storage of RBC units transfused to critically ill children is about 17 days in the USA and Canada [108, 109]. It is unknown whether these in vivo observations translate into clinically significant adverse outcomes. More than 20 observational studies have reported an association between age of blood and the incidence rate of nosocomial infections [110–113], while others have found no association [114–117]. Similarly some investigators reported an association between increased RBC length of storage and increased mortality in non-cardiac critically ill adults [44, 110, 118–120], while others find no association [121–123]. The same positive [124–128] and negative observations [115, 116, 129] have also been reported with respect to mortality in cardiac patients.

Tinmouth et al. [106] stated, "There is strong laboratory evidence suggesting that prolonged RBC storage may be deleterious". The results of many observational studies indeed suggest that an association exists between length of storage and outcome, but the published data are equivocal, and it must be underlined that observational studies overestimate the real benefit of a treatment by 30–60 % [130]. It is important to emphasize that finding an association does not imply a cause-effect relationship. Moreover, the number of RBC units and the severity of illness are also associated with increased mortality in transfused critically ill adults, and they are associated to each other. There is clearly some confounding by indication [131], which further increases the complexity of the relationship between RBC storage time and adverse outcome, and which no multivariate analysis can deconstruct. Only randomized clinical trials can uncouple the relationship between severity of illness, number of

transfusions and age of blood, and demonstrate a cause-effect relationship between RBC length of storage and adverse outcome in transfused critically ill patients. Several randomized clinical trials are presently addressing this question. The Age of Blood Evaluation (ABLE) study (ISRCTN44878718) is enrolling 2,510 critically ill adults since 2009 [132]. The Age of Red blood cell In Premature Infants (ARIPI) study (NCT00326924), which recruited 450 premature newborns who were allocated to receive either RBCs stored ≤7 days or transfusion therapy according to standard practice, was completed in Spring 2011 [133]. The "Red Cell Storage Duration and Outcomes in Cardiac Surgery" (NCT00458783) is a single-center RCT comparing outcomes in 2,800 patients allocated to receive RBCs stored for less than 14 or more than 20 days. The Red Cell Storage Duration Study (RECESS) (NCT00991341) is randomizing 1,434 cardiac surgery adult patients to receive either RBC units stored ≤10 days or ≥21 days [134]. The age of blood in children in PICU (ABC-PICU) study is in preparation and plans to recruit more than 1,500 critically ill children. Until hard evidence is available, the use of "fresh" rather than "old" blood cannot be recommended for ICU patients [135].

Practice Patterns: Determinants of RBC Transfusion

Laverdière et al. [136] undertook a survey of pediatric critical care practitioners to investigate stated RBC transfusion practices and clinical determinants that may alter transfusion thresholds in critically ill children. The transfusion threshold chosen by pediatric intensivists varied tremendously for a given scenario, ranging from less than 7 g/dL to more than 13 g/dL. The following patient characteristics were statistically significant stated determinants of RBC transfusion: low Hb concentration, primary diagnosis (bronchiolitis, ARDS, septic shock, corrected tetralogy of Fallot), young age (<2 weeks of age), low PaO_2, high blood lactate level, high PRISM score, active bleeding, thrombocytopenia, disseminated intravascular coagulation and emergency surgery. The results of a survey published in 2004 undertaken among European pediatric intensivists were similar [137].

While our beliefs affect what we teach and what we consider standard practice, the reality of what we actually do (observed practice pattern) can be quite different. The same group of investigators undertook an observational cohort study of 303 children consecutively admitted to an academic PICU and noted that 45 children (15 %) had received between 1 and 33 RBC transfusions each, for a total of 103 transfusions. The stated reasons for administering RBCs included the presence of respiratory failure (84/103), active bleeding (67/103), hemodynamic instability (50/103), blood lactate level >2 mmol/L (10/103) or sub-optimal DO_2 (6/103). In many cases, more than one reason was specified, but in seven cases, no specific reason was given [138]. In another cohort study involving 985 consecutive critically ill children, the most significant observed determinants of a first RBC transfusion were a low hemoglobin level, an admission diagnosis of cardiac disease, an admission PRISM score >10 and the presence of MODS during PICU stay [139]. The following determinants of perioperative blood product—not only RBC—transfusion were detected in a prospective cohort study of 548 children undergoing cardiac surgery: younger age, higher preoperative hematocrit, complex surgery, low platelet count and longer duration of hypothermia [140].

Goal-Directed RBC Transfusion Therapy

Goal-directed RBC transfusion therapy is frequently advocated. Its basic principle is simple—a RBC transfusion should be given with the aim of attaining a given "physiological" goal. Many goals are suggested in the medical literature. Some are related to biomarkers reflecting global O_2 delivery (DO_2) and/or O_2 consumption (VO_2): DO_2, VO_2, blood lactate, $Sv'O_2$ (mixed venous O_2 saturation), $ScvO_2$ (central venous SO_2), O_2 extraction rate, etc. Some are related to regional (tissue) markers: near-infrared spectroscopy (NIRS), regional or tissue SO_2 (rSO_2, StO_2), regional O_2 extraction rate, etc. Other goals have been considered, like heart rate variability, plethysmographic variability [141] and vascular endothelial growth factor levels [142]. Goal-directed RBC transfusion therapy might be the right clinical approach. There are indeed good data supporting goal-directed therapy and using $ScvO_2$ in unstable patients with severe sepsis and septic shock [143, 144], but the role of RBC transfusion in $ScvO_2$-directed goal therapy is unclear. There are no data supporting the use of other goals in other circumstances. Moreover, there is no consensus on what the best choice for a goal would be (maybe $ScvO_2$ in patients in severe sepsis and/or shock), nor any consensus on what threshold should be used for these goals.

There is consensus that the Hb concentration should not be the only marker used in the decision process to prescribe a RBC transfusion. In addition to considering the Hb level, many host-related and disease-related characteristics appear to account for the practice variation observed in PICU. Goal-directed transfusion therapy is a useful concept, but the appropriate goal remains to be determined and validated. There is however some evidence with regard to three potential determinants that deserves further elaboration: threshold Hb concentration, severity of illness (stable versus unstable patients) and case-mix (cardiac patients).

Red Blood Cell Transfusions in Non-cardiac Patients

Stable Critically Ill Children

In critically ill adults, there were no clinical studies documenting the safety of maintaining the Hb at a lower concentration before Hébert et al. [70] published a landmark paper in 1999. This randomized clinical trial involved

administration of non leukocyte-reduced RBC units and showed that a conservative strategy (RBC transfusion if the Hb concentration dropped below 7 g/dL to maintain a level between 7 and 9 g/dL) was as safe, in euvolemic critically ill adults, if not safer than a liberal strategy (RBC transfusion if the Hb concentration dropped below 10 g/dL to maintain a level between 10 and 12 g/dL). An adjusted MODS score as well as hospital mortality were statistically lower in the former than in the latter group.

Data from the adult population are important, but cannot be applied to pediatric patients without restriction because many host characteristics are specific to critically ill children and infants (different case-mix, normal range of Hb concentration that varies with age, different cardiovascular physiology, different energy requirements, better health status of children prior to PICU entry, etc.). There have been two randomized clinical trials that evaluated RBC transfusion in severely ill children. The first randomized clinical trial included 106 African children hospitalized for a malarial crisis who had no congenital hemolytic anemia. In these patients with hematocrit levels ranging from 0.12 to 0.17, RBC transfusion did not improve mortality (1/53 vs 2/53) if there was no respiratory or cardiovascular compromise [11].

The second randomized clinical trial, the Transfusion Requirements In Pediatric Intensive Care Units (TRIPICU) study, a large multicenter randomized non-inferiority clinical trial, included only stable or stabilized patients [145]. In this study, children were considered stable or stabilized if their mean arterial pressure was not less than two standard deviations below normal mean for age and if the cardiovascular support (vasopressors, inotropes and fluids) had not been increased for at least 2 h [145]. It must be underlined that in this definition of stable or stabilized patient, the respiratory and neurological status were not taken into account. The basic design of the TRIPICU study was quite simple. All critically ill children who presented a Hb level ≤9.5 g/dL within the first 7 days in the PICU were considered eligible for the study; they were included if they were hemodynamically stable and had no exclusion criteria. Children were randomized either to receive a transfusion only if the Hb was ≤9.5 g/dL (liberal group) or to receive a transfusion only if their Hb concentration was ≤7 g/dL (restrictive group). In the liberal group (320 patients), transfusion aimed for a post-transfusion Hb level of 11–12 g/dL while the aim was 8.5–9.5 g/dL in the restrictive strategic group (317 patients). Only pre-storage leukocyte-reduced packed RBC unit were used. The primary outcome measure was new/progressive MODS and death; all deaths were considered cases of progressive MODS. The number of new/progressive MODS in the restrictive and liberal groups where respectively 38 and 39. The 28-day of mortality was 14 in both groups. These results suggest that a threshold Hb of 7 g/dL can be safely applied to stable critically ill children. Accordingly, the principal recommendation of the TRIPICU study was to adopt "a restrictive transfusion strategy in PICU patients whose condition is stable in the ICU". One may challenge this recommendation and argue that some patient populations can differ from those in TRIPICU and require more RBC transfusions because they are sicker. Although not hard evidence, subgroup analyses have thus far found no justification to give more RBC transfusion to stable critically ill children even if their PRISM score is higher [145], if patients present with a septic states (sepsis, severe sepsis, septic shock) [146], or if they are in PICU after undergoing a non-cardiac surgery [147]. A before-after study also suggested that a restrictive policy is safe in burn children [148].

Unstable Critically Ill Children

Most experts in critical care medicine and in transfusion medicine believe that RBC transfusion is mandatory in hemorrhagic shock, regardless of the Hb concentration. The Hb level observed while a patient is actively and acutely bleeding does not immediately reflect the volume of blood that has been lost; thus, the Hb concentration is not the best marker to guide transfusion on an emergency basis in such patients. There is no consensus on what must be done in patients who are unstable, but are not actively or acutely bleeding, like critically ill patients with uncontrolled septic shock or uncontrolled intracranial hypertension. Intensivists believe that a higher threshold Hb concentration is required in unstable patients [136, 149]. Few hard data support this point of view, other than two randomized clinical trials conducted in adults with severe sepsis or septic shock by Rivers et al. [143] and in children by de Oliveira et al. [144] These trials suggest that intensivists should try to maintain the $ScvO_2$ over 70 % and that RBC transfusion is required if fluid challenge (up to 80 mL kg within 6 h) and inotropes or vasopressors do not succeed in increasing the $ScvO_2$ above 70 %.

Red Blood Cell Transfusions in Cardiac Patients

Patients with impaired ventricular function cannot increase their cardiac output as efficiently as other patients. Moreover, even at rest, O_2 extraction by myocardial cells is elevated, which implies a lessened coping capacity when anemia occurs. Thus, increasing the Hb level may be the only way to increase DO_2 and adequately support cardiac function in these patients. Support for this notion can be drawn from a retrospective study involving 1,958 adults who underwent surgery and refused blood transfusion for religious reasons. A substantially increased risk of death was associated with a low preoperative Hb level in cardiac patients when compared to those without cardiovascular disease [8]. In practice, the threshold Hb concentration observed before RBC transfusion is higher in the PICU during the postoperative period of cases of pediatric cardiac surgery than in other PICU patients [139].

Some recent publications question the statement that it is safe to give RBC transfusions to cardiac patients. Laboratory data suggest that RBC transfusion, even with fresh blood, can disturb the capacity of RBCs to release and capture nitric oxide, and to regulate the small blood vessels tone. Some clinical data suggest that critically ill adults with cardiovascular disease need a higher Hb concentration [150], but other data suggest that RBC transfusions can cause more ischemia in patients with cardiac illness. For example, Murphy et al. [151] reported a statistically and clinically significant association between RBC transfusions and ischemia in 8,518 adults transfused during post-operative care of a cardiac surgery: the adjusted odds ratio was 3.35 (95 % CI: 2.68–4.35). This held true regardless of the hematocrit level before transfusion. Indeed, the proportion of patients with a hematocrit <21 % who developed an ischemic episode was 1.9 % in non transfused patients while it was 13.4 % in transfused patients. In comparison, the proportion of patients with a hematocrit over 27 % who developed an ischemic episode was 3.5 % in non-transfused patients and 11.6 % in those who were transfused.

What determinants to use in the post-operative care of pediatric cardiac surgery patients and whether they are useful are matters of great debate. There is consensus that the need for RBC transfusion in patients without cyanotic cardiac disease during the post-operative period must be addressed separately from those of patients with cyanotic heart disease. Many experts in pediatric cardiology believe in maintaining elevated Hb levels in children without cyanotic heart disease and advocate Hb levels of 12–13 g/dL in neonates and 10 g/dL in infants and children [152]. Other experts in Britain and France do not share this view and advocate lower Hb thresholds of 7–8 g/dL in stable children with non-cyanotic heart disease [2, 153]. There is little evidence regarding this issue. In year 2009, Harrington et al. [154] completed a scenario-based survey among Canadian pediatric cardiac surgeons, cardiologists and intensivists in order to ascertain their stated practice pattern with respect to RBC transfusion during the post-operative care after a pediatric cardiac surgery. Two scenarios in the questionnaire involved patients with non-cyanotic heart disease: a 6-day old having undergone arterial switch surgery and a 5-month old having undergone correction of a complete atrioventricular canal. Most respondents replied that a Hb lower than 10 g/dL would prompt them to transfuse RBCs in these patients. Their transfusion threshold increased Hb by 2.5 g/dL if the patient was unstable, if he required ECMO, if active bleeding occurred, or if the $ScvO_2$ or the systemic blood pressure dropped suddenly. In the TRIPICU study, 63 patients with non-cyanotic cardiac disease were enrolled in the restrictive group and 62 in the liberal group [155]. New/progressive MODS was observed in eight patients in the former and four patients in the latter ($p=0.36$); there were two deaths in each group at 28 days post-randomization. Thus, the only presently available evidence from this subgroup analysis suggests that a Hb level above 7 g/dL is safe for critically ill children with non-cyanotic heart disease if they are stable. A higher threshold Hb level is probably required in unstable patients.

Neonates with cyanotic heart disease present Hb levels that are significantly higher than normal – Hb concentrations as high as 16–20 g/dL are frequently observed in these patients. In the survey by Harrington et al. [154] described above, two scenarios involved patients with post-operative cyanotic heart disease: a 6-day old patient with tetralogy of Fallot and a 5-month old with hypoplastic left heart syndrome – both underwent a Glenn procedure. Most respondents replied that they would prescribe a RBC transfusion for these patients only if their Hb dropped below 12 g/dL. Their transfusion threshold increased by 1.2 g/dL if the patient became unstable, if an active bleeding appeared, if the $ScvO_2$ dropped suddenly, or if the lactate level was high.

Few clinical studies have addressed this question. A case series of seven children with congenital cyanotic heart disease reported a decreased right to left shunt when increasing the Hb concentration from 13.0 to 16.4 g/dL. The authors specifically attributed the benefit seen to a decreased right to left shunt and did not consider the possibility that benefit could have been due to an increased VO_2 [61]. Interestingly, experience with bloodless surgery for complex cyanotic defects suggests that cardiac surgery can be safely performed with a lower level of Hb without evidence of increased risk [156, 157]. Cholette et al. [158] published a randomized clinical trial that included children with univentricular physiology among which 33 underwent a Glenn procedure and 27 a Fontan procedure: 30 patients were allocated to a restrictive strategy with a threshold for RBC transfusion of 9 g/dL and 30 patients, to a liberal group with a threshold of 13 g/dL. One death was observed in the liberal group. The median lactate blood level was 1.4 ± 0.05 mmol/L in both groups. Peak blood lactate was also almost identical (3.1 ± 1.5 versus 3.2 ± 1.3 mmol/L). However, the O_2 extraction rate was slightly higher in the restrictive group (31 % ± 7 % versus 26 % ± 6 %) with a difference that was statistically significant ($p=0.013$), but not necessarily clinically significant. These data suggest that it is safe not to give a RBC transfusion to patients with cyanotic cardiac disease as long as their Hb level is over 9 g/dL.

The evidence that RBC transfusion improves the outcome in children admitted to PICU after cardiac surgery is poor. Some evidence in adults suggests that a RBC transfusion may be detrimental. In spite of this, practitioners believe that a higher Hb threshold is required in children with cardiac disease, more so if a cyanotic heart disease is present. The appropriate transfusion thresholds Hb for children during the post-operative phase of cardiac surgery are unknown for

those with non-cyanotic as well as cyanotic heart lesions. Only a subgroup analysis involving 125 patients from the TRIPICU study has provided evidence which suggests that a Hb level of 7 g/dL is well supported by non-cyanotic patients and only one small randomized clinical trial conducted by Cholette et al. [158] has suggested that a Hb level of 9 g/dL is well tolerated by children with cyanotic heart disease. More studies on RBC transfusion must be done in the field of cardiac surgery.

Limiting Blood Product Transfusion

Whenever possible, it is always better not to administer any blood product. The concept of bloodless medicine and blood conservation are two aspects of blood management that all intensivists should integrate into their clinical practice. Blood conservation refers to limiting the volume of blood lost by patients. Repetitive phlebotomy may contribute significantly to blood loss (7.1 ± 5.3 mL/day, 34 ± 37 mL per PICU stay) [159]. Limiting and consolidating blood tests, closed blood sampling, use of pediatric blood collection tubes, and micro-analysis techniques requiring small sample volumes (<0.5 mL) can all be very effective ways to minimize blood loss [160, 161]. The concept of bloodless medicine refers to all the strategies that can be used to provide medical care without allogeneic blood transfusion. Both concepts are discussed in greater detail in a separate chapter in this textbook.

Although bloodless medicine and blood conservation are two concepts involving multiple strategies that should be applied whenever possible, there are several instances when a RBC transfusion must be considered. It is obvious that more research must be undertaken to provide scientific data before one can establish evidence-based guidelines. Meanwhile, decisions related to transfusion should be driven by physiological need rather than a specific Hb trigger, a decision making process advocated by the National Institutes of Health [162], the American College of Physicians [48] and a group of Canadian experts [163]. Because markers of "physiological needs" are not characterized in critically ill patients, the Hb level is still pivotal to the decision making process of intensivists who are considering RBC transfusion [1, 136, 137, 164]. In practice, we recommend the following strategy for hemodynamically stable critically ill children without cyanotic heart disease [165]:

Blood gas machines should not be used for Hb estimation on which to base a transfusion request.

RBC transfusion is required in most instances if the Hb concentration is <5 g/dL.

RBC transfusion is probably useful if the Hb concentration is between 5 and 7 g/dL.

For Hb levels ranging from 7 to 9.5 g/dL, there appears to be no overall benefit in transfusing RBCs.

No RBC transfusion is required if the Hb concentration is >9.5 g/dL.

It is probably appropriate to consider a higher threshold and/or to have a more aggressive RBC transfusion strategy in critically ill children who are hemodynamically unstable or who have significant cardiovascular disease. There is, however, no consensus on what this threshold should be. It is also possible that a higher Hb concentration may be required early in their course for patients with severe sepsis. Rivers et al. [143] in adults and de Oliveira et al. [144] in children showed that aggressive and early (first 6 h) goal-driven protocol therapy directed at attaining a $ScvO_2$ greater than 70 mmHg (equivalent to 65 mmHg for mixed venous saturation) [166] improves outcome in patients with severe sepsis. In the majority of patients, such early-goal therapy was achieved only if the hematocrit was kept above 0.30 during these six "golden" hours. The recommendations detailed above this paragraph apply after these golden hours, once the patient is stabilized. The decision to prescribe a RBC transfusion must be adapted to specific situations and must take into account determinants other than the Hb concentration, such as the severity of cases or the presence of mitochondrial dysfunction (high blood lactate level), a frequent occurrence in sepsis.

The "Nuts and Bolts" of Packed RBC Transfusion

Packed RBC units are stored in a preservative anticoagulant solution. CPD solution was previously a frequently used preservative that contains sodium citrate (C), citric acid, sodium diphosphate (P) and dextrose (D). In this solution, the dextrose provides energy for RBCs through glycolysis, the phosphate is utilized by RBCs to generate adenosine triphosphate (ATP) and the citrate chelates calcium, which inhibits coagulation, and is then metabolized to bicarbonate, which stabilizes the pH. Most countries have updated the constituents of the solutions used. CPDA–1 (anticoagulant citrate-phosphate-dextrose-adenine) solution contains a higher concentration of dextrose than CPD (2 g vs 1.6 g/63 mL) and some adenine (17.3 mg/63 mL). With this solution, ATP levels remain normal during 21 days of storage and decrease by 50 % after 35 days. Thus units with CPDA–1 can be stored up to 35 days while units with CPD may only be stored for 21 days (28 days fir CPD-2). Additive solutions containing more adenine, such as AS–1 (Adsol®), AS–3 (Nutricel®) and SAG–M are being used with increasing frequency in North American and European countries. The contents of AS–1 and SAG–M are similar to that of CPDA–1 except that they contain mannitol to decrease RBC lysis. Packed RBC units stored in additive solutions have a shelf-life of 35–42 days, depending on country-specific regulations for permitted storage (42 days in North-America, 35–42 in European countries) [167, 168].

The volume of each CPDA–1 unit is 250 mL, which includes 63 mL of preservative solution. Each unit may be diluted with 75 mL of saline immediately prior to

administration to the patient (this decreases the hematocrit from 0.70 to 0.55–0.60, allowing an easier administration). The mean volume of each AS–1, AS–3 or SAG–M unit is up to 350 mL, which includes 100 mL of preservative solution. These units have a hematocrit of 0.55–0.60; so they do not need to be diluted with saline prior to administration.

It is common practice to prescribe 10 mL/kg of packed RBCs stored in CPDA–1 and it can be expected that this should increase the blood Hb level by 2–2.5 g/dL if the patient is not actively bleeding. It is frequently unrecognized that these numbers hold true only for undiluted CPD/CPD–1 units: up to 15 mL/kg are required to get the same increase of the Hb concentration with CPD/CPDA–1 units to which saline (75 mL) has been added or RBCs stored in additive solutions. However, the optimal prescription should consider the Hb level prior to transfusion and should adjust the volume of the transfusion to attain a targeted Hb level. This can easily be done if there is no active bleeding by using the formula below to calculate the exact amount (volume) of packed RBCs that should be given:

$$\text{Volume (mL)} = \{(\text{Hb}_{\text{targeted}} - \text{Hb}_{\text{observed}}) \times \text{blood volume}\} / \{\text{Hb}_{\text{RBC unit}}\} \quad (19.1)$$

where $\text{Hb}_{\text{targeted}}$ is the Hb concentration targeted post-transfusion (for example, 10 g/dL), $\text{Hb}_{\text{observed}}$ is the most recently measured Hb concentration of the patient (g/dL), and $\text{Hb}_{\text{RBC unit}}$ is the average Hb concentration in the packed RBC units (g/dL) delivered by the blood bank.

The Hb concentration of RBC units may vary from one center to another and according to the different preservative solutions used. For non leukocyte-reduced RBCs in AS–3, the hematocrit is approximately 0.55, and the $\text{Hb}_{\text{RBC unit}}$ concentration is about 19.5 g/dL (usual range: 18–21 g/dL). For RBCs in CPDA–1, the hematocrit before dilution is about 0.65–0.75 and the $\text{Hb}_{\text{RBC unit}}$ concentration is about 25 g/dL. However, the Hb concentration does vary according to processing methods (e.g. there is RBC loss with leukoreduction filtration, buffy coat removal and/or washing) and between units, variation related to the variability of donor Hb concentrations. Where possible, to use this formula accurately, it is preferable to know the average Hb concentration of the units supplied by the local blood bank.

The blood volume can be calculated according to the formula:

$$\text{Total body blood volume} = \text{weight} \times \text{blood volume} \quad (19.2)$$

where weight is expressed in kg, and blood volume in liter/kg (0.08 L/kg for children aged <2 years, 0.07 L/kg for age 2–14 years). For example, in a child weighing 3 kg whose blood volume is 0.24 L (0.08 L/kg × 3 kg), who has a Hb level of 6.5 g/dL and for whom the desired Hb level is 10 g/dL ($\text{Hb}_{\text{targeted}}$), the volume of non leukocyte-reduced packed RBC unit to be transfused (in liters) would be calculated as shown below if the $\text{Hb}_{\text{RBC unit}}$ is 19.5 g/dL (AS-3):

$$\text{Volume} = \{(10 - 6.5\,\text{g/dL}) \times 0.24\,\text{L}\} / \{19.5\,\text{g/dL}\} = 0.043\,\text{L} = 43\,\text{mL}.$$

One can also use the following formula:

$$\text{Volume (mL)} = \{(\text{Ht}_{\text{targeted}} - \text{Ht}_{\text{observed}}) \times \text{blood volume}\} / \{\text{Ht}_{\text{RBC unit}}\} \quad (19.3)$$

In this latter formula, $\text{Ht}_{\text{targeted}}$ is the hematocrit (Ht) targeted post-transfusion (for example, 0.30), $\text{Ht}_{\text{observed}}$ is the most recently measured Ht of the patient (0.20), and $\text{Ht}_{\text{RBC unit}}$ is the average Ht in the packed RBC units delivered by the blood bank.

In stable patients, RBCs should be administered on a unit-by-unit basis to minimize exposure to multiple donors and to maintain the patient in the appropriate transfusion range. If the volume of packed RBCs needed to reach the $\text{Hb}_{\text{targeted}}$ is greater than the volume of one unit of packed RBCs, blood should be transfused one unit at a time and the Hb measured again prior to administration of additional packed RBCs. Given the fact that Hb and Ht values equilibrate within 30 min in transfused patients who are not actively bleeding [169], it would be appropriate to allow for this delay prior to verification of post-transfusion Hb level. A packed RBC unit can be subdivided into smaller units—either half units or four to five aliquots—to avoid waste (Pedi-Pak®, Genesis BPS, is frequently used in North-America). Sterile preparation of these fractionated or partial units may allow for remaining blood to be reserved for the same patient until the expiry date, thus minimizing exposure to multiple donors. A packed RBC unit must be given within 4 h after leaving the hospital blood bank. Fractionated units, which are prepared in a sterile manner, can be kept as long as the original unit.

Table 19.1 summarizes permissible choices of ABO/Rh blood components according to recipient ABO/Rh blood groups. An ABO/Rh blood group is mandatory before any blood component transfusion. In addition a cross-match (electronic or serologic according to institutional policy) is required before a RBC transfusion. It takes 5–10 min to ascertain the ABO and Rh status of a patient (type) and up to 60 min to complete pre-transfusion testing of a recipient including ABO/Rh typing, antibody screening and cross matching. In acute life-threatening situations requiring rapid transfusion, there may not be sufficient time for complete pre-transfusion testing. In these situations, ORh^- RBC and/or AB plasma should be administered. The risk of severe hemolytic reaction to non cross-matched RBC units is low in patients who have never been exposed to allogenic RBCs (i.e. who have never been transfused or pregnant); however in emergency situations, a reliable medical history is often

Table 19.1 Choice of ABO and Rh groups for blood product administration in children

Blood product(s) to be transfused[a]			
Recipient blood group	Red blood cells	Plasma	Platelets [b]
O	O	O, A, B, AB	O, A, B, AB
A	A, O	A, AB	A, AB
B	B, O	B, AB	B, AB
AB	AB, A, B, O	AB	AB
Rh^+	Rh^+, Rh^-	Not applicable	Rh^+, Rh^-
Rh^-	Rh^-	Not applicable	Rh^- [c]

Based on data from Refs. [2, 170, 171]

[a]The ABO subgroups suggested may not be appropriate in newborns and young infants (<4 months) if maternal antibodies are present in the recipient. The above suggestions also do not apply for bone marrow transplant patients grafted from an ABO mismatched donor [170]

[b]In emergency situations, if platelets of the recommended groups are not available, units with low titers of Anti-A or anti-B should be selected, or alternatively the majority of the plasma should be removed from the platelet concentrate

[c]Rh^+ platelets can be given to an Rh^- receiver when no Rh^- platelets are available. Anti-D immunoglobulins should then be considered, especially in women of childbearing potential

unavailable. For patients who have been previously transfused or who are pregnant, it is difficult to give a precise figure as to the risk, and this will vary with individual patients (e.g. number of previous transfusions, availability of previous records, nature of the underlying disease like immunosuppressed patient versus a sickle cell patient). The physician must weigh risks and benefits. However, in truly life-threatening situations, most physicians would proceed with transfusion of non cross-matched blood. If large amounts of uncross-matched packed RBC units are transfused, the hospital blood bank might recommend that similar units continue to be administered for a while (a protocol is usually implemented to deal with massive transfusion in most hospitals).

RBC units are stored at 1–6 °C and therefore represent a significant risk of hypothermia. All units are warmed to room temperature (about 20 °C) prior to administration. Warming to body temperature (37 °C) should be considered when significant volumes are given rapidly. In practice, packed RBC units are warmed to 37 °C before transfusion to a small patient (<10 kg) or if the amount given constitutes >20–30 % of the recipient's blood volume. In other situations (i.e. larger child, slower infusion rate), the blood will warm sufficiently at room temperature while being infused. Warming packed RBCs decreases viscosity (7 % decrease for each 1 °C increase), thus lowering the resistance through the catheter used; the clinical relevance of this remains to be determined. Standard blood-warmer must be used to rise the temperature of whole blood or packed RBC units, not micro-waves oven because they can cause severe hemolysis [172, 173].

All packed RBC units (even leukocyte-reduced units) contain fibrin, platelets and white blood cells, and must be filtered, using a standard blood bank filter with 180–260 µm pores. Some clinicians advocate using microaggregate filters (80 µm or less), but there are no studies that convincingly show an advantage to their use.

Poiseuille's law regulates the flow through a catheter: $Q' = \{\pi(P_1–P_2)r^4/8\ nL\}$ where Q' is flow (L/min), r is internal radius, $(P_1–P_2)$ is pressures difference, L is catheter length, and n is viscosity coefficient. Most of the resistance to flow attributable to a catheter is related to its radius (r^4) and its length. Moreover, the high viscosity of packed RBC units increases this resistance. It is therefore advisable that the biggest and shortest available catheter be used for RBC transfusion. A 14 G peripheral catheter in adults, a 20 G in infants, or even an intra-osseous catheter are acceptable; 22 G catheters [174] or 1.9 Fr NeoPICC™ [175] are too small unless the flow rate is decreased (<2.5 mL/kg/h) or the intraluminal pressure generated by a pump is increased. Significant hemolysis can occur with intraluminal pressures greater than 300 mmHg [174, 175]. Central vein catheters are appropriate.

A RBC transfusion must be completed within 4 h of removal of the unit from a monitored temperature controlled refrigerator. No medication should ever be administered into the same intravenous access and it is inappropriate to combine transfusion RBCs with a solution that contains dextrose (risk of hemolysis), Ringer lactate or calcium (risk of coagulation) [176]. Only physiologic saline (0.9 % NaCl) is compatible.

Patients should be closely monitored while receiving blood products and transfusion must be immediately stopped if a transfusion reaction is suspected (see section on reactions to blood product transfusion at the end of this chapter). Patient clinical data as well as information regarding the blood products received must be detailed in the hospital chart. If a transfusion reaction is suspected, it is important not to dispose of the remaining blood product as well as any filters and tubing and to forward all items to the blood bank. All possible severe transfusion reactions must be reported to the local blood blank. In some instances, it may be indicated to obtain a blood culture from the patient and from the remaining product, and to assess the patient for hemolysis.

Whole Blood

Whole blood stored for longer than 24 h contains few viable platelets. In addition, levels of Factors V and VIII (the labile coagulation factors) decrease with storage at 4 °C. Levels of the other clotting factors are however well maintained at 4° storage. Whole blood can be reconstituted by combining one unit of packed RBC with a compatible unit of fresh frozen plasma [84]. Worldwide, most blood suppliers do not routinely provide whole blood. However, the transfusion of

whole blood could be considered in the following four situations: (1) hemorrhagic shock; (2) exchange transfusion in a newborn; (3) administration of an autologous unit (i.e. blood collected from the patient a few days or weeks prior to reinfusion at the time of elective surgery); (4) administration of blood donated by a family member and dedicated to a given patient. Some investigators have claimed that the use of fresh whole blood is associated with less post-operative blood loss [177]. Whole blood less than 48 h old is systematically used in some hospitals for cardiac surgery, mostly to prime the cardiopulmonary bypass circuit [152]. However a randomized clinical trial has shown that "the use of fresh whole blood for cardiopulmonary bypass priming has no advantage over the use of a combination of packed red cells and fresh-frozen plasma during surgery for congenital heart disease" [178]. In other situations, it is preferable to administer RBC and plasma separately or, in the case of exchange transfusion, as reconstituted whole blood, if both RBC and coagulation factors are required.

Specific Types of Packed RBC Units

While in most instances, standard packed RBCs can be safely used, there exist various other available products indicated for specific clinical situations including washed, irradiated, dedicated, autologous and cytomegalovirus (CMV) seronegative units.

Washed units. – Washed packed RBC units have had more plasma extracted than usual. The hematocrit depends entirely on how much saline is used to reconstitute the solution after washing; it can be as high as 0.70–0.80, but usually is adjusted to give a hematocrit of 0.55–0.60. The volume of washed RBC units depends on the hematocrit. It generally takes 2 or 3 h to complete the washing process and these units must be used within 24 h after entering the unit to begin washing, unless processed with newly available equipment that maintains a close system and thus allows longer (7–14 days) storage post-washing. Washed RBC units can be used to prevent transfusion reactions in patients who have presented severe or recurrent allergic reactions. Some practitioners use washed RBC units because they believe they are free of potassium. However, strong hemolysis is observed in washed RBC units; the concentration of potassium units increased rapidly after they are washed, and get to the pre-washed potassium concentration within 24 h [179].

Irradiated units. – Patients at risk of contracting transfusion-associated graft versus host disease (TA-GvHD) must receive gamma-irradiated cellular blood components. Susceptible patients include those with congenital immunodeficiency, patients receiving immuno-suppressive therapy, recipients of directed transfusions from family members and possibly pre-term infants [152]. However, irradiation does lead to an increased leakage of potassium from the RBCs. The impact of this problem can be minimized if the blood product is administered soon after irradiation.

Autologous units. – A packed RBC unit is autologous when it was collected from the receiver. In the pediatric population, this is possible with older children who are healthy enough to give their own blood a few weeks before elective surgery. It is frequently believed both by lay people and by caregivers that the transfusion of autologous RBC units is absolutely safe. However, there are some complications that may occur with autologous transfusion, including bacterial contamination, transfusion overload and transfusion error.

CMV negative units. – CMV may be transmitted by the transfusion of cellular blood components, and this may cause serious infection in certain categories of transfusion recipients. Because more than 50 % of donors are CMV positive, it is impossible to procure CMV seronegative blood products for all recipients. This blood product is therefore usually reserved for CMV negative future transplant recipients or for already transplanted patients whose donor was CMV negative and who are themselves CMV negative. CMV is transmitted by white blood cells and consequently the risk of contracting a CMV infection is significantly decreased (but not absent) with leukocyte-reduced units.

Transfusion of Frozen Plasma

Plasma for transfusion is prepared from a whole blood donation by separation following centrifugation. Larger volumes of plasma may be collected using automated apheresis techniques. A typical unit of plasma has an approximate volume of 250 mL if obtained from a whole blood donation or approximately 500 mL when obtained by plasmapheresis.

Immediately following collection from a normal donor, plasma contains approximately 1 unit/mL of each of the coagulation factors as well as normal concentrations of other plasma proteins. Coagulation Factors V and VIII, known as the labile coagulation factors, are not stable in plasma stored for prolonged periods at 1–6 °C; consequently plasma is usually stored frozen at −18 °C or lower. Plasma frozen within 8 h of collection, known as fresh frozen plasma (FFP), contains about 87 % of Factor VIII present at the time of collection and, according to standards in most countries, must contain at least 0.70 UI/mL of Factor VIII. Several countries also use plasma frozen within 24 h of collection, known as frozen plasma (FP). Factor VIII levels in frozen plasma are approximately 70–75 % of the levels present at the time of collection. The levels of Factor V as well as the levels of other coagulation factors are not significantly decreased from baseline in plasma frozen within 24 h of collection [180, 181].

FFP and FP units are collected from a single donor, while units of virus inactivated frozen plasma—solvent detergent FFP (SD-FFP) (Octaplas, Octapharma) and methylene-blue treated FFP (MB-FFP)—are constituted from a pool of frozen plasma collected from approximately 700 donors; the SD process is used for inactivation of lipid-enveloped viruses. SD plasma is not currently licensed in the USA, but it is licensed and available in Europe. In some countries, only FP is available, but in many countries including the USA fresh FP is still available in 2011. Depending on the exact temperature at which plasma is stored, applicable national requirements/regulations and the precise product, frozen plasma can be stored from 3 to 24 months.

Indications for Frozen Plasma Transfusion

In 2006, approximately four millions unit of plasma were transfused in the USA [182]. In 2010, 292,884 FFP units and 57,487 SD-FFP units were transfused in the United Kingdom (www.shotuk.org). There is broad, general consensus that the appropriate use of FFP, FP and SD-FFP is limited almost exclusively to the treatment or prevention of clinically significant bleeding due to a deficiency of one or more plasma coagulation factors. Such situations potentially include the presence of (1) a diminution of coagulation factors due to treatment with vitamin K antagonists, (2) severe liver disease, (3) disseminated intravascular coagulation (DIC), (4) massive transfusion, (5) warfarin anticoagulation-related intracranial hemorrhage, (6) isolated congenital coagulation factor deficiencies for which a safer and/or more appropriate product does not exist [183]. A panel of experts could not "recommend for or against transfusion of plasma for patients undergoing surgery in the absence of massive transfusion" [183]. The same experts could not "recommend for or against" a plasma/RBC ratio of 1:3 or more (<1:3) in trauma patients requiring massive transfusion [183].

Plasma exchange with FFP, FP or cryosupernatant as the replacement fluid is the standard therapy for thrombotic thrombocytopenic purpura (TTP). Although no hard evidence supports this, some physicians also advocate plasma administration or exchange transfusion to treat patients with hemolytic uremic syndrome (HUS) who develop neurologic complications [184]. Plasma exchange may be used to treat Guillain-Barré syndrome [185] and acute disseminated encephalomyelitis (ADEM) [186], although intravenous immunoglobulins may be a better option [187]. Plasma exchange is also currently being studied as a therapeutic measure in sepsis [188, 189].

There is also a consensus among the experts developing guidelines that FFP and FP are not indicated in the following situations:

1. Intravascular volume expansion or repletion (where crystalloids, synthetic colloids or purified human albumin solutions are preferred) [84];
2. Correction or prevention of protein malnutrition (where synthetic amino acid solutions are preferred);
3. Correction of hypogammaglobulinemia (where purified human immunoglobulin concentrates are preferred);
4. Treatment of hemophilia A or B and von Willebrand disease (where desmopressin, virus-inactivated plasma-derived or recombinant factor concentrates are preferred);
5. Treatment of any other isolated congenital procoagulant or anticoagulant factor deficiency for which a virus-inactivated plasma-derived or recombinant factor concentrate exists;
6. Treatment of hemolytic uremic syndrome (HUS) unless plasma exchange is indicated;
7. As replacement fluid in therapeutic apheresis procedures for disorders other than TTP/HUS unless proven to be beneficial.

The "Nuts and Bolts" of Frozen Plasma Transfusion

The amount of FFP of FP initially prescribed ranges from 10 to 20 mL/kg. The coagulation profile should be verified before further plasma administration. Close monitoring of the respiratory and hemodynamic status of the recipient is mandatory because plasma transfusion is associated with increased risk of developing ALI and transfusion-associated circulatory overload (TACO) [190]. It may be necessary in certain patients to repeat transfusion or to initiate a continuous perfusion (at a rate of 10 mL/kg/h), if there is active bleeding. Repeated measurement of the activity of the coagulation cascade is the best way to determine whether more plasma is required. Indications for continuing plasma administration are the same as for starting plasma.

FFP and FP can be thawed in less than 10 min using microwave ovens specifically manufactured for this purpose. A unit of FFP/FP must be administered within 4 h after thawing. Standard blood administration filter must be used. Plasma prepared from whole-blood derived FFP expires as FFP 24 h after thawing if kept at 1–6 °C, but it can be converted to thawed plasma. This product expires 5 days after thawing if stored at 1–6 °C. Thawed plasma has reduced level of FVIII and is not suitable for Factor VIII replacement. However, concentrations of remaining factors are clinically adequate for transfusion to other patients [168].

Transfusion of Platelets

Three mechanisms combine their effect to stop bleeding from an injured vessel: (1) vasoconstriction, (2) platelet aggregation to form a plug and (3) plug stabilization by a fibrin clot [191]. A low platelet count and/or significant platelet dysfunction therefore places a patient at risk for bleeding because of an impaired ability to form a platelet plug. Platelet dysfunction is common in ICU. In most instances, it is attributable to toxins, drugs (for example, salicylate, nitric oxide), exposure to extracorporeal circulation and renal failure; rarely, unusual causes such as certain inherited diseases can be involved [191]. Treatment of platelet dysfunction, when required, includes administration of certain drugs (for example, antifibrinolytic agents) and/or platelet transfusion.

Thrombocytopenia is defined by a platelet count <150,000/mm^3. The prevalence of ICU-acquired thrombocytopenia is 44 % in critically ill adults [192]. Causes of thrombocytopenia in ICU are multiple and include sepsis [193], DIC, massive transfusion, bone marrow histiocytic hyperplasia with hemophagocytosis (acquired hemophagocytosis syndrome) [193, 194], as well as drug-related and heparin-induced thrombocytopenia [195]. Because correction of thrombocytopenia has been shown to be associated with reduced mortality [192], it is reasonable to administer platelet transfusions to critically ill patients with a low platelet count. However, the threshold below which a platelet transfusion should be given is a matter of debate.

Platelet concentrates are prepared from whole blood donations or by apheresis collections. Platelet concentrates prepared from whole blood contain about 55×10^9 platelets per unit, plus 50 mL of plasma, a small quantity of RBCs and about 10^8 white blood cells/unit. Apheresis platelet concentrates contain about 300×10^9 platelets per unit, plus 250–300 mL of plasma, up to 5 mL of RBCs and about 10^9/unit white blood cells. In many countries (Canada, United Kingdom, etc.), but not in the USA, all platelet units are leukocyte-reduced pre-storage, either by filtration or (in the case of apheresis platelets) as part of the automated processing. This decreases significantly the risk of HLA alloimmunization, non hemolytic febrile reactions and the transmission of CMV. Both types of platelet concentrates are stored at 20–24 °C for up to 5 days. In many countries, bacterial detection is performed to decrease the risk of bacterial contamination.

Indication for Platelet Transfusion

In 2010, 246,962 platelet units were transfused in the United Kingdom (www.shotuk.org). There is consensus that a platelet transfusion is indicated if the platelet count of a patient with an active hemorrhage falls below 50,000/mm^3 [196], or if the hemorrhage is severe and there is platelet dysfunction, as occurs frequently following cardiopulmonary bypass [197]. Many intensivists consider that the risk of pulmonary hemorrhage is significant in mechanically ventilated patients if the platelet count is <50,000/mm^3, and most will prescribe platelet transfusion in such instances (although this has never been substantiated by clinical studies). A threshold of 100,000/mm^3 is generally recommended for patients with multiple trauma, central nervous system injury [196], or for patients on extracorporeal membrane oxygenation (ECMO) [2, 84]. In patients with thrombocytopenia due to decreased platelet production, prophylactic platelet transfusion should be considered if the platelet count is <10,000/mm^3 or if there are additional risk factors for bleeding.

The administration of a large amount of crystalloids, packed RBCs and/or whole blood (more than one blood volume) can have a dilutional effect on the platelet count and warrants close monitoring [198, 199]. Platelets are associated with a sevenfold increased risk of acute transfusion reaction compared to RBC <www.shotuk.org>.

Platelet transfusion should not be used for the treatment of idiopathic thrombocytopenic purpura except in the presence of intracerebral or life-threatening bleeding [200, 201]. Platelets are also contra-indicated in cases of heparin-induced thrombocytopenia and of thrombotic thrombocytopenic purpura [196]. Alternatives to platelet transfusion, such as DDAVP or antifibrinolytic agents, should be considered as first choice therapies when appropriate [202].

The "Nuts and Bolts" of Platelet Transfusion

The amount of platelet concentrate (either whole blood derived or apheresis platelets) generally prescribed ranges from 5 to 10 mL/kg for infants weighing less than 10 kg. For older children weighing more than 10 kg, the usual starting dose is 1 whole blood derived unit per 10 kg (i.e. 1 unit for 11–20 kg child, 2 units for 21–30 kg child, etc.) or approximately 10 mL/kg up to a maximum of 1 pool of platelets if using apheresis or pre-pooled platelets. It can be expected that this should increase the platelet count by 50,000/mm^3 unless there is increased platelet consumption [84]. It is standard practice to give no more than five units of whole blood derived platelet concentrates or one apheresis platelet unit per transfusion. The recommended infusion time is 60 min or less. All platelet units must be administered within 4 h after delivery from the blood bank.

Platelets possess intrinsic ABO antigens and extrinsically absorbed A and B antigens [203]. Nevertheless ABO incompatible platelets (i.e. platelets with A and/or B antigens given to a donor with a corresponding antibody) are usually clinically effective. However there are several reports of acute

intravascular hemolysis following the transfusion of platelet concentrates containing ABO antibodies incompatible with the recipient's RBC [203, 204]. Therefore ABO-matched platelets should be used in pediatric patients especially for neonates and small children where the volume of plasma may be relatively large with respect to the patient's total blood volume. If ABO-matched platelets are not available, units with plasma compatible with the recipient's RBCs should be chosen. If this is also not possible, units with low titers of anti-A or anti-B should be selected or alternatively the plasma can be removed from the platelet concentrate (i.e. use a volume reduced platelet concentrate) [2]. Platelets do not carry Rh antigen, but concentrates contain RBCs in numbers sufficient to sensitize the recipient. An anti-D vaccine (Win Rho SDR®) should be given if the recipient is a Rh^- woman of childbearing potential and the donor is Rh^+ [2]. Each 120 mcg of Rh-immunoglobulin covers 12 mL whole blood (6 mL RBC) and lasts approximately 21 days [205]. Tobian et al. [206] reported that the incidence of allergic transfusion reactions to unmanipulated apheresis platelets is 5.5 %, and that concentrating and washing reduced this incidence to 0.5 %. Recipients of HLA-matched platelets should receive irradiated platelets in order to prevent graft versus host disease.

Serious Hazards of Transfusion

Labile blood products (RBC units, frozen plasma, platelet concentrates and cryoprecipitate) can cause early onset or late onset reactions and complications (Tables 19.2 and 19.3) [197]. By definition, immediate reactions occur while the transfusion is being given or within 24 h after the end of the transfusion. Late reactions and complications appear days, weeks or even years later. Severe reactions probably attributable to the transfusion of a blood product should be reported to the hospital blood bank.

The transfusion of a blood product can result in early as well as late onset death. The overall mortality rate attributed to the transfusion of a blood component dropped to 1/2,845,459 per transfusion in the United Kingdom in 2008 (Serious Hazards of Transfusion Group: (www.shotuk.org). [205]. The risk is higher with platelet concentrates: in 2000, the mortality observed in Canada and attributed to the transfusion of a blood product was 2.2 per 100,000 RBC units and 6.3 per 100,000 platelet pools [209]. The Center for Biologics Evaluation and Research of the Food and Drug Administration receives approximately 60–70 transfusion-related fatality reports per year [216]. The 13 deaths reported in 2010 by the "Serious Hazards Of Transfusion" (SHOT) system of the United Kingdom were caused by TACO (7), TRALI (1), hypotension (1), anaphylactic reaction (1), hyperhemolysis (1) and under-transfusion in a case of hemorrhagic shock.

Table 19.2 Reactions and complications related to blood product transfusions

	Frequency
1. Early onset reactions (<24 h)	
Transfusion-related acute lung injury (TRALI) [207]	1/31,960
Transfusion associated circulatory overload (TACO) [207]	1/34,091
Isolated hypotensive reaction [207]	1/102,273
Major allergic reaction (anaphylaxis) [207]	1/11,117
Minor allergic reaction [207]	1/100
Febrile non-hemolytic reaction [207]	1/50–1/200
Acute hemolytic transfusion reaction [207]	1/26,914
ABO incompatibility [208]	1/800,000
2. Early onset complications of massive transfusion [199][a]	
Coagulopathy	Frequent
Thrombocytopenia	Common
Hypothermia	Common
Hypocalcemia, hypomagnesemia, citrate toxicity	Common
Hyperkalemia	1/20
Metabolic alkalosis by citrate toxicity, metabolic acidosis	Rare
3. Late onset complications of transfusion	
Delayed hemolytic reaction [207]	1/255,682
Allo-immune thrombopenia	Unknown-rare
Post-transfusion purpura [207]	1/85,227
Infections	See Table 19.3
Transfusion associated graft versus host disease (TA-GvHD) [214]	1/1,000,000
4. Early and late deaths [215]	1/2,845,459

[a]Definition of massive transfusion : administration of more than one blood volume of blood products within a 24 h period

Acute Reactions

Any unexpected or unexplained change in the clinical condition of a patient during a transfusion or up to 24 h afterwards should be considered (and evaluated) as possibly being due to an acute transfusion reaction, and should be reported to the local blood bank [217].

Transfusion-Related Acute Lung Injury (TRALI)

TRALI is now a well-recognized reaction to transfusion of blood products and also one of the most serious. A TRALI is an acute lung injury (ALI) that appears during or within 6 h after the end of a transfusion. A panel of experts created a list of diagnostic criteria of TRALI that is detailed in Table 19.4. The criterion of "no pre-existing ALI before transfusion" means that TRALI cannot be diagnosed when an ALI is already present. Clinically, TRALI resembles ARDS and involves respiratory symptoms such as hypoxemia, dyspnea and frothy sputum as well as hypotension, tachycardia and fever [216]. Chest radiograph findings are also similar to those seen in ARDS and

Table 19.3 Infections potentially caused by blood product transfusion

Infection	Risk per transfusion[a]
HIV (AIDS) [207]	1/4,000,000
Hepatitis A [209]	<1/10,000,000
Hepatitis B [b] [210]	1/282,000–1/357,000
Hepatitis C [207]	1/2,800,000
Other hepatitis (D, E, etc.)	Unknown-rare
HTLV (Health Protection Agency) <www.hpa.org.uk>	1/17,000,000
Cytomegalovirus [209]	Unknown-rare
Parvovirus B_{19} [207]	1/5,000–1/20,000
TTBI (platelet) [209]	13–44/100,000 platelet pools
TTBI (RBC unit) [209]	0.02/100,000 RBC units
Other infections [c]	Unknown

HIV human immuno-deficiency virus, *HTLV* human T-lymphocyte virus, *RBC* red blood cell, *TTBI* transfusion transmitted bacterial infection

[a]Risk per transfusion of blood product: these figures are applicable only in countries where virus testing is systematically performed (testing for HIV, hepatitis B and C is systematically performed in less than 45 % of members states of the World Health Organization [211])

[b]The risk for transfusion-transmitted chronic HBV disease in Canada was estimated to be 1 in 2,240,000 transfusion in year 2003 [209]

[c]Other infections: zoonoses such as babesiosis [210], Colorado tick fever [210], Chagas disease [211], dengue [210], malaria [210], variant Creutzfeldt-Jacob disease [212], West Nile virus [213], etc.

Table 19.4 Diagnostic criteria of TRALI

The following diagnostic criteria of transfusion-associated acute lung injury (TRALI) were adopted during a Consensus Conference held in Toronto in 2004 [218]
Diagnostic criteria of TRALI: all six criteria must be present in order to diagnose a TRALI
1. Acute onset of acute lung injury (ALI)
2. Hypoxemia
Research setting:
PaO_2/FiO_2 ratio ≤300
or SpO_2 <90 % on room air
Nonresearch setting:
PaO_2/FiO_2 ratio ≤300
or SpO_2 <90 % on room air
or other clinical evidence of hypoxemia
3. Bilateral infiltrates on frontal chest radiograph
4. No evidence of left atrial hypertension (i.e., circulatory overload)
5. During or within 6 h of transfusion
6. No temporal relationship to an alternative risk factor for ALI
Diagnostic criteria of possible TRALI:
1. ALI
2. No preexisting ALI before transfusion
3. During or within 6 h of transfusion
4. A clear temporal relationship to an alternative risk factor for ALI

show generalized opacities. In 90 % of cases, the reaction appears within 1–2 h after a transfusion is started. HLA antibodies and/or granulocyte antibodies are positive in 65–83 % of tested donors [216, 219]. Respiratory symptoms usually disappear within 48–96 h, which is different from the progression typically seen in ARDS [220]. All blood products containing some plasma can cause a TRALI, but frozen plasma (50 %) and packed RBC units (31 %) are more frequently involved than platelet concentrates (17 %) [216].

The incidence of TRALI was between 1/1,000 and 1/8,000 transfusions in the 90s and the early 2000 [221–223]. A recent surveillance study completed in 2010 reported an incidence rate of 1.8 TRALI per 100,000 transfusions in Canadian children [224]. In this study, three out of the four cases of TRALI occurred in PICU patients. Furthermore, two cases occurred in neonates who underwent cardiac surgery, raising the possibility that these patients are at greater risk of TRALI.

The mechanisms involved in the physiopathology of TRALI are still being debated. The most popular hypotheses include: (1) a reaction between donor antibodies (anti-granulocyte, anti-HLA class I or II) and recipient antigens that initiates an inflammatory reaction in the lungs; (2) the neutrophils of a recipient primed by surgery, trauma or an infection overreact when exposed to inflammatory activators (anti-leukocyte, biologically active lipids, etc.) that are either present in the donor's blood or that were produced during storage [225, 226]. Recent studies suggest that the two theories might be somewhat linked [227]. This has lead to the development of a unifying model (the threshold model) by Bux et al. [228] According to this model, the level of priming of neutrophils, either directly or through activation of the pulmonary endothelium, by a patient clinical condition and by substances (including antibodies) present in the transfused component, is responsible for triggering TRALI in a recipient.

The treatment of TRALI involves cessation of the blood product deemed responsible and is otherwise the same as that of ARDS. When a TRALI is suspected, the transfusion must be stopped immediately, and supportive treatment must be started. Oxygen, mechanical ventilation and fluids may be required [229]. Diuretics are not recommended because they increase the risk of severe hypotension [230].

In some countries like the United Kingdom, Canada and USA (American Red Cross), blood collected from multiparous women is not used for transfusion, but sent to fractionation (production of albumin, IVIg) and/or a policy of preferential use of male donors has been implemented, the hypothesis being that this should reduce the exposure of blood receivers to donor antibodies (anti-granulocyte, anti-HLA) [231–233]. In the United Kingdom, provision of male plasma was associated with a reduction in TRALI reports from 36 in 2003 to 23 in 2004 and 2005 and 10 in 2006 [219]. The mortality rate of TRALI is approximately 6 % [221], but the prognosis is good in most cases. In survivors, resolution is usually rapid (within 96 h) and there are no

long-term sequelae [230]. However hypoxemia and pulmonary infiltrates persist more than 7 days in some patients (20 %) [229].

The diagnostic criteria advocated by the panel of experts in 2004 [218] exclude the possibility that a TRALI appears in a patient who already presents an ALI or an ARDS when a RBC transfusion is initiated, which is frequent in the PICU. There is indeed some evidence that a TRALI should also be considered in some patients with ALI/ARDS before a transfusion if their respiratory dysfunction deteriorates significantly during or after a transfusion. Marik et al. [234] suggested expanding the definition of TRALI in ICU to ALI/ARDS observed within 72 h after the transfusion of a blood product: they reported that such "delayed TRALI syndrome" occurred in up to 25 % of critically ill adults receiving a blood transfusion. Church et al. [235] also reported an association between the transfusion of plasma and/or packed RBC units and ALI/ARDS. The bioactive substances contained in packed RBC and plasma units can cause or add to the severity of cases of ALI/ARDS [235–237]. Further investigation is required to better characterize the epidemiology, the mechanisms and the clinical impact of transfusion-related delayed TRALI syndrome in PICU.

Transfusion-Associated Circulatory Overload (TACO)

TACO, also named transfusion-associated congestive heart failure, is probably underreported. The incidence rate of TACO collected by the SHOT system is 1/34,091 transfusion, but Popovsky believes that the real incidence rate can be up to 1 % [220], especially after massive transfusions. The incidence rate of TACO in PICU is unknown, but in 2010, TACO was the most common transfusion-related death in UK. According to the British Haemovigilance System (SHOT), a TACO is present if at least four of the five following criteria are met within 6 h after a transfusion: (1) acute respiratory distress; (2) tachycardia; (3) increased blood pressure; (4) acute or worsening pulmonary edema; (5) evidence of positive fluid balance <www.shotuk.org/shot-reports>. All patients with cardiac disease or chronic anemia (Hb < 5 g/dL) are at risk, including newborns. Circulatory overload can be prevented to some extent by slowing the rate of transfusion (to less than 1 mL/kg/h) in patients at risk. Other modalities include pre-emptive diuretics and splitting components into smaller aliquots. Treatment consists in cessation of the transfusion, attention to fluid balance, use of diuretics if necessary and supportive ventilatory measures.

Hypotensive Reaction

Hypotension following transfusion of a blood product is rare (1/102,273 transfusions in Canada [207]), but case reports have been published describing it both in adult and pediatric patients [238]. In most instances, these reactions seem to be caused by a bradykinin modulated metabolic reaction elicited when the blood product is exposed to a negatively charged surface like a transfusion filter. Patients receiving angiotensin conversion enzyme inhibitors as well as patients with an abnormal bradykinin catabolism, a common occurrence in cases of sepsis, are also at risk [197]. Hypotensive reactions usually appear quite soon after the transfusion is initiated and in most instances, there is no fever, although some flushing has been described. These reactions are more frequent after transfusion of platelet concentrates [238]. Pre-storage leukocyte reduction seems to decrease their incidence, although it does not eliminate them entirely [239]. Close monitoring of all patients receiving angiotensin conversion enzyme inhibitors is required.

Fever

Fever is the most frequent reaction to a blood product transfusion. It is not dangerous unless it is caused by a hemolytic reaction or a bacterial contamination. Its frequency after transfusion of a packed RBC unit is about 1 % [163, 240] and can be as high as 10 % after transfusion of platelet concentrates [241]. A **febrile non-hemolytic transfusion reaction** (FNHTR) is defined as a *de novo* rise in temperature equal to or greater than 1 °C that cannot be explained by the patient's clinical condition (i.e. other causes of fever must be ruled out). The fever can be accompanied by dyspnea, tachycardia, headache, anxiety, rigors (shivering) as well as nausea and vomiting [220]. These symptoms usually appear at the end or just after the end of transfusion. FNHTR is thought to be caused primarily by two mechanisms involving white blood cells. Firstly, FNHTR may occur when HLA antibodies present in a recipient react with donor white blood cells present in a RBC or platelet component. This leads to complement activation and cytokine release, which results in the typical symptoms of a FNHTR. Alternately (and likely more commonly, at least in the case of platelet transfusions) cytokines are released from white blood cells during the storage of blood components; when transfused, these cytokines can lead to a FNHTR in the recipient. The proportion of patients with fever episodes decreased from 24.7 % prior to the introduction of the pre-storage leukoreduction program to 22.5 % following its implementation in Canada (OR 0.88; 95 % CI 0.82–0.95; p = 0.001) [242]. It may be useful to use washed blood products for patients with a history of repeated and severe FNHTR to leukocyte-reduced blood products. Acetaminophen can be used to minimize fever, but premedication with acetaminophen, diphenhydramine or steroids is not helpful [243, 244].

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions are characterized by hemoglobinuria and/or hemoglobinemia (blood level of free Hb above normal range) with at least one of the following

symptoms and signs: *de novo* fever, dyspnea, hypotension and/or tachycardia, anxiety/agitation, pain [220]. Acute hemolytic reactions are rare (1/26,914 according to MacDonald et al. [207]), but may be fatal. The destruction of RBCs in the recipient is attributed to immunological incompatibility (donor RBC antigens reacting with recipient antibodies). Acute hemolytic reactions are usually caused by the transfusion of an incompatible blood product, an adverse event that is attributable to error in 86 % of cases. Acute hemolysis due to ABO incompatibility is the leading cause of severe reaction to RBC transfusion (1/108,968 RBC transfusions) [207]; however, other erythrocyte antigens can be involved (D/d, C/c, E/e, Kell, etc.). Hemolysis is associated with hemoglobinuria and acute anemia. Fever is also frequent, as well as shivering, discomfort and general pain. In severe cases, hypotension, shock, renal insufficiency and DIC can be observed. A mortality rate as high as 10 % is reported [197]. In order to prevent such hemolytic reactions, correct labeling of the blood sample for pre-transfusion testing is essential and, at the time of transfusion, compatibility between donor and recipient including ABO and Rh groups, the identification number of the unit as well as the identity of the recipient (name and hospital chart number) must be meticulously verified and routinely double-checked at the patient's bedside.

Non-immunologic Hemolysis

Non-immunologic hemolysis can be caused by mechanical trauma to RBCs (transfusion through a very small needle with high pressure), use of a cell-saver device or mechanical warmer (excessive warming), incorrect storage (e.g. if temperature goes below 0 °C), injection using lines that contain a hypotonic solution and bacterial contamination.

Allergic Reactions

Allergic reactions related to type I hypersensitivity reactions can occur when allergens from the donor react with antibodies from the receiver. Such reactions are usually minor (urticaria: 1/100 RBC units [163],) but may be severe (anaphylaxis: 1/20,000 RBC units) [163]. As reported by SHOT (2010 Annual Report <www.shotuk.org/shot-reports>), "anaphylactic reactions… occur most frequently during the first 15 min of a transfusion (mean time to onset 26 min in cases reported in 2010)", but the risk exists throughout the whole transfusion episode. At least one of the following signs/symptoms is present in severe cases: cardiac arrest, generalized allergic reaction or anaphylactic reaction, angioedema (facial and/or laryngeal), upper airway obstruction, dyspnea, wheezing, hypotension, shock, precordial pain, chest tightness, cardiac arrhythmia or loss of consciousness [220]. The risk for severe allergic reactions is greater in patients with IgA antibodies associated with IgA deficiency. Severe reactions usually occur more rapidly than mild reactions. Fever is usually not observed, but a rash is possible. Severe allergic reaction may be life-threatening [197]. It is advisable to administer antihistamines prior to transfusing patients who have presented repeated minor allergic reactions to blood products; the use of corticosteroids as well as using washed packed RBC units or platelet concentrates may also be considered particularly for severe or repeated reactions that do not respond to premedication with antihistamines. Patients with an IgA deficiency and anti-IgA should receive blood from donors with that same deficit or, in the case of cellular blood components, products that have been thoroughly washed. White blood cell reduction does not prevent allergic reactions.

Infections

All blood product administration involves a potential for transmission of infections. Bacterial contamination of blood products is the cause of 10 % of deaths attributable to transfusions. The risk of bacterial contamination is higher for platelets (1/31,189 units) than for RBC units (1/65,381 units) [207], as platelets are stored at 22 °C while RBCs are stored at 4 °C. Many preventive techniques have been implemented in the last years in order to decrease the risk of bacterial infections caused by platelet transfusions, which have significantly improved the safety of platelets transfusions. For example, the incidence in the Province of Quebec of probable and definite transfusion-transmitted bacterial infections associated with whole blood-derived platelets decreased from 1 in 2,655 in 2000 to 1 in 58,123 five-unit pools in 2008 ($p < 0.001$) [245]. It is estimated that transfusion-related sepsis occurs in 15–25 % of patients who receive contaminated platelet concentrates [211]. Potential sources of contamination include unrecognized bacteremia in the donor due to *Yersinia enterolytica* or *Salmonella* gastroenteritis, *Staphylococcus aureus* infection caused by dental manipulation, contamination of donated blood by normal skin flora during collection and infection occurring due to manipulation of blood products. The most common germs are: Gram negative bacteria like *Klebsiella pneumoniae*, *Serratia marcescens* and *Pseudomonas species*, and Gram positive like *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus cereus*. The reaction usually occurs during or within a few hours after transfusion and can cause milder symptoms such as fever and shivering as well as more severe complications such as septic shock. The risk of bacteremia is more important with prolonged storage time. When a bacterial contamination is suspected, the transfusion must be stopped immediately, wide spectrum antibiotics must be given (third generation cephalosporin or beta-lactam in combination with aminoglycoside) and supportive treatment administered. The blood bank must be informed immediately, as other blood products from the same donor may need to be withdrawn. Culture of the blood product itself is indicated. Several blood

suppliers now perform bacterial detection studies on platelet concentrates prior to their release into hospital inventories, but even this technique does not detect all contaminated units.

Acute Leukocytosis

Acute leukocytosis is rare after transfusion of leukocyte-reduced RBC units, but may occur after the transfusion of non filtered units [86]. White blood cells can reach values as high as 40×10^9/L, but return to normal within 24 h [86].

Acute Complications of Massive Transfusion

Massive transfusion is defined as the administration of more than one blood volume of blood products within a 24 h period, or more than 50 % of the circulating blood volume in 3 h or less, or ten RBC units in adults [199]. Serious acute complications of massive transfusion include fluid overload, hypothermia, coagulopathy and thrombocytopenia, acidosis, citrate intoxication, hyperkalemia and hypocalcemia [246].

Hypothermia

The massive transfusion of blood products can cause hypothermia, which can lead to problems like tissue hypoxia, arrhythmias, coagulation disorders (increased PT and PTT, platelet dysfunction), increased blood viscosity, high blood lactate level, hyperkalemia and decreased metabolism of drugs. Mortality is higher if the body temperature drops below 34 °C [247]. Treatment and prevention of hypothermia involve warming blood products as well as the patient (blanket, heating lamp, etc.).

Coagulopathy

The coagulopathy and thrombocytopenia observed after massive transfusion of RBC units is attributed to hemodilution, hypothermia, administration of blood products with a prolonged length of storage and DIC [248]. Transfusion-related coagulopathy can be diagnosed if at least one of the following criteria is observed during or shortly after a massive transfusion: INR (international normalized ratio) >2.0; activated partial thromboplastin time (aPTT) >60 s; positive assay for fibrin-split products; D-dimers >0.5 mg/mL [220]. It is frequently recommended to give plasma and platelets if a RBC volume corresponding to 1–1.5 times the circulating blood volume is administered within a short period of time.

Citrate Intoxication

Citrate can cause early onset acidemia, though metabolic alkalosis can also develop due to the liver metabolizing citrate [249]. Citrate intoxication occurs if the metabolic capacity of the liver is overwhelmed, which can occur with administration of packed RBCs at a rate greater than 3 mL/kg/min and of whole blood or plasma at a rate greater than 1 mL/kg/min [250, 251]. Citrate intoxication can cause severe hypocalcemia [252]. Callum et al. [205] recommended the following strategy in order to avoid complications related to massive transfusion: monitor core temperature and prevent hypothermia using a blood warmer for all intravenous fluids and blood components; monitor the coagulation profile and transfuse platelets, plasma or cryoprecipitate to maintain a platelet count >50,000/mm^3, an INR < 1.5–2.0 and fibrinogen level over 0.1 g/dL; monitor hyperkalemia, acidosis and hypocalcemia, and give $CaCl_2$ if necessary.

Hyperkalemia

Hyperkalemia is a potential complication with all RBC transfusions, especially if the transfusion is given rapidly. Potassium is released in the supernatant by RBC leak or lysis. Its level increases linearly and is approximately equal to the number of days of storage [253]. Potassium levels have been measured in CPDA-1 and SAGM: it increases from 5.1 to 78.5 mmol/L (1st–35th day) in the former, from 2.1 to 45 mmol/L (1st–42nd day) in the latter [253]. Irradiation further increases the potassium concentration in units stored following irradiation [254]. Monitoring of potassium levels in transfusion recipients is essential, and it is advisable to administer packed RBCs at a rate no greater than 0.3 mL/kg/min whenever possible. Notwithstanding these concerns, the frequency of hyperkalemia caused by RBC transfusion is low. Parshuram et al. [254] have shown that the transfusion of 11 mL/kg of packed RBC units to critically ill children increases the potassium blood level from 3.85 ± 0.55 to 3.94 ± 0.62 mmol/L, a difference that is not clinically, nor statistically significant.

Late Onset Reactions and Complications

Late reactions to transfusion occur days, weeks or even years after the transfusion. Serious late-onset non-infectious complications of blood transfusions include hemolysis (delayed hemolytic transfusion reaction), transfusion-transmitted infections, post-transfusion purpura, allo-immune thrombocytopenia, graft versus host disease, and possibly (though controversial) TRIM (see above).

Delayed Hemolytic Reactions

In 2006, the incidence rate of delayed hemolytic reactions was one per 255,682 transfusions in Canada [207]. Delayed hemolytic reactions are caused by antibodies in the recipient that are not detected during pre-transfusion compatibility testing and that developed either because of prior RBC transfusions or because of exposure to RBCs of fetal origin. The most frequently involved antibodies are: E, Jk^a, c, Fy^a, K [255]. The hemolytic reaction usually begins 3–14 days after

transfusion. Most cases are mild and resolve spontaneously, but severe cases can occur, especially in sickle cell patients (hyperhemolysis). There is no specific treatment. Erythrocyte alloimmunization following transfusion can occur in 1–8 % of recipients and is a particular concern in young girls who may then be at risk for hemolytic disease of the fetus/newborn in future pregnancies [163].

Post-Transfusion Purpura (PTP)

PTP is rare, but can be severe. It manifests itself by a low platelet count (below 10×10^9/L) any time between 1 and 24 days after transfusion in patients sensitized to platelet antigens by prior transfusion or pregnancy [197]. The pathogenesis is unclear and presumably is related to the presence of platelet-specific antibodies in the recipient following previous exposure to human platelets. These antibodies destroy both transfused platelets and the recipient's own platelets. Severe hemorrhage can occur in the gut, urinary tract and/or brain. The thrombocytopenia is refractory to platelet transfusion and the mortality rate is reported to be as high as 8 % [256]. Giving platelet concentrates that are free of the implicated platelet antibodies to susceptible patients can prevent this type of reaction. The thrombocytopenia appears suddenly, but it is usually self-limiting. Steroids, plasmapheresis and immunoglobulins may be required in severe cases. The acute onset of severe thrombocytopenia following transfusion can also occur when a plasma-containing component from a donor with anti-platelet antibodies is administered to a recipient possessing the corresponding platelet antigen.

Infections

Nowadays, non-infectious serious hazards of transfusion (NiSHOTs) are more frequent and more challenging to practitioners than transfusion-transmitted infectious diseases [58]. This does not mean that there is no risk. There will always be some residual risk of infections, attributable to the "window period" (time from the beginning of an infection to the time when tests can detect the infection) and to false negative results. Table 19.3 lists the most frequent or most important infections attributable to transfusions. Although transfusion transmitted hepatitis B virus (HBV), hepatitis C virus (HVC) and human immuno-deficiency virus (HIV) have become exceedingly rare, the risk of transfusion transmitted infectious diseases including the risk of bacterial contamination, cytomegalovirus (CMV) transmission and infection with emerging infectious disease agents and with viruses for which testing is not currently performed (e.g. human herpesvirus-8) [257] continues to be a major concern [258]. Transmission of insect-borne zoonosis is also a well-recognized problem (for example: West Nile virus [213], malaria [259], babesiosis [260], *Bartonella Quintana* [261]) A few cases of prion (agent causing variant Creutzfeld-Jacob disease or vCJD) transmission by a transfusion have been reported [212]. SD plasma has a reduced risk of infection related to enveloped viral pathogens, but the risk for non-enveloped viruses is not affected.

Transfusion Associated Graft Versus Host Disease (TA-GvHD)

TA-GvHD is a rare adverse event that can be extremely severe [214, 262]. The "Serious hazard of transfusion (SHOT) initiative" run in United Kingdom reported that 8 out of 22 deaths (36 %) attributed to a transfusion were caused by a TA-GvHD [263]. TA-GvHD has occurred in two settings. The first clinical setting in which TA-GvHD occurs is severely immunocompromised patients (such as those with congenital immune deficiency syndromes or cancer patients receiving chemotherapy) or preterm infants with immature immune systems unable to reject donor T lymphocytes found in cellular blood components [264]. Hence the donor T lymphocytes are able to engraft, proliferate, and then attack recipient tissues. An ICU group at particular risk is DiGeorge patients undergoing cardiovascular surgery for congenital cardiac anomalies associated with this syndrome. Surprisingly HIV infected patients are not at risk for TA-GvHD. The second clinical setting in which TA-GvHD occurs is the setting in which donor lymphocytes are able to engraft because they are not recognized as foreign by a non-immunosuppressed receiver. This occurs when the donor is HLA homozygous for one of the HLA haplotypes present in an HLA heterozygous recipient. This situation can occur in a population with relative HLA homogeneity (e.g. the Japanese) or in the setting of directed donations from biologic relatives or if HLA-matched platelets are given to treat a patient with immune refractoriness to unmatched platelets [2, 264]. Symptoms usually appear 8–28 days after transfusion and include fever, skin rash, diarrhea and hepatic dysfunction. A severe pancytopenia can be caused by bone marrow dysfunction. TA-GvHD is fatal in 90 % of patients if untreated, a fatality rate that is significantly higher than with GvHD related to bone marrow transplantation [84]. Lymphocyte multiplication can be blocked by irradiation, which dramatically reduces and probably eliminates the risk of contracting TA-GvHD. Leukoreduction of cellular components is not sufficient to prevent TA-GvHD.

Non-specific Treatment of Transfusion Reactions

When a transfusion reaction is suspected, the following actions must be undertaken immediately:

- Stop the transfusion immediately.
- Check if the patient received the correct unit.
- Maintain an intravenous access with NaCl 0.9 %.
- Insure patient stability.

- Re-check identification of patient and blood product.
- Report in detail the clinical data of the event in the hospital chart.
- Monitor the patient for at least a few hours.
- Collect blood cultures from the patient if bacteremia is suspected,
- Measure antibodies, antigens, free Hb or other markers of metabolic disturbance (acidosis, hyperkalemia, hypocalcemia, etc.) if appropriate.

Some attention must also be paid to the transfused unit:

- Look at the unit and describe your observation in the patient's hospital chart.
- Return the unit that was being transfused, the filter and the tubing being used, and the remaining blood product to the blood bank.

All possible transfusion reactions must be immediately reported to the appropriate blood agency, which is the blood blank in many hospitals.

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Hematologic Emergencies in the PICU

20

Martin C.J. Kneyber

Abstract

The pediatric critical care physician is frequently challenged by hematologic abnormalities in critically ill children admitted to the pediatric intensive care unit (PICU). The challenge is to differentiate between primary hematologic emergencies that require critical care interventions and abnormalities secondary to other disease conditions. It is therefore necessary for the pediatric critical care physician to collaborate with the pediatric hematologist when managing such patients. This chapter summarizes some of the most common hematologic emergencies of red blood cell (RBC), white blood cell (WBC), or platelet disorders observed in critically ill children that may require attention of the pediatric critical care physician.

Keywords

Hematologic emergency • Erythrocyte • Platelets • Sickle cell disease • White blood cells

Introduction

The pediatric critical care physician is frequently challenged by hematologic abnormalities in critically ill children admitted to the pediatric intensive care unit (PICU). The challenge is to differentiate between primary hematologic emergencies that require specific interventions and abnormalities secondary to other disease conditions. The purpose of this chapter is to summarize some of the most common hematologic emergencies seen in critically ill children that are associated with red blood cell (RBC), white blood cell (WBC) or platelet disorders. Transfusion medicine, oncologic emergencies, and coagulation disorders are discussed in other chapters. Of importance, many patients admitted for other reasons may have underlying disorders of elements of blood. It is beyond the scope of this chapter to go into detail about many of these disorders. The reader is kindly referred to books on pediatric hematology. As a consequence, it is therefore necessary for the pediatric critical care physician to collaborate with the pediatric hematologist when managing such patients.

Part 1: Red Blood Cell Disorders

Anemia is common in critically ill children. In a prospective multicenter observational study performed in 30 North-American PICUs it was observed that 33 % of the patients had anemia (defined by the Hb concentration two standard deviations below the mean normal Hb concentration for each group) upon PICU admission and 18 % developed anemia >48 h after PICU admission [1]. Acute anemia is mainly due to acute blood loss, aggressive fluid resuscitation with crystalloids, acute hemolysis, or acute splenic sequestration. Subacute anemia in critically ill children is frequently caused by repetitive daily blood sampling usually done in the PICU [2].

A large number of diseases will lead to some form of anemia (Table 20.1). In general these causes can be

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Table 20.1 Classification of anemia

Decreased production	Impaired development of red blood cells
	Aplastic anemia
	Bone marrow infiltration
	Bone marrow hypoplasia
	Pure red cell aplasia
	Transient erythrocytopenia of childhood
	Inadequate production of erythropoietin
	Chronic disease
	Endocrine disorders
	Malnutrition
	Renal disorders
Maturation impairment	Iron deficiency
	Lead poisoning
	Sideroblastic anemia
	Thalassemias
	Vitamine B12 or folate deficiency
Increased destruction or turn-over	(Auto-) Immune-mediated
	Drug-induced
	Dyshemoglobinemias
	Enzymopathy
	Hemoglobinopathies (sickle cell disease)
	Infection-related
	Spherocytosis
	Burns
	Hemophagocytic syndrome

Table 20.2 First-line diagnostic tests in anemia

	Test
Screening	Complete blood count
	Red cell indices (MCV, MCHC)
	Peripheral blood film
	Reticulocyte count
Confirmatory	Coombs test (direct and indirect)
	Hemoglobin electrophoresis
	G-6-PD assay
	Bone marrow aspirate
	Iron studies
	Serum B12 and folate
	Haptoglobin

MCV mean corpuscular volume, *MCHC* mean corpuscular hemoglobin concentration, *G-6-PD* glucose-6-phosphate dehydrogenase deficiency

classified as resulting from underproduction, impaired maturation, or increased turn-over or destruction (i.e. hemolysis) of RBCs. Hemolysis can be attributed to numerous causes originating from either intracellular or extracellular disorders, including RBC membrane defects, abnormal erythrocyte metabolism, immune mediated hemolysis (for instance ABO mismatch or auto-immune mediated hemolysis), and primary hemoglobinopathies such as thalassemias and sickle cell disease (SCD). Diseases leading to anemia can be identified by symptoms and diagnostic investigations (Table 20.2), of which the cell indices provide important information, in particular the mean corpuscular volume (MCV) (Table 20.3) [3].

Irrespective of its cause, anemia results in decreased O_2 carrying capacity and ultimately decreased O_2 delivery (DO_2). Clinical symptoms vary widely and include pallor, nausea, vomiting, weakness, fatigue, irritability, tachycardia, tachypnea and edema. However, it is not clear what the impact of anemia itself is on outcome of critically ill children. A Hb < 5 g/dL has been associated with increased mortality in non-critically ill children [4–6]. Furthermore, anemia was identified as an independent predictor for mortality in critically ill adults, whereas one group of investigators did not observe such an association in a heterogeneous group of critically ill children [7, 8]. Importantly, the landmark paper from the TRIPICU study has clearly shown that stable critically ill children can tolerate a Hb of 7 g/dL without serious complications [9]. In this multicenter prospective study comprising 637 stable critically ill children the occurrence of new or progressive multiple organ dysfunction syndrome was similar between patients randomized to a restrictive transfusion strategy (threshold Hb 7 g/dL) and liberal transfusion strategy (threshold Hb 9.5 g/dL) within 7 days of PICU admission. A post-hoc analysis of postsurgical PICU patients and children after cardiac surgery showed similar findings [10, 11]. At present, no data is available identifying a proper threshold for unstable critically ill children such as those with severe hypoxemia or hemodynamic compromise. Therefore, the decision to treat anemia is determined by the underlying cause, the acuteness, and the physiologic status of the child.

Anemias of Underproduction and/or Impaired Maturation

There are a number of diseases that lead to underproduction of erythrocytes and anemia, whereas iron deficiency or lead poisoning are well known causes of impaired maturation of RBCs. The majority of these conditions are chronic, with the exception of bone marrow failure affecting a single or even multiple cell lineages causing pancytopenia. The most common cause of acquired pancytopenia in the PICU is leukemia – either at presentation or as a consequence of chemotherapy or irradiation. Alternatively, many drugs often used in the PICU (e.g., antibiotics, ibuprofen, captopril and phenytoin) and infectious agents such as Parvovirus B19, hepatitis virus, Ebstein-Barr virus, cytomegalovirus, tuberculosis and human immunodeficiency virus are important causes of bone marrow failure. Of importance, pancytopenia

Table 20.3 Diagnosis of anemia using cell indices

	Low MCV	Normal MCV	High MCV
Normal RDW	Thalassemia trait	Lead toxicity	Aplastic anemia
High RDW	Iron deficiency Hemoglobin H disease	Liver disease	B12/folate deficiency
High RDW and high MCHV/HDW		Immune hemolysis Sickle cell disease Heriditary spherocytosis	

MCV mean corpuscular volume, *RDW* red cell volume distribution width, *MCHC* mean corpuscular hemoglobin concentration, *HDW* hemoglobin distribution width

may present as sepsis with bruising, hemorrhage, pallor and fatigue. Symptoms develop usually gradually, but aplastic crisis can ultimately result in cardiovascular collapse. Peripheral blood smear will show normocytic anemia with a low or absent number of granulocytes and platelets. Although many cases are mild and self-limiting, supportive therapy such as eliminating identifiable causative toxins or treating underlying infections or malignancy is indicated. Transfusion is indicated when there is cardiovascular compromise, though as discussed in the previous chapter, there are no standard threshold criteria for transfusion that can be applied in every situation.

Anemias of Increased Turnover or Destruction

Many hematological diseases may result in severe hemolytic anemia, such as sickle cell disease (SCD), thalassemias and (non-) immune mediated hemolysis.

Sickle Cell Disease

Sickle cell disease (SCD) is one of the most important causes of hemolytic anemia that may bring a patient into the PICU. SCD is the general term for all phenotypes related to mutations in the hemoglobin gene found at chromosome 11p15.4 that are characterized by red cell sickling following hemoglobin deoxygenation, chronic hemolysis, recurrent vaso-occlusion, and ischemic injury to various organs [12]. Sickle cell anemia (SCA) is the most common form of SCD. It is an autosomal recessive disease caused by the substitution of valine for glutamine at the sixth amino acid position of the beta chain of the hemoglobin gene. Sickle cell trait (SCT) differs from SCA in that it is a heterozygous condition and does not cause active disease. SCA primarily affects individuals from African, Mediterranean, Indian, and Middle Eastern descent, although there is also a high incidence among Hispanic individuals from the Caribbean, Central American and some South American countries [13].

Factors that promote sickling include desaturation of hemoglobin (either by failure to oxygenate in the lungs, diminished DO_2 or increased tissue extraction of oxygen), and increased microvascular transit time as seen in dehydration or vasoconstriction (Table 20.4). The number of RBCs that sickle depends on the extent and duration of deoxygenation, the proportion of abnormal ß-chain in the Hb (HbS) of affected cells, and the presence of fetal Hb in the erythrocytes. The conformational change in HbS enables polymerization between Hb molecules. Children with SCD may carry up to 90–100 % of HbS. HbF effectively reduces the concentration of HbS [14]. Hydroxyurea promotes the formation of HbF, hence its use is recommended in all patients with SCD to prevent SCD related complications [15]. Next to this, increased endothelial activity with production of endothelin and circulation of soluble cell adhesion molecules promotes sickle cell adhesion [16, 17]. Activation of platelets, adhesion of neutrophils, and proinflammatory cytokine release further promote sickling.

Table 20.4 Factors that may promote sickling

Hemoglobin desaturation	No oxygenation in the lungs (atelectasis, pulmonary infection, chronic lung disease, pulmonary vascular disease, high altitude)
	Diminished oxygen delivery (decreased cardiac output, severe anemia)
	Increased tissue extraction of oxygen (exercise, thyrotoxicosis, (malignant) hyperthermia, sepsis, seizures, shivering, acidosis)
Increased microvascular transit time	Increased viscosity of blood (transfusion, dehydration)
	Vasoconstriction (hypothermia, use of vasoconstrictor drugs)

Many life-threatening complications of SCD result from occlusion of the microcirculation. The first includes acute splenic sequestration crisis and transient aplastic crisis (TAC). TAC occurs in patients with SCD when there is a transient suppression of erythropoiesis following infection with a viral agent such as human parvovirus B19. This usually lasts for several days. Clinical symptoms rarely include hemodynamic instability; hence, clinical management is mainly supportive.

Acute chest syndrome (ACS), cerebrovascular accidents (CVA) and vaso-occlusive crises (VOC) are other manifestations of occlusion of the microcirculation.

Acute Splenic Sequestration

Acute splenic sequestration crisis is characterized by a sudden pooling of blood in the splenic sinusoids resulting in severe anemia. It typically occurs in children between 10 and 27 months of age, though it can also occur in young infants. It is relatively uncommon in older children because they develop functional asplenia over time, caused by repeated infarctions and subsequent fibrosis of the spleen, or autosplenectomy. Acute splenic sequestration crisis often occurs during bacterial or viral infection. Symptoms can range from mild to severe and include splenomegaly and symptoms of intravascular volume depletion. Laboratory investigations show an acute drop in Hb (>2 g/dL), reticulocytosis, thrombocytopenia, and leucopenia. The mainstay of treatment is to restore circulating blood volume and hemodynamic stability through infusion of volume expanders, and by repeated blood or exchange transfusions. One group of investigators has reported substantial mortality (35 %) when the Hb level dropped >4 g/dL. Performing a splenectomy after a first crisis is controversial because of the infectious risks associated with splenectomy. Alternatively, close long-term monitoring of the child may avoid the need for splenectomy.

Acute Chest Syndrome

ACS is one of the most common complications of SCD and is associated with significant morbidity and mortality (mortality rates ranging from 1.8 to 5 %) [18]. Pulmonary microvascular sequestration of sickled RBCs initiates ACS, leading to acute lung injury (ALI) or even ARDS necessitating mechanical ventilation [19]. Clinical symptoms include fever, (productive) cough, chest pain, dyspnea, hemoptysis, and hypoxia. Of note, these symptoms may not be present initially but frequently develop during disease course in response to other precipitating events. Laboratory investigations show leukocytosis and presence of mainly isolated upper or middle lobe consolidations on chest radiograph. Pleural effusions are less common, in contrast with adults. Repetitive episodes of ACS may have significant long-term consequences such as pulmonary fibrosis, pulmonary hypertension, or cor pulmonale. Pulmonary hypertension in ACS is associated with increased mortality in adults, but this does not seem to be the case for children and adolescents [20].

The exact pathophysiological mechanisms of ACS remains to be elucidated, but precipitating factors include bacterial and viral infections (especially in young children in winter months), higher steady-state Hb level, increased neutrophil count, and atelectasis (Table 20.5) [22]. Patients at risk for ACS may be identified by serum secretory phospholipase A2 levels [23], though this test is not widely available.

Table 20.5 Possible indications for red blood cell transfusion in sickle cell disease

Prophylactic	Pre-operative
	Post-stroke
	Abnormal transcranial Doppler flow rates
Therapeutic	Acute chest syndrome
	Transient ischemic attack
	Stroke
	Spinal cord infarct
	Persistent priapism
	Aplastic crisis
	Splenic sequestration crisis
	Refractory vaso-occlusive crisis

Based on data from Ref. [21]

Many patients with SCD also suffer from hyperreactive airways or asthma [24].

Treatment of ACS centers on treating the underlying pulmonary infection (if presumed present) and preventing infarction of lung tissue. Treating the infection prevents hypoxia and acidosis, two important risk factors of sickling; prevention of infarction minimizes pain and hypoventilation (which in itself is a risk for pulmonary infection). Therefore, conventional treatment includes oxygen, intravenous fluid hydration, broad-spectrum antibiotics, pain medications and transfusion therapy. Transfusion alone often results in significant clinical improvement [22]. Exchange transfusion aimed at decreasing HbS <30 % is indicated when the patient is severely hypoxemic or has widespread pulmonary infarction. Bronchoconstriction needs to be treated, if present. Adjunctive therapeutic interventions have emerged including corticosteroids and nitric oxide (NO). Dexamethasone limited the severity in one small study of 43 patients, but was also associated with increased rehospitalization after 72 h [25]. The use of NO in critically ill children with ACS has so far only been described in case reports; hence its routine use cannot be recommended.

Cerebrovascular Accidents

CVAs are the other predominant leading cause of morbidity and mortality in children with homozygous SCD admitted to the PICU [26]. By the age of 20 years, approximately 11 % of all patients will have suffered from infarcts, most frequently resulting from stenosis of large cerebral arteries (mainly the distal internal carotid artery and the proximal middle cerebral artery) [27]. Strikingly, approximately 15–25 % of patients with SCD have silent cerebral infarction [28]. Recent or recurrent ACS is a significant risk factor for the later development of stroke, which suggests that repeated damage to the endothelium may contribute. Abnormal cerebral flow on transcranial Doppler (TCD) ultrasound seems to be another risk factor in children [29]. Older children and adolescent suffer more often from hemorrhagic stroke caused

by ruptured aneurysms. Importantly, chronic transfusion therapy in children with SCA significantly decreased the occurrence of CVAs [30, 31]. The diagnosis of CVAs in patients with SCA is not different from other patients with CVA. Emergency management includes adequate oxygenation and exchange transfusion (targeted towards HbS <20 %) [32].

Vaso-Occlusive Crisis

VOC is a challenging and perhaps the most common complication of SCD. It is characterized by a vicious circle of sickling, micro-vascular occlusion and hypoxemia. It can occur in almost any organ in the body causing organ-specific symptoms, fever, leukocytosis and pain. The pain can be very severe. Bones are predominantly affected. Abdominal crises are difficult to discriminate from other acute or surgical abdominal diseases. Emergency management of VOC consists of adequate hydration, oxygenation, and pain control with analgesic and anti-inflammatory drugs (i.e. opioids and non-steroidal anti-inflammatory drugs). RBC transfusion may be indicated to break the vicious circle of sickling.

Functional Asplenia

Functional asplenia is common in SCD. Patient with SCD are therefore susceptible to sepsis caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Sepsis is a major cause of death in children with SCD. Preventive measures such as immunization against encapsulated bacteria and prophylactic antibiotic usage have significantly improved patient outcome [33]. Nonetheless, empiric broad-spectrum antibiotic therapy is indicated in children with SCD children when an infection is suspected.

Transfusion Therapy in Patients with SCD

The primary goal of transfusion therapy is to restore the appropriate Hb and hemotocrit (Ht) level. However, children with SCD are chronically anemic; hence, compensatory mechanisms have set in to ensure maintenance of adequate DO_2. In addition, higher Ht levels increase blood viscosity, enhancing the risk of sickling in the microcirculation. Thus, in general RBC transfusion should be used as little as possible in children with SCD except for specific indications (Table 20.6). However, exchange transfusions may be more indicated in critically ill children in order to minimize the risk of microvascular sickling; the primary goal would be to achieve an HbS <30 %. Children undergoing surgery under general anesthesia are at increased risk for severe complications such as acute chest syndrome, painful crises, neurologic complications (stroke, seizures) or renal failure.

Table 20.6 Commonly used drugs that need to be avoided in glucose-6-phoshate dehydrogenase deficiency

Antibiotics	Chloramphenicol
	Ciprofloxacin
	Sulfamethoxazole
	Nalidix acid
Antimalarials	Chloroquine
	Primaquine
Miscellaneous	Methylene blue
	Doxorubicin
	Vitamin K analogs
	Fava beans
	Moth balls

Schistocytosis

Schistocytes are fragments of RBCs formed by exposure to turbulence, shear stress, pressure fluctuation and collision with surfaces (schistocytosis). This form of hemolysis is caused by micro-angiopathic hemolysis (i.e. at the level of the arterioles), macro-angiopathic hemolysis (for instance in hemangiomas), and mechanical hemolysis in patients on extra-corporeal life support (ECLS). The most frequent causes of micro-angiopathic hemolysis in children presenting to the PICU include disseminated intravascular coagulation (DIC), hemolytic-uremic syndrome (HUS) and subacute bacterial endocarditis.

A triad consisting of hemolysis, thrombocytopenia, and acute renal failure (ARF) defines HUS. It is part of a spectrum that includes thrombocytopenic thrombotic purpura, which is seen more often in adults and is characterized by a more important neurologic involvement. Numerous – mainly infectious – agents trigger HUS; *Escherichia coli* O157:H7 is the most common, and it is frequently related to insufficient heating of meat. The pathophysiology of HUS is not clear, but likely involves injury to the endothelial cells involving ADAMTS-13 (a von Willebrand factor cleavage protein) and factor H (a complement C3 convertase inhibitor) [34]. This causes microthrombi and fibrin strands in arterioles that damage RBCs and cause platelet aggregation leading to anemia and thrombocytopenia. Children with HUS frequently present with acute renal failure. Other features include bowel involvement mimicking acute abdomen and central nervous involvement including seizures or altered consciousness. Therapy is mainly supportive and may require renal replacement therapy. Plasma exchange therapy may be beneficial [35] and is reviewed elsewhere in this textbook. Platelet transfusion is rarely indicated.

Macro-angiopathic hemolysis may be observed in patients in whom prosthetic heart valves have been implanted. Critical care intervention is only required in children with macro-angiopathic hemolysis when complications of the Kasabach-Merritt syndrome develop. Mechanical schistocytic hemolysis in patients on ECLS occurs when the blood flow is set above limits, small cannulas are used, large negative pressures are generated, and blood is exposed to foreign surfaces. Monitoring free Hb is used for evaluating the extent

of hemolysis in children on ECLS. It is also postulated that free Hb has clinical consequences such as renal impairment, but this has yet to be elucidated [36].

Red Cell Membrane Defects

Congenital and acquired intrinsic red cell membrane defects rarely require admission to the PICU, but may be observed in patients admitted to the PICU for other reasons. Acquired membrane red cell defects are caused by burns (either direct or indirect via oxygen radicals), toxins from streptococcal or staphylococcal infection, infection, drugs (such as antibiotics) or transfusion with plasma products [37–39]. Children with paroxysmal nocturnal hemoglobinuria (PNH) may present with venous thrombo-embolism in unusual locations and a history of recurrent sinopulmonary infection or septicemia. Thrombotic events, which can be lethal, are refractory to thrombolytic therapy [40]. Hereditary spherocytosis is a congenital red cell membrane defect that can be associated with life-threatening crises after parvovirus B19 infection, when there is an imbalance between inadequate production due to acquired bone marrow failure and hemolysis.

Red Cell Metabolism Defects

It is rare that patients with red cell metabolism defects need critical care, apart from patients with glucose-6-phospate deficiency (G6PD). G6PD is an X–linked inherited disease with high prevalence rates in tropical Africa, Middle East, tropical and subtropical Asia, and some areas of the Mediterranean Sea [41]. Patients become symptomatic when the enzyme activity is less than 60 %. Glucose-6-phosphate dehydrogenase handles oxidative stress in the erythrocyte. It catalyzes the reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH in the hexose-monophosphate shunt, which in turn converts glutathione disulfide to reduced gluthathione. Gluthathione is a scavenger for oxygen radicals. Patients with G6PD deficiency may present with severe acute hemolytic anemia caused by stressors such as drugs (Table 20.7), infection or notably ingestion of fava beans. Treatment consists mainly of eliminating (if possible) the precipitating agent; RBC transfusions may be indicated.

Immune-Mediated Hemolysis

Immune-mediated hemolysis is discriminated into alloimmune and autoimmune. Alloimune hemolysis occurs when the child passively acquires RBC antibodies during transfusion with RBC preparations containing donor antibodies. Autoimmune hemolytic anemia (AHIA) occurs when a child intrinsically develops antibodies against RBCs with (primary AIHA) or without (secondary AIHA) accompanying systemic illness.

Primary AIHA usually occurs after a viral infection. The child suffers from symptoms of anemia and dark urine. Because of the rapid onset, other symptoms such as jaundice or reticulocytosis may not be present. Laboratory studies show isolated anemia, low haptoglobin, spherocytes on peripheral blood smear and a positive direct antiglobulin (i.e. Coombs) test. The indirect Coombs test detects antibodies in the patients' serum. Supportive therapy includes plasma exchange. Transfusion should be avoided unless severe anemia with cardiovascular compromise occurs. Further therapy (e.g., high-dose corticosteroids) is dependent upon the type of primary AIHA, which is defined by the presence of IgG antibodies (suggesting warm-reactive AIHA) or complement (suggesting cold-reactive AIHA). Cold-reactive AIHA is then classified by which type of antibody (IgM auto-antibody or IgG) is detected. Secondary AIHA occurs in a wide variety of disease (Table 20.8).

Table 20.7 Causes of secondary autoimmune hemolytic anemia

Immune mediated	Evans syndrome
	Rheumatoid arthritis
	Systemic lupus erythematosus
	Evans syndrome
Infectious	*Clostridium difficile*
	Epstein-Barr virus
	Measles
	Mycoplasma pneumoniae
	Paramyxovirus
	Rubella
	Varicella zoster
Immunodeficiency	Congenital
	Acquired (human immunodeficiency virus)
Malignancy	Hodgkin's lymphoma
	Leukemia
	Myelodysplasia
Drugs	Acetaminophen
	Cephalosporins
	Ibuprofen
	Penicillins

Table 20.8 Differential diagnosis of secondary erythrocytosis

Hypoxia	Cyanotic congenital heart disease
	Obstructive sleep apnea
	Smoking and chronic carbon monoxide exposure
	High altitude
	High affinity hemoglobin
Renal	Renal artery stenosis
	Cysts
	Post-transplant
	Focal glomerulonephritis
Neonatal	Twin-to-twin transfusion
	Placental insufficiency
	Maternal diabetes
	Beckwith-Wiedemann syndrome
Miscellaneous	Erythropoeitin secreting tumors
	Growth hormone excess

Thalassemias

Thalassemias are a group of inherited disorders of hemoglobin synthesis. Although they are more common than SCD, patients with thalassemias are not often primarily seen in the PICU. Patients with the transfusion-dependent form of thalassemia (thalassemia major) may experience complications from iron overload sepsis. The risk of sepsis is increased because many patients underwent splenectomy or have indwelling vascular devices implanted for repetitive transfusion or chelation therapy [42]. Improved chelation therapy regimens have decreased the complication rate of myocardial iron overload necessitating inotropic support that was often required in adolescents with thalassemia major [42].

Secondary Hemoglobinopathies

Secondary hemoglobinopathies, or dyshemoglobinemias, include methemoglobinemia (MetHb) in patients treated with nitric oxide (NO), carboxyhemoglobinemia (COHb) in patients intoxicated with carbon monoxide (CO), or other toxins. Hb binds to CO 210 times more easily than O_2. This means that COHb cumulates until typical symptoms occur (threshold in adults is about 20 % but in children this may be lower). COHb cannot bind to O_2, and the oxygen dissociation curve shifts leftwards further contributing to anoxia. The vasodilatory drug nitroprusside is notorious because it contains five cyanide molecules and one molecule of NO bound to iron. Critically ill children and those with rapid infusion of nitroprusside cannot eliminate the cyanide quickly enough to prevent toxic effects.

Dyshemoglobinemias result in shifting of the oxygen dissociation curve, impairment of binding of O_2 by Hb and impairment of O_2 delivery. MetHb usually becomes symptomatic when concentrations approximate 35–50 %. Treatment consists of removing the toxin and providing antidote if applicable (i.e. ascorbic acid or methylene blue for MetHb or pure O_2 for CO intoxication). Exchange transfusion or hyperbaric oxygen therapy is indicated for life-threatening causes with clinically impaired DO_2.

Hemophagocytosis

Hemophagocytic lymphohistiocytosis (HLH) syndrome is a devastating multisystem disease with a poor prognosis [43]. The initiating event of reactive HLH is unknown, but it has been associated with infectious agents such as EBV or autoimmune disorders. Congenital HLH is a malignancy. Twenty percent of HLH is familial and associated with abnormalities of a natural killer cell-derived cytotoxin (perforin). HLH is characterized by aggressive destruction of RBCs and other blood elements by macrophages in bone marrow, liver and spleen. Clinical symptoms vary and are similar to the systemic inflammatory response syndrome (SIRS). The disease can be recognized if the patient meets at least five of the following criteria: (a) fever, (b) splenomegaly, (c) cytopenias of two or more lineages, (d) hypertriglyceridemia (>3.0 mmol/L) and/or hyperfibrinogenemia (≤1.5 g/L), (e) hemophagocytosis seen in bone marrow (no malignancy seen), spleen or lymph node, (f) low or absent natural killer cell activity, (g) ferritin ≥500 mcg/L), and (h) soluble CD25 ≥2,400 U/mL) [44]. Other supportive findings include CSF pleiocytosis, elevated serum transaminases, elevated bilirubin, and elevated LDH. Treatment in the PICU is supportive. The only curative option for congenital HLH is bone marrow transplantation.

Erythrocytosis

An increase in circulating RBCs is termed erythrocytosis. It very rarely primarily leads to critical care intervention, but may be seen in patients admitted for any other reason. Secondary erythrocytosis originates from hypoxia such as in patients with right-to-left shunting cardiac lesion or pulmonary disease and patients living in high altitude, whereas spurious erythrocytosis is caused by dehydration, hemoconcentration or polyuria. Patients with primary erythrocytosis have normal levels of erythropoietin, but it is increased in those with secondary erythrocytosis. Arterial hematocrit >65 % may aggravate tissue hypoxia, cause thrombosis and necessitate the use of reduction exchange transfusions. The volume of blood that needs to be exchanged is calculated by multiplying the child's estimated blood volume by the desired reduction in hematocrit. In the infant, the removal rate should not exceed 2 mL/kg/min.

Part 2: Non-malignant White Blood Cell Disorders

The type of leukocytosis is defined by specifying the WBC type along with the underlying cause of the increase. Stress mobilizes neutrophils from the bone marrow into the circulation or shifts marginated neutrophils. These are circulating neutrophils that were not active but can be mobilized in times of stress. True neutrophilia results from infection (both bacterial and viral), the band form is considered to be very suggestive for bacterial infection and thus routinely used in daily critical care [45]. In severe infections, neutropenia may occur because of insufficient formation of new neutrophils. Leukemoid reactions (i.e. neutrophils >50,000 cells/microL) can be triggered by various diseases but can only be discriminated from true leukemia through laboratory studies including marrow histology. Of particular concern are children with trisomy 21 who initially may have

leukemoid reactions that develop into myeloid leukemias. Lymphocytosis is classically known to occur in *Bordetella pertussis* infection and following viral infection, whereas lymphopenia is often transient resulting from viral, fungal or parasitic infections. Yet, one should be aware of chronic underlying diseases including HIV infection. Eosinophilia is associated with allergic conditions or parasitic infections. Monocytosis is commonly caused by infections (tuberculosis, subacute bacterial endocarditis, syphilis, brucellosis, infectious mononucleosis, malaria) or autoimmune disorders (such as systemic lupus erythematosus and sarcoidosis).

Part 3: Platelet Disorders

Thrombocytopenia

Thrombocytopenia in critically ill children is relatively common and results from underproduction, overconsumption, or both (as for instance during sepsis). In addition, it is not uncommon to observe thrombocytopenia caused by inadequate sampling or technical impairments in the laboratory. In general, the underlying cause is usually determined easily. If not, then additional investigations including thrombopoietin levels need to be measured [46]. The clinical spectrum of thrombocytopenia ranges from bruising, petechia and epistaxis to significant, life threatening bleeding. Hence, the decision when to transfuse platelets depends on the risk of bleeding and underlying disease.

Increased Consumption of Platelets

There are many causes of thrombocytopenia caused by increased consumption of platelets, of which DIC and HUS are the most predominant. Hemorrhage and cardiopulmonary bypass-related thrombocytopenia are also common. Burns causes sequestration of platelets in proportion to the area injured – persistence of thrombocytopenia in these patients may indicate DIC or sepsis. Meningococcemia is notorious for causing purpura fulminans, but this may occur also when infected with other agents. In patients with meningococcemia, the initial and serial assessment of platelet and neutrophil count may be used as a prognostic score [47, 48]. Likewise, platelet count is also predictive for the need of renal support in patients with Rocky Mountain spotted fever. Foreign surfaces in ECLS systems used in cardiac surgery activate and absorb platelets. This can be prevented by optimizing anticoagulant therapy and heparin coating of circuit components, timely changes of the circuit and post membrane platelet transfusion. Additional measures suggested include the use of aprotonin in young children [49].

Increased Destruction of Platelets

Idiopathic thrombocytopenic purpura (ITP) is caused by splenic phagocytosis of antibody-coated platelets [50]. The acute form is self-limiting; it cures spontaneously within several weeks following the precipitating viral infection. Approximately 20 % of affected children develop chronic ITP (i.e. < 150,000 cells/mcL). The mortality in ITP is very low (i.e. 1 %) and mainly caused by intracranial hemorrhage. Diagnosis and treatment is in adherence with guidelines from the American Society of Hematology [51]. Heparin-induced thrombocytopenia is relatively uncommon in critically ill children. It is caused by the formation of autoantibodies against heparin-platelet protein four complexes. In addition, the IgG antibodies activate platelets resulting in a prothrombotic state.

Decreased Production of Platelets

Reduced platelet synthesis rarely constitutes an acute problem.

Thrombocytosis

Thrombocytosis is defined as a platelet count >450,000 cells/mcL. Primary thrombocytosis is very uncommon in children, but secondary thrombocytosis has various causes including Kawasaki disease. The major complication of thrombocytosis is thrombosis, but it is unknown at what threshold to start preventive measures. In patients with Kawasaki, aspirin is initiated to prevent coronary thrombus formation.

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Coagulation Disorders in the PICU

21

Geoffrey M. Fleming and Gail M. Annich

Abstract

Critically ill patients often have alterations in the hemostatic milieu that require the pediatric intensivist to evaluate and treat clinical changes. Sometimes these alterations may be the primary clinical issue as seen in congenital factor deficiencies but more commonly are acquired and secondary to other systemic illnesses as is the case in disseminated intravascular coagulation. The goal of this chapter is to provide background into the normal components and function (both procoagulant and anticoagulant) of the hemostatic system including coagulation factors, platelets, thrombus formation and fibrinolysis. Using this background information, frequently encountered pathophysiologic clinical scenarios are reviewed including etiology and therapeutic options.

Keywords

Disseminated intravascular coagulation (DIC) • Coagulation cascade • Prothrombin time • Activated partial thromboplastin time • Thromboelastography (TEG)

Introduction

Life giving blood flows through our vasculature, bringing nutrients and oxygen to tissues as they perform their basic functions. The integrity of the vascular space is under complex control that modulates the balance between adequate anticoagulation to prevent thrombus formation in normal states and the need for hemostatic repair when the vascular integrity is breeched. As students we struggle to commit to memory all the basic components of this complex system, and as practitioners we are confronted with the life threatening derangements of this balance in critically ill patients. No discussion of coagulation can proceed without an understanding of the basic components, however knowledge of the interaction of these components is essential for patient management. This chapter will review the components of coagulation, including platelets, the coagulation cascade, inhibitors of thrombus formation, and fibrinolysis. Finally, we will address specific derangements of hemostasis encountered in the intensive care setting.

History

Today, we sit with textbooks that name and describe the coagulation system components, however, the evolution of our understanding of this process softens the sometimes confusing nomenclature of coagulation. The exact process of coagulation was largely elucidated in the twentieth century. At the end of the nineteenth century, it was presumed that the coagulation system consisted of four factors thrombokinase/

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thromboplastin (III, released by damaged tissues) – this reacted with prothrombin (II), which, together with calcium (IV), formed thrombin, which converted fibrinogen into fibrin (I) [1].

A first clue as to the complexity of the system of coagulation was the discovery of proaccelerin, later renamed Factor V, by Paul Owren in 1947. Factor VII, also known as serum prothrombin conversion accelerator or proconvertin, was discovered in a young female patient in 1949 and 1951 by different groups. Factor VIII turned out to be deficient in the clinically recognized but etiologically elusive hemophilia A; it was identified in the 1950s and is alternatively called antihemophilic globulin due to its capability to correct bleeding diathesis associated with hemophilia A.

Factor IX was discovered in 1952 in a young patient with hemophilia B named Stephen Christmas. The factor is hence called Christmas Factor or Christmas Eve Factor. An alternative name for the factor is plasma thromboplastin component, given by an independent group in California [1].

Hageman factor, now known as factor XII, was identified in 1955 in an asymptomatic patient with a prolonged bleeding time with the name of John Hageman. Factor X, or Stuart-Prower factor, followed, in 1956. In 1957, an American group identified the same factor. Factors XI and XIII were identified in 1953 and 1961, respectively [1].

The usage of Roman numerals rather than eponyms or systematic names was agreed upon during annual conferences (starting in 1955) of hemostasis experts. This committee evolved into the present-day International Committee on Thrombosis and Hemostasis (ICTH). Assignment of numerals ceased in 1963 after the naming of Factor XIII. The names Fletcher Factor and Fitzgerald Factor were given to further coagulation-related proteins, namely prekallikreins and high molecular weight kininogens respectively. The numerals III and VI remain unassigned, as a single thromboplastin was never identified, and in reality consists of ten factors, and accelerin was found to be activated Factor V [1].

Activation refers to conversion of blood zymogens to active enzymes, expression of blood cellular receptors, initiation of cell signaling, and release of vasoactive and cytotoxic substances; blood becomes reactive and "angry". With long-term exposures, a new equilibrium between activated blood elements and the body's ability to remove and control these substances must be reached. The patient's ability to neutralize cell signaling, vasoactive and cytotoxic substances, to replace consumed cells and proteins, to repair damage, and to restore homeostasis is influenced by age, comorbidities, organ reserves and other factors.

Thrombus Formation Overview and Review of Normal Coagulation Components

The formation of a thrombus normally occurs in response to loss of integrity of the vascular space. With injury to tissue, such as cutting ones finger in the kitchen, tissue factor is expressed on the injured endothelium, and sub-endothelial structural proteins are exposed to blood. Tissue factor initiates a cascade of events, which begins with zymogen conversion to active enzymes. These enzymes act in concert to produce thrombin. Thrombin cleaves fibrinogen to fibrin which is able to bind to receptors on platelets. Local platelets become activated, undergo many changes, and are recruited and adhere to the site of injury. Fibrin binds platelets together, and additional enzymatic activity cross-links these fibrin strands to form a stable clot. As soon as the injury occurs, the process of fibrinolysis is initiated, but remains relatively quiet until the endothelium is reconstructed. Then, fibrinolysis cleaves the fibrin cross-linking and the clot dissolves, platelets are cleared by the reticuloendothelial system, and the process awaits the next call to action.

Platelets

Platelets are the mainstay for hemostasis and preservation of vascular wall integrity. They are the bricks that are held together by a proteinaceous mortar and form the thrombus responsible for hemostatic control, as well as providing the attachment site for complexes responsible for the propagation of the coagulation cascade. These anuclear cellular fragments approximately 3–4 μm in size are derived from megakaryocytes in the bone marrow, and normally circulate in an inactivated state. Activation of platelets is initiated by a broad array of stimuli, including chemical and physical signals [2].

Platelet Activation

In the laboratory setting, activation is achieved with thrombin, collagen, laminin, fibronectin, von Willebrand factor (vWF), epinephrine, adenosine diphosphate (ADP), platelet activating factor (PAF), and thromboxane A_2 (T_XA_2). Mechanical stress, as occurs in turbulent flow states, is also responsible for activation. In vivo, disruption of the endothelium, sub-endothelium, or contact with artificial surfaces induces activation through receptor mediated binding of proteins exposed during this process, as well as through circulating and locally produced chemical messengers. Platelet activation is achieved through intracellular second messenger cascades of G-proteins which are linked to the binding surface receptors. G-protein activation produces a variety of end-products, including altered intracellular calcium levels,

kinase activation, and phospholipase activation [3]. These cascades induce changes in the platelet at the time of activation which are involved in the initiation and propagation of thrombus formation. There are at least five physiologic responses that occur during platelet activation, including alteration of platelet shape, expression and modulation of surface receptors, release of intracellular granule contents, and formation of tenase and prothrombinase complexes that incorporate components of the coagulation cascade necessary for its propagation [2, 4].

Quiescent platelets are discoid and relatively smooth, but in the face of activation, elongate and form pseudopods (Fig. 21.1). This shape change provides greater surface area for interaction with other platelets and thrombogenic surfaces, as well as providing ample space for receptor expression and tenase complex formation. It is also responsible for altered flow characteristics which brings the activated platelet into contact with the endothelial wall more readily [5]. Granular contents of platelets are released during activation, and include platelet factor 4 (PF4), thrombospondin, β-thromboglobulin, ADP and serotonin. These amplify the process by inducing further activation and chemotaxis of additional platelets.

Platelet Receptors

Surface receptors on platelets change during activation, both by expression of receptors not found in quiescence, and by conformational changes necessary for the activity of some receptors. P-selectin is expressed on the platelet surface after activation, and mediates adhesion to neutrophils, monocytes, and lymphocytes. Glycoprotein-Ib (GPIb) surface receptors are present during quiescence however undergo changes during activation. GPIb receptor changes include an epitope modification that alters binding to thrombin and the formation of the prothrombinase complex. GPIb receptors mediate platelet interaction with vWF as well as interact with thrombin to produce activation of the arachadonic acid pathway and subsequent T_XA_2 activity. This activation of the eicosanoid pathway results in the formation of prostaglandins and thromboxane, which contribute to further platelet activation. GPIb receptors are also intimately involved in the formation of the GPIb-IX-V prothrombinase complex which is integral to the propagation of the coagulation cascade.

GPIIb/IIIa (CD41/CD61) is the dominant platelet receptor with 40,000–80,000 of these receptors present on resting platelets and another 20,000–40,000 present inside the platelets within the alpha granules and the membranes of the open canalicular system. In resting platelets when the GPIIb/IIIa is in an inactive form, there is a low affinity binding site for adsorbed fibrinogen. Once the platelet is activated, and conformational shape change of the platelet occurs, the high affinity binding site of GPIIb/IIIa is exposed and binding of soluble fibrinogen occurs, which in turn leads to platelet aggregation and platelet-leukocyte aggregates by the cross-linking of two GPIIb/IIIa receptors, or by the cross-linking of GPIIb/IIIa with Mac-1 on the leukocyte; the crosslink is made by fibrinogen.

This activation process also includes the formation of platelet microparticles (PMPs), rich in factor Va, platelet factor 3, and phosphatidyl serine, a phospholipid-like procoagulant. The role of PMPs is unclear but in vitro they are shown to adhere to fibrinogen and fibrin enhancing further platelet aggregation [2]. In states of inflammatory activation of the coagulation system, these aggregates of activated platelets may form the basis for diffuse microvascular thrombus formation in conjunction with tissue factor presenting cells. This concept will be expanded in the section on disseminated intravascular coagulation.

Platelet activation can be inhibited and sometimes reversed in the laboratory through three mediators; matrix metalloproteinases, prostacyclin inhibitors, and nitric oxide. Although one can prevent activation of platelets through mechanical and chemical mediators in the laboratory, these mediators are felt to produce local platelet quiescence at the level of the endothelium. Best understood is nitric oxide, originally named endothelium derived relaxation factor. Nitric oxide has been shown to induce platelet resistance to activation, and is felt to modulate platelet activity at the blood-endothelium interface in vivo [6]. Reversal of activation requires exposure to nitric oxide longer than is likely to be found in vivo. Similar effects are seen with prostaglandins, as PGI_2 is released from the endothelium and prevents platelet activation [7].

Platelets are integral to the process of hemostasis, and their activation produces many changes that are responsible for thrombus formation. These include enhanced binding of platelets to damaged surfaces, platelet binding to other platelets, expression of receptors necessary for fibrin cross-linking, platelet chemotaxis, and location of tenase and prothrombinase complexes necessary for the propagation of coagulation. During critical illness, platelet number and function are affected. Thrombocytopenia reduces the numbers of the critical components for hemostasis, and platelet manipulation during infusion of donor cells causes activation. Contact with artificial surfaces such as indwelling catheters and extracorporeal circuits further activate platelets, as does exposure to circulating catecholamines. Platelets have no inherent regenerative properties, and once activated and degranulated these cells can no longer participate in the hemostatic complex. Hence, it is readily apparent that normal platelet numbers and an ability to respond to activation stimuli are crucial for normal hemostasis, both of which are adversely affected during critical illness.

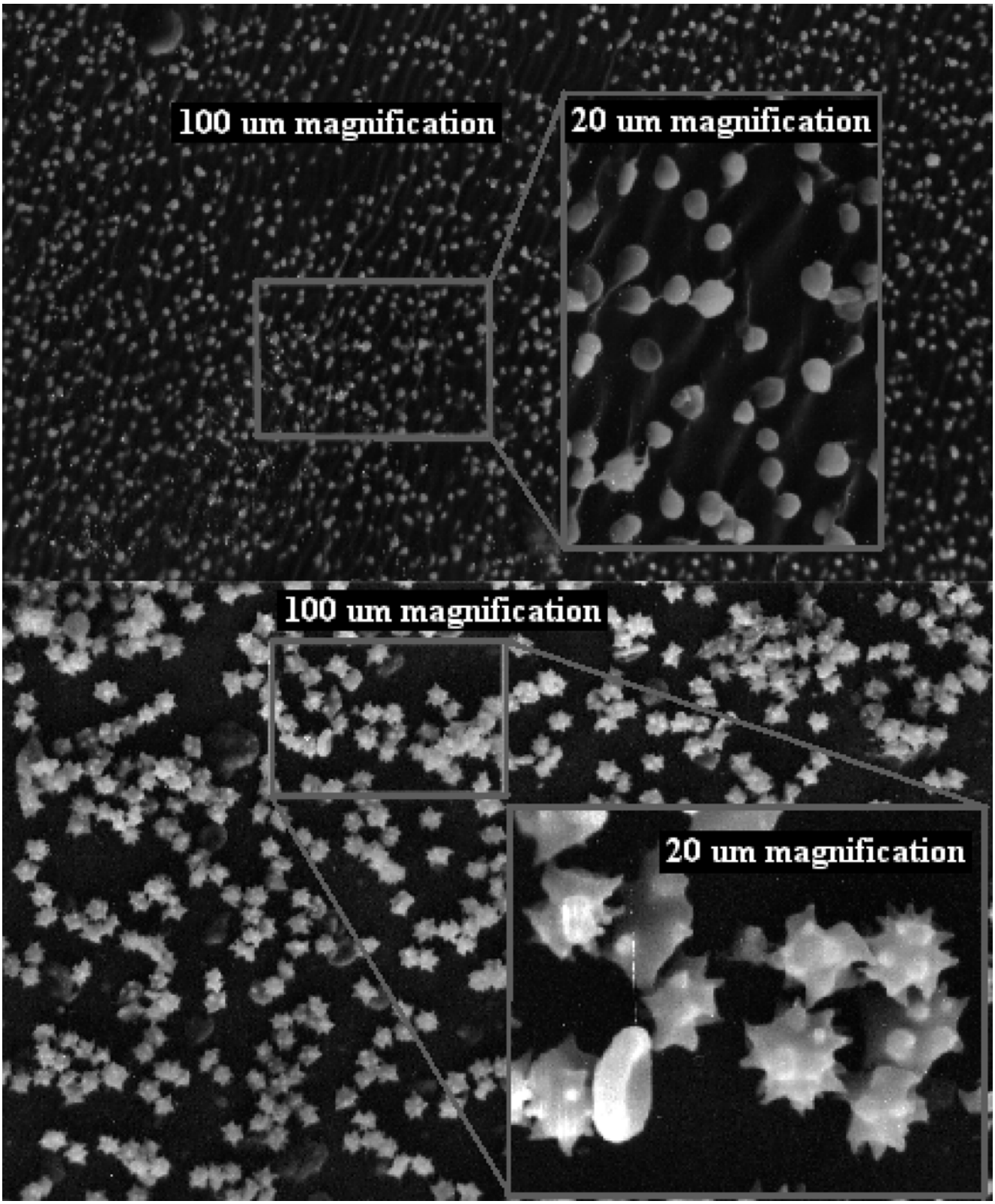

Fig. 21.1 Electron microscopy images of platelets, quiescent are smooth and discoid (*top* of figure), activated are irregular and elongated with pseudopod formation (*bottom* of figure)

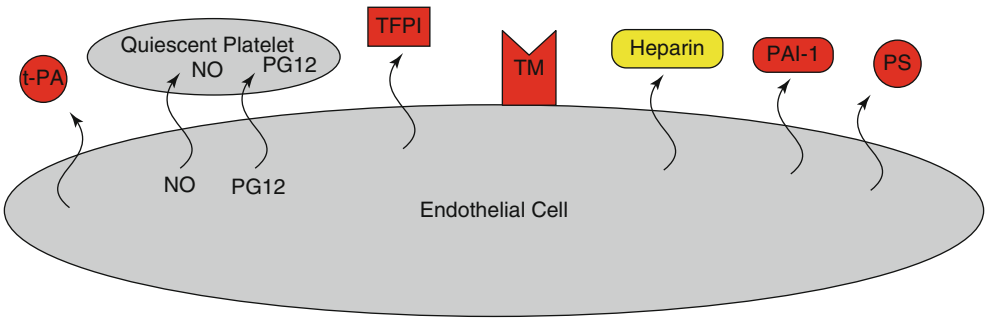

Fig. 21.2 Illustration of endothelial cell derived inhibitors of coagulation. Legend: *NO* nitric oxide, *PGI2* prostaglandin 2, *TM* thrombomodulin, *TFPI* tissue factor pathway inhibitor, *PAI-1* platelet activator inhibitor-1, *PS* protein S, *tPA* tissue plasminogen activator

Endothelial Cells

Under normal circumstances, blood proteins and cells interface at the endothelium that simultaneously maintains the integrity of the vascular system and the normal flow of blood. They cover an estimated area of about 1,000 m^2 in adults. Endothelial cells maintain this delicate balance between thrombosis and anticoagulation (hemostasis) by producing both anticoagulants and procoagulants. Much of the thrombogenic activity of the coagulation system is held in check by direct endothelial cell intervention, and endothelial damage releases this inhibition in addition to providing substrate for the coagulation cascade.

Disease states associated with diffuse inflammatory processes, such as sepsis and acute respiratory distress syndrome (ARDS), are now known to involve disruption of endothelial cell processes. Hence, such clinical entities also disrupt the balance of normal hemostasis, and this may result in abnormal coagulation function. Endothelial cells are activated by a variety of agonists including thrombin, C5a [8], IL-1, IL-6, and tumor necrosis factor [9, 10]. Activation of the endothelium increases platelet chemotaxis, promotes platelet binding to the endothelium, induces platelet activation, and removes inhibitory control of the coagulation cascade. Additionally, damage to the endothelium exposes collagen and fibronectin as well as tissue factor (TF) that stimulate thrombus formation.

Endothelial cells produce prostacyclin, Protein S, heparin sulfate, tissue plasminogen activator (t-PA) and tissue factor pathway inhibitor (TFPI), which regulate hemostasis through inhibitory modulation of the coagulation cascade (Fig. 21.2). Thrombomodulin and protease nexin-1, both produced by endothelial cells, remove thrombin. Endothelial cells also produce vasoactive substances and cytokines, such as nitric oxide, prostacyclin, endothelin-1 [11, 12], IL-1, IL-6 [13], and platelet activating factor (PAF), as well as inactivate others such as histamine, norepinephrine, and bradykinin [12]. Although an exhaustive review of the role of these substances is beyond the scope and focus of this chapter, protein S, heparin sulfate, t-PA, tissue factor pathway inhibitor (TFPI) and thrombomodulin will be discussed further in the section regarding control of hemostasis.

Coagulation Cascade

The coagulation cascade is the complex interaction of blood proteins, now labeled as factors and denoted with roman numerals, which produce thrombin. Fibrin is the final end-product of this process and is denoted as Factor I, and is responsible for binding platelets together and forming a thrombus via cross-linking. Classically, this cascade has been divided into the intrinsic and extrinsic pathways and is depicted as a linear progressive cascade. More recent data have broadened this understanding and reveal it is a complex circular cascade with both promoter and inhibitor feedback. It now is best divided into the (1) contact system, (2) extrinsic pathway, (3) intrinsic pathway, and (4) common pathway (Fig. 21.3).

Contact System

Four proteins, factor XII, prekallikrein (PK), high-molecular-weight-kininogen (HMWK) and complement-1 inhibitor (C1-INH) have been shown to play major roles in the activation and inhibition of the surface-mediated pathway, the "contact system" [14]. The role of this system in the initiation of the intrinsic pathway is of some question as only the deficiency of factor XI causes hemorrhagic abnormalities whereas deficiencies in the contact proteins (factor XII, HMWK, and prekallikrein) have not [2, 15–17]. It is more likely that this system primarily initiates the inflammatory response, complement activation, fibrinolysis, angiogenesis

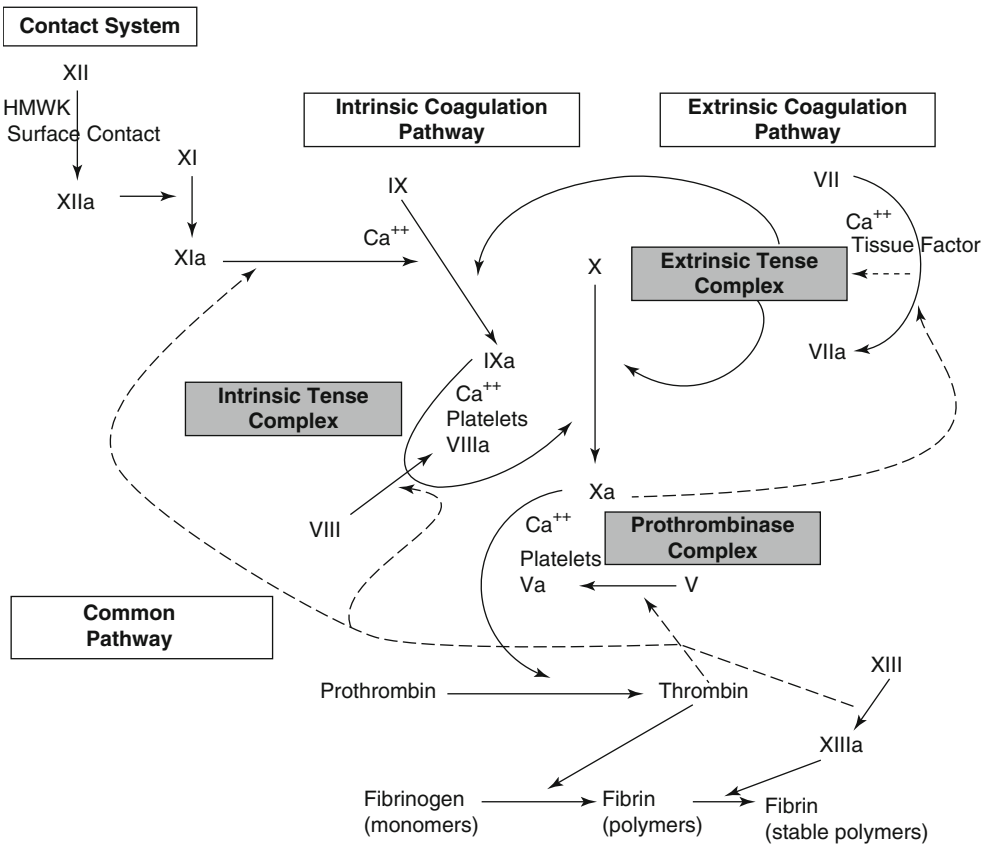

Fig. 21.3 Classical representation of the coagulation cascade. See text for detailed explanation of cascade. Legend: *HMWK* High molecular weight kininogen. Individual coagulation factors are represented by *roman numerals. Dotted arrows* represent agonists of an enzymatic reaction, *solid arrows* represent an enzymatic reaction

and kinin formation [14, 18, 19]. The heavy chain of factor XII binds to an endothelial surface, causing a local increase in enzyme concentration, auto-activation (XIIa formation), and resultant action on its substrates prekallikrein and factor XI to form kallikrein and factor XIa [14, 20]. Factor XIa activates the intrinsic pathway and the formation of the intrinsic tenase complex IXa-VIIIa which is attached to an activated platelet. It must be noted that factor XI can also be activated by thrombin once the coagulation cascade has been activated.

Factor XIIa also cleaves prekallikrein. The cleavage of prekallikrein, forms kallikrein and this creates a feedback loop whereby further cleavage of factor XII is accelerated [21]. Kallikrein is also a strong agonist for neutrophil activation. Both HMWK and C1-INH bind to the light chain of kallikrein [14, 22–24]. When C1-INH binds to kallikrein, its enzymatic activity is rapidly inactivated, whereas when HMWK binds to kallikrein it protects kallikrein from the inhibitory effects of C1-INH and other plasma protease inhibitors. The cleavage of HMWK by kallikrein forms bradykinin and activated HMWK, which binds to the surface tenfold greater than its cofactor, enhances prekallikrein activity, fibrinolysis and inhibits angiogenesis [14]. It is clear that the activation of factor XI by factor XIIa is a minor event in the initiation of the contact system and it is well known that deficiencies in factor XII have not been associated with abnormal bleeding. This suggests a more integrally related coagulation cascade with the extrinsic and intrinsic pathways interacting with one another rather than independently initiating thrombin formation.

Intrinsic Coagulation Pathway

The intrinsic system could be defined as coagulation which is initiated by components contained entirely within the vascular system [14]. It is the major player in the propagation phase of the cascade. Classically the initiation of the intrinsic pathway has been described as the activation of factor IX by factor XIa in the presence of Ca^{2+}, providing a pathway for fibrin formation that is independent of factor VII. Factor IXa can also be activated by factor VIIa, and this activation requires Ca^{2+} as well as tissue factor embedded within a lipid bilayer. Tissue factor is usually presented on damaged endothelium, but as in the case of inflammatory processes, may be expressed on circulating monocytes, as is seen in disseminated intravascular coagulation (DIC). Once factor IX is activated, it binds activated factor VIII on the phospholipid bilayer of a platelet, and forms the intrinsic tenase complex (Fig. 21.4) [25, 26]. The intrinsic tenase complex requires calcium as a cofactor, and binds factor X and activates it to factor Xa. It is a significant contributor to thrombin generation and a major player in the cascade's propagation phase.

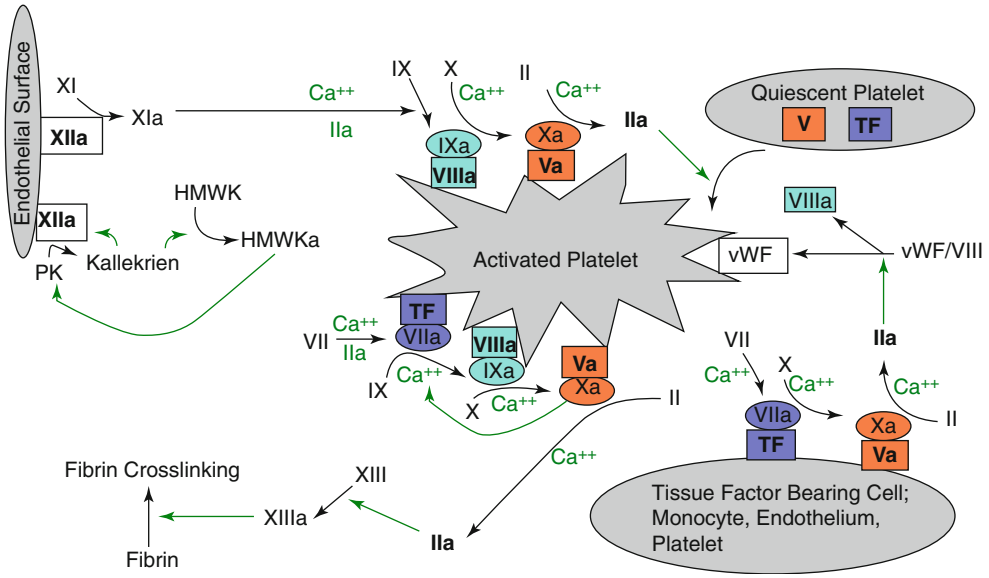

Fig. 21.4 Illustration of the coagulation cascade. This model emphasizes the central role of activated platelets and tissue factor bearing cells in providing a phospholipids bilayer necessary for formation of the tenase complexes. See text for detailed explanation of the cascade. Legend: Individual coagulation factors are represented by *roman numerals*. *Black arrows* represent enzymatic pathway. *Green arrows* and figures represent agonists of an enzymatic reaction. *TF-VIIa* Extrinsic Tenase Complex, *IXa-VIIIa* Intrinsic Tenase Complex, *Xa-Va* Prothrombinase Complex, *PK* Prekallekrein, *HMWK* High Molecular Weight Kininogen, *vWF* vonWillebrand Factor

Once factor X is activated it slowly cleaves prothrombin to produce thrombin; however this reaction becomes 300,000 times faster when Xa is anchored by factor Va in the presence of Ca^{2+} onto a phospholipid surface provided by platelets, monocytes, or endothelial cells [27, 28]. This complex is called the prothrombinase complex and initiates activation of the common pathway (Fig. 21.4). Factor V is activated by either factor Xa or thrombin.

Extrinsic System

The principal activator of the coagulation system in vivo is the extrinsic pathway that involves both blood and vascular elements. This system plays a major role when external injuries are the stimulating factor for activation of the coagulation pathway. The most critical component to the activation is tissue factor (TF), an intrinsic membrane protein that functions as a cofactor to factor VIII in the intrinsic system, and to factor V in the common pathway. Tissue factor is synthesized by macrophages/monocytes and endothelial cells and this synthesis is induced by cytokines such as interleukin-1, endotoxins, and tumor necrosis factor [14, 29, 30]. It is expressed on vascular subendothelium and many other cells such as stimulated monocytes and endothelial cells [31–34].

The major plasma component to the extrinsic system is factor VII, one of the vitamin K dependent prozymogens (the others being factors IX, X, prothrombin and protein C). The vitamin K dependent factors VII, IX, and X warrant special notation as they have conformational properties which assist in binding the factor to the phospholipid bilayer. Additionally, factor VII has the shortest half-life in plasma, approximately 6 h, and hence is the first to be affected by hepatic dysfunction. As a wound (surgical or otherwise) is created, tissue factor is expressed and rapidly binds and converts factor VII to factor VIIa, creating the TF/FVIIa complex or the extrinsic tenase complex (Fig. 21.4). This complex which forms upon either activated monocytes or "perturbed" endothelial cells has two main substrates, factor IX and factor X [14], and initiates the activation of the common pathway.

As stated above, this pathway plays a major role in thrombus formation when a wound is present. However it must be noted that in situations where the intrinsic pathway plays a major role in cascade activation such as extracorporeal circulation or DIC, monocytes will, over time, increase their expression of tissue factor. Thus both the intrinsic and extrinsic pathways contribute significantly to the onset and propagation of coagulation.

Common Pathway

As the extrinsic tenase complex cleaves either factor IX or X, these serine proteases remain membrane or phospholipid bound. The cofactor necessary for factor IXa to catalyze the conversion of factor X to factor Xa is factor VIII, while the cofactor for the factor Xa conversion of prothrombin to thrombin is factor V. Factor VIII exists in plasma, primarily as a noncovalent complex with von Willebrand factor (VWF). Factor V is supplied by activated platelets and is either excreted from the granules or fuses with the platelet membrane to bind factor Xa to the platelet, forming the

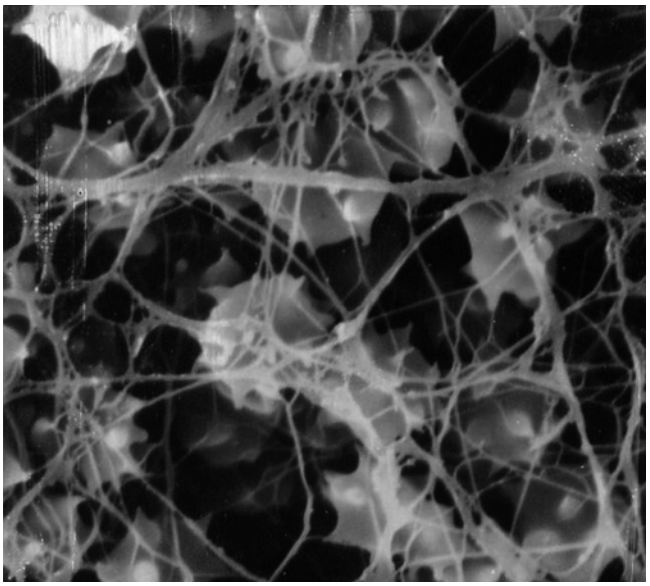

Fig. 21.5 Scanning electron microscopy image at 20 μm magnification of hemostatic plug demonstrating fibrin cross-linking

"prothrombinase complex" and thereby activating the common coagulation pathway by the cleavage of prothrombin (Fig. 21.4).

The cleavage of prothrombin produces thrombin and a useful marker of the reaction, protein fragments F1.2. Thrombin is a powerful enzyme most noted for its procoagulant functions by the cleavage of fibrinogen and activation of platelets, but it must be noted that its formation also leads to anticoagulant activity by the activation of protein C, the stimulation of endothelial cells to produce prostacyclin and tissue plasminogen activator, which initiates fibrinolysis [2, 9, 35]. In addition it also is involved in cellular proliferation, and inflammation. Within the common pathway however, thrombin's specific role is to cleave fibrinopeptides, activate factor XIII, potentiate the effects of factors VIII and V, activate protein C and factor XI.

Thrombin cleaves fibrinogen (fibrinopeptides). The formation of fibrin strands or monomers is the second phase of hemostasis (the first being platelet aggregation). Fibrinogen is present in high concentrations within plasma and platelet granules and interacts with many different proteins. During extracorporeal circulation a protein layer, predominantly fibrinogen, is rapidly deposited on the artificial surface which induces the formation of clot [2]. Thrombin binds to the central domain of fibrinogen cleaving it into fibrinopeptides A and B, producing monomers and polymers of fibrin. These fibrin monomers and polymers interact side to side and laterally to form a fibrin mesh which then is crosslinked by factor XIIIa to form a stable hemostatic plug (Fig. 21.5). Add to this the potentiation of factors VIII and V which produces more tenase and prothrombinase complexes and the result is a burst in thrombin activity and fibrin formation, and a rapidly propagating thrombus formation.

Physiologic Inhibitors of Coagulation

In order to control the coagulation cascade, which consists mainly of serine proteases, plasma contains several protease inhibitors to modulate and inhibit their activity. These include antithrombin III (AT), tissue factor pathway inhibitor (TFPI), thrombomodulin, and protein C (Fig. 21.6).

Antithrombin III (AT) is the most important of these as it neutralizes both factor Xa and thrombin by forming a complex with the enzymes and blocking their active sites [2]. Antithrombin III also inhibits factors IXa, XIa, and XIIa. Under conditions of diffuse inflammatory diseases, this inhibition by complex formation continues but is physiologically too slow to prevent thrombosis unless catalysis of antithrombin III activity is achieved by interacting with other agents innate to the endothelium such as protein C and protein S.

Other physiologic inhibitors of coagulation that warrant mention are tissue factor pathway inhibitor (TFPI), thrombomodulin, protein C and protein S. TF-VIIa is not efficiently inhibited by antithrombin III, and therefore has its own inhibitor, TFPI, which has its largest pool present on the luminal surface of the vascular endothelium. It is also present in the plasma, 10 % present in platelets, and also released by activated monocytes. It has two binding sites, one for factor Xa and one for TF-VIIa complex. The prevention of thrombosis is not preventable by this inhibition when TF-VIIa complexes are being formed at a high rate, such as during extracorporeal circulation and DIC.

The endothelium itself participates in thrombosis regulation by thrombomodulin. Thrombin binds to thrombomodulin on endothelial cells and the formation of this complex activates protein C, a vitamin K-dependent protein that inactivates factors Va and VIIIa. In order for protein C to function, its cofactor, protein S, another vitamin K-dependent protein, must present. Additionally, the endothelium regulates platelet activation by producing soluble inhibitors such as nitric oxide and prostaglandin (PGI_2).

Fibrinolysis

Fibrinolysis resembles the coagulation cascade with involvement of zymogen-to-enzyme conversions and feedback loops for potentiation and inhibition. Plasminogen is one of the main zymogens present in plasma for fibrinolysis, and thrombin is one of the main activators of this system. Thrombin activates protein C and this activation results in

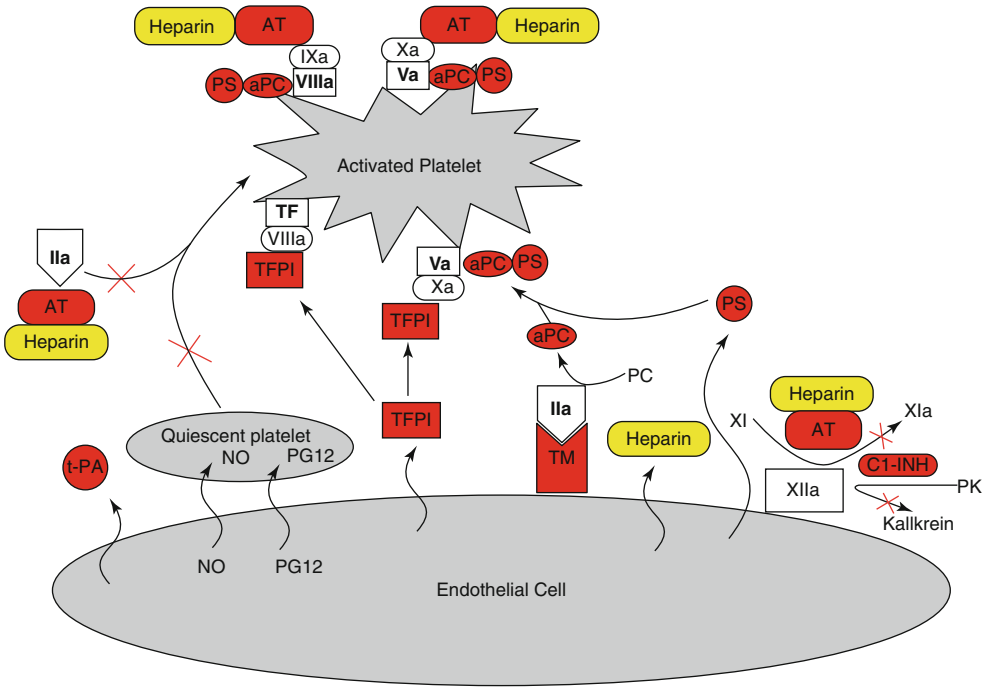

Fig. 21.6 Illustration of inhibition of the coagulation cascade. See text for detailed actions of inhibitors. Legend: *NO* nitric oxide, *PGI2* prostaglandin 2, *TM* thrombomodulin, *PC* protein C, *aPC* activated protein C, *PS* protein S, *TFPI* tissue factor pathway inhibitor, *AT* antithrombin III, *C1-INH* complement 1 inhibitor, *PK* Prekallekrein

the destruction of factors Va and VIIIa, therefore reducing the production of tenase and prothrombinase complexes. Thrombin also stimulates endothelial cells to produce tissue plasminogen activator (t-PA). Tissue plasminogen activator binds avidly to fibrin, cleaves plasminogen to plasmin and the result is the cleavage of fibrin by plasmin. The protein fragment produced from fibrin cleavage is a D-dimer, a useful marker of fibrinolysis. F1.2, D-dimer and fibrinopeptide A increase during unchecked intravascular inflammatory activation of the coagulation cascade, indicating ongoing thrombin production (F1.2), fibrin formation (fibrinopeptide A) and fibrinolysis (D-dimer) [9, 36], and a consumptive coagulopathy.

As with all other pathways within the coagulation system, fibrinolysis is regulated by a feedback loop controlled by the native protease inhibitors: α2-antiplasmin, α2-macroglobulin, and plasminogen activator inhibitor-1 (PAI-1). PAI-1 produced by endothelial cells, directly inhibits t-PA and urokinase, and its production is increased during endothelial injury such as in sepsis mediated disseminated intravascular coagulation. Alpha 2-antiplasmin rapidly inhibits unbound plasmin and prevents the enzyme from circulating, but poorly inhibits plasmin bound to fibrin. Alpha 2-macroglobulin is a slow inhibitor of plasmin.

In addition to fibrinolysis, plasmin is both an inhibitor and stimulator of platelets depending upon concentration and temperature [37]. At high concentrations of plasmin, under normothermic conditions, platelets undergo conformational changes which result in centralization of granules, and internalization of GPIb receptors, but not the GPIIb/IIIa receptors.

Complement and Leukocytes

The complex interaction of all components of whole blood responsible for the process of hemostasis requires a brief discussion of complement formation, neutrophils, monocytes, and leukocytes. Although their role in hemostasis is minimal during health, inflammatory processes induce prothrombotic stimuli from these components.

The complement system is also activated during periods of inflammation, and like the coagulation system, it is comprised of two separate pathways that lead to a common pathway. Although both the coagulation cascade and complement cascade are discussed as separate entities, the two interact significantly to modulate one another's activity [2, 38, 39].

The classical pathway is activated by a variety of stimuli that includes immune complexes, C-reactive protein and endotoxins. A cascade of enzymatic reactions produces C5a and C5b. C5a is a major agonist for neutrophils and monocytes [40, 41] while C5b in turn initiates the formation of the terminal complement complex (TCC) by sequentially binding C6, C7, C8, and several molecules of C9 [42]. TCC is capable of producing holes in cellular membranes, causing lysis and cell death. It also accelerates thrombin formation via its action on the prothrombinase complex [43].

The alternative pathway does not require antibody or immune complexes for activation. It is activated by foreign surfaces whether they be microbial organisms and/or elements, or whether they be particles or biomaterial surfaces. Complement activation via the alternative pathway occurs spontaneously at a low rate and as hydrolyzed C3 is formed by the classical pathway Factor B becomes activated and then initiates the cleavage

of C3 to form C3a and C3b. In the face of extracorporeal circulation, with a biomaterial surface to bind C3b covalently to its hydroxyl or amine groups, Factor B and D binding occurs and the alternative C3 convertase (C3bBb) is formed creating a positive amplification loop. Properdin stabilizes the C3 convertase and the clustering of C3b on the surface allows the formation of C5 convertase (C5b) with the assembly of TCC to follow as in the classical pathway [2].

Circulating leukocytes are comprised of neutrophils, monocytes, lymphocytes, basophils and eosinophils. For the scope of this chapter, we will be focusing on neutrophils, monocytes, and lymphocytes which are the main groups of cells involved in the inflammatory responses. Diffuse inflammatory processes activate these cell lines, and some of the indicators of this activation are L-selectin shedding, release of elastase and lactoferrin, the presence of cytokines such as IL-1 and TNF-α, and CD11b up regulation which has been widely demonstrated in hemodialysis and CPB [2, 44–52].

Neutrophils are the most abundant white blood cells, representing 40–60 % of the leukocyte population. Neutrophil agonists include factor XIIa, heparin, leukotriene B4, IL1-ß, IL-8, and TNF-α, many of which are also released by activated cells enhancing the activation process. Once activated, neutrophils release neutral proteases such as elastase, lysosomal enzymes, myeloperoxidase, hydrogen peroxide, hydroxyl radicals, hypochlorous acid, hypobromous acid, acid hydrolases, and collagenases. The released inflammatory mediators have various properties that include chemoattraction for leukocytes, promotion of adherence to endothelial cells, further platelet activation, and ongoing mediation of the systemic inflammatory response [2, 41, 53, 54]. Activated neutrophils express Mac-1 (CD11b/CD18) receptors. Mac-1 is an important receptor for binding neutrophils to endothelial cells and collagen. It also binds factor X and fibrinogen and thus facilitates thrombin formation. Monocytes when activated express tissue factor (TF) and agonists for activating monocytes include C5a, immune complexes, endotoxin, IL-6, γ-interferon, IL-1ß, TNFα, and monocyte chemotactic protein-1 (MCP-1). The activated monocytes are found to express Mac-1, L-selectin and MCP-1 [55–58], form aggregates with platelets [59], and produce MCP-1, IL-1ß, IL-6, γ-interferon, and TNF-α [60–62]. This results in monocyte and platelet microparticles which are able to sustain thrombin generation. Lymphocytes, like monocytes/macrophages, are largely responsible for cytokine expression which upregulates all phases of coagulation.

Laboratory Evaluation of Hemostasis in the Intensive Care Unit

Laboratory evaluation of the hemostatic system requires knowledge of the patient history and medication profile. Most routine laboratory testing is broad, and looks at the coagulation system in large portions (Table 21.1). An understanding of these routine laboratory tests provides insight in how to direct further testing. An excellent reference regarding laboratory evaluation of the coagulation system is invaluable in deciphering test results [63], and much of the following information is derived from such a source.

Table 21.1 Table of common laboratory tests of coagulation, normal values, and component of coagulation examined

Common laboratory evaluations of coagulation	
Laboratory test and normal values	Coagulation component evaluated
Platelet count	
150,000–400,000 cells/mm^3	Evaluates platelet number and size
Prothrombin Time (PT)	
12–16 s	Factors VII, X, V, II, I
Activated Partial Thromboplastin Time (aPTT)	
25–38 s	Factors XII, XI, IX, X, V, II, I
Thrombin Clotting Time (TCT)	
Fibrinogen 150–400 mg/dL	Fibrinogen level

Platelets are evaluated as part of the routine complete blood cell count in most institutions. Much can be derived from this routine screening, such as platelet number and size, however more advanced testing is occasionally required. Platelet count is now routinely performed using the Coulter Counter®, an automated process which uses cell size to differentiate cell lines. Counts are performed on whole blood as individual elements pass through a small aperture and their size is determined using differential light refraction. This process provides a platelet count, normally between 150,000 and 400,000 cells/mm^3 ($150–400 \times 10^9$ cells/l). Large platelets, aggregates of platelets, or platelet clumping may produce abnormal values or errors from the automated count, requiring a manual count. Manual counts are performed on thin blood smears, and platelets are counted per high power field, and may give additional information such as the presence of platelet aggregates or mega-platelets.

Skin bleeding time is a rarely used evaluation of platelet function in vivo whereby the skin is incised to a standardized length and depth, and the time to cessation of bleeding is measured. It is now largely out of favor due to more advanced laboratory evaluation of platelet function. Bleeding time also has the problems of interaction of other elements of whole blood, such as hematocrit and platelet numbers. Hence, platelet function is now more routinely measured using platelet aggregometry. In this process, platelet rich plasma is stimulated with an agonist for platelet activation. The activated platelets clump or aggregate, and using light spectroscopy the formation of aggregates is measured and compared to normal values. These studies can be invaluable to evaluate bleeding in a patient with suspected platelet dysfunction, such as Glanzmann's thrombasthenia, Bernard-Soulier

syndrome, or aspirin use. It is often helpful to enlist the aid of Hematologists in the diagnosis and management of platelet dysfunction.

Prothrombin time (PT) is a standard laboratory measurement in most hospital settings. It evaluates the extrinsic coagulation system and common pathway, factors VII, X, V, II, I, by evaluating the activation of factor X by factor VII in the absence of the intrinsic tenase, VIII-IX. Citrated, patient plasma is activated by the addition of tissue factor thromboplastin and calcium, and the time to clot formation is measured in seconds. PT results are affected by the levels and activity of factors involved, and is a sensitive marker for depletion of vitamin K dependent factors, II, VII, and X. PT does not, however, differentiate between diminished production and active consumption of factors, nor can one determine if an inhibitor is present, such as ATIII-Heparin complex in a heparinized patient. Normal values for adults are reported as 12–15 s, and age dependent normal values are used in pediatrics and range from 12 to 16 s [64]. Many clinicians use the International Normalized Ratio (INR) for PT results, with normal INR values of 1.0. This is a ratio of the patient PT to the normalized value calibrated to the World Health Organization reference thromboplastin used for testing. .

Activated partial thromboplastin time (aPTT) is also readily available as part of standard laboratory evaluations in most hospital settings. aPTT is used to evaluate the contact system, intrinsic coagulation, and common pathways, Factors XII, XI, IX, X, V, II, and I. The tissue factor thromboplastin added to the citrated patient plasma sample, in addition to calcium, lacks the apoprotein (tissue factor) component of thromboplastin used in the PT, hence provides only a phospholipid structure for the intrinsic tenase complex. This difference is what excludes the extrinsic coagulation pathway in the testing of aPTT. The addition of an activator, such as micronized silica, provides a surface area on which clot may form and greatly affects results, as does incubation time. Additionally, the reagent used in aPTT changes the sensitivity profile of the test in the face of certain inhibitors, such as heparin. Hence, it is necessary for individual laboratories to provide in-house reference standards for aPTT testing based on components used in testing. Normal testing provides results in seconds, with normal adult values usually in the range of 25–30 s, and for pediatrics the range is expanded to 26–38 s [64]. Prolongation of the aPTT may be due to deficiencies in the factors listed previously, active inhibitors of these factors, such as heparin sulfate, and low fibrinogen levels. As in the case of PT, abnormal results do not differentiate between consumption of factors and low levels of factors seen with congenital factor production deficiencies. Vitamin K dependent factors II, IX, and X are included in this assay, but the short half life of factor VII makes the PT the preferred test for hepatic synthetic dysfunction. Additionally, non pharmacologic inhibitors of factor function are tested by mixing patient plasma with normal plasma. That is, in the case of hemophilia A with normal factor VIII levels, factor VIII inhibitor presence is demonstrated by the normalization of aPTT results with a 50:50 mix of patient plasma and stored plasma. This type of mixing study is also used for other inhibitors, such as the lupus anticoagulant.

PT and aPTT look at the coagulation cascade in large portions, not differentiating specific factor deficiency. Advanced testing is available in most referral centers, and factor levels, expressed as a percent activity, are measurable. This testing is usually performed using substrate deficient in the specific factor under investigation. However, no such deficient substrate exists for factor XIII, and testing is done using clot dissolution assay by 5 M urea. A high degree of suspicion is necessary to order testing of factor XIII deficiency as abnormalities are not seen in routine coagulation evaluations.

Fibrinogen concentrations are measured using the thrombin clotting time (TCT), also named the Clauss reaction for its inventor. Citrated patient plasma is activated with the addition of thrombin, and time to clot formation is measured. Thrombin mediates this reaction through its protease activity on fibrinogen and the formation of fibrin. Abnormal results reflect low fibrinogen levels or a direct thrombin inhibitor, such as heparin. Additionally, fibrin degradation products have antithrombin activity, and will further prolong TCT results. Fibrinogen levels are determined from known standards, which are derived by serial dilution of a standardized fibrinogen solution and their resultant TCT results. Normal fibrinogen levels are 150–400 mg/dL. Heparin contamination of the TCT sample can be elucidated using the reptilase time, a test that mirrors the TCT, but uses snake venom in place of thrombin. Reptilase alters the conformation of fibrinogen cleaving and the results are unaffected by heparin. Fibrin degradation products are measured by direct assay, such as the D-dimer assay that measures circulating cross-linked fibrin produced by plasmin activity during fibrinolysis.

Further testing of the hemostatic process may be required. In the face of persistent thrombocytopenia after prolonged exposure to transfusion, platelet antibodies may be detected requiring specific donor platelets that are antigen matched. Heparin induced thrombocytopenia may require testing for platelet factor 4 antibodies. In the case of a prothrombotic state, genetic testing for mutations may be necessary as in the case of Factor V Leiden deficiency, methylenetetrahydrofolate reductase Mutation, and prothrombin 20210 mutations. Protein C and S activity are also measured in cases of a prothrombotic state. In thrombocytopenic purpura and hemolytic uremic syndrome, deficiencies in the von Willebrand cleaving protease ADAMS13 have been identified requiring specialized assays at reference centers. Again, specific testing of some aspects of the coagulation system is best done in conjunction with Hematology expertise.

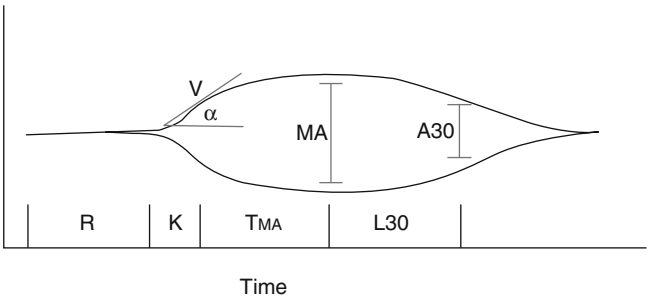

Fig. 21.7 An illustration of the thromboelastogram tracing. The output is an ellipse with multiple points of measurement. Factor deficiencies result in prolonged **R** period. The **K** time is prolonged with a lower **V**elocity in fibrinogen deficiencies. **MA** reflects the maximum strength of the clot and is affected by platelet function, number and fibrin cross-linking. Fibrinolytic activity is visualized in the area under the curve from MA to A30 and is reported as **L30**. Abbreviations: *R* Time to Clot Initiation, *K* Time to 20 mm amplitude (clot kinetics), *Velocity* Rate of Clot Formation measured using angle **α**, *MA* Maximum Amplitude, T_{MA} Time to Maximum Amplitude, *A30* Amplitude 30 min after MA, *L30* Area under the curve MA to A30

Assessment of the coagulation milieu done in clinical practice looks only at components of the process rather than the entire process. Currently one attempts to assess the coagulation profile of a patient using PT and PTT to evaluate the extrinsic and intrinsic pathway respectively and measuring levels of clotting components such as platelet counts and fibrinogen levels all with the hope of synthesizing a coagulation status assessment. Thromboelastography has been in existence since 1948 and is gaining rapid popularity as data acquisition methods have improved [65]. Thromboelastography has great advantages over the "static" assessment tools as it evaluates in a dynamic fashion multiple components of clot formation including time to initiation of clot, time to maximal clot, strength of clot and duration of clot and is able to provide information about factor levels/activity, platelet function, fibrin cross-linking and fibrinolytic activity [66, 67]. Two methods of thromboelastography are in popular use and are based on proprietary differences in methodology; TEG (Haemonetics Corporation, Braintree MA) utilizes an oscillating reaction chamber with a stable detection pin whereas ROTEM (Pentapharm GmbH, Munich Germany) utilizes an oscillating detection pin suspended in a stable reaction chamber. Impedance to movement created by the formation of clot is measured through the detection pin and generates a curve (Fig. 21.7). Multiple factors affect the measurements of thromboelastography and must be controlled to establish reliability for comparison of test results. The conditions affecting TEG/ROTEM measurements are numerous and a reference is provided for further reading [67]. A work group has formed to provide some standardization to TEG/ROTEM measurements which will be valuable for widespread clinical use [68]. In the interim, numerous reports are appearing in the literature of patient management, especially associated with surgical hemorrhage which includes cardiovascular surgery both intraoperative and postoperative and more recently it has become increasingly used for anticoagulation management during ECMO. Additionally, functional platelet mapping data available with TEG/ROTEM are used to manage anti-platelet therapies.

Modulation of the Coagulation System in the Intensive Care Unit

Oral anticoagulants are not often used in the intensive care unit setting for primary anticoagulation as their adsorption and peak effects are difficult to control and include many variables that alter coagulation. Warfarin (Coumadin) is the classic oral anticoagulant, and inhibits vitamin K dependent synthesis of factors II, VII, IX, and X as well as the inhibitors protein C and S. Hence, monitoring of warfarin therapy is achieved with measuring PT, and its effects are reversed with administration of vitamin K, replacement of factors with fresh frozen plasma, or with recombinant activated factor VII in cases of severe hemorrhage. Warfarin has interactions with many drugs that may increase or decrease the efficacy of the dosing regimen, making titration difficult. Hence, other forms of anticoagulation are often used in the acute setting.

Heparin sulfate remains the default anticoagulant and gold standard in the intensive care unit. It is far from an ideal drug. It has the advantage of being swiftly reversed by protamine or platelet factor 4 (PF4) and is widely available for parenteral use [69]. Heparin accelerates the action of antithrombin III (AT III) approximately 1,000-fold, but does not prevent thrombin formation, but inhibits thrombin after it is formed. Additionally, adequate levels of AT III are required for therapeutic effect of exogenously administered heparin for clinical anticoagulation. Heparin inhibits coagulation at the end of the coagulation cascade instead of the beginning; therefore many powerful serine proteases are already formed by the time heparin binds to AT III. Furthermore, the heparin-AT III complex only inhibits soluble thrombin and does not inhibit thrombin already bound to fibrin [70]. Heparin-catalyzed AT III weakly inhibits factors Xa and IXa but these reactions are relatively slow compared to inhibiting thrombin. Therefore, thrombin forms continuously and is circulated when heparin, low molecular weight heparin, or a heparinoid is used for anticoagulation [36, 71].

Standard (unfractionated) heparin has undesirable side effects. The drug activates several blood elements and may produce an important and sometimes devastating allergic reaction in some patients. Heparin increases the sensitivity of platelets to various agonists [72, 73]. Heparin is an agonist for factor XII [74], complement, neutrophils, and monocytes [75–77]. Heparin-induced thrombocytopenia (HIT) occurs

in 2–6 % of patients in both pediatric and adult patients who receive the drug (see subsequent sections). Although heparin is not a perfect anticoagulant, its cost, familiarity, ease of titration, and reversibility make it the preferred anticoagulant in the intensive care unit.

More recently, other heparinoids have gained popularity, especially in the prevention and treatment of non-life threatening thrombus formation. Low molecular weight heparins (LMWH) catalyze ATIII, are better factor Xa inhibitors than standard heparin [39], but are weaker blockers of thrombin [78], and are poorly reversed by protamine [79, 80]. There is evidence that LMWHs produce less microvascular bleeding than standard heparin and the plasma half-life is two to four times that of standard heparin [78]. Low molecular weight heparins may cause HIT, but the incidence is less than with standard heparin [81]. Heparinoids contain dermatan sulfate alone or are mixed with chondrin sulfate and heparin sulfate, the natural heparin produced by endothelial cells. By itself, dermatan sulfate catalyzes heparin cofactor II which is a direct thrombin inhibitor [82]. Heparinoids do not cause HIT and have been successfully used as an alternative for heparin during cardiac surgery [83]. The drawbacks to their use and the reason for them not being approved in the United States is their half-life is extremely long and their anticoagulant effects cannot be as easily reversed with protamine.

Many compounds have been investigated for anticoagulation efficacy. A large number of reversible and irreversible direct thrombin inhibitors are known [84], and a few have been used clinically in patients with heparin allergy. Argatroban is a potent reversible, direct thrombin inhibitor of both bound (fibrin) and unbound thrombin. Pharmacokinetic and pharmacodynamic data exist for Argatroban and suggest a volume of distribution of 174–180 ml/kg with 54 % of drug protein bound. The half life is 39–51 min in normal hepatic function and up to 181 min with hepatic dysfunction [85]. Additional data in adults suggest therapeutic serum concentrations of 0.5 mcg/ml achieved with a loading dose of 125 mcg/kg and a clearance rate of 4.7 ml/min/kg with the half life of effect 18–40 min [86, 87]. Argatroban is difficult to use clinically as the time to anticoagulation and steady state is anywhere from ½h to 3 h, and monitoring is done using activated partial thromboplastin times (aPTT) and anti IIa activity with the goal anti IIa level around 1.0 [88, 89]. Another direct thrombin inhibitor is recombinant hirudin. It was initially identified in leeches, and the anticoagulant that allows them to attach and siphon blood from their hosts. It binds irreversibly to both bound and unbound thrombin, and has a half-life of approximately 1.3 h with normal renal function, but this can increase substantially with renal insufficiency, and as with Argatroban, monitoring is often done using aPTT and anti IIa activity [90, 91].

In low volume extracorporeal therapies, such as continuous renal replacement therapy (CRRT) and plasmapheresis, regional anticoagulation may be employed instead of systemic heparinization as used in extracorporeal life support. The agent for anticoagulation and the reversing agent are simultaneously employed. The anticoagulant is infused into the circuit at the proximal venous port, and the reversal agent is infused at the distal port just prior to reinfusion of the circuit blood. Rarely, heparin may be used in this scenario with protamine infused to reverse the effects [92]. However, regional citrate based anticoagulation is gaining popularity in CRRT [93]. In this case, anticoagulation is achieved by citrate effectively binding free or ionized calcium in whole blood. As is evident from Fig. 21.4, calcium is a necessary cofactor for most of the coagulation cascade enzyme activity. Sequestration of this calcium renders the coagulation cascade and platelets ineffectual. Because of the obvious cardiovascular effects of hypocalcemia, this essential element must be returned to the patient at the time of reinfusion of circuit blood. Calcium is administered either at the distal circuit or in a separate lumen as dictated by blood flow rates in the circuit and the size of catheter. Small children on CRRT with low blood flow rates often experience catheter clotting if calcium is re-infused in the dialysis catheter. Hence, in small patients an additional central venous catheter may be necessary for regional citrate anticoagulation. Although this may complicate care, citrate regional anticoagulation has been shown to reduce hemorrhagic complications of CRRT and is gaining popularity [94]. The choice of anticoagulation must be tailored to the individual patient and the expertise of the staff caring for the patient [95].

Modulation of platelet function is not common as an intended therapy in the acute setting, although patients may present to the intensive care unit setting having been administered such drugs, or have side effects to platelet function from agents used for other purposes. Although not often used as a primary anticoagulant, aspirin is the mainstay of therapy for adults with acute myocardial infarction. It causes an irreversible inhibition of cyclo-oxygenase through acetylization of the enzyme, preventing prostaglandin formation. However, the non-steroidal anti-inflammatory drugs such as ibuprofen, produce finite inhibition of the cyclo-oxygenase, and effects dissipate. Ticlodipine, an adenosine diphosphate receptor antagonist also inhibits platelet function that will persist for 7–10 days after therapy is ceased. B-blockers, such as propranolol may affect platelet aggregation and activation by agonists, but do this weakly. Milrinone, a phosphodiesterase inhibitor frequently applied in the post cardiopulmonary bypass group has been demonstrated to affect platelet activation response in TEG platelet mapping and may affect function in the at risk patient for bleeding [96]. Angiotensin converting enzyme inhibitors, such as captopril have been noted to affect platelet aggregation by decreasing thromboxane production, and finally, furosemide, surprisingly, is also known to inhibit platelet function. Finally, any nitric oxide

donor such as nitroglycerine or nitroprusside not only have vasodilatory effects, but also promote platelet quiescence through nitric oxide release. It must be noted that these various platelet inhibitors, affect only specific platelet activation pathways. Each platelet can be activated by a variety of pathways and therefore no inhibitor provides complete inhibition of platelet function [97].

Bleeding in the Intensive Care Unit

Disorders of Platelets

Thrombocytopenia is seen in a variety of clinical conditions encountered in the intensive care unit setting. Bleeding due to isolated thrombocytopenia is classically reported as cutaneous bleeding, i.e. petechiae, epistaxis, and bleeding gums, although hemorrhage can be severe in the post surgical setting, or if platelet counts are <20,000/mm^3. It results from insufficient production of platelets, increased destruction of platelets, or sequestration of platelets. Decreased production of platelets is seen in bone marrow suppression due to chemotherapy, a variety of medications, Fanconi Anemia, thrombocytopenia with absent radius (TAR syndrome), and Wiskott Aldrich syndrome. Thrombocytopenia may also be due to increased consumption as seen in infection/sepsis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and extracorporeal therapies. Antibody mediated platelet destruction is seen in cases of idiopathic thrombocytopenic purpura, transfusion induced platelet antibody, and heparin induced thrombocytopenia (HIT). Sequestration of platelets may occur with hypersplenism, or locally in the giant hemangiomas of Kasabach-Merrit syndrome. Finally, with massive transfusion, thrombocytopenia may be due to a combination of blood loss and dilution by crystalloid and packed red cell transfusion [98]. Thrombocytopenia is treated by infusion of pooled donor platelets, usually 10 ml/kg body weight, or as a number of units with 60 ml in each unit. In the case of specific platelet antibodies, single donor platelets may be more effective in producing the desired rise in platelet numbers.

Factor Deficiencies

Deficiencies of coagulation factors may present in the intensive care unit with bleeding. As compared to isolated thrombocytopenia, factor deficiencies tend to produce deep tissue hemorrhage. Although any factor may be reduced in isolation, factor VIII, factor IX, and vWF deficiencies are the most commonly affected by congenital deficiencies, and factor VII deficiency is the most commonly acquired factor deficiency.

Patients with Hemophilia A (factor VIII deficiency) have an X-linked recessive deletion on the long arm of the X chromosome at the Xq28 locus. The incidence is 1:5,000–10,000 male births and the phenotypic expression ranges from mild to complete absence of factor VIII activity. Approximately 50–60 % of affected patients have < 2 % factor VIII activity and suffer from severe hemorrhage, presenting at birth. A family history of hemophilia A, reduced factor VIII activity, and genetic testing are the mainstay for diagnosis. Therapy in the setting of acute hemorrhage is replacement of factor VIII, which is now done predominantly with intravenous recombinant human factor VIII products that also contain vWF. A variety of recombinant factor VIII products are available, and dosing has been standardized to International Units of clotting factor activity per milligram of purified protein. The half life of recombinant factor VIII is approximately 12 h, but may be shorter in the face of ongoing hemorrhage and consumption. Dosing is based on the severity and location of presenting hemorrhage, ranging from 10 to 20 IU/kg/24 h for hemarthrosis to 50 IU/kg every 6–12 h until bleeding resolves. In the case of severe trauma or surgery, factor replacement is achieved through a continuous infusion. Goal factor VIII activity levels achieved with factor infusion therapy ranges from 30 to 100 %, again depending on the location and severity of hemorrhage. Adjunct therapy for factor VIII replacement may include 1-deamino 8-D-arginine vasopressin (DDAVP), which causes a release of VIII-vWF from storage pools in platelets and endothelium, and antifibrinolytic therapy such as ε-aminocaproic acid (Amicar®). Additionally, cryoprecipitate may be used as it is rich in factor VIII, vWF, and fibrinogen, although viral transmission from pooled donors makes recombinant factor replacement preferable. Factor VIII inhibitors which develop in 15–35 % of Hemophilia A patients are alloantibodies, and severely complicate therapy by reducing the efficacy of infused factor VIII. The effect of inhibitors on therapy is related to the titer of antibody, and standard therapy may be efficacious, however some patients require porcine factor VIII or recombinant activated factor VII. Hence, it is important to determine the inhibitor status of all hemophilia patients requiring therapy for severe hemorrhage, and consultation with the primary hematologist is invaluable [99].

Hemophilia B is due to an X-linked recessive deletion on the long arm of the X chromosome at the Xq-26 locus that codes for factor IX. It too presents with variable degrees of factor IX activity, but is much less common than factor VIII deficiency, occurring in 1:30,000 male births. Like hemophilia A, severe hemorrhage is treated with recombinant human factor IX and may require adjunct therapy with antifibrionlytic drugs such as ε-aminocaproic acid (Amicar®). Cryoprecipitate contains little factor IX, hence its use in hemophilia B is not efficacious. Factor IX inhibitor alloantibody occurs less frequently than in hemophilia A, but may be present [93].

von Willebrand disease (vWD) may present in both males and females, and is transmitted in an autosomal fashion with variable penetrance. It is a rare disorder of coagulation, affecting 1–2 % of the population, however most do not suffer from severe disease or go undiagnosed. The incidence of severe type III vWD is estimated at 0.5–3.5 per million population. The gene for vWD resides on the short arm of chromosome 12 and encodes for the production of von Willebrand factor (vWF). vWD presents with a broad variability in clinical symptoms, and is divided into three types I, II, III. Type III is total absence of vWF and is most likely to present in the intensive care unit setting with significant hemorrhage, although all types and subtypes of disease may present with severe hemorrhage. Therapy for mild hemorrhage includes DDAVP, however in the case of severe hemorrhage, recombinant factor VIII is utilized as it contains significant amounts of vWF. Recombinant factor VIII is dosed upon the severity of hemorrhage, with a loading dose of 40–80 IU/kg followed by additional doses every 8–12 h. Ristocetin cofactor levels can be followed to titrate therapy with goals of >50 IU/L [100].

Factor VII deficiency is most commonly acquired by hepatic failure, or overwhelming consumption as seen in severe trauma with massive transfusion and DIC. The availability of activated recombinant factor VII has let to its use in many clinical situations such as severe hemorrhage after surgery and trauma, although it's indicated usage is primarily for hemophilia patients with specific inhibitors. Off label uses for activated recombinant factor VII (rFVIIa), NovoSeven®, have expanded dramatically since its introduction representing up to 97 % the overall use [101]. Although individual centers have created usage and dosing guidelines for these off label uses many cited indications are without large study results to guide appropriate patient selection and usage [102–104]. The most often cited indications for off-label use are: Hemophilia with inhibitors, hepatic failure with life threatening hemorrhage, hemorrhage into a closed space such as intracranial hemorrhage or retroperitoneal hemorrhage, severe hemorrhage with multiple trauma or surgery, or rarely for acute emergent anticoagulation reversal such as with warfarin overdose. rFVIIa use is indicated only after adequate replacement of platelets, standard factor replacement with fresh frozen plasma, and fibrinogen replacement with cryoprecipitate has been attempted. It is not indicated for use in futile care, prophylaxis for potential bleeding except in the case of hemophilia with factor inhibitors, or cutaneous bleeding as seen with angiodysplasia or mucositis. rFVIIa dosage is 70–90 micrograms/kg intravenously, rounded to the nearest 1,200 microgram dose as each vial contains 1,200 micrograms. The dose is administered over 2–5 min, and is usually given with platelet transfusion to maximize the formation of extrinsic tenase complex.

Massive Transfusion Syndrome

Bleeding may occur in the intensive care unit setting in the face of massive transfusion [105]. This loss of factors, fibrinogen, and platelets in whole blood is not replaced by packed red blood cell infusion alone. Hence, abnormal laboratory values and overt bleeding may occur, and require replacement. Platelet transfusion has been discussed in the section on thrombocytopenia. Specific factor replacement has been discussed for single factor deficiencies, however most patients with diminished factor activity in the ICU have a more generalized consumption, or as in the case of hepatic failure, have deficiencies in the vitamin K dependent factors II, VII, IX, and X. Fresh frozen plasma will replace most factors adequately and is usually given in doses of 10–15 ml/kg body weight. Plasma should be infused soon after warming and as rapidly as the patient will tolerate because delays result in a decline in factor activity. Hypofibrinogenemia is treated with cryoprecipitate at doses of 0.1 units per kilogram body weight up to the usual adult dosage of 10 units. Although cryoprecipitate contains factor VIII and vWF, it does not contain additional factors.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is an adequate descriptor of one portion of the process involved, but is an incomplete and inadequate title for the clinical state. It might better be labeled as uncontrolled thrombin generation leading to microvascular thrombotic disease with resultant end organ dysfunction and a generalized bleeding diathesis related to consumption of coagulation proteins and fibrinogen, in addition to the down regulation of prothrombotic mediators of normal hemostasis. Although adequately descriptive, this label is not easily shortened for the purposes of communication, hence we will use the acronym DIC for the purposes of this discussion.

DIC or consumptive coagulopathy is recognized classically in conjunction with sepsis, but is also seen in other forms of diffuse inflammatory processes that alter the cytokine milieu and affect the balance between pro and anti-thrombotic regulators in normal hemostasis. It is a complex process which is not all or none, but is a continuum from mild to severe, hence its clinical definition has been difficult. Clinical scoring systems have been developed and subsequently validated and improved to aid the clinician in the diagnosis of DIC [106–109]. It is now felt that in adult patients with sepsis, severe DIC defined by these scoring systems is a marker for the risk of mortality [106, 110].

Pathophysiology of DIC

DIC is now recognized to result from diffuse inflammatory processes, and includes elements of thrombin generation, accelerants for the process of thrombin generation, and down regulation of the normal inhibitors of thrombin generation. In sepsis, thrombin generation begins with expression of tissue factor, usually on activated or damaged endothelial cells in addition to activated monocytes and macrophages. Tissue factor expression appears to be the driving mechanism for thrombin formation in DIC, through activation of the extrinsic tenase complex (TF-VIIa) and induction of the common pathway by activation of factor X to Xa. Factor Xa binds to factor Va and the prothrombinase complex is formed, resulting in the cleaving of prothrombin to thrombin. The extrinsic tenase complex also activates conversion of factor IX to IXa which binds to factor VIIIa and forms the intrinsic tenase complex (VIIIa-IXa). The intrinsic tenase complex provides further stimulus for activation of the common pathway increasing thrombin generation. Thrombin further amplifies its own production by enhancing conversion of factor V to Va, factor VIII to VIIIa and finally, by activation of factor XI to XIa which further amplifies the intrinsic pathway through enhanced conversion of factor IX to IXa. Phospholipids are necessary for the formation of tenase complexes, and this occurs normally on cell surfaces. However, in sepsis, additional phospholipids are available from bacterial degradation, cellular destruction, and increased levels of very low density lipoproteins (VLDL), which aid in the tenase complex formation outlined above. The result of this entire process is generation of large amounts of thrombin that act to cleave fibrinogen to fibrin.

The large amount of thrombin and fibrin generated by TF induction of the coagulation cascade results in additional changes. Further prothrombotic actions are the activation of platelets and endothelial cells that enhance the formation of the tenase complexes. Fibrin binds to activated platelets and monocytes, creating soluble microparticles that are poorly cleared by the reticloendothelial system, and are capable of sustaining thrombin generation. These microparticles are also responsible for further damage to endothelial cells, which accentuates tissue factor and cytokine production. Activation of the complement cascade during sepsis enhances the destructive and propagative role of cytokines in DIC.

The production of thrombin and fibrin also play a role in removal of the restraining effects of antithrombotic controls on hemostasis. Normally, thrombin is quickly inactivated by antithrombin III (ATIII) binding, and by the binding of thrombin to thrombomodulin on the endothelial surface. However, in sepsis the binding of ATIII to thrombin is quickly overwhelmed by the rapid rise in thrombin, and the increased inactivation of ATIII by neutrophil elastase. In response to activation and injury, endothelial cells express less thrombomodulin, which in turn reduces the activation of protein C normally released from the thrombin-thrombomodulin complex. The cofactor for protein C function, protein S is additionally inhibited by its binding to complement 4b binding protein. Finally, endothelial cell activation and injury decreases the expression and release of tissue factor pathway inhibitor (TFPI), which normally inhibits activity of factor VIIa and Xa. The removal of the antithrombotic control of TFPI further enhances the generation of tissue factor mediated thrombin formation.

Activated protein C is not only responsible for the inhibition of factors V and VIII, it neutralizes plasminogen activator inhibitor type-1 (PAI-1). The lack of negative control of PAI-1 limits fibrinolysis, and fibrin cross-linking is enhanced. Sepsis induces other changes in the fibrinolytic cascade as well, for instance, PAI-1 production is not only increased from protein C inhibition, but also from endothelial cell responses to endotoxin and tumor necrosis factor-α. Sepsis also reduces the release of tissue plasminogen activator, which further reduces fibrinolytic activity. Finally, α2-antiplasmin levels are increased in sepsis, which binds plasmin and limits its ability to cleave fibrin. Hence, fibrinolysis is suppressed in sepsis through multiple mediators.

Clinical Scoring Systems in DIC

The clinical diagnosis of DIC has been difficult, and as outlined above, includes many phases and a continuum of severity. It has also been noted that individual components of the scoring system did not provide adequate sensitivity and specificity. The International Society of Thrombosis and Haemostasis Scientific Standardization Sub-committee on DIC developed a clinical scoring system to help clinicians and investigators in the diagnosis of DIC. This scoring system has subsequently been modified, and in its most recent validated form has been presented by the Japanese Association for Acute Medicine [111]. The scoring system looks at four laboratory components and calculates an aggregate score in the presence of the Systemic Inflammatory Response Syndrome; absolute and change in platelet count, levels of fibrin degradation products/D-dimers, prothrombin time, and fibrinogen level [112]. The scoring systems have not been specifically validated in the pediatric population. Additional laboratory values may be obtained, such as fibrin 1.2 fragment, fibrinopeptide A assays, and PAI-1 levels, although their measurement is currently restricted to specialized laboratory facilities, making their use in clinical practice impractical.

Treatment for DIC

The primary therapy for DIC is to treat the underlying inflammatory disease, such as antimicrobial therapy in sepsis. However, after the initial inciting agent is removed, DIC may persist due to its own self propagating mechanisms. Hence, additional therapy targeting DIC specifically are

under investigation. A recent review of therapeutic stratagem in DIC has been published, and we summarize the data in the following paragraphs. [113]. A disclaimer is however required, as these studies often do not include pediatric patients, extrapolation to the pediatric population may be risky, additionally, this area of investigation is rapidly evolving, and review of the current literature is necessary prior to initiating therapies.

Antithrombin III infusions have demonstrated improvement in some animal models of sepsis, and have led to promising phase II trials in humans. However, a large multicenter placebo controlled trial of ATIII infusion (KyberSept Trial) demonstrated no improvement on mortality despite adequate ATIII levels in septic patients, as well as more bleeding complications in the treatment group. Sub-group analysis suggested concomitant heparin sulfate infusion was associated with this higher risk of mortality and bleeding. Thus far no data support the use of ATIII infusions as first line therapy for DIC. Activated protein C (drotecrogrin alfa) has been investigated, and an improvement in mortality was seen for adult patients with severe sepsis in the PROWESS trial. However, this improvement in mortality was associated with an increased hemorrhage risk. Pediatric data for the use of drotecrogin alfa includes a small open label trial that demonstrated results similar to the PROWESS trial [114]. However data from a phase III randomized placebo controlled trial (RESOLVE) did not duplicate the adult studies with no significant efficacy noted in the intervention group [115]. In this same trial serious adverse bleeding events were similar in both the intervention and control group for the entire cohort, but differences neared statistical significance. In the intervention arm, serious bleeding events were more common in infants less than 60 days of age with a significantly increased risk of serious bleeding event. The maker of drotecrogrin alfa, Xigris® (Eli Lilly and Company Indianapolis IN), announced in October 2011 a voluntary market withdrawal of the product citing safety concerns concurrent with a meta-analysis from the Cochrane Collection© that does not support routine use of drotecrogrin alfa in severe sepsis [116]. Tissue factor pathway inhibitor (TFPI) demonstrated improvement in DIC and mortality in animal models. This led to a large randomized double blind placebo controlled trial in humans (Optimized Phase 3 Tifacogin in Multicenter International Sepsis Trial) demonstrated an attenuation of DIC, but there was no improvement in mortality. As in the ATIII trial, an increased risk of hemorrhage was noted, however it was not associated with concomitant heparin infusion. At this juncture, no data support the use of TFPI administration in sepsis induced DIC. Data regarding C1-INH administration in sepsis is limited to a small randomized, double blind placebo controlled pilot study. C1-INH improved organ dysfunction but had no effect on coagulation, and was too small to detect mortality differences.

Current data in the literature show definitive benefit only for activated protein C infusions for sepsis induced DIC in a select group of adult patients. The clinician is therefore limited to supportive replacement of components of the hemostatic milieu, such as plasma, platelet infusions, and fibrinogen replacement with cryoprecipitate. Even in these supportive replacement therapies, there exists a debate about replacement of substrate in the face of uncontrolled thrombin generation, in that it may simply further amplify the process and worsen end organ dysfunction. This debate is not supported by clinical trial data and remains theoretical. Excessive correction of laboratory values is unwarranted, but clinical evidence of hemorrhage must be treated. There are no firm guidelines for when replacement is necessary, although many clinicians worry about significant hemorrhage if the platelet count is <20,000/mm^3, the PT is > 30 s, and fibrinogen levels are <50–100 mg/dL.

Extracorporeal Life Support (ECLS)

Platelet activation and adhesion as described above are well known to occur during both cardiopulmonary bypass and ECLS, as well as with vascular access catheters and grafts. Both adherent platelets and platelet microparticles are procoagulant in nature and therefore provide continual, ongoing stimulus for the above described physiologic platelet responses to occur. The number of adherent platelets to a surface is proportional to the amount of surface adsorbed fibrinogen [117], but this density can vary with the chemical and physical composition of the surface. For example rough surfaces accumulate more platelets than smooth surfaces [118], and fewer platelets adhere to polyurethane than to silicone rubber [119]. It is well known that during extracorporeal life support (ECLS) [2] platelet adhesion and aggregate formation reduce the circulating platelet count. High consumption and formation of microemboli can occur rather than occlusive thrombi. As ECLS continues, adherent platelets detach leaving fragments of platelet membrane behind; these will also detach and circulate. The circulating platelet pool during ECLS consists of decreased numbers of morphologically normal platelets, increased numbers of platelets at various stages of activation (pseudopod formation, degranulation, membrane receptor loss), and new larger platelets released from the bone marrow. Bleeding times increase in the presence of structurally normal appearing platelets [120–122] and as ECLS continues beyond 24 h, platelet consumption continues. In addition to these platelet changes, there is a diffuse inflammatory response mediated by complement and circulating leukocytes. These effects are not unlike those reviewed in DIC, however are partially controlled by heparin anticoagulation. Current research is investigating extracorporeal circuits that attempt to mimic the normal endothelial

inhibitory function of nitric oxide by releasing it from the polymer or utilizing pre-existing nitroso-thiols within the blood to produce NO *de novo* at the blood biomaterial interface [123, 124]. At approximately 5–7 days of ECLS therapy, fibrinolysis increases, and clinically relevant hemorrhage may persist despite a reduction in heparin dosing, platelet transfusions, and reduction in activated clotting times. At this juncture, fibrinolysis inhibitors such as ε-aminocaproic acid (Amicar®) may be employed. Aprotinin is a protease inhibitor that was commonly used in cardiopulmonary bypass surgery to treat and prevent fibrinolysis related bleeding and was also used as an adjunct in ECLS related bleeding. Aprotinin has been removed from the marked after safety concerns noted with its use in cardiac surgery [125]. A more detailed discussion of ECLS anticoagulation and bleeding is available within the chapter dedicated to ECLS as well as other sources [126].

Along the lines of systemic heparinization as for ECLS, it must be briefly noted that heparin induced thrombocytopenia (HIT) is a significant, but extremely rare side effect to heparin. The incidence of PF4 antibodies appears to be 2–6 % in both the pediatric and adult population [127, 128]. Heparin-induced thrombocytopenia and thrombosis rarely occur but cause catastrophic complications when they do [81, 129–132]. Additionally, fewer than 10 % of those patients with positive anti-PF4 antibodies have the clinical syndrome of thrombocytopenia or thrombosis [131]. Heparin binds to platelets and causes some minor aggregation and thrombocytopenia in many normal patients receiving heparin. However, in patients with HIT, antibodies, specifically IgG, are formed and the Fc portion binds to platelet factor 4. Platelet factor 4 (PF4) is secreted from platelet alpha granules, and is normally expressed on the platelet surface and binds heparin during activation. The insertion of IgG antibodies between heparin and PF4, changes the configuration of heparin-PF4 binding and causes platelet aggregation and clearance, resulting in thrombocytopenia [133]. The diagnosis of HIT requires demonstration of antibody presence by enzyme-linked immunosorbent assay, and significant thrombocytopenia in patients receiving heparin with additional adjunct testing such as the serotonin release assay. In the scenario of thrombosis or severe thrombocytopenia, alternative anticoagulation should be entertained and may be achieved with direct thrombin inhibitors. Warfarin use in HIT is contraindicated due to reduced protein C synthesis and a significant increase in thromboembolic risks [134]. If this is necessary, consultation with a hematologist is helpful.

Conclusion

The fragile balance between prothrombotic and antithrombotic mediators of the coagulation system is easily disrupted in the face of critical illness. Understanding the basic physiology and interactions of these components demystifies derangements that lead to hemorrhage or thrombus formation. Additionally, the therapeutic mechanism and site of action of drugs that modulate the coagulation system are more readily understood with this knowledge. We have addressed a few of the disease states that are sources of concern for the practitioner, however this review is not intended to be a definitive review of all coagulation derangements. There are detailed textbooks dedicated entirely to the coagulation system, and these are an invaluable resource for the practitioner. Additionally, Hematology consultation may provide additional diagnostic and therapeutic insight for the intensive care unit practitioner.

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Therapeutic Apheresis in the Pediatric Intensive Care Unit

22

Stuart L. Goldstein

Abstract

In its most general sense, apheresis refers to techniques for large-scale removal of selected components of the blood. "Plasmapheresis" refers to removal of plasma, "erythrocytapheresis" to removal of red blood cells, and "leukapheresis" to removal of white blood cells. The provision of apheresis for critically ill children is becoming more commonplace as the immunobiology of various acute diseases is becoming elucidated, yet remains challenging due to a number of un-modifiable factors. However, given the relative infrequency of these disorders, prospective randomized trials to evaluate the efficacy of therapeutic apheresis are lacking. In addition, critically ill children develop their maximal organ failures and mortality very early in the intensive care unit time course, so waiting to see if a disease will resolve is often not a clinical option for many of these patients. Finally, many diseases do not have a biological marker to follow, so reliance on clinical improvement can be very subjective. The aim of this chapter is to describe the technical pediatric specific considerations and typical indications for apheresis provision for children seen in the pediatric intensive care unit setting. In addition, a framework for consideration of when to initiate, continue and discontinue therapeutic plasmapheresis is provided.

Keywords

Plasmapheresis • Plasma exchange • Red cell exchange • Children

Introduction

The term "apheresis" is derived from a Greek word meaning "removal." In its most general sense, apheresis refers to techniques for large-scale removal of selected components of the blood. "Plasmapheresis" refers to removal of plasma, "erythrocytapheresis" to removal of red blood cells, and "leukapheresis" to removal of white blood cells. The rationale for provision of therapeutic apheresis in children is challenged by the lack of studies with adequate sample size or design to make evidence-based inferences regarding benefit.

Nearly all pediatric apheresis applications and protocols are extrapolated from adult studies, which are limited by sample size as well [1]. In addition, the critically ill child develops his or her maximal number of failed organs and illness severity very rapidly compared to adult patients [2–4]. As a result, aggressive intervention is often chosen to provide maximal support early [5] without the benefit of confirmatory tests or "tincture of time", since diseases which may be amenable to apheresis have rapid and often catastrophic consequences.

Provision of apheresis procedures to children is also challenged by a number of technical considerations. Apheresis is feasible regardless of the size of the child, as long as adequate vascular access can be established. However, apheresis procedures in young children must be customized to the situation and to the size of the patient since apheresis equipment and the software that controls it are, in general, designed for

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use in adults. The aim of this chapter is to describe the technical pediatric specific considerations and typical indications for apheresis provision for children see in the pediatric intensive care unit setting.

Automated Apheresis Technology

Principle of Separation

Since apheresis technology is based on the use of automated cell separators, it is helpful to understand how these instruments work. The basic task of automated cell separators is to separate red blood cells, buffy coat, and plasma while maintaining sterility, such that one or more of the components can be returned to the patient. In most instruments, this separation is accomplished by mechanical centrifugation. It is also possible to separate plasma from cells by filtration across a membrane, but these machines can only be used for plasmapheresis [6]. Centrifugal devices separate whole blood into components on the basis of density differences, while membrane separators work on the basis of differences in particle size. All apheresis systems have single use disposable circuits that maintain sterility during centrifugation and that incorporates safety features such as air traps to prevent embolism, filters to prevent reinfusion of aggregates, pressure monitors for access pressure and a means to infuse an anticoagulant to prevent clot formation in the extracorporeal circulation.

Quantification of Removal

Plasmapheresis is the most commonly indicated apheresis treatment in the pediatric intensive care unit (PICU). The general rationale for plasmapheresis is to remove soluble substances in the plasma that might play a role in the patient's disease process, e.g., the pathogenic anti-glomerular basement membrane antibody in patients with Goodpasture syndrome. As plasma is removed from the patient, a replacement fluid must be given to maintain intravascular volume and oncotic pressure, which becomes admixed with the patient's plasma (of note, some of this replacement fluid is subsequently removed as the plasmapheresis proceeds). At the start of a plasmapheresis, most of what is removed is the patient's plasma, whereas at the end of the plasmapheresis, much of what is removed is replacement fluid. The amount of plasma removed (expressed as multiples of the patient's plasma volume) in a plasmapheresis treatment is related to the fraction of the original plasma remaining in the patient [7]. A plasmapheresis procedure that removes a volume equal to the patient's plasma volume will achieve about 63 % removal of the original plasma, with 37 % remaining in the patient. Removal of twice the patient's plasma volume will remove 86 % of the original plasma. Thus, it is apparent that the additional benefit of prolonging a plasmapheresis past two volumes is marginal. Finally, the overall efficiency of a single plasmapheresis procedure, or of a series of treatments is also affected by the distribution between intra-and extravascular compartments of the targeted substance and on other metabolic characteristics such as rate of resynthesis and degradation [7].

Anticoagulation

An anticoagulant must be added to the blood as it enters the extracorporeal circuit in order to prevent clotting in the machine's tubing. Sodium citrate is the most commonly used anticoagulant for apheresis. Sodium citrate chelates calcium to prevent in vitro activation of the clotting cascade. When infused into the patient, the citrate may cause transient hypocalcemia in the patient. The severity of this side effect depends on the rate of citrate infusion, the capacity for hepatic metabolism of citrate, and the patient's state of calcium homeostasis (i.e., baseline hypocalcemia or hypoparathyroidism). In many apheresis protocols, the rate of citrate infusion to the patient is the limiting safety factor in determining how rapidly blood can be drawn and returned, and ultimately how long the procedure will last.

The symptoms of reduced ionized calcium related to citrate [8] are usually referred to as "citrate toxicity". The mildest and most common symptoms are peri-oral or hand and foot tingling and paresthesias. Some patients experience nausea, an unusual taste in the mouth, or lightheadedness. More severe hypocalcemia may lead to tremors, twitching, muscular spasm, tetany, seizures, arrhythmias and hypotension related to myocardial dysfunction [9–11]. In the PICU setting, patients undergoing apheresis should be monitored for early signs of citrate toxicity by measurement of ionized calcium levels. In small children or sedated or unconscious patients, frequent vital sign measurement including blood pressure and ECG monitoring are necessary. Prevention of hypocalcemia can also be achieved using a regional anticoagulation protocol, adapted from continuous renal replacement therapy protocols [12], in which a calcium chloride (8 g per 1 l of normal saline) is infused in the return line at 1.5–2 times the blood pump rate in ml/h. For example, if the blood pump rate is 60 ml/min, the calcium chloride rate would be 90 ml/h. In general, mild symptoms can be relieved by reducing the rate of citrate infusion or by stopping the procedure temporarily until symptoms subside.

Procedures

As noted above, there are three basic therapeutic apheresis procedures: Plasmapheresis, erythrocytapheresis, and leukapheresis. These three procedures are modified in various ways for the therapeutic goal at hand and for safety considerations in small children.

Plasmapheresis

Plasmapheresis involves separation of the plasma from the cellular elements of blood, collecting the patient's plasma into a waste bag, and returning to the patient his own cells mixed with a fluid to replace the discarded plasma. The replacement fluid must contain colloid to maintain the patient's intravascular oncotic pressure. When 5 % albumin is used as the only replacement fluid, the plasmapheresis procedure can be performed with minimal concern for transfusion-transmitted infectious disease or transfusion associated acute lung injury (TRALI) [13]. Removal of plasma and replacement with 5 % albumin will result in depletion of most plasma proteins including immunoglobulins and the components of the coagulation cascade. Plasmapheresis of one plasma volume will reduce the levels of coagulation proteins by about 70 %, which can be associated with a fibrinogen level below 100 mg/dl and prolongation of the PT and aPTT but not usually with clinically significant bleeding. If the rate of hepatic regeneration of these lost coagulation factors is normal, a schedule of plasmapheresis procedures every other day generally does not require exogenous replacement with fresh frozen plasma (FFP). However, if daily plasmapheresis is necessary or if the patient has a concomitant coagulopathy, the replacement fluids must include FFP. If the pre-plasmapheresis fibrinogen level is less than 150 mg/dl, FFP should also be included as part of the replacement fluids. If FFP is used as the replacement fluid, the patient's plasma proteins and coagulation parameters will remain within normal limits.

Erythrocytapheresis

Erythrocytapheresis involves separation of the plasma from the cellular elements, collecting primarily the patient's red cells into the waste bag and returning the patient's own plasma mixed with donor packed red blood cells. This technique can be of great value for hemoglobinopathies, and occasionally for diseases caused by intra-erythrocytic parasites such as malaria. The principal applications of erythrocytapheresis are in sickle cell disease. The pheresis machines can be programmed to calculate the necessary volume of packed red blood cells needed to achieve a desired post-procedure hemoglobin S level, as long as the patient's pre-procedure hematocrit, hemoglobin S and packed red cell hematocrit concentrations are known. The patient's total hemoglobin can also be raised without a large volume of intravascular fluid. Common indicators for erythrocytapheresis in sickle cell disease include emergent preparation for surgery, severe acute chest syndrome, or cerebrovascular event. Typically, a post-procedure hemoglobin S of 25 % is desired in these acute situations.

Leukapheresis

Leukapheresis involves separation of the whole blood into three fractions - plasma, red cells, and white cells from the buffy coat. The plasma and red cells are returned, and only the leukocyte fraction is retained as a leukocyte product. With the standard leukapheresis procedure using the automated cell separators, a replacement fluid is not needed since both donor and therapeutic leukapheresis are collection procedures, not exchange procedures. For any leukapheresis procedure, a replacement fluid may be needed to compensate for the volume of leukocytes and red cells removed in the waste or collected product especially in small children. This technique can be applied as therapeutic leukocyte depletion to patients with hyperleukocytosis from leukemia as a rapid means of reducing blood viscosity associated with extremely high peripheral white blood cell counts [14–16]. In, general, two blood volumes are processed, and the procedure may he expected to remove approximately 50 % of the circulating platelets along with the leukocytes [17]. Variations of this leukapheresis technique can be used to harvest peripheral blood mononuclear cells from an allogeneic or autologous donor, as sources of either hematopoietic stem cells for stem cell transplantation [18–24], dendritic cells, T-lymphocytes for donor lymphocyte infusions [25–29] and other cell based therapies. Another variation of the leukapheresis procedure is termed "photopheresis", in which the mononuclear cells harvested by leukapheresis are treated with a photoactivatible chemical (a psoralen), subjected to irradiation under ultraviolet-A light (UVA), and returned to the patient. This therapy is used for cutaneous T-cell lymphoma [30–35] and may have broader applications as immunologic therapy for other autoimmune diseases [36, 37], solid organ graft rejection [38, 39] including kidney allograft rejection [38, 39] and graft-versus-host disease [30, 40, 41].

Technical Issues in Pediatrics

Use of apheresis in children is feasible regardless of the size of the patient, as long as an adequate vascular access can be established. However, apheresis procedures in young

Table 22.1 Patient and catheter size guide

Patient size (kg)	Catheter size (French)
Neonate	Dual-lumen 7.0
3–6	Dual-lumen 7.0
6–12	Dual-lumen 8.0
>12–20	Dual-lumen 9.0
>20–30	Dual-lumen 10.0
>30	Triple-lumen 11 or 12

children must be customized to the situation and to the size of the patient because apheresis equipment and the software that controls it are, in general, designed for use in adults.

Access

Successful pheresis provision depends on a well-functioning venous access. The access for drawing blood into the cell separator is the most critical, and critically ill children will usually require a double lumen venous catheter designed for hemodialysis to permit adequate flow of 2 ml/kg/min; Table 22.1 provides a guide to match access and patient size [42]. The softer single and double lumen catheters, such as the Broviac™ catheter, commonly used in oncology patients and in intensive care units, are not suitable for apheresis procedures. It is preferable to draw from the proximal ports and reinfuse at the distal point to minimize recirculation although in practice the better functioning port is usually chosen for the drawing access. The length, gauge and positioning of the tip of the catheter will depend on the child's size. However, the wall of the catheter must be resilient enough to withstand the negative pressure generated during the apheresis procedure.

Volume

Extracorporeal volume (ECV) is the most important consideration in adapting apheresis instruments designed for adults to use in children. The ECV for cell separators in clinical use varies from 200 to 400 ml depending on the machine and the procedure to be performed. Unless specific measures are taken to compensate for this volume, the patient's blood volume will be depleted by this amount during the apheresis procedure. While an adult may easily tolerate the temporary loss of 200–400 ml of whole blood, this ECV may be too much for a small child. As a general guideline, modification of the procedure in the interest of patient safety is required if the ECV exceeds 15 % of the patient's total blood volume (TBV) and should be considered if the ECV exceeds 10 % of the TBV.

The ECV for an apheresis procedure is a fixed specification of the instrument and tubing, and can be determined precisely. The patient's TBV, however, must be estimated in order to plan the apheresis procedure. The TBV estimate is a basic parameter for the algorithms that control the pumps on an automated apheresis instrument. The traditional formula used by most pediatricians to estimate TBV is 70–75 cc/kg. More complex, empirically derived formulae [43] for blood volume estimation that take into account gender, weight and height are available. These formulae are programmed into the software of some automated apheresis instruments, while these formulae may be more accurate than a weight-based TBV estimate in adults, they may yield overestimates of TBV in children, especially prepubertal males.

Blood Priming

In addition to the ECV, there is an obligate extra-circulatory red cell mass (ECRCM), a volume of packed red blood cells which must be held in the apheresis instrument in order to achieve the separation of plasma from red cells. Two decisions arise with respect to this ECRCM. First, can the patient tolerate the temporary loss of this red cell mass during the procedure? The answer to this question depends not only on the patient's total blood volume, but also on the patient's hematocrit and cardiovascular and pulmonary reserve. Second, can the patient tolerate the bolus of fluid which is associated with returning the red cells, or "rinsing back" the red cells from the machine to the patient at the end of the apheresis procedure? The answer to this question also depends on a clinical assessment of the patient's blood volume cardiopulmonary reserve and kidney function.

The procedure modifications that compensate for the ECV and ECRCM for young children undergoing apheresis are often referred to as "priming". While it is possible to prime the apheresis instrument by filling all of the tubing with red blood cells at a predetermined hematocrit before starting, priming is usually accomplished by infusing additional red cells or fluids at the start of the procedure during the time that the machine is filling with blood from the patient. With proper planning, it is possible to perform an apheresis procedure in a small child with no change in the patient's blood volume or red cell mass during the procedure.

In general, the method of priming for an apheresis procedure affects the patient's blood volume during the procedure and also the final amount of fluid administered at the end of the procedure. The patient's ability to tolerate volume depletion, loss of red cell mass, and volume overload must be assessed as part of the planning before the procedure is started. For children weighing <20 kg or for patients who are anemic or hemodynamically unstable, red cell priming is usually indicated.

Anticoagulation (Dose)

The need for anticoagulation to prevent clotting in the extracorporeal circuit was discussed above. For apheresis procedures in pediatrics, one must pay particular attention to the dose rate at which the anticoagulant is administered to the patient. Since the anticoagulant is added to the blood drawn from the patient in a constant ratio of volume of anticoagulant per volume of blood, the rate of blood draw determines the dose of anticoagulant that the patient ultimately receives. Apheresis procedures in children are often performed at higher flow rates than adults, when the rate is expressed on a per kilogram basis. Using typical values as an example, a 70-kg adult undergoing plasmapheresis with flow rates of 90–120 cc/min experiences blood draw rates in the range of 1.3–1.7 cc/kg/min but a 20-kg child undergoing plasmapheresis using a central line that permits a flow of 40 cc/min experiences a draw rate of 2.0 cc/kg/min. Thus, the dose rate of citrate will be higher in the child than in the adult. For many apheresis protocols, the dose rate of citrate is the limiting parameter for how fast the procedure can be run. Procedure modifications including calcium supplementation based on regional citrate anticoagulation protocols used in continuous renal replacement therapy (CRRT) [12] to prevent citrate toxicity are commonly used in pediatric plasmapheresis.

Hypothermia

Children and adults experience some degree of hypothermia during apheresis procedures because of cooling of blood in the extracorporeal circuit. This side effect may be more pronounced in younger children since the flow rate per kilogram is higher than for adults, as discussed above. A blood warmer is commonly incorporated into the return line in most pediatric apheresis procedures. Depending on the model used, the warmer increases the ECV by 20–50 cc.

Cooperation

The aspects of apheresis that children tolerate least well are the needles, the need to remain seated and still, the restriction of one or both arms, the operation of the blood pressure cuff, and boredom. The apheresis staff must be expert in phlebotomy and IV placement to gain the trust and cooperation of young patients. The staff must also be able to provide age-appropriate explanations of what is going on, and should encourage parental involvement wherever possible. Space and resources to provide distracting entertainment for children undergoing apheresis are a necessity. With a sensitive and experienced apheresis staff, it is rare that children are so frightened, inconsolable, or uncooperative that sedation must be used.

Disease-Specific Indications

The evidence that demonstrates the clinical efficacy of apheresis-based treatments is compelling in some disease states and marginal in others. For this reason, the Journal of Clinical Apheresis has published, most recently in 2010 [1], a categorized listing of the indications for therapeutic apheresis. The indications are placed into one of four categories, as shown in Table 22.2, based on the strength of evidence that therapeutic apheresis is effective for that disease process. Although this system of categories is imperfect, it is helpful in guiding clinical decisions about the use of apheresis. When therapeutic apheresis is applied to diseases seen

Table 22.2 Indication categories of the American society of apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Example: plasma exchange in Guillain-Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease
III	Optimum role of apheresis therapy is not established. Decision making should be individualized Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances Example: plasma exchange for active rheumatoid arthritis

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Table 22.3 Application of plasmapheresis for diseases seen in children

Diagnosis	ASFA category	Typical treatment plans		
		Volume treated	Frequency	Duration/endpoint
TTP [45]	I	1–1.5 FFP or cryopoor plasma	Daily	Normalized LDH and platelet count
HUS, atypical [46–48]	I (anti-factor H antibody) II (complement mutations) IV (diarrhea associated)	1–1.5 FFP or cryopoor plasma	Daily	Normalized LDH and platelet count
Goodpasture syndrome [49, 50]	I	1–1.5 5 % albumin	Every other day for 6 treatments	Reduction in anti-GBM antibody/cessation of pulmonary hemorrhage
Rapidly progressive glomerulonephritis with antibodies (ANCA) [51, 52]	I	1–1.5 5 % albumin FFP when pulmonary hemorrhage is present	Daily or every other day	6–9 procedures
SLE [53, 54]	II (CNS Disease)	1–1.5 5 % albumin	Daily or every other day	3–6 treatments
Lupus nephritis [55]	IV	1–1.5 5 % albumin	Three times a week	3–6 treatments
Recurrent FSGS [56, 57]	I	1–1.5 % Albumin/FFP	Daily ×3 then every other day	Minimum 9 treatments until resolution/improvement or resolution of proteinuria, taper treatments on individual basis
Solid organ allograft rejection (antibody-mediated) [58, 59]	I	1–1.5 5 % albumin	Daily or every other day	6 treatments minimum, consider more if donor specific antibodies still elevated
Thrombocytopenia-Associated Multi-organ Failure (TAMOF), sepsis [6, 60]	III	1–1.5 5 % albumin/plasma	Daily or every other day	2–14, assess for resolution of MOF, improvement in platelet count

Based on data from Szczepiorkowski et al. [1]
TTP Thrombotic Thrombocytopenic Purpura, *ASFA* American Society for Apheresis, *HUS* Hemolytic Uremic Syndrome, *FFP* Fresh Frozen Plasma, *LDH* Lactate Dehydrogenase, *FSGS* Focal Segmental Golmerulosclerosis, *GBM* Glomerular Basement Membrane, *ANCA* Anti-Neutrophil Cytoplasmic Antibody, *SLE* Systemic Lupus Erythematosus, *CNS* Central Nervous System, *MOF* Multi-Organ Failure

in the PICU either plasmapheresis or plasma exchange is most commonly indicated. The diseases for which therapeutic apheresis may be indicated are shown in Table 22.3, along with commonly used treatment schedules. Of course, these schedules must be individualized based on the patient's clinical condition. It is important to establish at the start of a course of apheresis how the success or failure of the therapy will be monitored and judged. This is often difficult to determine with certainty, because many diseases do not have a discrete identifiable marker to follow clinical response to treatment.

For many native immunological diseases and antibody-mediated solid organ transplant rejection, corticosteroids, other immunosuppressive agents, and intravenous immunoglobulin are commonly used in conjunction with plasmapheresis. In addition, critically ill children requiring apheresis are often receiving multiple organ support therapy including CRRT, extracorporeal membrane oxygenation and/or left-ventricular assist devices [5]. The apheresis machine can be connected in-line with many of these devices in order to obviate the need for separate dual lumen venous access or interruption of CRRT [5]. A number of technical issues require careful consideration when providing tandem therapies, which include matching the blood pump flow rates of each machine when possible, close attention to pressure and flow changes and most importantly, prevention of recirculation by ensuring the direction of blood flow is the same between the apheresis equipment and other extracorporeal device.

Apheresis and ACE Inhibitors

One unusual interaction of medications with apheresis therapy is relevant to the care of patients with kidney disease. Antihypertensive agents of the angiotensin converting enzyme (ACE) inhibitor class have been associated with an atypical and potentially severe reaction occurring shortly after the start of apheresis procedures. The symptoms include flushing and hypotension in most patients, and abdominal cramping, diarrhea, nausea, and diaphoresis in some. The reactions were first reported in patients taking ACE inhibitors

who underwent staphylococcal protein A column therapy, but have been associated with plasmapheresis [44] and other therapies involving extracorporeal circuits. The postulated mechanism of these reactions is that during an apheresis procedure elevated levels of bradykinin are generated. In most apheresis patients this is inconsequential because of rapid degradation of bradykinin by kininase II. However, if the patient is receiving ACE inhibitors, the degradation mechanism may be blocked by the drug and the vasodilatory and gastrointestinal effects of bradykinin give rise to the symptoms. Many ACE inhibitors drugs have been implicated, and it is recommended that ACE inhibitors be withheld at least 24 h before an apheresis procedure.

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Thromboembolic Disorders in the PICU

23

Ranjit S. Chima, Dawn Pinchasik, and Cristina Tarango

Abstract

The burden of thromboembolic disease in hospitalized children appears to be increasing. This is likely a reflection of increased survival of children with complex medical problems with increased utilization of invasive procedures and central venous catheters. Infants and teenagers appear to be at the highest risk for thromboembolic disease due to age-associated changes in the hemostatic system. Venous thromboembolism in the PICU usually presents as deep vein thrombosis and requires a high index of suspicion for diagnosis; pulmonary embolism may occur as a consequence. Numerous inherited and acquired risk factors are associated with venous thrombosis in children, notably the use of central venous catheters and the presence of underlying diseases such as trauma, malignancy, congenital heart disease and congenital thrombophilic disorders. Radiologic studies are needed to make the diagnosis of venous thromboembolism, and evaluation for underlying thrombophilia should be considered. Anticoagulation is the mainstay of treatment for venous thrombosis and pulmonary embolism in children, while systemic or site-directed thrombolysis is reserved for life or limb threatening thrombosis. Management strategies and duration of anticoagulation therapy are extrapolated from adult data. While the role of thromboprophylaxis remains unclear in critically ill children, its use in high risk patients should be considered. Long term outcomes are not known, however recurrent thromboembolism and post thrombotic syndrome are known complications of venous thrombosis in children.

Keywords

Venous thromboembolism • Central venous catheter related thrombosis • Pulmonary embolism • Anticoagulation • Thrombolysis

Introduction

Venous thromboembolism (VTE) constitutes an important morbidity in patients admitted to pediatric intensive care units (PICU). The magnitude of the clinical impact of this entity remains unclear in critically ill children. However, critically ill children frequently have the presence of risk factors such as central venous catheters (CVC), immobility, malignancy, trauma and congenital heart disease that place them at disproportionately higher risk for the development of VTE. The clinical consequences of venous thrombosis can be life threatening with the development of pulmonary embolism (PE). More commonly, venous thrombosis impacts

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venous access and impedes the delivery of care in patients with complex medical problems who are dependent on reliable vascular access for their survival.

Epidemiology and Incidence

VTE usually presents as deep vein thrombosis (DVT) or rarely PE, specific venous beds such as the cerebral sinuses, renal veins or portal veins may also be the site of thrombosis. The incidence of VTE in children is highest in infants and teenagers and, unlike adults, is almost always associated with an underlying medical condition such as malignancy, surgery, trauma, congenital thrombophilic states or congenital heart disease [1–5]. In the PICU, the most common risk factor for VTE is the presence of a CVC [1, 2, 6]. The incidence of VTE appears to be increasing in hospitalized children; recent data demonstrates a 70 % increase in the annual rate of venous thrombosis from 2001 to 2007 with an incidence as high as 58 cases per 10,000 hospital admissions [4]. More importantly, the incidence of VTE in children admitted to the PICU appears to be even higher, with a recent study estimating the incidence of radiographically confirmed VTE to be 74 per 10,000 admissions [7]. These data demonstrate a markedly higher incidence of VTE in children when compared to reports from Canadian and Dutch registries from the 90s which estimated the annual incidence of 0.07 and 0.14 cases per 10,000 children respectively and estimated the incidence of VTE to be 5.3 per 10,000 hospital admissions [1, 2].

The incidence of CVC related thrombosis varies between 13 and 66 % in both adults and children [8]. The largest retrospective data set from the Canadian Childhood Thrombophilia Registry identified 241 children with CVC related thrombosis, an incidence of 3.5 per 10,000 hospital admissions [6]. Central venous catheters appear to be the most important risk factor for VTE in children admitted to the intensive care unit [7]. Prospective studies performed in both pediatric critical and non-critical care settings utilizing ultrasound, contrast venography or both estimate an incidence of CVC related thrombosis between 13 and 35 % (Table 23.1) [9, 11–14]. This variation likely relates to differences in patient population, types of catheters, catheter placement sites and diagnostic studies utilized. More recently there has been a trend towards greater utilization of peripherally inserted central catheters (PICC) in critically ill children; however there is limited data on the incidence of VTE in this setting. A recent prospective study estimated 9.3 % of VTE following PICC placement which is lower than that associated with central venous catheters [15].

PE is a rare entity in children when compared to adults. The incidence of PE in children is not clear given the paucity of prospective studies; however the incidence maybe increasing especially in tertiary care centers with increased survival of children with complex medical conditions with increased dependence on CVC's. Data from the Canadian and Dutch registries estimated the incidence of PE to be 0.86 and 0.14 per 10,000 hospital admissions respectively [1, 2]. However, a recent review from a tertiary care center estimates the incidence to be higher at 5.7 per 10,000 hospital admissions [16]. Raffini et al. in their retrospective cohort observed an incidence of 11 % over an 8 year period [4]. However, there appears to be a wide variation in the incidence of PE from 1 to 40 % in different subsets of pediatric patients [17]. This is a reflection of differences in clinical suspicion, diagnostic tests and underlying disease processes. Notably, the incidence of PE in children admitted to the ICU is not known.

Overview of Coagulation

The prevention and management of VTE in the critically ill child requires an understanding of how coagulation proceeds in a normal setting and common intrinsic or acquired hypercoagulable states in children. Furthermore, age-based differences in hemostasis must be considered, as the balance of procoagulant and anticoagulant factors is dynamic during development and can contribute to the age-specific risks of thrombosis [18]. Normal hemostasis requires the controlled and localized formation of an impenetrable platelet and fibrin plug at sites of vascular injury. Current models of hemostasis have moved beyond the parallel intrinsic and extrinsic pathways and have elucidated the importance of tissue factor-bearing cells, platelets, and endothelium to coagulation. In this cell-based model, coagulation occurs in overlapping stages of clot initiation, amplification, and propagation [19, 20]. In the initiation phase, tissue factor-bearing cells have contact with blood at sites of vascular injury; the

Table 23.1 Incidence of catheter-related thrombosis in children in prospective studies utilizing ultrasound or venography

Reference	Age (years)	Diagnostic testing	Catheter location	Incidence
Male et al. [9]	1–17	Ultrasound and venography	Upper venous system	29/85 (34 %)
Massicotte et al. [10]	0–16	Venography	Upper and lower venous system	21/158 (13 %)
Jacobs et al. [11]	0–6	Ultrasound	Lower venous system	12/44 (27 %)
Beck et al. [12]	0–18	Ultrasound	Upper and lower venous system	17/93 (18 %)
Talbott et al. [13]	0–21	Ultrasound	Lower venous system	7/20 (35 %)

factor VIIa-tissue factor complex that forms can activate small amounts of factors IX and X. This in turn, results in a small amount of thrombin generation. During the amplification stage, this generated thrombin can activate more platelets that have leaked out of the intravascular space as well as activate cofactors such as V and VIII. Finally, in the propagation phase, activated protease complexes assemble on the surface of platelets and large-scale thrombin generation occurs, and this is sufficient to form a fibrin clot.

This cell-based model highlights the importance of coagulation localization on specific cell surfaces, which prevents the coagulation process from spreading and resulting in pathologic thrombosis. This tight regulation of thrombus formation in normal circumstances is also mediated by protein C, protein S, thrombomodulin, antithrombin and tissue factor pathway inhibitor (TFPI), which confine thrombus formation to sites of injury [21, 22]. In patients with sepsis or other life-threatening disorders, this tightly controlled process is deranged as acidosis, hypothermia, disseminated intravascular coagulation and endotoxin can result in increased tissue factor expression, endothelial damage, and consumption of anticoagulant factors [23, 24].

Pathophysiology of Pulmonary Embolism

PE is characterized by partial or complete obstruction of the pulmonary artery by a thrombus that embolizes from a remote site or develops *de novo*, or by fat that embolizes from a fractured bone. The subsequent physiologic consequences are dependent on the degree of obstruction, underlying cardiopulmonary disease and vasoactive mediators [25]. Ventilation-perfusion mismatch develops resulting in increased dead space ventilation leading to an increase in arterial pCO_2. Clinically this may present as an increased end-tidal CO_2 ($ETCO_2$) to arterial pCO_2 gradient. Hypoxemia may occur with PE as a consequence of intra-cardiac shunting in the presence of right to left shunts or as a result of right heart failure and low cardiac output leading to mixed venous desaturation. In the latter, the right ventricle, which is thin walled and exposed to a low pressure pulmonary vascular bed is exposed to increased pulmonary artery pressure due to obstruction; additionally, vasoactive mediators and systemic hypoxemia may lead to pulmonary vasoconstriction thereby increasing right ventricular impedance [26]. This increase in right ventricular impedance leads to increased right ventricular end diastolic volume and consequently dilation with increased wall stress. Due to ventricular interdependence there is a bowing of the inter-ventricular septum thereby reducing left ventricular preload and leading to a reduction in cardiac output and consequently hypotension. Furthermore, an increase in right ventricular volume and pressure and associated systemic hypotension may affect coronary blood flow causing right ventricular ischemia and right ventricular failure. Hence, a combination of physiologic changes associated with increased right ventricular impedance leads to reduced cardiac output and thereby reduced oxygen delivery to the tissues resulting in mixed venous desaturation.

Risk Factors for VTE

Risk factors are frequently identified in children who have VTE (Table 23.2); identification of these factors is crucial not only to management of the acute event, but to the prevention of primary or recurrent VTE.

Inherited Risks

Inherited thrombophilic risks exist in children and may confer an increased risk for the development and recurrence of VTE [27]. The cleavage of factor V by activated protein C is an important control point in clot development, preventing ongoing clot propagation. Factor V Leiden results from factor V alleles that contain a point mutation which confers resistance to activated protein C [28]. Thrombosis risk increases even in those who are heterozygous for such a mutation, and this disorder represents the most commonly encountered intrinsic thrombophilia in children who have had thromboembolic events [29]. The prothrombin gene mutation G20210A mutation has also been described as a common heritable thrombophilia. Patients with such a mutation have been demonstrated to have higher prothrombin levels when compared with normal controls, and their risk for developing thrombolic disease is increased [30].

Antithrombin is an inhibitor of numerous clotting factors and deficiency of this hepatic protein impairs an individual's ability to limit clot formation; deficiency encountered in critically ill children outside of early infancy is typically due to heterozygosity, as the rare homozygous form of antithrombin deficiency is likely to yield catastrophic thrombosis in utero or death early in life [31]. Most patients with inherited,

Table 23.2 Risk factors for venous thromboembolism

Inherited	Acquired
Antithrombin deficiency	Central venous catheters
Protein C deficiency	Surgery
Protein S deficiency	Congenital heart disease
Factor V Leiden mutation	Systemic infection/illness
Prothrombin mutation	Trauma
	Malignancy
	Nephrotic syndrome
	Immobility

Multiple factors may be present in a given patient

heterozygous antithrombin deficiency have antithrombin activity levels in the range of 40–60 % [31].

Protein C, in its activated form, plays an important role in the prevention of clot propagation. Heterozygous deficiency is associated with deep vein thrombosis in children, particularly teenagers. The homozygous (or compound heterozygous) form of deficiency leads to purpura fulminans in infancy and can be a devastating, life-threatening disease [32]. Deficiency of protein S, an important cofactor for protein C, can also lead to thromboembolic disease in the heterozygous state or purpura fulminans in the homozygous or compound heterozygous state [33].

Acquired Risks

Central venous catheters (non-tunneled, tunneled and peripherally inserted central catheters) play an important role in delivering care to critically ill children and constitute by far the most common risk factor for the development of VTE in critically ill children. These devices are being used with increasing frequency in the management of children with acute and chronic diseases who are admitted to hospital wards and intensive care units. CVC related thrombosis may present as a partial or complete catheter occlusion. The former is defined by the ability to infuse but not withdraw fluid from the catheter while complete occlusion refers to the inability to infuse or obtain fluid from a catheter. The spectrum of thrombus related occlusion includes a fibrin sheath (or fibrin sleeve), intraluminal clot, or a venous thrombosis [34]. Fibrin sheath refers to the accumulation of fibrin and fibronectin on the catheter surface which may completely encase the catheter [35]. Most CVC's will develop a fibrin sheath within 5–7 days of placement [35]. Generally these present as a partial occlusion by creating a one way valve wherein the catheter can be flushed but will not draw blood. A fibrin tail is a variation of the fibrin sheath; this tail is formed by the adherence of fibrin to the tip of the catheter. An intraluminal clot forms within the catheter lumen and maybe related to retrograde blood flow into the catheter tip; this may present as a complete occlusion. Catheter-related venous thrombosis is defined by the presence of a mural thrombus adhering to the vessel wall, which may partially occlude the catheter and vessel lumen or a deep vein thrombus, which completely occludes the catheter and the vein. The catheter related factors that may play a role in the thrombus formation include catheter composition, location, size and duration. Central venous catheters are manufactured from a variety of materials including polyurethane, polyethylene, silicone and polyvinyl chloride. Catheters made of stiffer materials (polyethylene and polyvinyl chloride) have been shown to be more thrombogenic [36, 37]. The surface characteristics of catheters can be quite variable and may affect the thrombotic tendency of a device [38]. The catheter insertion site may also be associated with the incidence of thrombosis. Beck et al. noted a 25 % incidence of thrombosis for catheters inserted in the jugular and subclavian veins in comparison to 41 % incidence for catheters placed in the femoral vein [12]. Male et al. noted a 44 % catheter-related thrombosis incidence in those catheters placed in the subclavian vein in comparison to a 20 % incidence for those catheters placed in the jugular vein [9]. A larger catheter diameter relative to the vessel in which it is placed, increases the risk of thrombosis [12]. These circumstances are most commonly seen in infants who have smaller vessel lumen diameter [6]. There is not a consistent relationship between catheter duration and incidence of thrombosis. Beck at al. noted that thrombi developed in most patients with CVC's by the fourth day following placement [12].

Specific disease states can also predispose children to VTE. Children with congenital heart disease have a known increased incidence of VTE. A recent review of children undergoing cardiac surgery demonstrated an 8 % incidence of venous thrombosis [39]. This increased risk is likely related to perturbations of pro and anti-thrombotic factors and platelet activation/dysfunction associated with cardiopulmonary bypass [40–42]. Malignancy and chemotherapeutic agents may also predispose children to VTE. The mechanisms by which malignancy results in hypercoagulability are likely variable and related to the type of cancer. Increased expression of tissue factor by tumor cells, hyperviscosity and increased microparticle formation have all been implicated in malignancy associated thrombosis [43]. L-asparaginase, a mainstay of leukemia treatment, contributes significantly to hypercoagulability by decreasing antithrombin levels [44]. These effects are augmented in children greater than 9 years of age and are hastened by concomitant administration of corticosteroids, as is standard practice during induction chemotherapy for patients with acute lymphoblastic leukemia [45]. The monoclonal antibody family of anti-VEGF agents has also been associated with increased rates of thrombosis [46, 47].

In addition, acquired antithrombin deficiency may be present in critically ill patients with sepsis related to decreased production and increased consumption of antithrombin. Furthermore children with nephrotic syndrome may become significantly deficient in antithrombin, as well as proteins C and S, predisposing them to thrombosis [48]. The antiphospholipid syndrome (APS) is another acquired disorder that can result in thrombosis in children [49]. This autoimmune disorder may be primary or seen in association with other autoimmune disorders such as systemic lupus erythematosus. APS can also be accompanied by other findings such as thrombocytopenia, hemolytic anemia, or Raynaud's

phenomenon. Of note, a positive lupus anticoagulant may be present in patients without evidence of or a history of thromboembolic disease and the presence of these antibodies do not necessarily indicate a diagnosis of APS or a predisposition to thrombosis [50]. In teenage girls the use of estrogen-containing medications are an important risk factor for the development of thrombosis, however it should be noted that this risk is augmented in the presence of thrombophilic states such as factor V Leiden, prothrombin gene mutations and other heritable thrombophilias [51, 52].

Diagnosis of Venous Thrombosis

Clinical Diagnosis

The clinical diagnosis of venous thrombosis is dependent on the location of the thrombus. DVT of the extremities will often present with extremity swelling, plethora or color change, and pain. Prospective studies in children indicate that 59–86 % of CVC related thrombosis are asymptomatic [12, 13, 53]. Hence, a high index of suspicion is required to make a clinical diagnosis. Most commonly, repeated occlusion of a CVC should arouse suspicion of thrombosis. CVC related thrombosis may also present as unexplained fever or thrombocytopenia, sepsis unresponsive to therapy or unexplained cardiopulmonary decompensation with hypoxemia [54, 55]. Catheters located in the upper venous system may, in addition, present with superior vena cava syndrome, pleural and/or pericardial effusions, chylothorax or chylopericardium [55–57].

The clinical presentation of PE is non-specific and may mimic a host of other disorders especially in patients who are critically ill. Moreover the underlying disease itself may mask or confound the presentation. Hence, a high degree of suspicion is required to make the diagnosis. The classical clinical presentation of PE is pleuritic chest pain, cough, dyspnea and hemoptysis, however patients may present with hypoxia, cyanosis, right heart failure, pulmonary hypertension and shock. Reports suggest that in critically ill patients on mechanical ventilation a PE maybe clinically silent [58]. In adolescents, pleuritic chest pain appears to be the most common symptom, followed by dyspnea, cough and hemoptysis [59]. PE may also present with persistent tachypnea in children who have risk factors for VTE [60]. Most patients in a recent review had signs and symptoms of PE at the time of diagnosis with dyspnea and pleuritic chest pain being the most frequent; nearly half of the patients were hypoxemic [16]. Other signs noted were unexplained tachycardia and fever [16]. Hence, in the critical care setting, the diagnoses of PE should be considered in patients with thrombotic risk factors, especially those with underlying VTE in the setting of any cardiorespiratory deterioration.

Radiologic Diagnosis

Given the unreliable nature of clinical signs and symptoms, radiologic studies are needed to confirm the diagnosis and extent of VTE. Historically, contrast venography has been considered the gold standard for the diagnosis of venous thrombosis [61, 62]. Contrast venography requires the injection of contrast media into a superficial vein distal to the area of suspicion, and visualization of a filling defect or cut-off in the vein is consistent with this diagnosis [62]. The use of venography in children is limited by the invasiveness of the procedure as well as the risks of bleeding, infection, and exposure to contrast and radiation. Currently, the most common imaging modality for venous thrombosis in children is compression ultrasonography with Doppler imaging [63]. Non-compressibility of the vessel lumen during this examination is considered to be the diagnostic hallmark for venous thrombosis (Fig. 23.1). Ultrasound offers the advantages of being non-invasive, easily available and portable; however study findings may be subject to operator bias. Furthermore, intrathoracic venous structures and deep veins in the abdomen and pelvis may be difficult to visualize. Numerous studies in adults have demonstrated ultrasound to be sensitive and specific when compared to contrast venography in diagnosing VTE in the lower extremity [64, 65]. There have been no studies comparing ultrasound to venography in children with CVC related thrombosis. A prospective study comparing ultrasound to venography in the upper venous system in children noted overall venography sensitivity of 79 % in comparison to 37 % with ultrasound [66]. However, ultrasound was more sensitive in detecting thrombi in the internal jugular vein while venography had improved sensitivity for detection of thrombi located in the superior vena cava, subclavian and brachiocephalic veins. Other radiologic techniques that are being employed include computed tomography (CT) venography and magnetic resonance venography. These are especially useful for imaging thrombi located in deep veins in the pelvis and abdomen. In adults, CT venography has been shown to have a greater than 95 % sensitivity and specificity for diagnosing thrombi in the lower extremities. However, there is little data available regarding the sensitivity and specificity of CT venography or MRI venography in children with DVT.

Radiologic imaging for PE includes chest radiographs, echocardiography, computed tomography with pulmonary angiography (CTPA), ventilation perfusion (V/Q) scintigraphy, pulmonary angiography and magnetic resonance angiography. Chest radiographs are non-specific especially in critically ill children and are of little value in confirming the diagnosis of PE. They may demonstrate wedge shaped infiltrates, atelectasis or effusion, all of which maybe secondary to the underlying disease process. In children with proven PE nearly 50 % of children have been found to have normal chest radiographs [67]. Another easily performed bedside study is

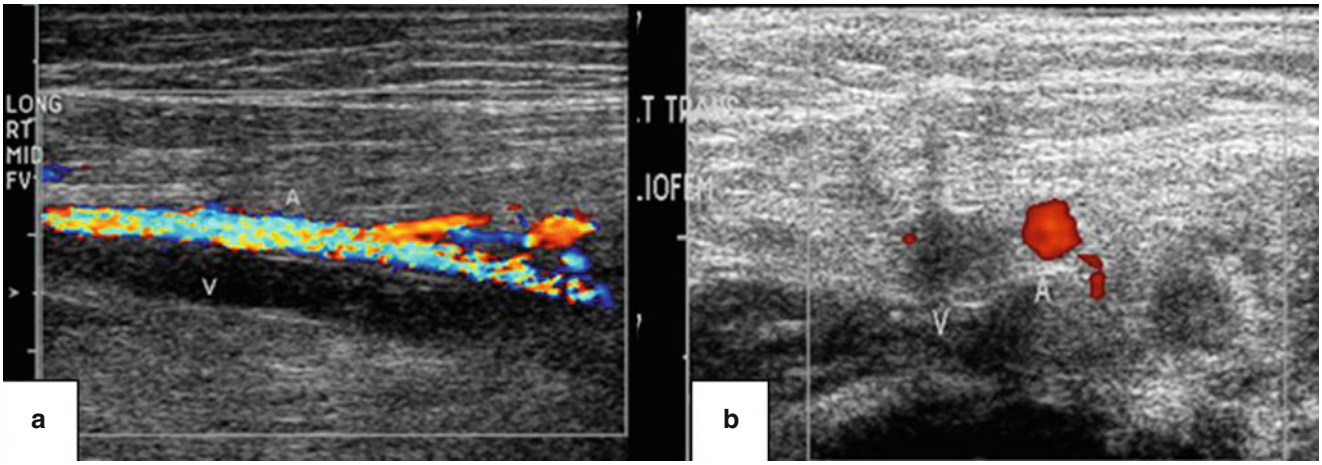

Fig. 23.1 Ultrasound with color Doppler images of femoral vein and artery in a child with catheter-related thrombosis. (**a**) Longitudinal view: flow is noted in the artery (*A*) but is absent in the vein (*V*). (**b**) Transverse view: flow is noted in the artery (*A*) but is absent in the vein (*V*), suggesting the presence of a thrombus

echocardiography. The utility of this study lies in its abilities to detect thrombi that are located within the central pulmonary arteries, assess for pulmonary hypertension and right ventricular size and function, especially in patients with hemodynamic compromise. In adults echocardiography for PE has been shown to have low positive likelihood ratio and is indicated only for patients with hemodynamic compromise [68].

Pulmonary angiography, which has long been considered to be the gold standard for diagnosing PE, is limited by its invasiveness and inability of detect thrombi in smaller vessels [69]. Recent studies show that CTPA is significantly more sensitive than pulmonary angiography in the detection of PE [70]. Hence, in adult patients it is suggested that pulmonary angiography be performed when other tests are equivocal [68]. With newer generations of multidetector row scanners, CTPA of the chest has become the diagnostic modality of choice in adults and children replacing V/Q scintigraphy. Numerous recent studies in adults have established the role of this modality in adults when compared to V/Q scintigraphy [69, 71–74]. This modality offers the advantage of being quick and easy to perform allowing detection of thrombi down to subsegmental vessels and delineation of other pathology in the pulmonary parenchyma and mediastinum [75]. This is especially important in critically ill children who commonly have abnormal chest radiographs with ongoing cardiorespiratory disease. Intraluminal defects within the arterial lumen that have a sharp interface with contrast media are diagnostic of PE [75] (Fig. 23.2). Furthermore, in children, wedge shaped peripheral consolidation on CTPA has been demonstrated to be significantly associated with PE [76]. Disadvantages of CTPA include the need for iodinated contrast material especially in patients

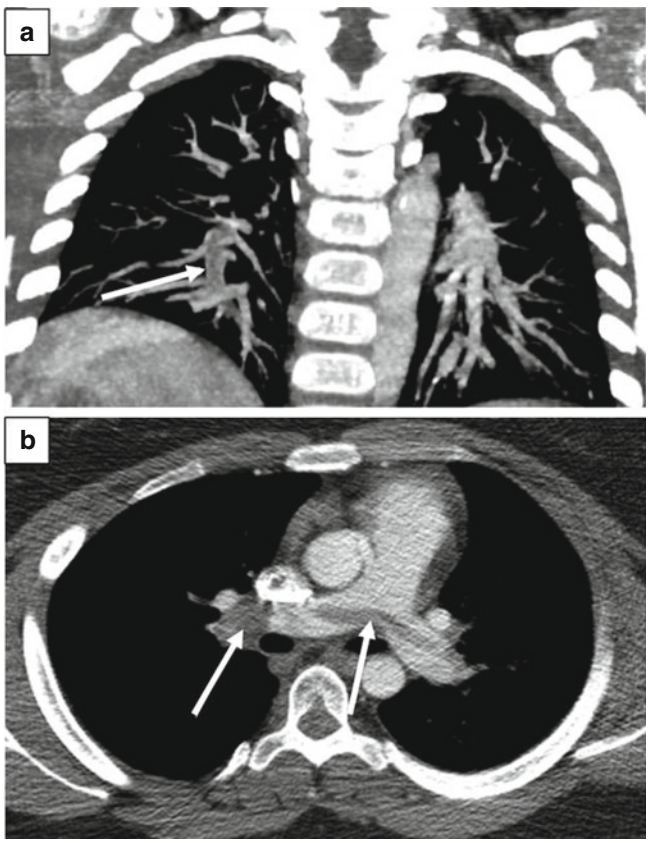

Fig. 23.2 Computed tomography with pulmonary angiogram (CTPA) of the chest showing pulmonary embolism. (**a**) Coronal image showing thrombus (*arrow*) in right lower pulmonary arterial vessels, note well defined vessels on the left with no thrombus. (**b**) Transverse image showing saddle embolus (*arrows*) at the pulmonary artery bifurcation with extension into both pulmonary arteries (Image courtesy Dr. Daniel J Podberesky, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

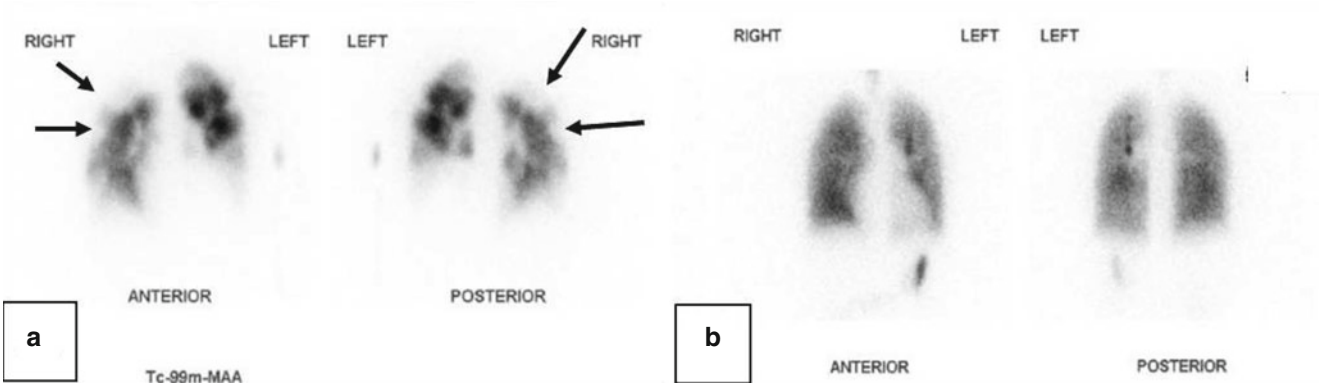

Fig. 23.3 Ventilation perfusion (V/Q) scan of the lung in an adolescent with pulmonary embolism. Perfusion scan (**a**) showing multiple filling defects (*arrows*) over both lung fields; corresponding ventilation scan shows (**b**) homogenous appearance of the lungs (Image courtesy Dr. Daniel J Podberesky, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

with kidney injury and radiation dose. Prudent use of CTPA as a diagnostic tool for PE in children may need risk-factor assessment as it is unlikely to be positive in children with no VTE risk factors [77]. V/Q scintigraphy has been used extensively: historically it has been the primary screening modality for PE [78]. During the perfusion phase radiolabeled albumin is injected and the distribution of these particles delineates pulmonary blood flow, while ventilation is assessed using inhaled radiolabeled aerosol [75]. V/Q mismatch is noted as defects on the perfusion phase (Fig. 23.3). This test is limited by a high rate of non-diagnostic tests, wherein the test is unable to exclude or confirm a diagnosis of PE because of matched ventilation perfusion defects [79]. Additionally its use may be limited in young children who are unable to inhale aerosol and in patients with underlying diseases associated with V/Q mismatch (such as pneumonia, pulmonary artery stenosis, sickle cell disease and collagen vascular disease) and congenital heart disease with right to left shunts [75]. Hence, the role of V/Q scintigraphy is limited to patients with normal chest radiographs and those with kidney injury or allergy to iodinated contrast material. MRA is a newer technique that can be utilized in clinically stable patients in whom ionizing radiation and iodinated contrast is contraindicated [69]. Negative MRA's do not rule out PE as small thrombi may be missed, and in adults, it has been shown to be technically inadequate, hence limiting its use to centers that perform it routinely and in patients in whom standard testing is contraindicated [69, 80].

Laboratory Evaluation

As discussed, children may experience VTE for a variety of reasons, including the presence of reversible risk factors, the presence of a medical condition that is associated with increased risk for venous thrombosis, and the presence of an underlying heritable thrombophilia. Children with VTE should have a basic laboratory evaluation that includes a complete blood count, prothrombin time (PT), partial thromboplastin time (aPTT), fibrinogen, fibrin degradation products (FDPs) and a D-dimer. Additionally any patient suspected of a PE in the intensive care unit should have an arterial blood gas, troponin, and EKG. Blood gas values other than an elevated alveolar arterial oxygen gradient are not useful in determining the presence of PE [81]. Similarly, EKG findings include sinus tachycardia, right axis deviation with right bundle branch block and ST-T wave changes are of little diagnostic utility [82]. D-dimer, a breakdown product of cross linked fibrin, is elevated with thrombosis and is commonly utilized in assessing the diagnosis of PE in adults. Despite its high sensitivity (high negative predictive value) this test is non-specific and values maybe elevated in conditions such as infection, malignancy, trauma and surgery [83]. Furthermore in children with PE, the D-dimer levels may be a poor discriminator for the presence of PE [67, 84]. Given the non-specificity of isolated clinical signs and symptoms, clinical prediction rules have been developed in adults which utilize a combination of history, physical examination and diagnostic tests that determine the pretest probability of PE [79, 85, 86]. Hence, in adults suspected of having PE, an unlikely or low/intermediate probability of having PE by a clinical decision rule along with a normal D-dimer excludes the presence of PE and obviates further testing [79]. However, these rules may have little predictive ability in children. A recent retrospective cohort study evaluated the Wells simplified probability score for PE in a cohort of children with radiologically proven PE and found that it lacked the utility in determining the pre-test probability of PE in children [84].

Further laboratory testing involves measurement of levels and activities of antithrombin, protein C, and protein S, and if found to be significantly low, replacement with recombinant product or fresh frozen plasma can be considered. Additionally, genetic testing for heritable mutations in factor V or prothrombins can be run at the time of diagnosis. Controversy exists regarding the extent of laboratory thrombophilia work up that should be undertaken when a child or adolescent presents with VTE [87–89]. Heritable thrombophilia traits are more common in children with thrombosis; a meta-analysis in children with first-onset venous thrombosis observed an increased incidence of protein C deficiency, protein S deficiency, antithrombin deficiency, Factor V Leiden, or the prothrombin G20210A than controls [27]. Yet, except for the severe homozygous deficiencies of protein C, S or antithrombin presenting with purpura fulminans, the management of a first thrombotic event is not altered by the presence of a thrombophilic defect. Whether testing for thrombophilia changes clinical management or outcomes remain unclear. As there are currently no pediatric or adult guidelines for the duration of anticoagulant therapy based on heritable thrombophilia, testing should be considered on an individual basis.

Treatment of Venous Thromboembolism

The treatment of VTE in children requires careful consideration of the overall clinical status and risk factors for bleeding as well as ongoing or recurrent thrombosis. In the acute phase, VTE therapeutic options include anticoagulation, thrombolysis and thrombectomy. Since there is a paucity of therapeutic studies in children much of the data is extrapolated from adults and is based on published guidelines for antithrombotic therapy in children [90]. Recent guidelines also suggest involvement of a pediatric hematologist preferably one with experience in VTE in managing these patients [90].

Anticoagulation

Anticoagulation is recommended for all patients with DVT, including those with PE. Commonly used anticoagulants in the acute setting include unfractionated heparin (UFH) and low molecular weight heparin (LMWH), and in certain conditions direct thrombin inhibitors may be considered. Following initial anticoagulation, vitamin K antagonists (VKA) or LMWH are used for long term anticoagulation. For children in the PICU who develop a CVC related thrombus, a suggested treatment algorithm is presented in Fig. 23.4.

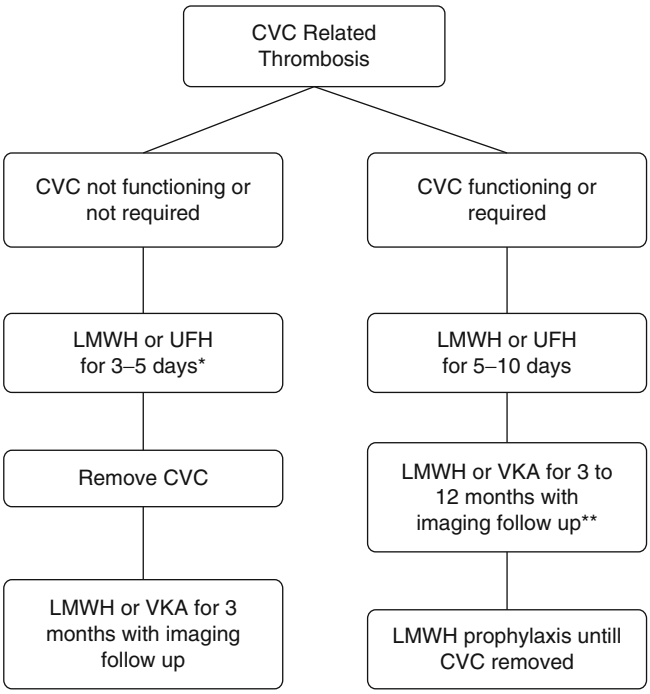

Fig. 23.4 Management algorithm for central venous catheter (*CVC*) related thrombosis. *CVC* central venous catheter, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *VKA* vitamin K antagonists. **Therapy prior to CVC removal may not be required if there is low risk of embolization;**longer duration of therapy suggested in presence of prothrombotic risk factors such as malignancy*

Unfractionated Heparin

Initial anticoagulation therapy in critically ill children with VTE is often with UFH. All heparins act by increasing antithrombin activity with subsequent inactivation of the serine proteases IIa, Xa, and to a lesser degree IXa and XIa. UFH's short half-life (4 h) and easy reversibility with protamine are appealing features in the setting of critical illness. Additionally, UFH can be used in patients with renal insufficiency with close monitoring. Suggested dosing and monitoring guidelines are presented in Table 23.3. Infants often require higher doses of UFH due to a larger volume of distribution and lower antithrombin levels. As children can frequently have transient nonspecific inhibitors/antiphospholipid antibodies that can prolong the aPTT, managing heparin dosing on aPTT alone is suboptimal and UFH anti-Xa levels may need to be followed. The major risk of UFH use is bleeding, with a recent prospective study reporting a major bleeding rate of 24 % in pediatric intensive care patients [91]. UFH is also associated with heparin-induced thrombocytopenia (HIT) in 2.3 % of critically ill children; hence monitoring of platelet counts is necessary while on UFH [92]. HIT is a prothrombotic, immune-mediated

Table 23.3 Dosing for anticoagulants and thrombolytics for acute venous thromboembolism and pulmonary embolism

Drug	Dose	Monitoring
Unfractionated heparin (UFH)	Loading dose 75 units/kg followed by: Age <1 year 28 units/kg/h 1–16 year 20 units/kg/h >16 year 18 units/kg/h	Titrate to keep anti-factor Xa level 0.35–0.7 activity units/ml[a]
Enoxaparin (LMWH)	Age <2 months: 1.5 mg/kg/dose every 12 h SQ >2 months to 18 years:[a] 1 mg/kg/dose every 12 h SQ	Titrate to keep anti-factor Xa level 0.5–1 activity units/ml[b]
Warfarin	0.2 mg/kg/dose (max 10 mg) once daily	International normalized ratio (INR): 2–3
Tissue plasminogen activator (tPA)	Low dose: 0.03–0.1 mg/kg/h for 6 h High dose: 0.1–0.6 mg/kg/h for 6 h Adults: 100 mg IV over 2 h	Fibrinogen, PT, aPTT, thrombin clotting time, imaging q12 h

[a]Titrate to aPTT (1.5–2 times normal) if UFH anti-Xa level not available
[b]Higher doses at initiation may be needed in children up to 5 years of age

adverse side effect of heparin therapy. It is most often associated with antibodies against complexes of heparin bound to platelet factor 4 that result in platelet activation and thrombin generation [93]. Long term use of UFH is limited by need for continuous infusions and the high risk of osteopenia with extended administration. The duration of UFH therapy for VTE is dictated by the clinical scenario. In patients transitioning to vitamin K antagonists, it is recommended that administration of UFH be continued for a minimum of 5 days and continued until a therapeutic INR has been reached. In patients transitioning to LMWH, UFH can be discontinued 4 h following the first dose of LMWH. This transition can be done at any time following initiation of UFH therapy and is most commonly based on the anticipated clinical course of a patient.

Low Molecular Weight Heparins

LMWH such as enoxaparin have become more frequently used in pediatric patients and are being utilized commonly as first line agents for treating VTE especially in stable patients who do not require invasive procedures. When compared to UFH they have clear advantages. A longer half-life and more predictable pharmacokinetics due to less nonspecific protein binding result in twice daily administration and decreased monitoring requirements. LMWH also have a lower risk of osteoporosis on long term administration, better ability to inhibit thrombin, and have a lower incidence of HIT when compared to UFH [90, 94–96]. However unlike UFH, in the event of LMWH overdose or bleeding, protamine only partially reverses its anti-Xa effect [97]. LMWH is most often administered subcutaneously, but has been administered intravenously in critically ill infants, although the different routes of administration result in dissimilar pharmacodynamics [98]. Suggested dosing and monitoring guidelines are presented in Table 23.3. Recent studies suggest that a higher starting dose of enoxaparin may be needed to attain therapeutic levels in infants and children [99, 100]. Bleeding is the main complication of enoxaparin therapy with a 3 % rate of major bleeding in children [101]. As described above, LMWH can be used for chronic anticoagulation in children. Unlike warfarin, LWMH has few drug interactions and no influence of diet on dosing; however, subcutaneous administration for prolonged periods can be difficult in children.

Direct Thrombin Inhibitors

Direct thrombin inhibitors such as bivalirudin, argatroban and lepirudin are a relatively new class of anticoagulants that bind directly to thrombin and block its interaction with its substrates. Currently, the only clear indication for their use in children with VTE is the presence of HIT. Despite their documented use in pediatrics, argatroban is the only approved anticoagulant for adult patients with HIT [102–104], and it is currently the recommended treatment for VTE in children with HIT. The suggested dose for argatroban is 0.75 mcg/kg/min as a continuous infusion, with a goal PTT of 1.5–2.5 times baseline. Lower doses of 0.2 mcg/kg/min are recommended in hepatic impairment [103].

Vitamin K Antagonists

VKAs inhibit gamma carboxylation of vitamin K dependent proteins (Factors II, VII, IX, X, protein C, protein S), thereby reducing plasma activity. As Protein C and Protein S have shorter half-lives than the hemostatic proteins, heparin therapy must continue until warfarin is in the therapeutic range (INR 2–3) to avoid a transient increase in hypercoagulability. VKAs are administered orally and are subject to multiple drug and food interactions, which may limit their use in patients with changing dietary intake or frequent medication changes [97]. Suggested dosing and monitoring guidelines are presented in Table 23.3. In addition, VKAs require

frequent monitoring of the INR, and patients often require multiple dose adjustments. Bleeding is the major adverse effect of warfarin therapy. Children on oral anticoagulation have been reported to have a bleeding risk between 0.05 % and 3.2 % per patient year [97]. Treatment of bleeding and supratherapeutic doses of VKAs includes holding VKA therapy, dosing with vitamin K, and administration of fresh frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa.

Duration of Anticoagulation for VTE

Recommendations for the duration of anticoagulant therapy in pediatric VTE are derived from adult data. Often, the duration of therapy will be influenced by ongoing thrombotic risk factors, persistent thrombus, or a history of recurrent thrombosis. For infants and children who have a known and reversible risk factor for VTE, the recommended duration of anticoagulation therapy is 3–6 months, with continued therapy advised if the patient still has the risk factor present once the anticipated duration of therapy has been completed [90].

Thrombolysis

Given the risk of bleeding, thrombolysis or clot destruction is reserved for children with VTE who have life or limb threatening thrombosis involving major vessels [90]. In the setting of PE it should be considered in children with shock or hypotension. The use of thrombolytics for PE in children is based on adult data; adults with PE are stratified as high, intermediate or low risk based on early mortality risk [68]. High risk (massive PE) patients have the presence of shock or hypotension while intermediate risk (submassive) patients have normal blood pressure with markers of RV dysfunction and/or elevated markers of myocardial injury (troponin I) [68, 105]. Patients with normal blood pressure with no markers of RV dysfunction or myocardial injury are described as low risk [68, 105]. Adult guidelines for PE suggest anticoagulation across all risk strata while thrombolysis is reserved for high risk patients. Recent data in children with PE has demonstrated poor response to thrombolytic therapy with a significant risk of bleeding [16]. Thrombolysis should also be considered for children with significant DVT that compromises vascular access. In addition to salvaging vessels in children that are dependent on stable vascular access, thrombolysis may afford reduction in long-term sequela of venous stasis [106–109].

Thrombolysis can be performed utilizing thrombolytic agents (such as plasminogen activators), mechanical devices or a combination of both (Fig. 23.5) [110]. Of the available thrombolytic agents, tissue plasminogen activator (tPA) is the agent of choice in children; tPA converts plasminogen to plasmin which enzymatically cleaves fibrin leading to clot dissolution [90]. Notably, replacement of plasminogen with fresh frozen plasma may be required prior to starting systemic tPA therapy [90]. Suggested dosing and monitoring guidelines for systemic tPA are presented in Table 23.3 [90, 110]. Bleeding is a major risk with tPA, contraindications to tPA therapy include ongoing bleeding, recent surgery or trauma, thrombocytopenia and presence of active intracranial disease (neoplasm, aneurysm or and vascular malformation). Utilizing a lower dose in a site directed manner can attenuate the bleeding risk. Mechanical thrombolysis by itself is reserved for patients who have significant thrombosis with contraindications to anticoagulation and thrombolytics. This involves interventional procedures using specialized catheter based devices which disrupt the clot and simultaneously aspirate clot fragments [111]. Risks of these procedures include vessel damage and clot embolization. Surgical thrombectomy is also an option but is reserved as a last therapeutic resort.

Thromboprophylaxis

Although there is strong evidence that mechanical and pharmacologic thromboprophylaxis decreases the risk of VTE in adults there is no such data in critically ill children [112–114]. Furthermore, guidelines in children recommend against thromboprophylaxis in patients with CVC's [90]. Hence, it remains unclear whether thromboprophylaxis should be routinely used in critically ill children. A recently published North American survey assessing prescribing practices for pharmacologic thromboprophylaxis in critically ill children showed that pediatric intensivists were more likely to prescribe thrombophrophylaxis for adolescents compared to children or infants [115].

LMWH's are often used in the prevention of VTE in adults and is usually the drug utilized in critically ill children for thromboprophylaxis. Prophylactic dosing regimens for enoxaparin in infants and children have been published and it has been demonstrated to be safe and efficacious in children [90, 116]. Recent data from the PROphylaxis for ThromboEmbolism in Critical Care Trial (PROTECT) in adults demonstrated no differences in the incidence of proximal DVT in patients receiving LMWH or UFH; whether such a strategy would benefit critically ill children remains unclear.

While anticoagulant prophylaxis can decrease the risk of VTE in hospitalized patients, the benefit is offset by a small but definite risk of hemorrhage, especially in surgical, neurosurgical or coagulopathic patients. For such cases, mechanical thromboprophylaxis with compression boots should be considered. Pneumatic compression boots help prevent venous stasis by squeezing blood from underlying deep veins during inflation with refilling during deflation. While all intermittent compression systems augment blood flow in proximal veins for the brief time while they compress,

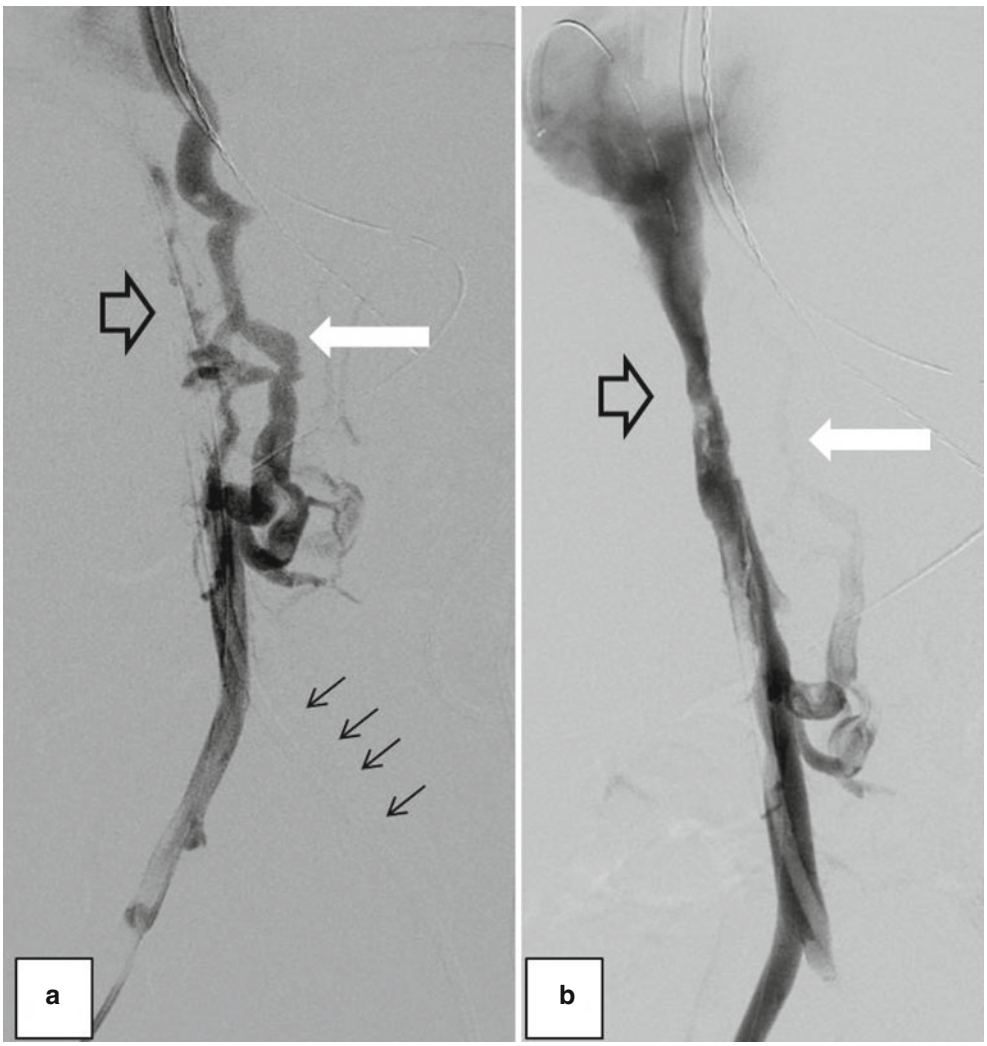

Fig. 23.5 (**a**) Digital subtraction (DSA) venogram showing complete occlusion of suprarenal inferior vena cava (*black arrowhead*) with drainage via collaterals (*white arrow*). Faint outline of left femoral venous catheter is seen (*black arrows*). (**b**) DSA venogram after pharmacomechanical thrombolysis and angioplasty shows significant improvement in contrast flow and caliber of suprarenal inferior vena cava (*black arrowhead*), reduction in collaterals (*white arrow*) (Image courtesy Dr. Kamlesh Kukreja, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

different pressures can be used and the air can be inflated uniformly or sequentially with graded pressures, allowing for more patient comfort [117]. Like graded compression stockings, these devices are limited to older children and adolescents due to limited sizes. The use of pneumatic compression boots has yet to be thoroughly studied in children. Another option for thromboprophylaxis in pediatric patients greater than 10 kg with lower extremity DVT who have a contraindication to anticoagulant therapy is a temporary vena caval filter. In such cases, anticoagulation should be started as soon as the risk of anticoagulation decreases, and filters should be removed as soon as possible [90].

Outcomes

Long term outcomes for children who develop VTE remain unclear. Notable long term issues with patients who develop DVT are recurrence and post-thrombotic syndrome (PTS). Data from the Dutch and Canadian registries demonstrated a 7–8 % incidence of recurrence, which appears to be lower than adults [2, 3, 63]. However, risk of recurrence may be higher in children with underlying thrombophilic disorder [118]. PTS in characterized by the chronic venous insufficiency following DVT that results in pain, edema, superficial vein dilation, stasis dermatitis and ulceration. Recent reviews have suggested the incidence to be 26 % in children, which is similar to adults [107]. Outcome data for children who develop PE are limited, with the Dutch and Canadian registries estimating 10 % mortality; however 21 % mortality was observed in a recent cohort [1, 2, 16]. In children who develop massive PE mortality is extremely high, estimated at 80 % [119].

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Part V

Oncologic Disorders in the PICU

Robert F. Tamburro Jr.

Care of the Oncology Patient in the PICU

24

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Abstract

There are numerous malignant conditions that place the pediatric patient at great risk requiring the need of critical care services. Therefore, it is essential that the pediatric critical care provider possess a sound understanding of these conditions such that they may be anticipated, recognized and treated effectively. Of these conditions, perhaps none requires the prompt, well conceived care of a pediatric intensivist as much as a malignant mediastinal mass. A definitive diagnosis must be established balancing the likelihood of a definitive result with the risk of the diagnostic procedure and the associated sedation. A clear understanding of the findings that suggest a patient is at high risk for airway compromise is essential. Hyperleukocytosis is another malignant condition associated with significant morbidity and mortality as a result of leukostasis. Leukostasis is a clinical condition characterized by progressive and potentially severe neurologic or respiratory disease attributable to small vessel infiltration and occlusion by leukemic blasts. Hypercalcemia is another disorder that may be associated with a variety of malignant processes. Although relatively rare in children, it may result in a number of life-threatening conditions including cardiac dysrhythmias, neurologic impairment, and renal failure. Additionally, it is well-established that varying degrees of coagulopathy are present in most patients with advanced malignancy. Perhaps most notable, acute promyelocytic leukemia is associated with such a high incidence of death near the time of presentation secondary to intracranial and pulmonary hemorrhages that it is viewed as a medical emergency. Other forms of leukemia may be associated with other pathophysiological consequences that may also be life-threatening. For example, lactic acidosis resulting from a high rate of glycolysis is a very rare, but life-threatening complication of hematologic malignancies. A heightened sense of alertness for these rare conditions may result in earlier detection, more effective therapy, and better outcomes for these children.

Keywords

Mediastinal mass • Hyperleukocytosis • Hypercalcemia • Acute promyelocytic leukemia • Differentiation syndrome • Lactic acidosis of malignancy • Palliative care • Pediatrics

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Introduction

Cancer is responsible for more deaths in children over 1 year of age than any other disease, but through clinical research outcomes have improved dramatically in the past three decades [1, 2]. Today, children diagnosed with cancer have a projected survival rate of approximately 80 %, compared with less than 20 % in 1970 [2]. This improvement is not only due to research oriented towards curing cancer, but is also due to improved supportive care when children undergoing intense therapy for cancer experience life-threatening problems. Nearly 40 % of pediatric cancer patients require intensive care services and pediatric cancer patients account for approximately 3 % of all children requiring admission to a PICU [3, 4]. In the past, these patients were considered to be poor candidates for critical care services. However, recent data suggest that overall PICU survival does not differ between cancer and non-cancer pediatric patients [3]. In one report, 87 % of non-operative pediatric oncology patients survived through their PICU course and 81 % survived to hospital discharge [3]. Comparable survival rates have been published elsewhere [5]. Hospital survival for pediatric oncology patients requiring PICU admission following surgery is well in excess of 90 % including 70 % survival among those post-operative patients who require both mechanical ventilation and vasoactive infusions [3]. Likewise, PICU resource expenditure in terms of lengths of stay does not appear to differ between cancer and non-cancer patients [3]. In light of these findings, the pediatric critical care provider should have a sound foundation of knowledge regarding the unique aspects associated with the care of the pediatric cancer patient. This chapter will highlight several conditions unique to the oncology patient that may require critical care services.

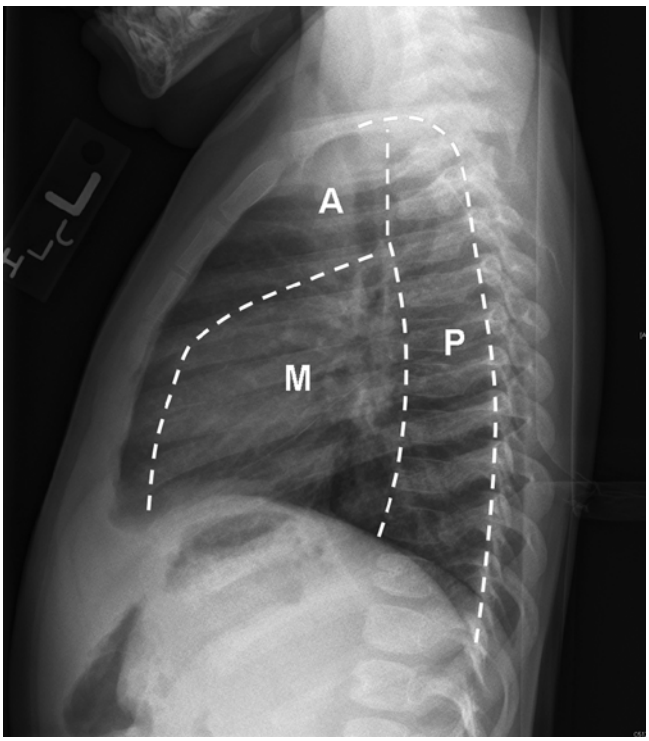

Fig. 24.1 Mediastinum and its compartments. The anterior (*A*), middle (*M*), and posterior (*P*) mediastinal compartments. The anterior mediastinum lies anterior to the heart and extends cephalad into the anterior half of the thoracic inlet, where it meets the posterior mediastinum. Therefore, the anterior mediastinum primarily contains the thymus. The posterior mediastinum lies posterior to the heart and extends cephalad to the posterior half of the thoracic inlet, where it meets the anterior mediastinum. The posterior mediastinum contains the descending aorta, the esophagus, the thoracic duct, and the sympathetic chain. Finally, the middle mediastinum is a wedge-shaped area between the anterior and posterior mediastinal compartments and is bound inferiorly by the diaphragm and superiorly by the apex of the heart. The middle mediastinum contains the heart, pericardium, aorta, trachea, and main bronchi

Mediastinal Mass

Introduction

The mediastinum is the area of the thorax that extends from the thoracic inlet superiorly to the diaphragm inferiorly and from the sternum and costal cartilages to the anterior surface of the 12 thoracic vertebrae and includes the parietal pleura [6]. It may be subdivided into anatomic compartments: anterior, middle, and posterior mediastinum (See Fig. 24.1) although others also include a superior compartment [6, 7]. Although relatively uncommon in children, masses may arise in the mediastinum from a variety of both benign and malignant disorders (See Table 24.1) [7–11]. A review of several large series reveals non-Hodgkin lymphoma, Hodgkin lymphoma, and neuroblastoma to be the most common diagnoses of mediastinal masses in children [8–14]. Lymphomas typically arise from the anterior, superior or middle mediastinum and can be associated with significant cardiopulmonary compromise [8, 9, 12]. Neural tumors arise from the posterior mediastinum and rarely produce any significant airway obstruction [8, 9, 12].

Pathophysiology

Mediastinal masses can result in life-threatening complications. Masses that arise in the anterior, superior and middle mediastinum can compress the tracheobronchial tree, the heart, and the great vessels (including the superior vena cava). The clinical presentation varies based on the site of anatomic obstruction or compression [8]. For example, compression of the tracheobronchial tree can result in dyspnea, stridor, cough, wheeze, orthopnea [15] or can present with a normal respiratory exam. One report suggests that 60 % of children with mediastinal masses will present with respiratory symptoms [15]. Likewise, compression of the superior

Table 24.1 Mediastinal masses in children

Anterior Mediastinum
Thymus
Normal thymus
Thymic cyst
Thymoma
Adenopathy
Infectious adenopathy
Lymphoma or leukemia
Sarcoidosis
Tumors
Germ cell tumors (e.g. teratoma)
Thyroid or parathyroid tumors
Hamartoma
Hemangioma
Infections
Mediastinitis
Sternal osteomyelitis or abscess
Vascular abnormalities
Vascular malformations
(Lymphatic, venous, or mixed)
Other
Histiocytosis
Morgagni hernia
Hematoma
Middle mediastinal mass extension
Middle mediastinum
Adenopathy
Infectious (e.g. tuberculosis)
Metastatic disease
Lymphoma or leukemia
Sarcoidosis
Tumors
Thyroid or parathyroid tumors
Cardiac tumors
Hamartoma
Hemangioma
Infections
Mediastinitis
Vascular abnormalities
Vascular malformations
Vascular rings
Aneurysm
Other
Bronchopulmonary foregut anomaly
(e.g. esophageal duplication cyst)
Histiocytosis
Hematoma
Anterior mediastinal mass extension
Posterior Mediastinum
Tumors of the nervous system
Neuroblastoma
Ganglioneuroma
Ganglioneuroblastoma
Nerve sheath tumors
Paraganglioma
Adenopathy
Infectious adenopathy
Metastasis
Sarcoidosis
Tumors
Osseocartilaginous tumors
Thoracic duct cyst
Hemangioma
Infections
Mediastinitis
Vertebral osteomyelitis
Discitis
Vascular abnormalities
Vascular malformations
Other
Hematoma
Bochdalek hernia
Extramedullary hematopoiesis
Lateral meningocele
Extension of normal thymus
Histiocytosis

Adapted from Franco [192]. With permission from Elsevier

vena cava (SVC) causes venous engorgement, head, neck and/or upper extremity edema, and/or altered mental status known as SVC syndrome [7, 16]. Direct cardiac compression may decrease cardiac output resulting in cyanosis, syncope, dysrhythmias, and death [15, 17, 18]. "Critical mediastinal mass syndrome" is a complex syndrome where the mediastinal mass causes acute airway compromise *and* SVC syndrome which can lead to decreased right ventricular output [7], heart failure, hypoxia, and death [8, 12, 15–19].

Although establishing a definitive diagnosis is essential for appropriate treatment, a logical approach to the diagnostic work-up of a mediastinal mass should be implemented balancing the likelihood of a definitive result with the risk of the diagnostic procedure [18, 20] and the associated sedation/anesthesia. There are often several options for securing a definitive diagnosis, and ideally, the diagnosis needs to be made in the least invasive manner possible. Anesthesia increases the risk of airway obstruction and vascular compression in this patient population [12, 15–20]. Approximately 7–19 % of patients with a mediastinal mass will develop an airway complication with the induction of anesthesia or deep sedation [14, 18–21]. The pathophysiology of this airway compromise with anesthesia is multifactorial [20]. With the induction of anesthesia, lung volumes are decreased secondary to weakened inspiratory muscle tone and increased abdominal muscle tone [20, 22]. In addition, bronchial smooth muscle relaxes resulting in increased compressibility of the large airways and decreased expiratory flow rates [20, 23].

This exacerbates the effects of any extrinsic compression to the tracheobronchial tree [20, 23]. Furthermore, the use of neuromuscular blockade eliminates the caudad movement of the diaphragm observed during spontaneous respiration, thereby, decreasing the transpleural pressure gradient [20, 23]. This transpleural gradient opens the airways during spontaneous inspiration, and when decreased, results in decreased airway caliber augmenting the effect of any extrinsic compression [15, 20]. The end result of neuromuscular blockade is the potential for decreased airway caliber, decreased lung volumes and the inability to appropriately ventilate and/or oxygenate.

The presence of SVC syndrome and evidence of vessel compression on chest CT is an important variable as mediastinal masses may cause direct superior vena cava, pulmonary artery or myocardial compression leading to decreased venous return. General anesthesia, potentiated by supine positioning, may worsen venous return to the right heart, decrease flow to the pulmonary arteries, leading to acute right sided heart failure. These physiologic parameters are often worsened by the application of positive pressure ventilation versus spontaneous respiratory effort [7, 24].

Identification of High Risk Patients

The actual sedation and anesthetic risks in this population remain an area of controversy as recent retrospective studies vary in reporting no serious cardiopulmonary complications [25] to a 15 % occurrence of serious cardiopulmonary complications including emergent tracheostomy and death [24]. Risk stratification is difficult as each study varies in patient population, tumor pathology, diagnostic procedures and depth/mode of sedation or anesthesia [7, 24–26].

Despite the conflicting data, it is crucial to identify patients at highest risk from life-threatening complications. A comprehensive review of pediatric patients with mediastianal masses revealed a 9.4 % anesthesia related complication rate [27]. The main complications were hypoxia and difficulty ventilating and were primarily alleviated by repositioning and intubation. The authors identified four preoperative factors significantly associated with increased risk: (1) orthopnea, (2) upper body edema, (3) great vessel compression and (4) mainstem bronchus compression. Ng reported a 15 % anesthetic complication rate including difficulties with ventilation and cardiovascular collapse resulting in two deaths [24]. None of these patients received neuromuscular blockade; however, all of the patients were intubated and received positive pressure ventilation. All children with complications had tracheal compression and the presence of three or more respiratory symptoms prior to general anesthesia. A history of any symptoms of respiratory distress prior to sedation should raise concern of airway compromise with deep sedation or anesthesia [15]. The presence of pre-operative respiratory symptoms is clearly one factor that has been associated with an increased risk of airway complications with anesthesia [14, 15, 17–19]. Orthopnea may be a particularly important finding in distinguishing patients at increased risk of compromise with anesthesia [14, 15, 17–19].

Despite the usefulness of a detailed pulmonary history and physical examination, it is equally important to note that airway obstruction may occur with the use of anesthesia despite no history of respiratory symptoms [14, 15, 28]. Thus, other information should be assessed in the evaluation of a child with a mediastinal mass. A standard chest radiograph establishes the presence of a mediastinal mass as often these children are considered to have asthma or another similar process prior to the initial chest radiograph [7]. In addition, the radiograph may reveal associated pleural effusions, tracheal compression and/or tracheal deviation (See Fig. 24.2). The presence of a pleural effusion in association with a mediastinal mass has been reported to identify patients at increased risk of airway compromise [7]. Moreover, masses that exceed 45 % of the thoracic diameter (measured at the diaphragm) on chest x-ray are more likely to be symptomatic than those that are less than 30 % of the diameter [12, 28]. It should be noted again, however, that patients at risk for airway compromise may have no tracheal compression observed on chest x-ray [28]. Computed tomography of the chest may be more useful for accurately depicting mediastinal involvement, anatomical distortions and the degree of tracheal compression [8, 9, 15, 29] (See Fig. 24.3). In fact, data suggest that general anesthesia may be safely administered if the tracheal cross sectional diameter is greater than 50 % of the expected size on CT scan [13–15].

These studies are static tests of a dynamic process, and thus, dynamic studies may provide additional data [20]. Pulmonary function tests have been used to identify patients with a mediastinal mass at increased risk of airway compression [12, 13, 15, 20]. Decreases in the peak expiratory flow rate (PEFR), total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV1) have all been reported in patients with a mediastinal mass suggesting both obstructive and restrictive deficits [12, 13]. The PEFR appears to be a useful predicator of airway compromise with a predicted PEFR <50 % of predicted for age, sex, and height identifying patients at high risk of lower airway obstruction with the use of anesthesia. Also, a 12–14 % decrease in pulmonary function can be anticipated when placing the child with a mediastinal mass in the supine, rather than, the upright position [12, 13]. It is important to

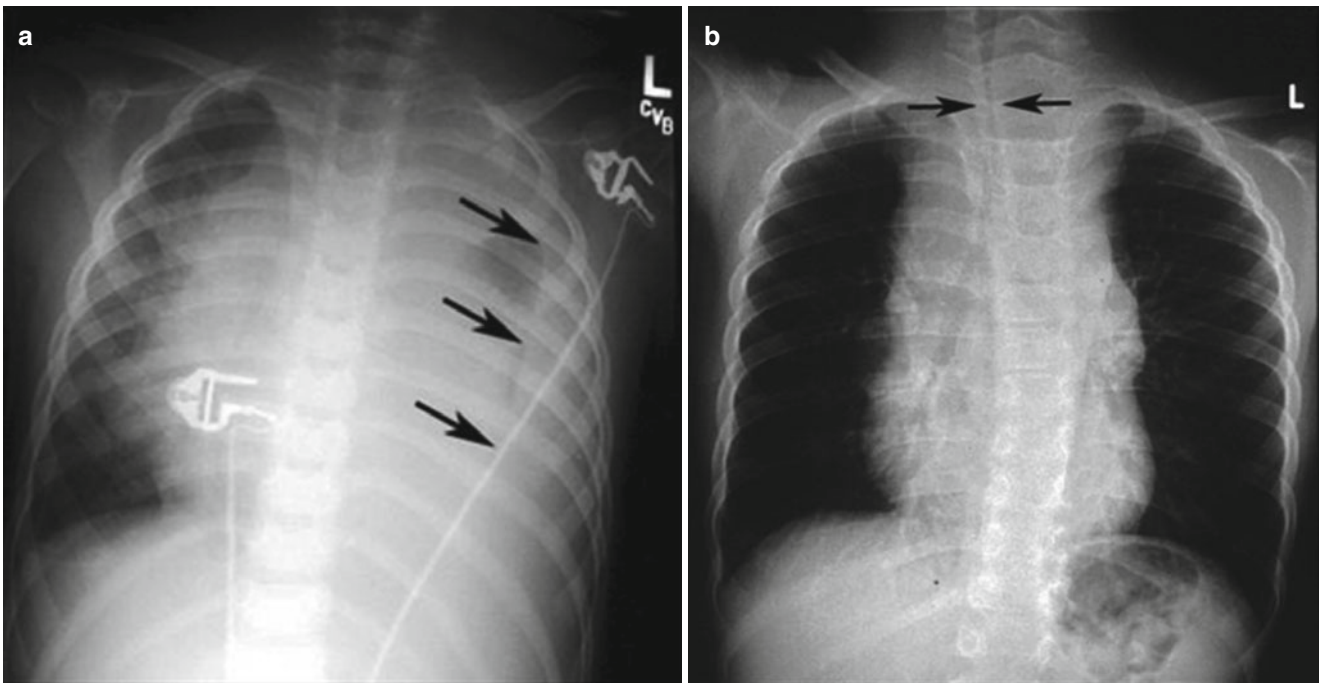

Fig. 24.2 Chest radiographs demonstrating pleural effusion (**a**) and tracheal compression (**b**) associated with a mediastinal mass. In (**a**), the *arrows* demonstrate the edge of a large pleural effusion in a child with a large malignant mediastinal mass. In (**b**), the *arrows* demonstrate significant narrowing of the trachea secondary to a malignant mediastinal mass

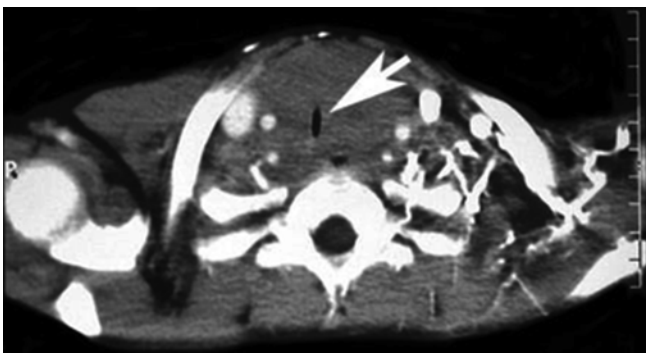

Fig. 24.3 Computed tomography of the chest depicting significant tracheal compression from a mediastinal mass. The *arrow* is pointing to the significantly narrowed trachea

remember that these tests require patient cooperation often making their use impractical particularly in young or symptomatic children. Figure 24.4 demonstrates the flow volume loops of a child with a mediastinal mass before and after therapy [13]. Echocardiography is another dynamic test that may be used to assess cardiac function, the presence of a pericardial effusion, impending tamponade, and the integrity of the pulmonary outflow tract [15, 20].

Management and Approach to the Diagnostic Work-Up

Utilizing the data obtained from these clinical, radiological, and functional assessments, the definitive work-up and treatment of the mass can proceed in a manner balancing risk and benefit. Several algorithms for the diagnostic work-up and management of a mediastinal mass have been published [15, 18, 20]. All involved clinical services (nursing, oncology, anesthesia, surgery, pathology, radiation oncology, intensive care) should communicate effectively with one another to ensure the optimal course of action and the appropriate, timely handling of diagnostic specimens [15, 30]. Although never ideal, presumptive, pre-biopsy therapy may be required in cases of severe airway compromise [15, 28, 31]. This obviates the risks of anesthesia and delays in treatment associated with a diagnostic work-up. However, it may reduce the ability to make a definitive diagnosis, result in unnecessary therapy, and lead to improper staging of the disease [18, 19, 31]. Borenstein reported 23 patients with probable mediastinal lymphoma who were treated with steroids prior to securing a definitive diagnosis [31]. In 18 of the patients (78 %), the diagnosis could still be established. Of the other five (22 %), two had a delayed diagnosis, two failed to have

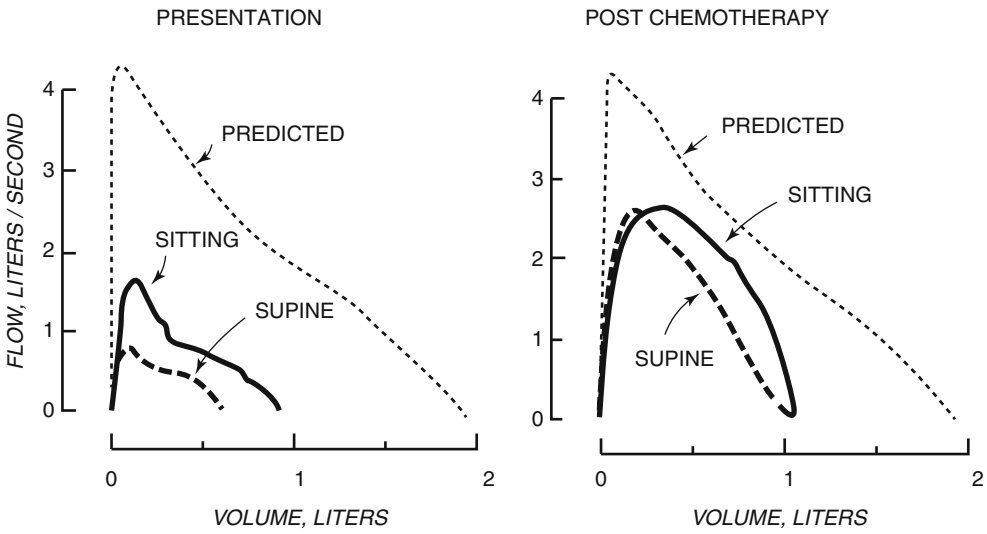

Fig. 24.4 Expiratory flow-volume loops of an 8-year old girl who presented with a large mediastinal lymphoblastic lymphoma. There was significant reduction in maximum flows, but this was markedly improved 4 days after onset of chemotherapy (*right*). Note that the impairment was greater in the supine rather than upright position (Adapted from Shamberger et al. [13]. With permission from Elsevier)

a definitive diagnosis, and one had a potential inaccurate staging. Pre-biopsy radiotherapy has also been found to obscure the diagnosis [19, 32].

In pursuing a definitive diagnosis, obtaining tissue from areas that are remote from the mediastinum may be performed and offer less risk [14, 15, 18–20]. Such procedures may be performed under local anesthesia or with minimal sedation, but with extreme caution nonetheless. For example, bone marrow aspiration may be used to ascertain a diagnosis, particularly for non-Hodgkin lymphoma. Ebie found that 48 of 176 non-Hodgkin lymphoma patients (28 %) had bone marrow involvement at diagnosis [33]. Unfortunately, this test may have less utility in other patient populations; Munker reported that only 5 % of Hodgkin lymphoma patients have bone marrow involvement [34]. Thoracentesis is another diagnostic test that may also be useful in determining the etiology of a mediastinal mass when associated with a pleural effusion [35]. Among malignant masses, pleural effusions are more common in lymphoblastic lymphoma than Hodgkin lymphoma and this diagnosis has been secured using cytological and flow cytometric analysis of the pleural fluid [35]. Fine needle aspiration and core needle biopsies of superficial lymphadenopathy have also been used to diagnose lymphoblastic lymphoma precluding the need for more invasive procedures [14, 26, 36–38]. Excisional biopsies of these lymph nodes are more invasive, but still may be performed with local anesthesia and potentially yield more definitive results. If these other diagnostic approaches are unsuccessful, then a mediastinal biopsy must be considered. This may be performed via a percutaneous fine needle aspiration, via a CT-guided core needle biopsy, via mediastinoscopy, or via an open surgical excision [8, 39–41].

Use of Anesthesia or Deep Sedation

If general anesthesia is deemed necessary, it must be approached with great caution in these high risk children. First, secure intravenous access must be established and consideration should be given to lower extremity placement as the superior vena cava may have poor inflow [19, 29]. Next, pre-anesthesia sedation or narcotics should be avoided. Both a flexible and rigid fiberoptic bronchoscope should be available and femoral-femoral cardiopulmonary bypass should be on standby [15, 19, 20, 41–44]. The rigid, ventilating bronchoscope is the instrument of choice for the unstable airway. However, it is important to note that if the mediastinal mass is compressing the airway near or beyond the carina, a bronchoscope may be ineffective as it may not be able to bypass the distal airway occlusion. Induction of anesthesia should ideally be performed in an upright or semi-recumbent position; however, if the patient cannot tolerate this, then a lateral or prone position should be considered as supine positioning may be associated with worsening airway obstruction and vascular compression. Anesthesia should only be deepened once it is demonstrated that the patient can be easily ventilated with a bag mask set-up. Neuromuscular blockade should be avoided [20, 29, 45]. Maintenance of a natural airway with spontaneous ventilation minimizes further alterations to the already distorted cardiopulmonary physiology [24, 25, 44]. If necessary, the airway can be maintained with a laryngeal mask airway (LMA) [46, 47] or with a reinforced endotracheal tube that is passed beyond the obstructed region of the tracheobronchial tree [29].

In the event of an acute airway occlusion, several maneuvers may be implemented that can be life-saving. Anesthetic effects should be promptly reversed and the patient returned to a state of spontaneous ventilation. Repositioning of the

child, in particular utilizing a prone position, may alter the effect of the mass on the airway and facilitate air movement [15, 43]. Heliox may also improve air movement through the narrowed airway [47]. Bag valve mask ventilation in a spontaneously breathing patient using high positive end expiratory pressure (PEEP) has been reported to be useful [15]. In addition, the ventilating rigid bronchoscope may be advanced beyond the area of obstruction. An emergent thoracotomy with bulk resection of the tumor may need to be performed to relieve pressure on the airway. However, this should be performed only in extremis as the bleeding and tissue edema involved may actually worsen the effects upon the mediastinum. If the above noted interventions are unsuccesful in restoring adequate ventilation within minutes, the patient will need to be placed on cardiopulmonary bypass or extracorporeal membrane oxygenation [15, 19, 20, 41–43]. There are reports of successfully using ECMO as the primary means of stabilizing pediatric patients with critical mediastinal masses [44].

Even after a successful biopsy of the mass or lymph node, the post-operative recovery phase represents a time of continued high risk [19, 29]. During the immediate, post-anesthetic period, the patient may still have impaired respiratory muscle function, altered level of alertness, and increased airway obstruction secondary to edema post-biopsy or partial resection. Extubation should be attempted only after effective, spontaneous breathing has been documented. The patient will continue to require close monitoring for several days following initiation of therapy assessing for transient worsening from the edema associated with tumor lysis and to ensure response to treatment.

Conclusion

Although relatively uncommon in children, mediastinal masses may arise from a variety of disorders most commonly non-Hodgkin lymphoma, Hodgkin lymphoma, and neuroblastoma [8–14]. Lymphomas typically arise from the anterior, superior or middle mediastinum and can be associated with significant cardiopulmonary compromise [8, 9, 12]. A patient presenting with, or acutely developing airway obstruction from a mediastinal mass needs cautious care and planning using a multidisciplinary approach prior to proceeding with diagnostic interventions and therapy. If intubation is required, it is preferable to have it performed in the controlled environment of the operating room as described above. If emergent intubation must be performed outside the operating room, it should be performed without the use of neuromuscular blockade by the most experienced person [20, 29, 45]. Once the patient is successfully intubated, the use of PEEP, repositioning of the tube, and/or repositioning of the patient may be needed to facilitate optimal air movement [15]. A focused history, appropriate diagnostic imaging, and physiologic testing will assist in identifying patients at highest risk of cardiopulmonary compromise although extreme caution must be exercised in caring for any child with a mediastinal mass.

Hyperleukocytosis

Hyperleukocytosis is defined as a peripheral leukocyte count greater than 100,000/μL, although it may only become clinically significant when it surpasses 200,000/μL [48]. It commonly occurs in conjunction with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML). It may be responsible for significant morbidity and mortality occurring early in the course of these malignancies seemingly secondary to its associated hyperviscocity. Hyperleukocytosis is a presenting finding in 9–13 % of children with ALL, in 5–22 % of those with AML, and in virtually all children with chronic myelogenous leukemia (CML) in the chronic phase [48–50]. Hyperleukocytosis involving lymphoid blasts is better tolerated than that of myeloid blasts as reflected by fewer complications attributable to leukostasis or hemorrhage [48].

Leukostasis is the clinically significant manifestation of hyperleukocytosis. The leukostasis syndrome is characterized by progressive neurologic or respiratory signs and/or symptoms attributable to small vessel infiltration and occlusion by leukemic blasts [51–55]. Central nervous system (CNS) hemorrhage is the most feared complication of hyperleukocytosis [56, 57]. The incidence of CNS hemorrhage is associated with higher leukocyte counts and is more common among patients with AML than those with ALL. It has been reported in 5–33 % of patients with AML and hyperleukocytosis [48, 53, 58–61] versus only 2 % of children presenting with ALL and hyperleukocytosis [62]. In one series, each of the children with ALL who experienced a CNS hemorrhage had a white blood cell (WBC) count greater than 400,000/μL [62]. Pulmonary leukostasis has been widely reported in the adult AML population [53, 63]. In children with hyperleukocytosis, symptomatic pulmonary leukostasis occurs in 8 % of patients with AML and in 6 % of patients with ALL [48, 62]. Of note, pulmonary leukostasis can occur without hyperleukocytosis [64].

Hyperviscosity is only one of the mechanisms postulated in the pathophysiology of the hyperleukocytosis leukostasis syndrome and does not appear to account for all the findings [65–68]. For example, the whole blood viscosity may not necessarily be elevated in hyperleukocytic leukemias since the erythrocrit usually falls in response to an increasing leukocrit [69, 70]. Moreover, as stated above, leukostasis can

occur without hyperleukocytosis [64]. Additionally, in this setting, compensatory mechanisms such as vasodilation are triggered to help mitigate the potential deleterious effects of hyperviscosity [71]. Furthermore, leukostasis does not solely depend on the number, but also the size, deformability, surface markers, and tissue invasiveness of the leukemic cells, as well as their volume fraction [53, 67]. Thus, there is increasing evidence that other mechanisms must contribute to the pathophysiology of leukostasis. Specifically, there is data suggesting that through the release of cytokines, leukemic myeloblasts are able to promote their own adhesion to vascular endothelium and enhance blast cell recruitment [54]. The resulting interactions may contribute to vascular disruption and the local release of chemo-attractant factors. These locally released chemo-attractant factors may stimulate bleeding thereby influencing the distribution and severity of the damage [54, 72, 73]. This up-regulation of endothelial cell adhesion receptor expression by myeloblasts is time-dependent [54]. This finding not only supports the clinical principle that leukocytoreduction must be achieved rapidly since the longer leukemic blasts interact with the endothelium, the "stickier" they become, but also suggests that adhesion molecule–blocking antibodies may be an attractive future therapy [74].

Any child with a WBC count greater than 100,000/μL should be evaluated for signs and symptoms of leukostasis. Pulmonary leukostasis usually presents with nonspecific symptoms such as exercise intolerance, tachypnea, dyspnea, and hypoxia with diffuse interstitial or alveolar infiltrates on chest radiographs (See Fig. 24.5). Caution must be practiced when diagnosing hypoxemia based on an arterial blood gas alone because hyperleukocytosis can lead to spurious hypoxemia if the blood sample is not immediately cooled (i.e. in crushed ice) and analyzed due to oxygen consumption by the leukocytes [75]. The differential diagnosis of pulmonary leukostasis includes pneumonia, pneumonitis, pulmonary edema, and/or pulmonary hemorrhage; all of which occur more frequently than leukostasis in this patient population. Signs of CNS leukostasis may range from subtle symptoms of confusion, blurred vision, tinnitus, somnolence, headache and dizziness, to more dramatic findings including visual field defects, gait instability, seizures, stupor, delirium and coma. Papilledema, retinal vein distention, retinal hemorrhages, cranial nerve defects, and neck stiffness have also been reported [76]. Cardiac symptomatology tends to be less common, but important findings may include neck vein distention, a gallop rhythm and electrocardiographic signs of right ventricular overload and myocardial ischemia. High fever (usually greater than 39 °C) is virtually always present and rarely represents an infection since most cultures remain negative. Disseminated intravascular coagulopathy (DIC), thrombocytopenia, and renal failure related to tumor lysis syndrome (see below) represent other potential complications

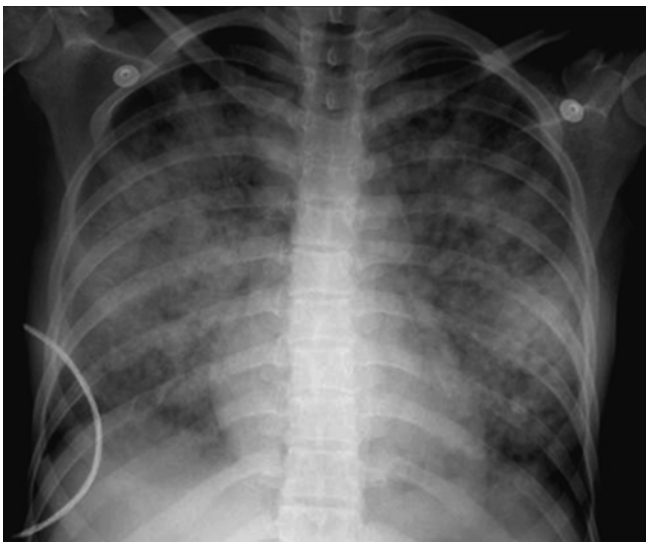

Fig. 24.5 Chest radiograph of a patient with hyperleukocytosis and pulmonary leukostasis

of hyperleukocytosis. DIC may occur in as many as 30–40 % of patients with AML and 15–25 % of patients with ALL. Thrombocytopenia may be underestimated because WBC fragments are often counted as platelets in the automated cell analyzers [77].

There is no uniform consensus in the management of hyperleukocytosis and there are no controlled studies to advocate any particular therapy. Standard tumor lysis therapy should be implemented promptly with immediate initiation of hydration [78]. Patients with platelet counts of less than 20,000/μL should receive platelet transfusions to decrease the risk of intracranial hemorrhage; platelets do not significantly increase blood viscosity. Packed red blood cell transfusions, on the other hand, should be avoided because they do increase blood viscosity and have been associated with an increased incidence of CNS hemorrhage [62, 79]. The hemoglobin level should not be raised above 10 g/dL and most children will tolerate a hemoglobin concentration of 7 g/dL without complication. Particular care should be taken when planning general anesthesia because these children are at significant peri-operative risk [80].

Cytoreduction is commonly recommended for patients with hyperleukocytosis and appears reasonable, although there is little data to support the potential benefit and no prospective study has determined the preferred modality [81, 82]. Most complications of hyperleukocytosis are observed at presentation before cytoreduction can be initiated, and therefore, are not preventable by cytoreduction. Moreover, the reversibility of these complications with cytoreduction is debatable. One study of children with ALL and hyperleukocytosis concluded that leukapheresis could be safely reserved for patients with a WBC count exceeding 400,000/μL, or for those presenting with complications of hyperleukocytosis

[62]. Determining the appropriate role of leukapheresis in patients with AML is more challenging since these patients present more often with complications. There are published guidelines on the indications for leukapheresis, however there are no widely accepted criteria regarding the optimal time of initiation, the duration of therapy, or the clinical or laboratory parameters to be followed to guide therapy [74, 83]. More recent retrospective studies have found a trend towards reduction in early mortality with leukapheresis; however, that may also be attributable to improvements in other means of supportive care. Moreover, data on improvement in long term outcomes is lacking [84–87]. Further, there is no linear correlation between the leukocyte count and the risk of clinical events (stroke, pulmonary leukostasis) [59]. Additionally, exchange transfusion and leukapheresis are only temporizing measures, as the WBC counts often rebound. However, they may be important in tumor debulking and decreasing the incidence of tumor lysis pneumopathy [88, 89]. The role of cranial irradiation is controversial and currently discouraged in pediatric patients because of acute and chronic neuropsychiatric complications [90]. Interestingly, a single case report described the successful use of inhaled nitric oxide in treating the hypoxemic respiratory failure of pulmonary leukostasis associated with hyperleukocytosis [91].

In summary, the leukostasis syndrome is a potentially life-threatening condition occurring in conjunction with hyperleukocytosis. It may be associated with significant morbidity affecting most notably the neurologic and respiratory systems. Although a consensus treatment plan has not been defined, standard of care should include immediate hydration, appropriate tumor lysis therapy and correction of coagulopathy and thrombocytopenia. If available, leukapheresis should be performed in selected patients as long as induction chemotherapy is not delayed. Chemotherapy is the single measure that will cause sustained cytoreduction and prevent further damage resulting from leukostasis [74]. Adhesion molecules, soluble cytokines and chemotactic ligand-receptor pairs are potential targets for future therapies [74].

Hypercalcemia

Incidence

Metabolic derangements are commonly associated with cancer and its treatment. Tumor lysis syndrome is the classic example with a number of different metabolic abnormalities including hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. However, several malignant conditions are associated with metabolic derangements such as hypercalcemia resulting from mechanisms different than those occurring in tumor lysis. Hypercalcemia is one such example occurring in up to 20–30 % of adult cases of cancer, although it is relatively rare in children with a reported incidence of 0.4–1.3 % [92–95]. It may be associated with a wide spectrum of malignancies; acute leukemias, neuroblastoma and rhabdomyosarcomas are a few of the more common diagnoses [92, 95]. It is present in approximately half the patients at the time of the diagnosis of cancer with the others developing it later in the course of their malignancy [92, 95]. Several reports describe hypercalcemia as the presenting symptom of pediatric malignancy, and thus, cancer must be considered in the differential diagnosis of any child presenting with hypercalcemia [96–98].

Hypercalcemia may result in a number of life-threatening conditions including cardiac dysrhythmias, progressive mental impairment including coma, and renal failure. Other reported symptoms tend to be non-specific and include back or abdominal pain, fatigue, hypertension, anorexia, nausea, vomiting, dehydration, acidosis, polyuria, polydipsia, and constipation [92, 93, 99, 100]. In general, the symptoms worsen with the severity of the hypercalcemia. However, other factors including the rate of the rise of the calcium level and pre-existing medical conditions influence the symptomatology [99, 101]. The renal failure observed in these patients is often multifactorial. Hypercalcemia can reduce the glomerular filtration rate by reducing the ultrafiltration coefficient, a major determinant of the single-nephron glomerular filtration rate [100]. Hypercalcemia also impairs renal concentrating capacity, resulting in increased salt and free water loss, polyuria, and dehydration [99, 100]. The anorexia, nausea, and vomiting may also contribute to dehydration and a decreased glomerular filtration rate. The cardiac manifestations of hypercalcemia include a shortened corrected QT interval (specifically, the beginning of the QRS complex to the apex of the T wave (Q-aTc)) and a predisposition for arrhythmias primarily bradydysrhythmias [102, 103].

Pathophysiology

Insights into normal bone and calcium homoestasis have improved the understanding of the hypercalcemia of malignancy. Osteoclastogenesis is mediated through the receptor activator of nuclear factor kappa B (RANK) signaling pathway which is likely to be the common pathway for hypercalcemia. Known regulators of the RANK pathway include parathyroid hormone (PTH), parathyroid hormone related protein (PTHrP), 1,25-dihydroxyvitamin D, IL-1 and tumor necrosis factor (TNF); all of which have been implicated in the hypercalcemia of malignancy [104]. The mechanisms of hypercalcemia associated with cancer can be classified into four types: (1) local osteolytic hypercalcemia, (2) humoral hypercalcemia of malignancy, (3) secretion of vitamin D, in its active form, 1,25-dihydroxyvitamin D, and (4) ectopic

secretion of authentic parathyroid hormone [99]. In local osteolytic hypercalcemia, the hypercalcemia results from marked osteolysis secondary to increased osteoclastic bone resorption in areas surrounding the malignant cells. Humoral hypercalcemia of malignancy results most commonly from the systemic secretion of PTHrP by malignant tumors; more frequently associated with solid tumors. It is this peptide, and not parathyroid hormone, which is the major mediator of humoral hypercalcemia of malignancy [99, 105]. PTHrP shares some homology and similar biologic activity to parathyroid hormone causing increased bone resorption and enhanced renal retention of calcium [99, 105]. Numerous cytokines such as IL-1, IL-6, TGF-ß(beta) and TNF-α(alpha) as well as calcitriol have also been implicated in humoral hypercalcemia of malignancy [106]. Tumors, most notably lymphomas, may also result in hypercalcemia secondary to the secretion of the active form of vitamin D, 1,25-dihydroxyvitamin D [107]. Finally, ectopic secretion of parathyroid hormone itself by malignant cells may result in hypercalcemia, but this is extremely rare [108].

Table 24.2 Treatment of malignant hypercalcemia

Effective elimination and reduction of tumor burden
Eliminate exogenous sources of calcium
Discontinuation of any other form of oral calcium
Discontinuation of calcium in intravenous fluids and parenteral nutrition solutions
Elimination of medications that contain calcium
Discontinue medications that may lead to hypercalcemia
Antacids
Calcitriol
Lithium
Thiazide diuretics
Vitamin D
Increasing the renal clearance of calcium
High volume intravenous volume expansion with normal saline
Loop diuretics such as furosemide (after euvolemia/hypervolemia is attained)
Inhibition of osteoclastic bone resorption
Bisphosphonate therapy
Calcitonin
Other
Glucocorticoids
Gallium nitrate
Dialysis

Treatment

The definitive therapy for hypercalcemia of malignancy is effective elimination and reduction of tumor burden, and thus, appropriate anti-neoplastic therapy must be initiated promptly. Antihypercalcemic therapy is a temporizing measure aimed at decreasing calcium levels, and thereby, limiting life-threatening symptomatology and allowing time for the anti-neoplastic therapy to take effect. Since true hypercalcemia occurs through three basic mechanisms (enhanced osteoclastic bone resorption, enhanced renal tubular reabsorption of calcium, and enhanced intestinal absorption of calcium), principles of therapy should include inhibiting osteoclastic bone resorption, increasing renal clearance and preventing intestinal absorption (See Table 24.2) [99, 100].

Minimizing intestinal absorption of calcium is straightforward and obviously requires discontinuation of the use of oral calcium supplements in enteral feeding solutions, elimination of medications that contain calcium, and discontinuation of any other form of oral calcium supplementation. Additionally, any calcium in intravenous fluids including parenteral feeding solutions must also be removed [99]. Medications that may also lead to hypercalcemia such as lithium, calcitriol, vitamin D, antacids and thiazide diuretics should be discontinued [99].

Increasing the renal clearance of calcium may be accomplished with vigorous hydration. Patients with hypercalcemia associated with cancer are substantially dehydrated as a result of impaired renal concentrating ability induced by hypercalcemia and/or by decreased oral hydration resulting from anorexia, nausea, and/or emesis. The dehydration leads to a reduction in the glomerular filtration rate that further reduces the ability of the kidney to excrete the excess serum calcium [99, 100]. Therefore, intravenous volume expansion should be considered first-line therapy and initiated immediately. Normal saline should be administered at high rates (with rates as high as 3 l per body surface area per day and 10 mL per kilogram per hour up to total volumes as high as 500 mL/h in adults) depending on the baseline level of dehydration and renal function, the cardiovascular status of the patient, and the severity of the hypercalcemia [93, 99, 100]. Monitoring for clinical signs of fluid overload is imperative during this therapy.

This vigorous hydration will increase the glomerular filtration rate thereby increasing the filtered load of calcium that passes through the glomerulus into the tubular lumen [99]. The saline will also serve to inhibit calcium reabsorption in the proximal nephron [99]. Moreover, by increasing the glomerular filtration rate to, or above the normal range, loop diuretics may be used to further increase the renal excretion of calcium [99]. Loop diuretics such as furosemide block calcium reabsorption in the loop of Henle. The augmented diuresis induced by the loop diuretics helps guard against symptomatic fluid overload and may permit increased administration of saline facilitating further calcium excretion, although there is limited data to support this practice [109]. In light of the fact that loop diuretics can promote dehydration, thereby resulting in a decline in the glomerular filtration rate and the filtered load of calcium, and other electrolyte disturbances, bisphosphonate therapy is quickly

replacing furosemide as front line therapy. Diuresis should be reserved for the management of fluid overload from aggressive hydration [110]. Moreover, thiazide diuretics stimulate, rather than inhibit, renal calcium reabsorption, and therefore, their use is contraindicated in the treatment of hypercalcemia [99].

If enhanced renal excretion of calcium fails to correct hypercalcemia, or in cases of severe hypercalcemia, inhibition of osteoclastic bone resorption must be utilized. Bisphosphonates are medications that work by blocking osteoclastic bone resorption and are currently considered the most effective, safest treatment of hypercalcemia [93, 99]. A number of randomized clinical trials have confirmed the superiority of bisphosphonates [99, 111]. Pamidronate disodium is a bisphosphonate that has been extensively studied and widely used for malignancy associated hypercalcemia in adults for many years [112, 113]. It is an analog of endogenous pyrophosphate that binds to hydroxyapatite crystals in the bone inhibiting osteoclastic activity via several postulated mechanisms. The use of pamidronate for the treatment of severe hypercalcemia in children is limited, based on anecdotal reports and small series [93, 100, 114–120]. Its use in children for the prevention or treatment of bone complications of osteogenesis imperfecta, however, has been much better established [118, 121, 122]. Pamidronate is estimated to correct serum calcium levels in 60–90 % of cases within 3–4 days, with an effect persisting for 3–4 weeks [112]. Its use should be initiated as soon as hypercalcemia is discovered because a response requires 2–4 days and the nadir in serum calcium generally occurs within 4–7 days after therapy is initiated [99]. Hypocalcemia, moderate and delayed hypophosphotemia, hypomagnesemia, and hypokalemia have all been associated with its use, and thus, monitoring of electrolytes is essential for as long as 2 weeks [93]. Azotemia was noted in animal studies of bisphosphonate, but acute renal failure is rarely observed after its administration (0–4 %) and is usually multifactorial in origin and/or associated with multiples doses [93, 99, 113]. Few other adverse effects have been reported consisting of fever, muscle pain, and an inflammatory syndrome [93]. Zoledronate, a newer FDA approved bisphosphonate, is more effective and simpler to administer than pamidronate; however, its use in children has not been well established. One recent, small, retrospective series suggests that its use in children with cancer is safe, well tolerated, and may be associated with improved bone strength and pain control [123]. However, much more prospective study is needed to fully assess its efficacy and safety in children with hypercalcemia of malignancy [123]. Interestingly, significantly elevated levels of PTHrP may predict resistance to bisphosphonate treatment [124].

Several other therapies, many of which were used extensively prior to the advent of bisphosphonates, may also be of benefit. Calcitonin, which reduces serum calcium levels by also inhibiting bone resorption, may be useful as it results in a more rapid reduction than other agents [93, 100]. However, its effect unfortunately tends to be small and transient, and tachyphylaxis limits its use. The combination of calcitonin and pamidronate has been suggested for cases of life-threatening hypercalcemia [100, 125]. Mithramycin remains an effective therapy, but its use has been limited by its potential for severe toxicity and the greater efficacy of pamidronate [126]. Glucocorticoids may be useful because of a specific anti-tumor effect or for tumors such as some lymphomas that produce 1,25-dihydroxyvitamin D [99]. Gallium nitrate is also approved for the treatment of hypercalcemia, but the need for an infusion over 5 days and a worse toxicity profile limits its use [127]. In certain situations, including renal failure, the inability to use the above described therapies, or with severe, symptomatic, unresponsive hypercalcemia, dialysis against a dialysate containing little or no calcium is a reasonable and highly effective therapeutic option [99]. New and novel approaches to directly target the RANK pathway including denosumab, a RANK-L antibody, demonstrate promise, but there is currently no data on their use in children [128].

Acute Promyelocytic Leukemia (APL) – Leukemia-Associated Coagulopathy

It is well-established that varying degrees of coagulopathy are present in most patients with advanced malignancy. The incidence of disseminated intravascular coagulation (DIC) in solid tumors has not been uniformly described to date. In acute leukemia, DIC is initially present in approximately 15–20 % of patients with acute lymphoblastic leukemia (ALL), 30–40 % of patients with acute myelogenous leukemia (AML), and in more than 90 % of patients with acute promyelocytic leukemia (APL; M3-AML according to the French-American-British classification) [129–131].

APL accounts for 4–8 % of pediatric AML in the United States [132] and given the relatively high incidence of death around the time of presentation secondary to intracranial and pulmonary hemorrhages (estimated at 65 % and 32 %, respectively), it must be viewed as a medical emergency [133–135]. Despite rapid sensitive molecular techniques such as reverse transcription-polymerase chain reaction (RT-PCR), which detects the presence of the *PML-RARa* fusion protein (or rare molecular variants) characteristic of APL, the diagnosis of APL still requires a high index of suspicion so that appropriate therapy can be initiated. The introduction of all-*trans* retinoic acid (ATRA), a differentiating agent, as therapy for APL has reduced the incidence of fatal hemorrhage as a major cause of morbidity and mortality at presentation due to the associated coagulopathy. ATRA not only effectively treats this rare form of leukemia, but also

helps ameliorate the coagulopathy [136–139]. Although aggressive and immediate supportive care is typically administered to patients at the time of APL diagnosis, hemorrhage continues to be the most common cause of death during induction therapy (5 %), followed by infection (2.3 %), and differentiating syndrome (1.4 %, discussed below) [133–135].

Although it is a well-known side effect of ATRA therapy, significant or persistent headache should prompt brain imaging studies such as CT or MRI. A lumbar puncture should be avoided until any coagulopathy is resolved or at least significantly improved; CNS disease is very uncommon in APL and the risk of hemorrhage after lumbar puncture during coagulopathy generally outweighs the benefit of the procedure and implementation of CNS intrathecal chemotherapy [133–135]. Although a fair number of patients with APL present with significant leukocytosis, leukapheresis should be avoided until the coagulopathy resolves or is significantly improved due to the risk of massive hemorrhage, particularly intracranial hemorrhage [133–135].

In patients presenting with a WBC count less than 100,000/μL and severe coagulopathy, consideration should be given to starting ATRA for 1–3 days prior to introducing chemotherapy. Provided that the WBC count is not rapidly rising, this may help to improve the underlying coagulopathy. Patients presenting with a WBC count greater than 100,000/μL and coagulopathy are best treated with concurrent ATRA and chemotherapy as treatment with ATRA alone places them at risk for ATRA-induced differentiating syndrome (discussed below) [133–135].

The pathophysiology of the APL-induced coagulopathy is complex and involves several mechanisms: (1) procoagulant activity through the expression of high levels of tissue factor (TF) and cancer procoagulant; (2) abnormal fibrinolysis characterized by a high expression of annexin II on the surface of APL cells, which acts as a cofactor for plasminogen activation by tissue plasminogen activator (tPA), increasing the efficiency of plasmin formation; (3) production of proteolytic enzymes (e.g. elastase) and the release of cytokines (IL-1ß(beta) and TNF-α(alpha)), which affect the prothrombotic potential, adhesive properties and permeability of the vascular endothelium; and (4) thrombin generation of ATRA-treated APL cells that undergo apoptosis which heightens the hypercoagulable state [137, 140, 141].

The clinical characteristics and bleeding symptoms at the onset of APL present with varying degrees of severity [138, 142]. Severe DIC with life-threatening bleeding and rapid consumption of coagulation factors and platelets is due to the massive activation of intravascular clotting. Routine laboratory findings characteristic of the coagulopathy in APL are thrombocytopenia, hypofibrinogenemia, increased circulating levels of fibrin degradation products (FDPs), increased D-dimers, and prolonged prothrombin, thrombin and partial thromboplastin times [143, 144]. A primary thrombocytopenia due to bone marrow replacement of megakaryocytes by leukemic cells is exacerbated by platelet consumption during clot formation, and potentially by the direct toxic effects of secondary bacterial or viral infections if present [140].

The management of the coagulopathy in patients with APL must always be balanced with treatment of the underlying malignancy taking into account the fact that effective chemotherapy may exacerbate the DIC and bleeding syndrome by worsening the thrombocytopenia [140]. Aggressive supportive care, especially with blood products, is thus strongly recommended, with a platelet goal of at least 30,000–50,000/μL and a fibrinogen goal of at least 100–150 mg/dL. Cryoprecipitate is the product of choice for fibrinogen replacement, although aggressive use of fresh frozen plasma (FFP) for clotting factor replacement in the context of DIC should also be used liberally until the coagulopathy has resolved [133–135, 138, 140, 145–147].

The role of heparin in this patient population remains controversial. The theoretical benefit of limiting bleeding by inhibiting intravascular fibrin formation and reducing the consumption of clotting factors and platelets has never been demonstrated in large, randomized, controlled trials [147, 148]. Hence, the routine use of heparin is not recommended [143]. The use of anti-fibrinolytic agents (epsilon-aminocaproic acid or tranexamic acid) or protease inhibitors (aprotinin) to counteract fibrinolytic activators and other proteases appears logical, however, they have never been proven effective and have even been implicated in cases of thromboembolism [149, 150]. ATRA therapy during induction for APL may not only treat the underlying disorder, but may also have a direct effect on hypercoagulation and hyperfibrinolysis [138, 139, 151]. However, caution is recommended, as thromboembolic events may occur if the retinoic acid syndrome or hyperleukocytosis develops secondary to ATRA treatment [137]. At the present time, there is no consensus indication regarding the use of either heparin or antifibrinolytics to treat leukemia-associated coagulopathy and the use of such agents should not be routinely implemented unless in the context of a clinical trial.

Differentiation Syndrome

The introduction of all-*trans* retinoic acid (ATRA) combined with chemotherapy to the treatment of APL has made this leukemia very curable with an expected 4–5 year disease-free survival rate of 70–80 % [152, 153]. In contrast to most chemotherapeutic agents which are cytotoxic, the mechanism of action of ATRA is not to destroy leukemic cells, but rather, to stimulate their differentiation into mature cells (See Fig. 24.6) [152]. Although ATRA is generally well tolerated, some patients develop differentiation syndrome (DS), formally

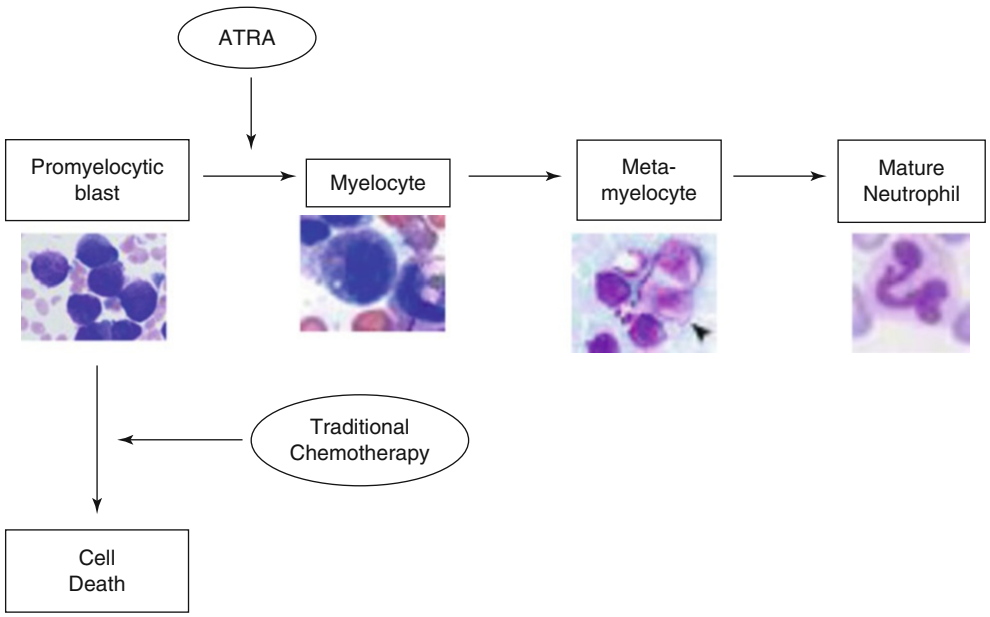

Fig. 24.6 Mechanism of all-*trans* retinoic acid (*ATRA*) in treating acute promyelocytic leukemia. The figure depicts the difference between ATRA and traditional chemotherapy in treating leukemia. ATRA therapy results in the differentiation of malignant promyelocytic blasts cells into mature neutrophils in contrast to traditional chemotherapy which results in cell death

known as retinoic acid syndrome: a cardiorespiratory syndrome with dyspnea, pulmonary infiltrates, pleural or pericardial effusions, episodic hypotension, and occasionally acute renal failure [154]. Initial studies with ATRA as a single agent for induction therapy for APL reported an approximate incidence of differentiation syndrome of 2–25 % depending on the diagnostic criteria used; however, more recent studies in children suggest a lower incidence of 13 % for severe DS [152, 155–157]. Differentiation syndrome may be severe and associated with significant morbidity and mortality. Encouragingly, mortality associated with this condition appears to be decreasing with rates declining from approximately 30 % to 5 % or less in recent trials [132, 152, 158, 159].

The diagnosis is based on a constellation of clinical findings with some authors suggesting that the diagnosis may be secured by the presence of at least three of the following signs and symptoms in the absence of an alternative explanation: fever, weight gain, respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, hypotension and renal failure [160, 161]. A high index of suspicion is essential since the diagnosis can be subtle and often findings are mistakenly attributed to iatrogenic fluid overload, pneumonia or sepsis [161].

Differentiation syndrome commonly develops 10 days after the initiation of treatment with a bimodal peak in the first and third week, but has been described as early as 2 days after treatment [157]. Fever and respiratory distress occur in about 75–95 % of the patients, pulmonary infiltrates in 50–80 %, and pleural or pericardial effusions in 30–60 % depending on the diagnostic criteria for severe or moderate DS. Acute renal failure can develop in up to 46 % of the patients with severe DS often requiring dialysis [157, 161]. Sweet syndrome with elevated vasoactive cytokines has also been described with ATRA therapy and is believed to be induced by differentiating leukemic promyelocytes [162, 163]. The etiology of pulmonary alveolar hemorrhage in patients with APL can be difficult to discern; however, in the setting of a resolving coagulopathy during treatment with ATRA, it may be considered another manifestation of the differentiation syndrome [164, 165].

The pathogenesis of this syndrome is mediated, in large part, by the effects of ATRA-treated, differentiating leukemic cells [161]. Myeloid precursors and mature granulocytes, presumably the differentiating ATRA-treated APL cells, infiltrate into organs due to ATRA-induced changes in their adhesive capacity and their chemokine production [161, 166]. This tissue infiltration is an essential component of the pathophysiology of the differentiation syndrome [161]. Post mortem histologic studies of the lungs of patients with differentiation syndrome support the theory that ATRA therapy results in leukemic cell differentiation, endothelial cell damage, and leukocyte infiltration into the lungs [154, 167]. ATRA causes increased expression of adhesion molecules on the surface of the APL cells resulting in increased binding to adhesion molecules on the endothelium [158, 168]. Additionally, soluble factors such as interleukin-1-ß (IL-1- ß), TNF-α, and IL-6, which are known to promote leukocyte activation, play an important role in the hypotension and pulmonary infiltrates associated with the differentiation syndrome [169].

The most important aspect in the management of differentiation syndrome is its early recognition. Dexamethasone is the primary therapy and its prompt implementation at the first sign or symptom of differentiation syndrome may be life-saving, decreasing mortality rates to approximately 5 %

[154, 170]. Unfortunately, no risk factors have been established to identify patients at highest risk for differentiation syndrome [154, 171]; however a higher white blood cell count at presentation may be predictive of severe DS [157]. In one trial, the use of steroids in all patients receiving ATRA decreased the incidence of severe differentiation syndrome, but did not impact DS-related mortality [132]. Thus, the use of dexamethasone to potentially mitigate the consequences of differentiation syndrome must be carefully weighed against potential steroid-associated toxicity [171]. The impact of the concomitant administration of chemotherapy with ATRA on differentiation syndrome appears equivocal. In the European APL Group trials, chemotherapy combined with ATRA reduced the incidence of the syndrome, but also had no effect on mortality [158, 160]. Finally, it is important to note that the differentiation syndrome has only been observed during induction therapy and not with ATRA use during maintenance therapy [152, 154, 171–173].

Lactic Acidosis of Malignancy

There are several relatively rare conditions associated with cancer and its treatment that may impact upon the pediatric critical care provider. For example, lactic acidosis resulting from a high rate of glycolysis is a very rare, but life-threatening complication of hematologic malignancies that has been long identified [174, 175]. It has been reported in solid tumors as well, but rarely so [176]. Even in the presence of oxygen and adequate perfusion, malignant cells can maintain a high rate of glycolysis producing lactate at a rapid pace [177]. This high rate of glycolysis may, in part, be the result of overexpression or aberrant expression of glycolytic enzymes including hexokinase, the initial rate-limiting enzyme in the glycolytic pathway [178]. The condition tends to be associated with hypoglycemia (40 % of the cases reviewed in the literature) and there is data to suggest that the insulin-like growth factor system may contribute to the overexpression of enzymes of the glycolytic pathway in malignant cells [174]. Neoplastic involvement of the liver is also noted in the majority of cases suggesting that hepatic underutilization of lactate is an important factor in the pathogenesis of this condition [174]. The overall mortality rate for this condition approaches 95 % [174]. The vast majority of patients present with lactate levels well in excess of 10 mmol/L with reports of levels over 40 mmol/L [174, 179, 180].

The primary treatment is cytoreductive therapy of the underlying malignancy. In the published literature, all patients whose disease was not treated or was not responsive to chemotherapy died with active lactic acidosis; lactic acidosis resolved only when chemotherapy resulted in cytoreduction of the underlying malignancy. Alkalinization may be needed to prevent the adverse cardiovascular effects of severe acidosis resulting from the elevated lactate levels until chemotherapy can take effect [174]. However, alkalinization is often ineffective and may actually potentiate lactate production in these patients [174, 181, 182]. In one report, the use of hemofiltration with a bicarbonate-based replacement fluid rapidly normalized the pH allowing for better hemodynamics, although lactate levels remained unchanged until chemotherapy began to take effect [174]. Renal replacement therapy has been used with varying success. One case reported the successful treatment of lactic acidosis with sustained low efficiency dialysis until definitive treatment could be initiated [183].

Balancing Therapy at the End of Life

For the family and for the medical care team it is often difficult to recognize and accept the reality that a child will not survive despite best efforts. A recent review of top-selling textbooks from multiple specialties revealed that most textbooks, and most disease-oriented chapters, had no or minimal information on caring for patients at the end of life [184]. Physicians and staff in the pediatric intensive care unit are especially likely to care for children at the end of life. It is established that children who die in the hospital with complex chronic conditions are more likely to experience longer periods of mechanical ventilation and hospitalization before death [185]. As caregivers who are often present in these situations, the pediatric critical care clinician has an obligation to provide excellent end of life care and to diligently attend to the relief of suffering in children with cancer.

It has been reported that children who die of cancer, many of whom receive aggressive treatment at the end of life, often have substantial suffering in the last month of life [186]. Although there are models for end of life care in pediatric oncology, there is a stark lack of formal courses or training in caring for the dying patient, and there is a high reliance on trial and error as a means of learning how to deal with such situations [187–189]. Although there is need for more formal training, a few simple principles can help to guide decisions about the care of oncology patients at the end of life in the PICU [190].

First, it is important that decisions be made in a multidisciplinary manner. End of life care for pediatric patients with cancer requires integrated, coordinated service that involves the primary oncology team, the PICU team, the family and often community resources such as a family pastor [191]. Second, the complexities of prognosis should be considered as the team communicates to a family. For example, in a patient who has a progressive malignancy, global prognosis may be grim even if the disease process that required intensive care services is improving. The opposite may also be true; the cancer may be in remission, but the disease process

requiring intensive care services is deteriorating. In these cases, it is easy for families to experience 'mixed messages' regarding the condition of the patient, and this may significantly impact and impede the decision-making process. Third, when a patient is moving towards the end of life, it is important to clearly establish goals of care in light of prognosis, and then to consider all medical decisions in light of these goals of care. For example, the decision of whether or not to use mechanical ventilation should not be made in isolation from other factors, but rather, should be formulated by determining whether or not that intervention helps the patient and family to achieve their goals of care. Finally, it is important for families to be reassured that it is never the case that 'there is nothing more that we can do'. Even if there is no curative interventions for a child with cancer, there is always something that can be done to aggressively relieve pain and non-pain causes of suffering, to ensure that the family has access to the appropriate support services, and to re-affirm that the medical care team is present as a child progresses towards death. The goal set by Dr. Edward Trudeau in the 1800s still holds today: "To cure sometimes, to relieve often, to comfort always."

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Critical Illness as a Result of Anti-Neoplastic Therapy

25

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Abstract

Although cancer is responsible for more deaths in children over 1 year of age than any other disease, outcomes are improving as a result of many factors including better supportive care and increasingly aggressive anti-neoplastic regimens. As a result, the pediatric intensivist will likely encounter many complex clinical challenges related to the therapy for childhood cancer. Chemotherapy can, in the course of reducing tumor burden, also bring about life-threatening changes in organ function, metabolism and electrolyte levels. The destruction of tumor cells results in the release of intra-cellular contents in tumor lysis syndrome, and this may lead to a range of problems including cardiac arrhythmias, tetany and renal failure. In addition, the chemotherapy may produce life-threatening toxicity to otherwise healthy tissues. An understanding of these toxicities enables the intensive care physician to anticipate problems and intervene in a timely manner. Radiation therapy can also lead to a wide variety of organ dysfunction, most notably, lung injury. Radiation pneumonitis presents a true diagnostic challenge requiring a clear understanding of both the use and timing of anti-neoplastic therapy in conjunction with an appreciation for the clinical and radiographic findings suggestive of this disorder. Additionally, the impact of anti-neoplastic therapy on the immune system has been well established. Neutropenic enterocolitis (typhlitis) is an acute, potentially life-threatening, necrotizing inflammation of the cecum and colon reported to occur in children treated for leukemia as well as other malignancies. Furthermore, the myelosuppression associated with many forms of anti-cancer therapy predisposes the child with cancer to bacteremia and sepsis. Encouragingly, with timely critical care interventions, the outcomes from severe sepsis in non-transplant oncology patients now approximate those of the general pediatric population. In sum, therapy for cancer in children can profoundly impact physiology and the pediatric intensivist must have a sound working knowledge of these effects.

Keywords

Tumor lysis syndrome • Chemotherapy • Radiation pneumonitis • Typhlitis • Sepsis Pediatrics • Oncology

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Introduction

Cancer is responsible for more deaths in children over 1 year of age than any other disease; however, outcomes are improving [1, 2]. Today, children diagnosed with cancer have a projected survival rate of approximately 80 % [2]. This improvement is due in large part to the use of more aggressive anti-neoplastic treatment regimens and improved supportive care of the toxicities associated with these therapies. As such, nearly 40 % of pediatric cancer patients require intensive care services and pediatric cancer patients account for approximately 3 % of all children requiring admission to a PICU [3, 4]. Therefore, it is imperative that the critical care provider have a clear understanding of the potential anti-neoplastic treatment toxicities and the therapies available to ameliorate these conditions.

Tumor Lysis Syndrome (TLS)

Pathophysiology

Tumor lysis syndrome (TLS) is a potentially life-threatening complication that can occur during anti-cancer therapy. It is associated with severe metabolic derangements (See Fig. 25.1) [5–18]. The pathophysiological basis for the syndrome is the release of intracellular contents upon the lysis of tumor cells. Tumor cells, which have high intracellular concentrations of potassium, phosphate, and purine nucleic acids, are rapidly lysed [5–7, 12–19]. This lysis leads to the release of potassium and phosphate into the bloodstream resulting in hyperkalemia and hyperphosphatemia. Hypocalcemia can follow as calcium quickly binds to the excess phosphate [5, 6, 12–20]. Additionally, xanthine oxidase ultimately metabolizes released nucleic acids into uric acid producing hyperuricemia, which in turn leads to the risk of crystallization in the renal tubules and decreased kidney function [5, 6, 12–18, 21].

Because the syndrome results from the lysis of tumor cells, the patients at highest risk are those with large, rapidly proliferating tumor burdens that have a high sensitivity to anti-neoplastic therapy [5–7, 12–18]. It is not surprising, therefore, that the syndrome is most commonly associated with high-grade lymphoproliferative malignancies such as Burkitt lymphoma, acute lymphocytic leukemia, and other high-grade lymphomas and leukemias [5, 6, 8, 12–19]. The overall incidence of TLS is unknown, but it has been reported to be as high as 40 % in patients with high-grade non-Hodgkin lymphoma. Typically, it occurs 12–72 h following the initiation of anti-neoplastic therapy. However, it may occur spontaneously and there are reports of hyperuricemia with acute renal failure as the presenting symptom of occult lymphomas [5, 22–26]. It may occur following any anti-neoplastic therapy including corticosteroids, interferon α(alpha), intrathecal methotrexate, rituximab, and ionizing radiation [27–34]. Clinicians should be especially vigilant in monitoring the metabolic status of those patients at highest risk including those with large tumor burdens, extensive bone marrow involvement, high tumor sensitivity as well as pre-existing renal dysfunction, acid-concentrated urine, elevated pre-treatment serum uric acid and lactate dehydrogenase levels [5–7, 12–19, 35].

One potential consequence of acute TLS is renal failure, and this can further worsen the metabolic derangements. Often the etiology of renal failure in this clinical setting is multifactorial [5, 6, 36]. Of primary concern is uric acid nephropathy [5, 6, 35]. In the context of an acidic urine and elevated concentrations of uric acid in the collecting duct, crystallization of uric acid is fostered [6]. For this reason, it is important not only to decrease uric acid levels, but also to avoid and aggressively treat pre-renal conditions such as volume depletion that contribute to uric acid crystallization [6]. Renal function may be further impaired by the formation of calcium-phosphate crystals [5, 6, 20]. Compounding the renal derangements directly attributable to tumor lysis, acute tubular necrosis resulting from hypovolemia, hypoperfusion, hypotension, cytokinemia and/or nephrotoxic medications can lead to renal dysfunction in these patients [5, 6]. In addition to these factors, renal impairment from tumor infiltration of the kidneys and/or obstructive nephropathy from the tumor itself may also worsen renal failure in this clinical setting [5, 19].

Treatment

Effective prevention and treatment of TLS requires careful monitoring of hydration, urine output, and the metabolic abnormalities [5, 12–18]. Patients at risk for tumor lysis syndrome should receive aggressive fluid therapy and have reliable venous access established [5, 6, 12–19, 37–40]. There are data suggesting that a high urine flow is the primary mechanism of protection in acute uric acid nephropathy [41]. In the attempt to decrease solute concentration in the renal tubules and make precipitation less likely, approximately twice maintenance intravenous fluid therapy (~3 L/m^2/d) should be utilized to increase renal blood flow, glomerular filtration rate, and ultimately, urine volume [5, 6, 12, 13, 15, 19]. The urine specific gravity should be maintained at ≤1.010 [5]. The composition of the fluid may be varied, but should contain at least a sodium concentration of 77 mEq/L (1/2 normal saline) and absolutely **no** potassium nor phosphorus [5]. Those patients at risk for volume overload should have their fluids adjusted accordingly and/or receive concomitant diuretic therapy [5]. Mannitol and furosemide can be used as needed to maintain an adequate urine flow [5, 19].

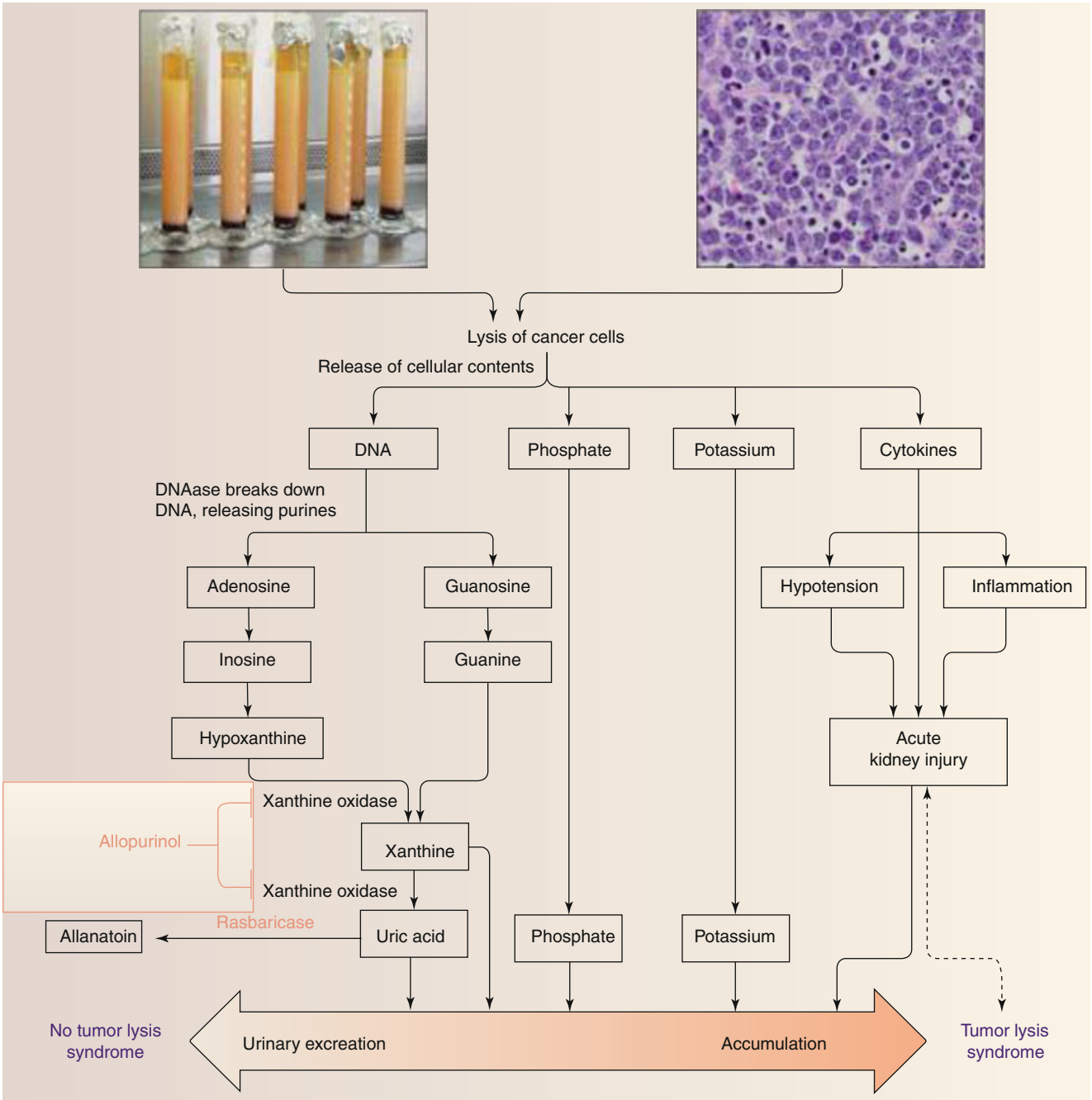

Fig. 25.1 Tumor lysis syndrome. The figure depicts the metabolic consequences of tumor lysis syndrome. The figure also illustrates the mechanism of action of allopurinol; namely, blocking the formation of uric acid by acting as a competitive inhibitor of the enzyme xanthine oxidase. The role of rasburicase which catalyzes the conversion of uric acid to allantoin to decrease uric acid levels is also depicted (Reprinted from Howard et al. [14]. With permission from Massachusetts Medical Society)

Hyperkalemia

Perhaps the most life-threatening electrolyte disturbance found in tumor lysis syndrome is hyperkalemia. Potassium levels >6.5 mEq/L or rapid increases in potassium (>2 mEq/L) can be associated with life-threatening dysrhythmias and must be treated emergently [6, 7]. Sodium bicarbonate may be used to acutely decrease serum potassium levels by increasing the pH which drives potassium intracellularly [6, 36]. Glucose and insulin may also be used to drive potassium intracellularly [5, 6, 19, 38]. Beta-agonist aerosol therapies may have the same effect [6]. Sodium polystyrene sulfonate resins may be used to exchange sodium for potassium in the gastrointestinal tract [36, 39]. Loop diuretics may facilitate

the urinary excretion of potassium [6, 19]. Renal replacement therapy may be needed in extreme and/or refractory cases [6]. Exogenous sources of potassium must obviously be eliminated as well as any medication that may result in elevated potassium levels (e.g., heparin, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors) [5].

Hyperuricemia

Hyperuricemia can occur either spontaneously or after the onset of chemotherapy as a consequence of the lysis of malignant cells which release their contents into the bloodstream at a more rapid rate than the kidneys can eliminate them. Aggressively treating hyperuricemia is crucial in the management of TLS and in maintaining adequate renal function [12–19]. The goals of therapy should be to prevent the formation of uric acid and to augment its elimination [6]. In part, because malignant cells have a high cellular activity and turnover, they contain large quantities of nucleic acid products that are rapidly released into the bloodstream during tumor lysis [5–7]. These purine nucleic acids are initially converted to hypoxanthine, and then, into uric acid via the enzyme xanthine oxidase (See Fig. 25.1) [5, 6]. Hyperuricemia has generally been defined as a plasma uric acid level exceeding 8 mg/dL [42]. Allopurinol, a structural analogue of hypoxanthine, is a competitive inhibitor of the enzyme xanthine oxidase [5, 6, 12–18, 43]. By competitively inhibiting xanthine oxidase, allopurinol decreases production of uric acid and results in a decrease in systemic uric acid levels (See Fig. 25.1) [12–18, 42, 44, 45]. However, allopurinol has three key limitations [5]. First, it only prevents the formation of new uric acid, and does not enhance the elimination of uric acid formed prior to its administration [5, 12–18, 46]. Second, it increases the levels of both xanthine and hypoxanthine, which in turn increases the potential for xanthine crystallization and obstructive uropathy since xanthine is even less soluble in urine than uric acid [12–18, 38, 45, 47, 48]. Fortunately, this potential complication is rarely clinically manifested. Third, allopurinol reduces the degradation of other purines requiring dose reductions in medications such as 6-mercaptopurine [5, 46].

The elimination of uric acid can be augmented by alkalinization of the urine [5, 6, 19]. Uric acid is insoluble at a pH <6.0 and will crystallize in the renal tubules, collecting ducts, and renal parenchyma. Systemic alkalinization can be used to produce an alkalotic urine (pH between 7.0 and 7.5) that increases the solubility of uric acid and facilitates renal elimination [5, 6]. However, systemic alkalinization can have untoward effects. The solubility of xanthine and hypoxanthine significantly decreases in an alkalotic pH placing the patient at risk for the formation of urinary xanthine crystals and xanthine obstructive uropathies [5, 12–18, 40, 49]. In addition, the metabolic alkalosis may contribute to lower ionized calcium levels and/or foster the formation of calcium and phosphate precipitants [19, 40, 49]. It may also cause a leftward shift in the oxygen disassociation curve potentially resulting in decreased release of oxygen at the tissue level [50]. Given the potential consequences described above, it is generally believed that alkalinization of urine no longer plays a role in the management of TLS [12–18].

A relatively recent innovation in the management of this complication, especially in patients at high-risk of TLS, is the development of a recombinant form of urate oxidase, rasburicase, which catalyzes the conversion of uric acid to allantoin (See Fig. 25.1) [12–18, 46, 51, 52]. Allantoin is approximately five times more soluble in urine than uric acid facilitating elimination [5, 12–18, 53, 54]. Rasburicase effectively reduces uric acid levels within 4 h of administration and is more effective than allopurinol, which generally reduces uric acid levels within 48–72 h after the first dose [12–18, 42, 52, 54]. Several different reports have recently underscored the dramatic impact that rasburicase has on uric acid levels and it is now generally considered the treatment of choice to prevent TLS in children at high risk for this metabolic complication and warrants strong consideration in children at intermediate risk as rasburicase so rapidly decreases the uric acid levels that the need for additional therapy may not be warranted [5, 12–18]. The recombinant form of rasburicase appears to be well tolerated [42, 55, 56], however, it should not be used in patients with glucose-6-phosphate dehydrogenase deficiency as it may induce a hemolytic anemia [5, 12–18, 52, 57, 58]. Rasburicase may yield inaccurate determination of serum uric acid levels as it may continue to breakdown uric acid in the laboratory collecting tube; a process that may be stopped by promptly placing the collecting tube on ice [6, 57].

Hyperphosphatemia

Hyperphosphatemia is often difficult to treat. Malignant hematologic cells may contain up to four times more intracellular phosphorus than normal lymphoid cells [9, 19]. The increased intracellular phosphorus, in conjunction with poor renal function, can make hyperphosphatemia a considerable clinical challenge. Moreover, anti-neoplastic therapy prevents the rapid reuse of phosphate for newly synthesized tumor cells [6]. Calcium phosphate precipitants form when the calcium phosphorus solubility product (determined by multiplying the phosphorus concentration by the total calcium concentration) exceeds 60 [59]. The first step in treatment is to eliminate exogenous sources of phosphorus including any unnecessary medications with a phosphorus base [5, 19]. Phosphorus binding medications such as aluminum hydroxide and sevelamer should be administered [5, 12–19].

Sevelamer offers the advantage of not containing calcium nor aluminum (that may accumulate in the face of renal failure); however, it is expensive [60]. Hypertonic glucose and insulin may also drive phosphorus into the intracellular space [19]. It is important to ensure adequate intravascular volume. Hemodialysis can aid in the control of hyperphosphatemia, but it can be associated with significant rebound [6, 19, 61]. Continuous veno-venous hemofiltration dialysis has been found to effectively decrease serum phosphorus levels and has been used following dialysis to prevent rebound [61].

Hypocalcemia

Hypocalcemia can result from the hyperphosphatemia and must be treated cautiously in order to prevent the formation of calcium phosphorus precipitants [5, 20]. Asymptomatic hypocalcemia should simply be monitored [5, 19]. Symptoms of hypocalcemia requiring treatment include seizures, tetany, and arrhythmias [6].

Monitoring

While executing the specific measures to prevent and treat the electrolyte disturbances of tumor lysis, vigilant clinical and laboratory monitoring is essential [5, 12–19]. Clinical assessment should include a focus on neuromuscular symptoms including, but not limited to, muscle cramps, tetany, Chvostek and Trousseau signs, carpopedal spasms, paresthesias, twitching, weakness, lethargy, confusion, and seizures [5, 6, 19]. Continual electrocardiographic monitoring should be utilized to detect rhythm disturbances associated with the electrolyte imbalances [5]. In tumor lysis syndrome, many electrocardiographic changes may occur, especially in patients with potassium imbalances. Hyperkalemia is most often associated with peaked T-waves and a widened QRS complex [6]. Daily weights and frequent assessments of fluid balance with particular attention to urine output are critical [6]. Laboratory determinations that should be performed at least two or three times daily, and more frequently if the clinical status warrants, include complete blood cell counts as well as levels of uric acid, potassium, phosphorus, calcium, blood urea nitrogen, creatinine, lactate dehydrogenase, and urinary pH [6, 19]. Ionized calcium levels should also be performed as concomitant hypoalbuminemia may result in normal functional calcium levels [5, 20].

Classification

TLS can be managed effectively with early identification of patients at risk, vigilant monitoring, and appropriate therapeutic interventions (See Fig. 25.2) [5, 6, 12–18]. One of the most critical factors is the early identification of patients at risk because this allows for the implementation of preventive measures and minimizes the risk of renal failure and electrolyte derangement [5, 8, 12–18]. As anti-neoplastic therapy continues to improve, the risk of TLS may expand into other malignant diseases [6]. Moreover, as therapies for the prevention and treatment of tumor lysis advance, the need for clear, specific definitions of the syndrome will become progressively more important [5]. Perhaps the most widely utilized classification system has been proposed by Cairo and Bishop [5, 12–18], which is a modified version of a previously established classification schema [8]. Patients are categorized as having no tumor lysis, laboratory tumor lysis, or clinical tumor lysis syndrome [5, 8, 12–18]. Patients classified as having no tumor lysis syndrome have neither laboratory nor clinical evidence of the syndrome and can be further categorized as being at high or low risk. Patients with laboratory tumor lysis syndrome have baseline levels above or below normal or experience a 25 % change in the levels of two or more of the four critical serum parameters (uric acid, potassium, phosphorus, calcium) 3 days before or 7 days after the initiation of chemotherapy [5, 12–18]. Patients with clinical tumor lysis syndrome must satisfy laboratory tumor lysis criteria and have one or more of the three most significant clinical complications; renal insufficiency, cardiac arrhythmias/sudden death, and/or seizures [5, 12–18].

Chemotherapy Adverse Effects

There are a number of chemotherapeutic agents used in pediatric oncology that have the potential for untoward side effects that may result in the need for critical care services or complicate the care of a critically ill oncology patient (See Table 25.1). For example, one of the most common adverse effects of traditional cytotoxic chemotherapeutic agents is myelosuppression. A notable exception is vincristine which is commonly used in patients with acute lymphoblastic leukemia. Myelosuppression will often necessitate the use of red cell and platelet transfusions along with increasing the risk for opportunistic infections. The extent and duration of myelosuppression will vary based on the agents and dosages administered.

A number of anti-neoplastic agents may impede normal respiratory function. Bleomycin, used primarily for lymphomas and sarcomas, has been noted to induce interstitial pneumonitis that may progress to fibrosis while busulfan, used in many HSCT conditioning regimens, has been associated with an interstitial fibrosis after long term or high dose therapy [62–64]. Cytarabine has been associated with pulmonary toxicity causing acute respiratory distress secondary to a capillary leak pulmonary edema [65]. Cytarabine, as well as

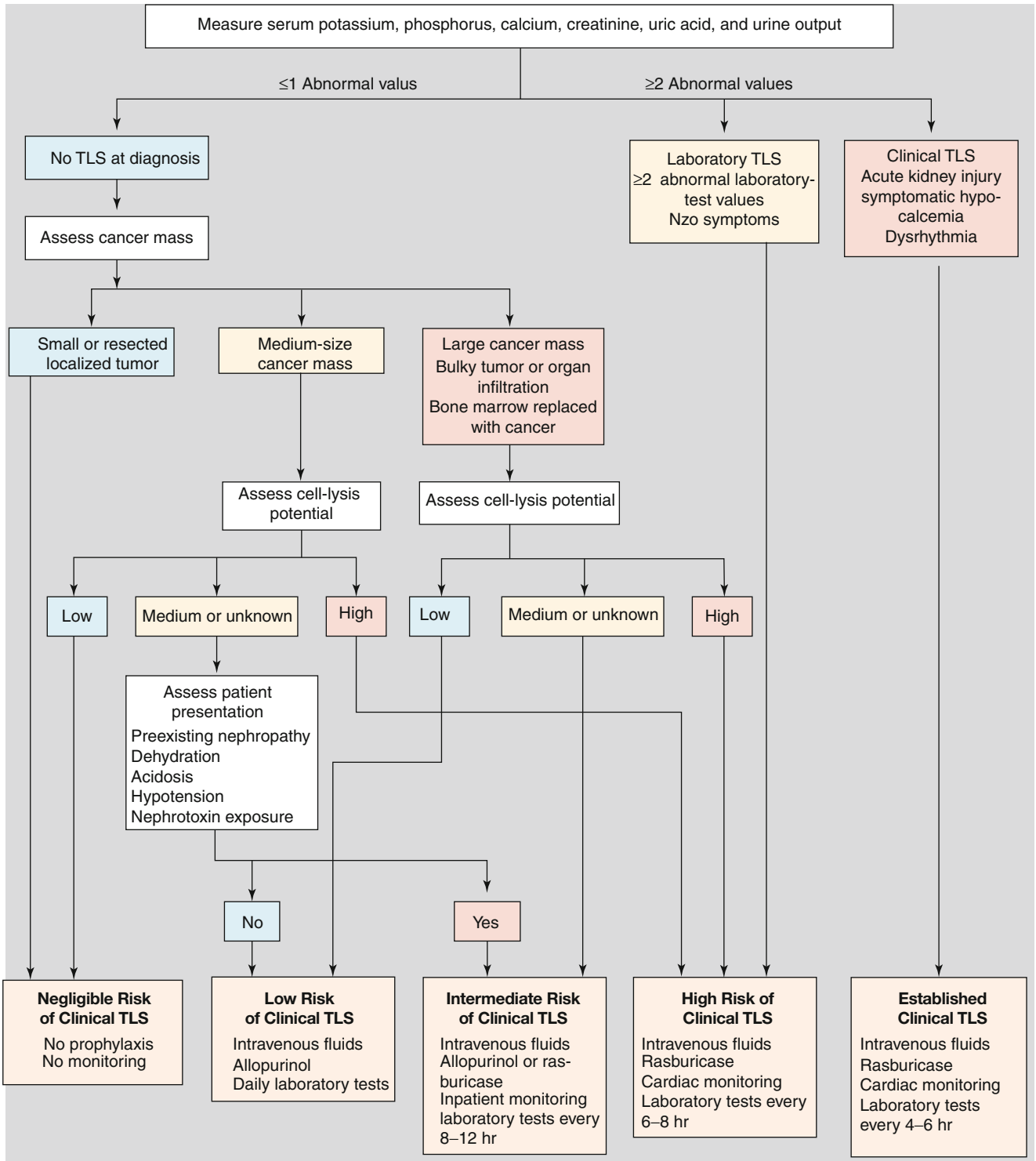

Fig. 25.2 Assessment of tumor lysis risk (Reprinted from Howard et al. [14]. With permission from Massachusetts Medical Society)

a number of other agents such as methotrexate and fluorouracil, has been associated with severe mucositis that may create respiratory difficulties secondary to oropharyngeal edema and inflammation [66]. Leucovorin (folinic acid) can be used to decrease the severity of methotrexate-induced mucositis [67]. In rare instances, this severe mucositis may progress and result in life-threatening airway obstruction [68]. Noncardiogenic pulmonary edema may be induced by gemcitabine as well as by high-dose cytarabine. This can be acutely life-threatening, but may respond to management

with diuretics and steroids [69]. Vincristine, a vinca alkaloid commonly used in the treatment of a number of pediatric malignancies has been reported to cause laryngeal nerve paralysis resulting in vocal cord paralysis and stridor [70–75]. The vocal cord paralysis may occur alone or in conjunction with generalized neurotoxicity; it may be bilateral or unilateral [70, 71]. The stridor generally resolves after discontinuing or decreasing the dose of vincristine [70–72]. Given the varied causes of stridor in the pediatric oncology patient, this reversible condition may easily be overlooked [70]. Direct laryngoscopy of the airway not only confirms the diagnosis, but also rules out other treatable causes of stridor in the immunocompromised patient [71]. Vinblastine has also been reported to induce vocal cord paralysis [72, 73].

A number of agents are associated with cardiac toxicity, either acutely or after long-standing therapy. It is estimated that survivors of childhood cancer have a significantly higher risk of developing congestive heart failure [relative risk =15.1] [76]. The anthracyclines, daunorubicin and doxorubicin, have long been known to result in a delayed cardiomyopathy. While potentially cardiotoxic at any dose, the incidence begins to significantly risk as cumulative doses exceed 300 mg/m^2 [76–78]. Idarubicin, a second generation anthracycline analogue, has been associated with an improved therapeutic index although the risk of cardiomyopathy and congestive heart failure is not eliminated [79]. Anthracyclines may also be associated with dysrhythmias. Mitoxantrone, used for leukemias, lymphomas, and pediatric sarcomas, is structurally similar to the anthracyclines, but associated with less cardiotoxicity [80]. While its use in pediatrics is still controversial, dexrazoxane can potentially be utilized to bind to the free oxygen radicals believed to be responsible for anthracycline-induced cardiomyopathies [81, 82]. Cyclophosphamide, used in a number of treatment protocols and in conditioning regimens for HSCT, has been noted to cause cardiac dysfunction at higher doses including myocarditis, congestive heart failure, exudative pericarditis, myocardial necrosis and hemorrhagic myocarditis [80, 83]. Although its cardiotoxicity may be exacerbated by the anthracyclines, unlike the anthracyclines, cyclophosphamide-associated cardiac toxicity does not appear to be cumulative [83]. A number of other agents may also cause hemodynamic compromise independent of significant cardiac toxicity. Vincristine and vinblastine both can cause orthostatic hypotension seemingly secondary to autonomic neuropathy while etoposide is frequently associated with a hypotension that is related to the rate of infusion [84, 85]. Administration of biologic agents such as aldesleukin (interleukin-II), rituximab, infliximab, and alemtuzumab may create a clinical condition mirroring septic shock with tachycardia, fever, decreased vascular tone, and hypotension requiring vasopressor support [86–88]. This syndrome can also be seen with the purine analogue clofarabine [89]. Interferon α(alpha), used in the treatment of chronic myelogenous leukemia, has been associated with acute cardiovascular collapse and pulmonary edema [90].

A number of neurological manifestations may result from chemotherapy. Fludarabine, used in some HSCT conditioning protocols, may result in neurotoxicity, particularly at higher doses. Central demyelinization, blindness and coma may all emanate from this therapy [91–93]. Ifosfamide at high doses has been associated with altered mental status and a metabolic encephalopathy [94]. Methylene blue and thiamine have been used to reverse the symptoms of ifosfamide related encephalopathy in case reports [95, 96]. In addition, methotrexate, given intrathecally or systemically, can result in neurological toxicity [97]. Intrathecal methotrexate, an integral part of many leukemia protocols, has long been reported to cause arachnoiditis with fever, headache, and meningeal signs [98]. Seizures and acute mental status changes have also been reported to occur following high dose and intrathecal methotrexate [99]. Vincristine may be associated with significant peripheral neuropathy [100]. Cisplatin and carboplatin can cause significant peripheral neuropathy and permanent hearing loss [101–103]. When used in the setting of high-dose therapy for HSCT, busulfan is associated with such a high-risk of seizures that the use of anticonvulsant prophylaxis is required [64]. High-dose cytarabine used primarily in leukemias, has been associated with a syndrome of cerebellar toxicity. It is more likely to occur in patients with underlying renal insufficiency. This cytarabine-induced syndrome often responds to treatment with dexamethasone [104]. Nelarabine, used in T-cell leukemias and lymphomas can cause peripheral neuropathy, ataxia, seizures, and coma [105].

Renal and hepatic dysfunction may also be side effects of anti-neoplastic therapy. Cisplatin and carboplatin may injure the kidney endothelium resulting in a consistent loss of electrolytes creating systemic hypokalemia, hypocalcemia, hypomagnesemia, and/or hyponatremia [106]. Cyclophosphamide and ifosfamide may cause a hemorrhagic cystitis due to the irritant properties of a common acrolein metabolite. Acrolein-induced hemorrhagic cystitis can be prevented with the medication MESNA to bind to the acrolein, and aggressive hydration and diuresis to prevent acrolein irritation of the bladder. High cumulative doses of ifosfamide can cause hypophosphatemia, and potentially, renal failure [80, 107, 108]. Methotrexate may also be associated with renal dysfunction that may be avoided with forced alkaline diuresis [67]. No longer investigational Glucarpidase, which metabolizes methotrexate, may be considered for the treatment of life-threatening methotrexate toxicity or overdoses [109]. Aldesleukin may be associated with oliguria and elevated creatinine levels [110, 111]. Hepatic toxicity including sinusoidal obstruction syndrome may be associated with a number of chemotherapeutic agents including busulfan

Table 25.1 Common chemotherapeutic agents and their toxicity relevant to critical care medicine[a]

Chemotherapy agent	Common toxicities of greatest relevance to PICU[a]
Aldesleukin	Cardiovascular: sinus tachycardia, arrhythmias including SVT with hypotension, pulmonary congestion, hypotension and hemodynamic changes resembling septic shock (within 2 h of administration), angina, myocardial ischemia, edema
	CNS: cognitive changes, disorientation, paranoid delusion
	Dermatologic: exfoliative dermatitis
	Renal: oliguria, anuria, renal failure
	Respiratory: dyspnea, pulmonary edema
Alemtuzumab	Cardiovascular: hypotension, cardiac arrest (<1 %), cardiac arrhythmias
	Respiratory: dyspnea, respiratory arrest
Asparaginase preparations (E. coli derived, pegylated, and Erwinia derived)	CNS: somnolence, depression, hallucinations, agitation, disorientation, seizures,
	Gastrointestinal: acute pancreatitis
	Hematologic: hypofibrinogenemia and decreased clotting factors V, VII, VIII, and IX, severe protein C deficiency, decreased anti-thrombin III
	Hypersensitivity: acute allergic reactions consisting of fever, rash urticaria, arthralgia, hypotension, angioedema, bronchospasm, and/or anaphylaxis
Bleomycin	Respiratory: interstitial pneumonitis
Busulfan	CNS: seizures
	Hepatic: Sinusoidal Obstruction Syndrome (SOS)
	Respiratory: interstitial pulmonary fibrosis
Carboplatin	Allergic: anaphylaxis
	CNS: seizures
	Renal: electrolyte abnormalities hypocalcemia, hypomagnesemia, hyponatremia, hypokalemia
Cisplatin	Allergic: anaphylaxis
	Renal: acute renal failure, azotemia (dose related), electrolyte abnormalities hypocalcemia, hypomagnesemia, hyponatremia, hypokalemia
Clofarabine	Cardiovascular: hypotension, capillary leak syndrome/systemic inflammatory response syndrome
	Hepatic: acute liver failure
Cyclophosphamide	Cardiac: cardiac dysfunction (<1 %) at higher doses – cardiac necrosis or hemorrhagic myocarditis, may potentiate the cardiotoxicity of anthracyclines
	Endocrine: syndrome of antidiuretic hormone
	Genitourinary: hemorrhagic cystitis
	Hepatic: jaundice
Cytarabine	High-dose therapy toxicities (doses ≥1,000 mg/m2): cerebellar toxicity, conjunctivitis, hyperbilirubinemia, pulmonary edema, pericarditis and tamponade
	Respiratory: sudden respiratory distress (1–10 %) progressing to pulmonary edema/pneumonitis
Dactinomycin	Hepatic: ascites, hepatomegaly, hepatitis
Daunorubicin/ doxorubicin	Cardiac: early and late – congestive heart failure (1–10 %) (cumulative doses >300 mg/m^2)
	Genitourinary: urine discoloration (red)
Etoposide	Gastro-intestinal: severe mucositis at high doses used in HSCT, anorexia
	Cardiovascular: hypotension (often related to the rate of infusion)
Etoposide phosphate	Cardiovascular: hypotension (at the time of infusion)
Fludarabine	CNS: demyelination; somnolence, blindness, coma, severe neurotoxicity (at higher doses)
	Respiratory: dyspnea
Gemcitabine	Cardiovascular: peripheral edema
	Hepatic: hepatic failure
	Respiratory: acute respiratory failure
Gemtuzumab ozogamicin	Cardiovascular: peripheral edema, hypertension, hypotension
	Hepatic: hepatic failure, Sinusoidal Obstruction Syndrome (SOS)
	Respiratory: dyspnea, pleural effusions, pulmonary edema and acute lung injury
Idarubicin	Cardiac: early and late – congestive heart failure (1–10 %) (cumulative doses 137.5 mg/m^2)
	Genitourinary: urine discoloration (red)

Table 25.1 (continued)

Chemotherapy agent	Common toxicities of greatest relevance to PICU[a]
Ifosfamide	Cardiovascular: PAC, PVC, SVT atrial fibrillation
	CNS: encephalopathy: somnolence, confusion, hallucinations, coma (usually at higher doses), polyneuropathy
	Genitourinary: hemorrhagic cystitis, metabolic acidosis, hypophosphatemia acute renal failure with high doses
Interferon α (alpha) 2a	Cardiovascular: <1 % tachycardia, arrhythmias, chest pain, hypotension SVT, edema
	Genitourinary: azotemia
	Respiratory dyspnea
Irinotecan	Gastrointestinal: severe secretory diarrhea resulting in electrolyte disturbances
Isotretinoin	CNS: psychiatric disturbances, pseudotumor cerebri
	Endocrine: hypercalcemia
Mechlorethamine	Dermatologic: erythema multiforme
	Hematologic: hemolytic anemia (<1 %)
Methotrexate	CNS: subacute toxicity (2nd or 3rd week of therapy) motor paralysis of extremities, cranial nerve palsy, seizures or coma; Demyelinating encephalopathy (late onset usually associated with cranial irradiation or other systemic chemotherapy); With itrathecal doses: arachnoiditis (headache, nuchal rigidity, vomiting and fever);
	Dermatologic: exfoliative dermatitis, Stevens-Johnson syndrome
	Gastrointestinal: intestinal perforation
	Renal: renal failure, azotemia
Mitoxantrone	Cardiovascular: abnormal EKG, arrhythmias, edema, congestive heart failure (cumulative doses >140 mg/m^2)
	Gastrointestinal: gastrointestinal hemorrhage
	Respiratory: dyspnea
Nelarabine	CNS: severe neurologic toxicity (seizures, coma, death), peripheral neuropathy, headache, blurred vision, nystagmus
Procarbazine	Cardiovascular: orthostatic hypotension (<1 %), hypertensive crisis
	CNS: ataxia, CNS stimulation, confusion, disorientation, dizziness, hallucinations
	Hematologic: hemolytic anemia
	Ocular: nystagmus
	Respiratory: pleural effusion, pneumonitis
Rituximab	Cardiovascular: hypotension, capillary leak syndrome, arrhythmia, angioedema, anaphylaxis, infusion reactions (fever, rigors)
	Respiratory: bronchospasm
Thioguanine	Hepatic: hepatitis, jaundice, Sinusoidal Obstruction Syndrome (SOS),
Thiotepa	Dermatologic: severe rash/skin desquamation with high-dose therapy such as that used with HSCT
Tretinoin	Cardiovascular: arrhythmias, chest discomfort, edema, flushing, hypertension, hypotension, edema
	CNS: anxiety, confusion, depression, dizziness, insomnia, malaise, pain, pseudotumor cerebri (<1 %)
	Gastrointestinal: gastrointestinal hemorrhage
	Hematologic: disseminated intravascular coagulation, hemorrhage
	Renal: renal failure
	Respiratory: expiratory wheezing, pleural effusion, pneumonitis, respiratory insufficiency
Vinblastine/ vincristine	Cardiovascular: orthostatic hypotension
	CNS: peripheral neuropathy, loss of deep tendon reflexes, headache, convulsions, weakness, vocal cord paralysis
	Gastrointestinal: constipation, paralytic ileus
	Genitourinary: urinary retention
	Endocrine: syndrome of inappropriate antidiuretic hormone (SIADH)

[a]For additional details please see appendix

thioguanine and dactinomycin [64, 112, 113]. Reversible hepatotoxicity has been reported as a dose-limiting toxicity for 6-mercaptopurine as well as with clofarabine [89, 114, 115].

Multiple other significant toxicities exist with anti-neoplastic agents that may be relevant to the critically ill child. When high-dose thiotepa is used in the setting of HSCT, rash and skin depigmentation commonly occurs. However, even more worrisome is that thiotepa may be secreted via sweat glands placing the patient at risk for skin desquamation. This adverse effect can be reduced by avoiding unnecessary occlusive dressings and gently bathing the patient with mild soap three to four times daily immediately after administration [116]. Vincristine and cyclophosphamide may both induce a temporary state of inappropriate anti-diuretic hormone release (SIADH) [11]. The peripheral neurologic effects of vincristine can also induce severe constipation and/or an ileus [117]. This is in contrast to

irinotecan, used in several refractory malignancies, which can induce a potentially severe secretory diarrhea. Potential treatment options for irinotecan-induced diarrhea include loperamide, octreotide, and prophylaxis with a third generation oral cephalosporin such as cefixime [118]. A variety of unique toxicities can be caused by asparaginase products which are commonly used in acute lymphoblastic leukemia. It is available in two products derived from *E. coli* (one pegylated) that may induce allergic/anaphylactic reactions. Patients experiencing allergic/anaphylactic reactions may be able to tolerate an Erwinia-derived formulation, but allergic reactions are still possible [119]. All asparaginase formulations can also cause acute pancreatitis, induce disturbances in insulin regulation, and cause life-threatening coagulopathies (more commonly thrombosis) [119–121].

It is also important to realize that many of the anti-neoplastic agents are vesicants which can cause severe tissue necrosis when extravasated. All agents should be administered via central venous catheters whenever possible. Extravasations of anthracyclines (doxorubicin, daunorubicin, idarubicin) can be managed with systemic administration of dexrazoxane [122, 123]. Extravasations of vinca alkaloids (vincristine, vinblastine) can be managed with warm compresses and local administration of hyaluronidase [124]. Other potential vesicant and irritant anti-neoplastic therapies include but are not limited to melphalan, dactinomycin, and cisplatin [124, 125].

Radiation-Associated Toxicty

In addition to chemotherapy, radiation therapy can induce a variety of complications that may be pertinent to the care of critically ill pediatric oncology patients. Generally, younger children are more at risk for long-term effects of radiotherapy than older children [126]. Moreover, radiation therapy can affect a variety of body tissues [126]. It has long been known that radiation can affect the cardiovascular system [127–129]. Radiation can affect all structures of the heart including the coronary arteries, the valves, and the conduction system, but particularly, the myocardium and the pericardium [80, 130, 131]. Clinically evident cardiac toxicity has been reported to occur in as many as 30 % of patients receiving mediastinal irradiation [128]. In fact, cardiac toxicity has even been associated with craniospinal irradiation for brain and central nervous system tumors [132]. A recent analysis of 19 published reports on the effect of radiation therapy on cardiac disease suggested that trials conducted after 1980 may be associated with a lower incidence of cardiac toxicity. However, after controlling for length of follow-up in that report, those differences were no longer evident with all trials with a median follow-up of more than 10 years reporting an excess of cardiac morbidity regardless of the treatment era [133].

Pericardial disease is the most common acute manifestation of patients receiving mediastinal irradiation in several reports [127, 130, 131]. Other presenting symptoms of radiation-associated cardiac disease include angina, dyspnea, congestive heart failure, and peripheral embolization from intracardiac clot [134]. A number of risk factors for the development of radiation-induced heart disease have been identified including the total radiation dose, the age of the patient, the volume of cardiac tissue exposed, the dose fractionation, the time period of radiation, the presence of pre-existing cardiovascular risk factors, and the use of adjuvant chemotherapy [135–137]. Cardiac effects of radiation therapy may also occur years after therapy manifested by coronary artery disease, a restrictive cardiomyopathy, valvular disease and diastolic dysfunction [131, 138–140].

In addition to cardiac toxicity, neurologic toxicity may be associated with radiation therapy [141]. This radiation-related neurologic injury can affect every level of the nervous system and may occur during the course of radiation treatment or only years later [141]. The clinical manifestations of these radiation-related injuries are vast and range from acute encephalopathy to delayed cerebral radionecrosis and late-onset dementia. They may include such entities as radiation-induced brain tumors as well as endocrine dysfunction [141–143]. Pulmonary toxicity with radiation therapy has also been extensively studied and will be discussed in detail in the following section.

Radiation Pnuemonitis

Epidemiology

Radiation-induced pulmonary injury is one of the most common complications in patients receiving radiation therapy for tumors in and around the thorax [144]. Patients receiving total body irradiation as part of their preparative regimen for HSCT may also be at risk [145]. The incidence of radiation pneumonitis in children has not been extensively studied. In one pediatric study, three of eight children who received whole lung irradiation for the Ewing sarcoma family of tumors and pulmonary metastases developed radiation pneumonitis [146]. The pneumonitis developed at a median of 14 weeks (range 7–22 weeks) after radiation treatment and each of these patients experienced a brisk clinical improvement in their respiratory symptoms with initiation of steroid therapy [146].

Pathophysiology

Classical radiation pneumonitis represents a dose-related pulmonary toxicity with a pathophysiology that has been well described dating back to the late 1960s [147]. It consists

of three phases: (a) an early, clinically latent phase of pneumonitis occurring during the first month after treatment; (b) an intermediate phase of acute exudative pneumonitis occurring approximately between the second and sixth month after therapy; (c) and a late phase of fibrosis occurring 6 months after radiation therapy [147–150]. In sum, radiation pneumonitis results primarily from injury to capillary endothelial and alveolar pneumocytes (Type I and Type II alveolar cells) [148, 151–153]. Several mechanisms have been offered to explain this injury including the generation of free radicals, the activation of a stress response resulting in upregulation of specific nuclear transcription factors such as nuclear factor κ(kappa)-B, the activation of specific signal transduction pathways including sphingomyelin hydrolysis, and direct genetic damage to these cells causing apoptosis [151, 152, 154]. This initial damage results in a loss of integrity of pulmonary capillaries, a loss of surfactant production, and exudation of fluid into the alveoli and interstitium [151–153, 155]. Tissue hypoxia, macrophage activation, oxidative stress, profibrogenic and angiogenesis activity mediated by transforming growth factor- ß (TGF-ß), hypoxia inducible factor 1-α (HIF-1α), and vascular endothelial growth factor (VEGF) activity all serve to foster inflammation and fibrosis [156]. TGF- ß has also been demonstrated to antagonize the ability of keratinocyte growth factor (KGF) to induce Type II pneumocyte proliferation and differentiation [155].

Damage to bronchial epithelial cells results in bronchiolar atelectasis while the decreased production of surfactant results in collapse of the alveoli [151]. Vascular endothelial cell damage and dysfunction causes microthrombus formation and narrowing of the vascular lumen ultimately leading to pulmonary hypertension [151]. With a continuing inflammatory response, the alveolar septa become thickened and the alveolar space becomes smaller [153]. Pathophysiologically, these changes result in a loss of compliance, decreased gas exchange, and potentially, respiratory failure [152]. In time (approximately 6 months), fibrosis may develop together with loss of capillaries, further thickening of the alveolar septa and obliteration of the alveolar space [153].

Clinical Signs and Symptoms

The primary symptoms of radiation pneumonitis are dyspnea, shortness of breath, and a cough that is usually non-productive [149, 152, 153, 156–158]. Fever may also accompany the condition [149, 153, 156–158]. It is very important to note that the clinical symptoms of acute radiation pneumonitis usually manifest 2–3 months **after** the completion of therapy [152–154]. In fact, they may not manifest until as late as 6 months after treatment and only rarely occur within the first month following treatment [152, 156, 157]. Thus, at the time of presentation of respiratory symptoms, it will usually have been several weeks since the course of radiation therapy, and this potentially treatable condition can easily be overlooked in the differential diagnosis. Other than dyspnea, specific physical findings of pulmonary disease may be limited and only appreciated in the area of irradiated lung [149, 152]. The pneumonitis may be self-limited or may progress to severe respiratory distress depending on the extent and intensity of the lung injury [152, 153]. In fact, some patients may present with radiation fibrosis without a history of acute pneumonitis. Cor pulmonale and respiratory failure may result late in the course from fibrosis of large areas of irradiated lung [149, 152].

Radiographic findings may be important in establishing the diagnosis of radiation pneumonitis, as often, the changes are confined to the outline of the radiation field (See Fig. 25.3) [149, 152, 153]. The early changes commonly include a ground-glass opacification, diffuse haziness, or indistinct pulmonary markings over the irradiated area [149, 152]. Alveolar infiltrates or dense consolidation with or without air bronchograms predominate later [152]. Computed tomography is also useful in detecting and monitoring radiation-induced lung injury [149, 156, 159].

Diagnosis

The diagnosis of radiation pneumonitis can be difficult to establish and is often a diagnosis of exclusion [149, 157, 160]. At times, the condition may be diagnosed based on the time of presenting clinical symptoms in relation to the radiation therapy, in conjunction with radiographic findings limited to the area of radiation [152]. It is often difficult to differentiate radiation pneumonitis from recurrent malignancy, infection, or non-infectious pulmonary conditions associated with cancer and its treatment [149, 152, 157, 160]. Although there are no pathognomonic histopathologic findings, a lung biopsy may be useful in distinguishing radiation pneumonitis from other etiologies. The acute histologic changes of this condition (i.e., fibrin exudate in the alveoli) when detected adjacent to the more chronic findings (i.e., alveolar fibrosis and subintimal sclerosis) support the diagnosis of radiation pneumonitis particularly when observed in the appropriate clinical setting [152]. Bronchoalveolar lavage (BAL) does not appear to provide clinically useful data to confirm the diagnosis, however, bronchoscopy detected bronchial stenosis occurred in 6 % of patients considered to have radiation pneumonitis/fibrosis [157]. Also, although not clinically useful at this point, transforming growth factor- ß 1 (TGF- ß1) and IL-6 concentrations in the BAL fluid recovered from irradiated areas of lung are significantly increased in comparison to levels assessed in non-irradiated areas of lung [161]. There is also data to suggest that serum TGF- ß1 levels, as well as serum soluble intercellular adhesion molecule-1, may be useful markers for the early detection of

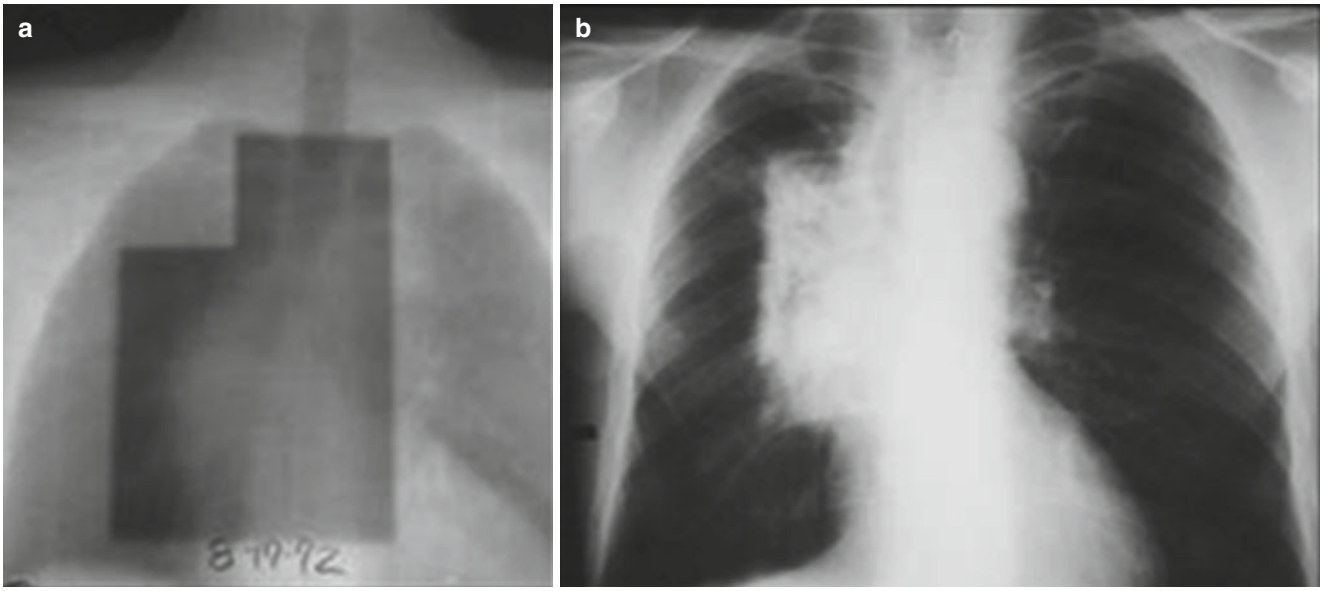

Fig. 25.3 Radiation pneumonitis. (**a**) depicts the port for radiation therapy. (**b**) illustrates the radiographic findings of the subsequent radiation pneumonitis experienced by the patient (Published with permission from LearningRadiology.com. http://www.learningradiology.com/notes/chestnotes/radiationpneumonitispage.htm)

radiation pneumonitis [148, 162]. Pulmonary function tests may be useful in assessing and monitoring the effects of radiation pneumonitis. In particular, deficits in the diffusing capacity of the lung for carbon monoxide (DLCO) and the forced expiratory volume in 1 s (FEV1) are most likely to be abnormal [156]. Chest radiography may reveal a variety of findings depending upon the phase of the radiation injury, but findings limited to the radiation port may help confirm the diagnosis in conjunction with the appropriate clinical scenario. Computed tomography may be more sensitive than routine chest radiography. In fact, computed tomography has recently been found to be as effective as KL-6 and surfactant protein-D (SP-D) levels in identifying patients with interstitial lung disease at high risk of deterioration following radiation therapy [163].

The phenomenon of radiation recall pneumonitis is a condition that the pediatric critical care provider should also be familiar with when caring for children with cancer. In brief, certain types of chemotherapy may produce pneumonitis when given to patients who have previously received radiation to the lungs [164]. The clinical presentation is the same as radiation pneumonitis with radiographic findings limited to the irradiated areas of the lungs. Common examples of chemotherapeutic agents that have been associated with this condition include adriamycin, etoposide, gemcitabine, and paclitaxel.

Treatment

Although there are no controlled human clinical trials available on the efficacy of steroid therapy in radiation pneumonitis, corticosteroids are the mainstay of therapy and a long history of use supports their effectiveness [146, 147, 149, 152, 154, 165]. Steroids have been demonstrated to improve physiologic abnormalities and to decrease mortality in mouse models of radiation pneumonitis [166, 167]. The effects of steroids can be dramatic although severe or well established cases may be refractory to even high doses of steroids [147, 149, 168]. There exists a case report describing the successful use of inhaled steroids in this setting [165]. When effective, steroids must be weaned very cautiously monitoring for exacerbations of the pulmonary symptoms [150, 152, 169]. The prophylactic use of steroids to prevent radiation pneumonitis does not appear to be effective and it is generally believed that corticosteroids have no place in the treatment of radiation fibrosis [147, 149, 152, 170].

Few other therapies have been suggested for the prevention and treatment of radiation pneumonitis/fibrosis. Cyclosporin A has been used effectively in treating a case of steroid resistant radiation pneumonitis [171]. Azathioprine was found to be effective therapy for radiation pneumonitis in an elderly patient who could not receive further steroid therapy secondary to myopathy [172]. There is some animal data to suggest that nonsteroidal anti-inflammatory agents, particularly those that affect lipoxygenase products, may be useful in treating radiation pneumonitis; however, human data is lacking [173]. Also, the use of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers has been demonstrated to effectively protect lungs from radiation-induced pneumonitis and the development of lung fibrosis in rat models of radiation injury [174, 175]. However, in a human study, the concomitant use of angiotensin-converting enzyme inhibitors

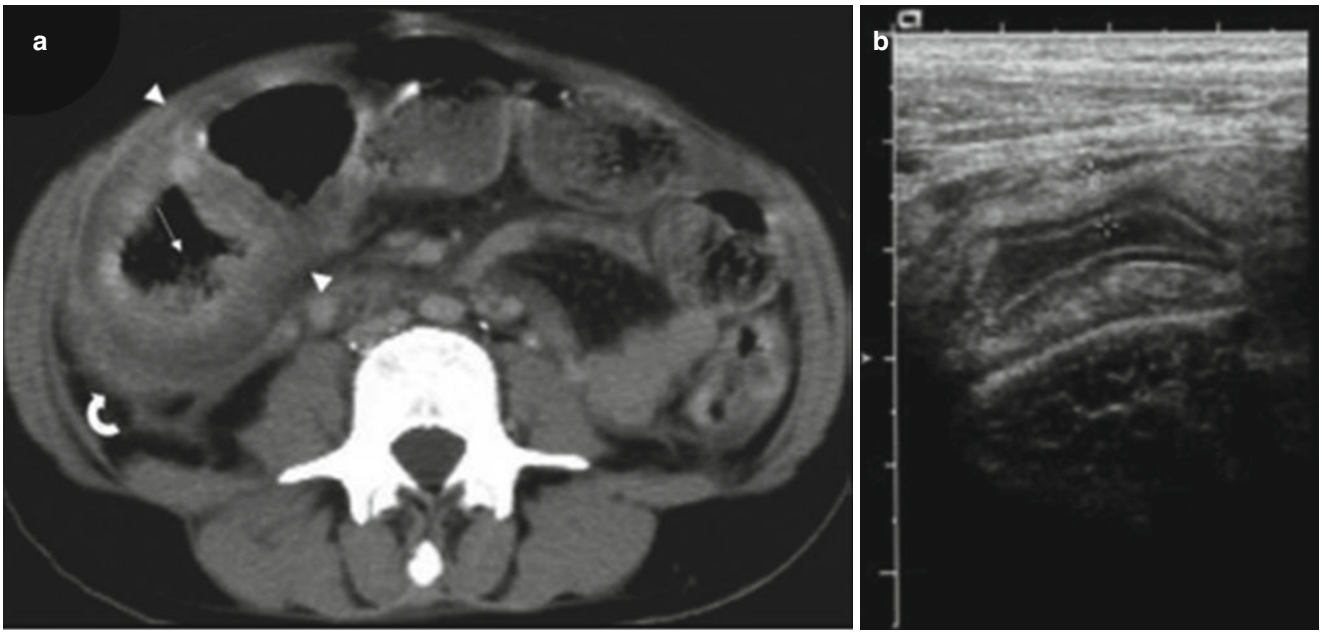

Fig. 25.4 Radiographic images of typhlitis. (**a**) is a computed tomogram of the abdomen demonstrating thickening of the hepatic flexure of the colon (*arrowheads*). Intraluminal contents (*straight arrow*) and surrounding inflammatory changes (*curved arrow*) make accurate measurement of the bowel wall thickness difficult. (**b**) is a transverse ultrasound image of the cecum demonstrating the gut signature as alternating hyperechoic and hypoechoic layers corresponding to the five layers of the bowel wall. Electronic calipers placed on the mucosal and serosal surfaces allow accurate measurement of bowel wall thickness (0.50 cm) (Reprinted from McCarville et al. [187]. With permission from John Wiley & Sons, Inc.)

with thoracic irradiation failed to decrease the incidence or to delay the onset of symptomatic radiation pneumonitis as compared to patients not receiving this medication [176]. Amifostine and pentoxyphylline, on the other hand, have been found to have a protective effect against radiation-induced pulmonary injury in randomized, double-blind human clinical trials [156, 177, 178]. However, recent data have not been able to confirm the protective effect of amifostine, and thus, current guidelines do not advocate its use to prevent radiation pneumonitis [179].

Sporadic Radiation Pneumonitis

The pathophysiology of classical radiation pneumonitis does not appear to explain all of the published reports of radiation pneumonitis and there is data to support a second form of radiation-induced pulmonary injury [148]. This form of radiation-induced lung injury, named sporadic radiation pneumonitis, is characterized by a bilateral lymphocytic alveolitis and appears similar to an immunologically mediated hypersensitivity pneumonitis [148]. Several published reports have demonstrated both an increase in BAL lymphocyte counts in patients with radiation pneumonitis as well as bilateral disease despite unilateral radiation supporting this concept [180–183]. In fact, in one report, BAL sampling from patients receiving unilateral radiation revealed significantly higher lymphocyte counts among patients with clinical radiation pneumonitis as compared to patients who did not develop pneumonitis [180]. These lymphocyte counts were also significantly higher than the pre-irradiation levels [180]. Moreover, the patients with clinical radiation pneumonitis also displayed an increase in the gallium lung scan index, a decrease in vital capacity, and a reduction in diffusion capacity as again compared to both patients without clinical pneumonitis and to pre-irradiation baselines [180]. Of note, there was **no** difference in any of the BAL findings or the gallium lung scan studies between the irradiated and non-irradiated sides of the lungs [180]. The pathophysiology of sporadic radiation pneumonitis may more plausibly explain radiation-induced dyspnea and hypoxemia that is out of proportion to the volume of irradiated lung, the reports of bilateral pneumonitis in the setting of unilateral therapy, and radiographic findings that occur outside the field of irradiation [148, 180–182, 184].

Typhlitis

Gastrointestinal complications resulting from the treatment of leukemia and lymphoma have long been established [185, 186]. Typhlitis, also known as neutropenic enterocolitis, is an acute, potentially life-threatening, necrotizing inflammation of the cecum and colon reported to occur in 3–9 % of children treated for leukemia [187, 188]. Although it is most commonly associated with the treatment of acute leukemia and lymphoma, it has also been reported to occur in children treated for solid tumors, in children with aplastic

Table 25.2 Common etiologies of shock in the child with cancer

Hypovolemic shock
Sepsis
Hemorrhage
Bladder (medications, viruses)
Intestine (typhlitis, *Clostridium dificile*)
Massive hemoptysis (*Aspergillus*, tumor invasion)
Intractable emesis
Pancreatitis
Asparaginase
Glucocorticoid
Central nervous system lesion
Addisonian crisis (after glucocorticoid therapy)
Diabetes mellitus
After glucocorticoid therapy
After pancreatitis
Malignant hypercalcemia
Distributive shock
Anaphylaxis (etoposide, teniposide, carboplatin, asparaginase, cytosine arabinoside, amphotericin-B, blood products, gamma globulin, vitamin K, interleukin-2, tumor necrosis factor)
Sepsis
Veno-occlusive disease
Syndrome of inappropriate secretion of antidiuretic hormone
Cardiogenic shock
Treatment-related
Anthracycline
Cyclophosphamide (HSCT)
Radiotherapy
Cardiac tamponade
Intracardiac tumor
Intracardiac thrombus
Pericardial effusion
Constrictive pericarditis
Fungus ball
Myocarditis
Viral
Fungal
Bacterial
Metabolic
Hyperkalemia
Hypokalemia
Hypocalcemia

Adapted from Rheingold [203]

anemia, in patients with the human immunodeficiency virus, and as a complication of stem cell transplantation [187, 189–192].

Clinically, the condition classically presents as a triad fever, abdominal pain, and severe neutropenia. However, a significant number of patients do not present this way, and thus, clinicians must maintain a very high index of suspicion for this entity in severely neutropenic patients who have recently received myelosuppressive chemotherapy [187, 189, 193–199]. Other gastrointestinal complications such as diarrhea and vomiting may also be observed [187, 193, 194]. Ultrasonography and computed tomography are used to detect the characteristic macroscopic finding of the condition, namely bowel wall thickening [187, 193, 195, 200, 201]. In children, a bowel thickness ≥0.3 cm on ultrasound exam is considered abnormal (See Fig. 25.4) [187, 188, 195, 200–202]. Although typhlitis may occur at any age, the median age at diagnosis has been reported to be 10 years with some data to suggest that children older than 16 years are at an increased risk for developing the condition [187, 195].

The mainstay of treatment for typhlitis is medical management with bowel rest, total parenteral nutrition, and broad spectrum anti-microbial coverage covering gram-negative enteric organisms and anaerobes [187, 193, 194]. Surgical intervention is utilized in only a fraction of the cases with rates varying from 1 to 20 % based on the date, size and patient population of the study [187, 188, 193, 194]. The most recent pediatric studies noted the use of surgery in relatively few cases, approximately 4 % [187, 196]. Surgery should be reserved for the treatment of worsening signs and symptoms of peritonitis associated with bowel ischemia or perforation and criteria have been proposed to guide the use of surgical intervention [194, 195]. Although initially believed to be a pre-terminal event, outcomes have improved over time with mortality rates of 2–8 % being reported in pediatric series [186, 187, 189, 194, 196].

Sepsis in OncologyPatient Population

Shock is a common concern for the pediatric oncology patient. The differential diagnosis of shock for these children is quite varied with several etiologies unique to this patient population (See Table 25.2). Of the many possibilities, sepsis appears to be the most common cause of shock, and thus, it is important for the pediatric critical care provider to have a sound understanding of this pathophysiologic process [203]. As this pathophysiology has been discussed in detail elsewhere, this section will focus on sepsis as it pertains to the oncology and HSCT patient, focusing on predispositions and outcomes.

In their landmark study, Watson et al. reported that children with neoplasia accounted for nearly 13 % of all cases of severe sepsis in children 1–9 years of age and approximately 17 % of cases in children 10–19 years of age [204]. However, oncology patients should not be considered a homogenous group as there are significant differences in their predisposition to sepsis. Leukemia/lymphoma patients have disease of their bone marrow, and therefore, tend to receive more intensive myeloablative therapy resulting in disruption of normal immune function [203]. Solid tumor patients may also receive myeloablative therapy, however, usually less so. Anatomic obstruction and functional impairment tend to predispose these children to sepsis [203]. As a result of these factors, neutropenic bacteremia appears to occur more

frequently among leukemia patients. Viscoli reported that 84 % of the bloodstream infections detected among leukemia patients were associated with neutropenia as compared to only 47 % of solid tumor patients and 55 % of the bone marrow transplant patients [205]. Others have made similar observations and data suggest that children with acute myelogenous leukemia may be at particular risk [206–208].

In addition to the type of cancer, the state of the disease and its treatment may also influence the predisposition to sepsis. Haupt has reported that infection rates are significantly higher in patients receiving intensive protocols [209]. Ammann found that children with bone marrow involvement of their malignancy more than doubled their risk of bacteremia [210]. In that report, children receiving more intensive chemotherapy than pre-B cell acute lymphoblastic leukemia maintenance therapy had an 11-fold increased risk of bacteremia. In addition, the length of time from the last chemotherapy treatment appears to be related to the likelihood of bacteremia [207]. Others have also demonstrated an association between disease status and outcome from sepsis [211]. In a prospective study of 438 adult neutropenic and bacteremic cancer patients, Gonzalez-Barca found uncontrolled neoplasia to be one of only four factors associated with an increased risk of mortality in multivariate analysis [211]. Further, the need for long term, indwelling central intravenous access also appears to increase the risk of sepsis in this patient population [212, 213]. The use of Hickman/Broviac type catheters appears to present a greater risk than Port-type catheters, but both types are less likely to be infected than non-tunneled temporary central venous catheters [212, 213]. In the majority of cases (54–87 %), the infection can be effectively treated without removal of the catheter [212–214]. However, persistent bacteremia, previous stem cell transplantation, hypotension, multiple catheter associated bloodstream infections in the same catheter, exit-site infections, inappropriate empiric antibiotic therapy, and Candida infection were all associated with an increased risk of catheter removal in one report [212].

Other clinical findings have also been used to predict both the presence of culture positive sepsis and the severity of illness among children with cancer. Hematologic parameters, particularly neutropenia, have long been used to identify oncology patients at risk for sepsis. Dating back to Bodey's landmark study, a relationship between decreased leukocytes and an increased risk of infection in cancer patients has been well established [215]. Moreover, it is well established that a temperature >39.0° C in neutropenic cancer patients increases the likelihood that the patient is bacteremic [206, 210, 216, 217]. In fact, one single center report suggests that the height of the temperature and a prolonged capillary refill time predict most strongly which children with fever and treatment-induced neutropenia will require critical care therapies [216]. Additionally, a single-center study suggested that by employing a combination of C-reactive protein, interleukin-8 (IL-8), and monocyte chemotactic protein-1-a (MCP-1-a) levels, febrile neutropenic pediatric patients with hematologic malignancy and documented infection could be distinguished from those without an infectious etiology [218]. In another report, IL-6 levels were found to be a useful predictor of bacteremia in the febrile neutropenic pediatric oncology patient [219].

Although neutropenia clearly predisposes patients to bacteremia and sepsis, its impact on outcome is less well established [205, 220, 221]. In addition to neutropenia, the absolute monocyte count appears to be useful in identifying patients at high risk for bacteremia [217, 222]. Furthermore, the presence of a co-morbidity has also been found to predispose children with cancer to sepsis and contribute to the severity of the illness [205, 210, 220, 223].

In addition to understanding the predisposition to sepsis, it is also important to consider the outcomes of sepsis in this patient population. Watson reported a case fatality rate of 16 % among the sub-group of children with neoplasia in his epidemiologic study while the case fatality rate for the entire study cohort of children 1–19 years of age approximated 10 % [204]. In that study, there was no attempt to distinguish between oncology patients who had received a HSCT and those who had not, although it would appear important to distinguish between these two groups. For example, Kutko performed a retrospective chart review of all children admitted to the PICU with a diagnosis of septic shock and reported an overall mortality rate of 13.5 % [221]. Among children with cancer, there was a significant difference in the mortality rate between HSCT patients and non-transplant oncology patients (38.5 % vs 5.5 % respectively, $p<0.05$) [221]. Additionally, Fiser has reported similar findings in a 13-year retrospective review of 446 admissions with severe sepsis admitted to the ICU of a pediatric oncology hospital [220]. He observed a 17 % overall mortality rate with a notable difference in outcomes between the patients who had undergone HSCT (30 %) and those who had not (12 %) ($p<0.0001$) [220]. In fact, the 12 % mortality rate among the non-transplant oncology patients is quite consistent with the mortality for sepsis in children overall [204, 220]. In a multicenter study, Viscoli et al. prospectively evaluated 191 consecutive admissions of children with cancer who experienced a bloodstream infection [205]. They also noted a difference in the overall 30-day mortality rate between bone marrow transplant patients and children with solid tumors and acute leukemia (21 % vs 6 % and 11 % respectively, $p<0.001$). Moreover, the combined mortality rate of 9 % among the non-transplant patients in their study again approximates that of the general pediatric population [204, 205]. In a case control study, Pound also demonstrated no difference in PICU mortality between pediatric oncology patients and non-oncology patients admitted with septic shock (15.9 % vs 11.6 %, respectively, $p=0.61$) [224].

In summary, oncology patients account for a relatively high proportion of severe sepsis in children with several reported factors identifying patients at increased risk. Children who have undergone HSCT are clearly at increased risk of dying as compared to the non-transplant oncology patient. However, and of note, the outcomes of sepsis in the non-HSCT oncology population are not substantially different from that of the general population.

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Hemophagocytic Lymphohistiocytosis Syndromes

26

Stephen W. Standage and Alexandra H. Filipovich

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a non-malignant, life-threatening hyperinflammatory condition resulting from dysregulation of normal innate and adaptive immune responses. Defects in immune effector cell cytotoxic mechanisms have been identified in many HLH syndromes. Infants and children most often present with this condition, but new onset disease may be observed in adults as well. Presenting signs and symptoms include the classic triad of fever, hepatosplenomegaly, and cytopenias, but neurologic impairment, respiratory and cardiovascular embarrassment, liver disease with coagulopathy, diarrhea, and rash may feature prominently. Diagnosis relies upon fulfilling clinical criteria and laboratory assessments including serum ferritin, soluble IL-2 receptor levels, and natural killer (NK) cell function studies. Treatment consists of excellent supportive care for the critically ill. Specific disease modifying therapy employs immunosuppressant medications and often hematopoietic stem cell transplant. HLH syndromes are frequently fatal if untreated. With current interventions survival ranges 60–70 %.

Keywords

Hemophagocytic lymphohistiocytosis • Familial hemophagocytic lymphohistiocytosis • Macrophage activation syndrome • Natural killer cell • Cytotoxic T cell

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a non-malignant, life-threatening hyperinflammatory condition resulting from dysregulation of normal innate and adaptive immune responses. In the years since its first description, HLH has been recognized as a clinical syndrome with an unusual constellation of presenting features. It is caused by many disparate, but related etiologies, rather than as a single, discrete, unified disease process. In this regard and others, HLH bears resemblance to sepsis, which also has a multitude of pathologic processes at its root. Indeed, HLH may often be mistaken for culture negative sepsis.

Based on current knowledge, HLH is separated into two general classes: primary and secondary. Primary HLH is caused by defined genetic mutations in genes whose protein products participate in immunologic regulatory pathways. These diseases often present with classic familial inheritance patterns. Secondary HLH is believed to occur sporadically, induced by specific infectious or inflammatory insults. However, as more is discovered about the immune mechanisms involved, the distinction between these subsets is blurring. It may be that many individuals with presumed secondary HLH have subtle defects of immune regulation that predispose to disease activation by specific immunologic challenges.

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Table 26.1 Diagnostic guidelines for Hemophagocytic Lymphohistiocytosis (HLH)

The diagnosis of HLH can be established by fulfilling either or both of the two criteria below

1. A molecular diagnosis consisted with HLH
2. Diagnostic criteria (five out of the eight criteria must be met)
   - (a) Fever
   - (b) Splenomegaly
   - (c) Cytopenias (affecting at least two of three lineages in the peripheral blood)
     - (i) Hemoglobin <90 g/L (in infants < 4 weeks: hemoglobin <100 g/L)
     - (ii) Platelets $<100 \times 10^9$/L
     - (iii) Neutrophils $<1.0 \times 10^9$/L
   - (d) Hypertriglyceridemia and/or hypofibrinogenemia
     - (i) Fasting triglycerides ≥3.0 mmol/L (i.e., ≥ 265 mg/dl)
     - (ii) Fibrinogen ≤1.5 g/L
   - (e) Hemophagocytosis in bone marrow, spleen, lymph nodes, or cerebrospinal fluid
   - (f) Low or absent NK-cell activity
   - (g) Ferritin ≥500 μg/L
   - (h) Soluble CD25 (soluble IL-2 receptor) above normal limits for age

HLH was first described by Farquhar and Claireux in 1952. They named the condition "familial haemophagocytic reticulosis," [1] but through the years it has also been called familial erythrophagocytic lymphohistiocytosis, [2] viral-associated hemophagocytic syndrome, [3] and malignancy associated hemophagocytic syndrome [4]. It is believed by many that the macrophage activation syndrome (MAS), observed in association with rheumatologic disorders, is likely a variant of HLH as both have similar clinical phenotypes and share some underlying mechanisms [5–11]. The International Histiocyte Society formally adopted the name of hemophagocytic lymphohistiocytosis in 1998 and defined criteria for its diagnosis which were updated in 2007 (Table 26.1) [4,12,13].

The true incidence and prevalence of HLH are unknown and would appear difficult to ascertain accurately; however, they do seem to vary by ethnicity. The diagnosis of HLH is problematic due to its variable presentation and the many nonspecific clinical features it shares with other disease processes. HLH is considered to be rare, but increasing awareness and recognition of the syndrome is leading to more frequent diagnoses. Currently, it is estimated that the autosomal recessive forms of familial HLH have a prevalence of 1/50,000 live births. A recent report estimated the incidence of HLH in tertiary care pediatric hospitals at one case of HLH per 3,000 inpatient admissions [14].

Pathogenesis

The principle characteristic of HLH is one of intense, prolonged, systemic inflammation. It is this underlying inflammation that drives the clinical features and contributes to the multisystem organ failure observed in this disorder. Histiocytes are phagocytic antigen presenting cells derived from the bone marrow mononuclear myeloid/granulocyte progenitor lineage. Monocytes, macrophages, and dendritic cells are considered histiocytes. In the normal immune response to infection or tissue injury, these cells function to activate and direct the innate and subsequent adaptive responses through cytokine/chemokine signaling and antigen presentation to their lymphoid counterparts. B cells, as well as helper and effector T cells, contribute to the inflammatory milieu through their own cytokine elaboration. They also assist with pathogen elimination via antibody production, activation of phagocytic killing, and by direct assassination of infected cells. Beyond coordinating the specific activities of various immune cells, cytokines exert systemic effects on various organs to initiate a stress response designed to protect tissue integrity and function, mobilize metabolic substrate necessary for the increased immunologic demand, and to establish an environment conducive to pathogen eradication. Natural killer (NK) cells are crucial to all aspects of this process. They help coordinate the initiation, effector, and resolution phases of the immune response by modulating initial histiocyte signaling, eradicating infected/damaged cells, and by ultimately culling the expanded effector lymphocyte and histiocyte population. They accomplish these effects through their own cytokine signaling and by utilizing granule-mediated activation-induced apoptosis.

NK cells share with cytotoxic T cells the ability to induce apoptosis in target cells by releasing granules whose constituents permeate the target cell plasma membrane and activate an intrinsic apoptotic cascade within that cell. This process begins as the effector T cell or the NK cell 'surveys' the target cells by sampling their surface proteins and receptor repertoire. Inappropriate epitopes displayed within major histocompatibility complex (MHC) molecules or abnormal surface protein patterns activate the effector cell and induce the formation of a circular immunologic synapse. This circular immunologic synapse is created with tight junctions fashioned at the periphery by interactions between effector cell lymphocyte function-associated antigen 1 (LFA1) and target cell intercellular adhesion molecule 1 (ICAM1) proteins. The effector intracellular cytoskeletal scaffold microtubule organizing center (MTOC) is oriented toward the synapse, reorganizing and directing the intracellular secretory apparatus, to direct specialized membrane bound vesicles at the target cell. These vesicles, which contain cytotoxic granules, are transported down the microtubule fibers, fuse with the plasma membrane, and exocytose their contents into the immunologic synapse. The granules contain several cytotoxic constituents most notably perforin and granzyme proteins. The tight junctions bounding the synapse prevent diffusion of these toxic substances away from the target cell. Perforin inserts itself into the target cell plasma membrane and facilitates the internalization of the various granzyme proteins. The granzyme proteins then trigger target cell

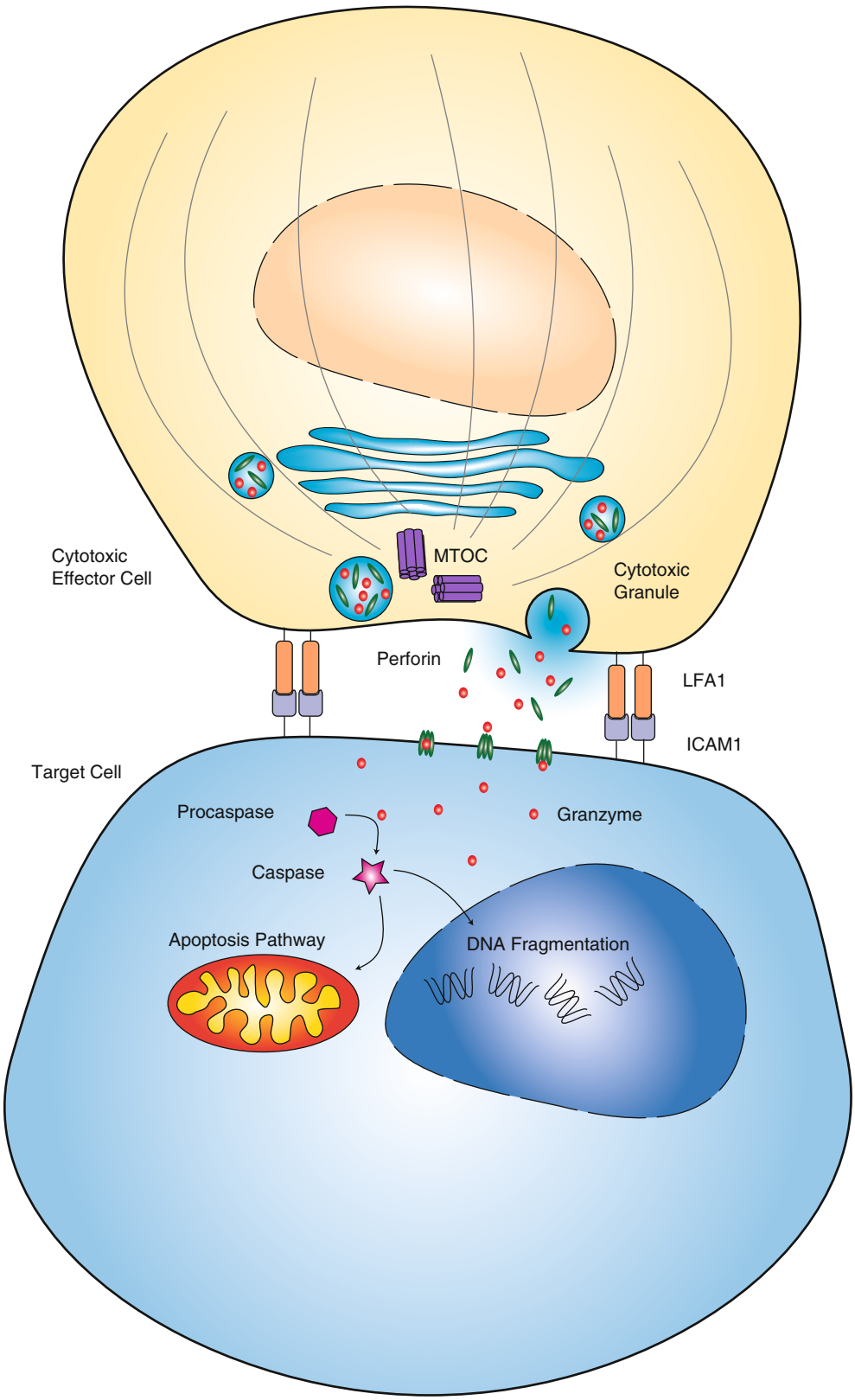

Fig. 26.1 Granule mediated activation-induced apoptosis. After binding to an abnormal target cell, immune effector cells release perforin and granzyme from their cytotoxic granules to trigger target cell apoptosis

apoptotic mechanisms, in part via activation of caspase enzymes, thereby killing the target cell (Fig. 26.1). The effector cell subsequently releases the synapse and moves on to survey other cells [15–17].

This process is essential to both the NK and T cell effector functions including the ability of NK cells to quell excessive or unnecessary immunologic activation. Defects in these mechanisms underlie the various forms of familial HLH and

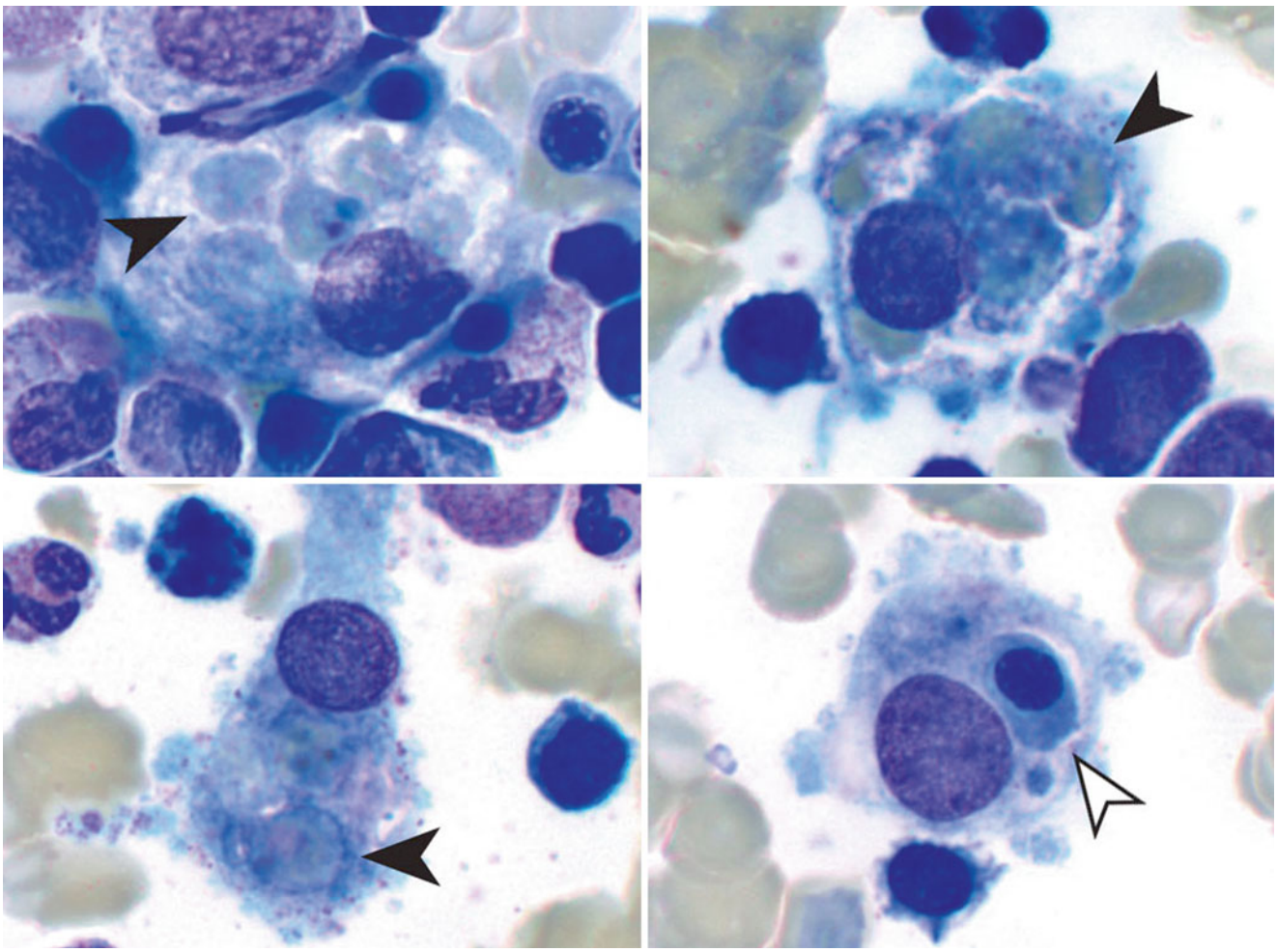

Fig. 26.2 Photomicrograph of hemophagocytic macrophages in bone marrow from a patient with HLH. *Solid arrowheads* indicate engulfed *red* blood cells. *Open arrowhead* indicates a nucleated erythroid progenitor that has been phagocytosed

relative dysfunction in these pathways may contribute to secondary forms of HLH. Indeed, some degree of abnormality of NK cell function (although rarely in NK cell number) has been observed in all forms of HLH [18].

In HLH, a fundamental deficit in the regulation of proinflammatory signaling, due in part to NK cell dysfunction, leads to intense activation and proliferation of histiocytes and CD8 cytotoxic T cells. It is possible that excessive signaling through macrophage toll like receptors (TLRs) may contribute to this pathogenesis. Recent research has demonstrated that repeated stimulation of TLR9 induces a cytokine storm and that disruption of MyD88, a protein involved in the intracellular propagation of TLR signaling, can suppress HLH in a mouse model [19,20]. The ensuing hypercytokinemia and tissue infiltration of activated cytotoxic T cells induces the clinical features observed in HLH and contributes to the severe multisystem organ failure through mechanisms yet to be elucidated. Hemophagocytosis, the ingestion of red blood cells, is a prominent feature of macrophages driven by excessively elevated cytokine levels (Fig. 26.2) [21].

There are many genetic causes of HLH; the majority of which are inherited in an autosomal recessive manner. Mutations in the perforin gene were the first to be directly associated with HLH [22]. Without perforin, the granzyme enzymes cannot enter target cells to initiate apoptotic cascades. Perforin mutations account for 15–20 % of HLH in certain geographic areas. HLH secondary to mutations in the perforin gene is known as familial hemophagocytic lymphohistiocytosis 2 (FHL2). FHL2 has both mild and severe phenotypes; the severity inversely correlating with the amount of mature perforin protein that is produced [23,24]. MUNC 13-4, a protein essential to the exocytotic process whereby cytotoxic granules are released by effector cells, is mutated in FHL3 [25]. FHL3 has a worldwide distribution and accounts for 15–20 % of all inherited forms of HLH. FHL4 is caused by mutations in the protein syntaxin 11, a member of the SNARE family of proteins, which is necessary for the fusion of cytotoxic vesicles with the plasma membrane and release of their granules [26–28]. A mutation in the syntaxin binding protein 2, also related to NK cell degranulation, has been initially

designated FHL5 [29]. The genetic defect responsible for FHL1 has not been identified and no mutations in granzyme proteins have been associated with HLH. An X-linked variant of familial HLH has recently been described that is associated with XIAP (X-linked inhibitor of apoptosis protein) deficiency [30]. The exact pathologic mechanism has not been elucidated, but it may be related to accentuated T cell receptor-mediated T cell survival during an immune response.

Immunodeficiencies caused by defects in lysosomal trafficking have also been linked to life-threatening episodes of HLH. These include Chediak Higashi syndrome, Griscelli syndrome, and Hermansky-Pudlak syndrome type II [17,31–33]. The HLH syndrome has occasionally been observed as well in DiGeorge syndrome, chronic granulomatous disease, X-linked agammaglobulinemia, and X-linked nuclear factor-κ(kappa)B essential modulator (NEMO) defects [34–36]. In the X-linked lymphoproliferative syndrome (XLP), an immunodeficiency characterized by malignant lymphomas, dysgammaglobulinemia, and Epstein-Barr virus- (EBV) triggered HLH, a deletion in the SH2D1A gene disrupts the signal transduction protein which is necessary for normal T and NK cell activation and proliferation [37]. Lymphocytes from individuals with XLP demonstrate decreased activation-induced apoptosis. This pathophysiology is similar to that of familial HLH which may, at least in part, explain the underlying predisposition of patients with XLP to develop HLH [38].

Secondary HLH has also been associated with a variety of microbial agents. As mentioned above, EBV triggers a secondary HLH syndrome in XLP, but EBV and many other viruses can also induce HLH in individuals without prior known familial mutations [39]. The incidence of EBV-associated HLH appears to be higher in Asia for unknown reasons [4,39]. Additional members of the herpes virus family have also been observed to trigger HLH including cytomegalovirus, varicella zoster virus, human herpes virus 6 (HHV6), and HHV8 [40–43]. Other viruses reported sporadically in the literature to be associated with HLH include human immunodeficiency virus (HIV), influenza, parvovirus, adenovirus, and hepatitis B [43–47]. Non-viral infectious agents have been described with HLH as well including mycobacteria, leshmania, malaria, candida and aspergillus [45]. It is important to note that in considering infection associated HLH, a recent study of Chinese children with EBV-associated HLH revealed seven novel mutations in the perforin, MUNC 13-4, and XIAP genes. These findings suggest that many forms of secondary HLH triggered by a specific infectious insult may be due to a genetic predisposition [48].

Malignancies associated with HLH are predominantly lymphoid in nature with a tendency toward T and NK cell lymphomas. These, however, are described primarily in adults rather than in children [49]. HLH type syndromes can also be observed in autoimmune conditions such as juvenile idiopathic arthritis, systemic lupus erythematosis, and Crohn's disease, but in the context of autoimmune disease, it is often referred to as the MAS [6,7,9,50].

Clinical Features

The classic presentation of HLH consists of prolonged, high fevers (usually present for 1–2 weeks prior to diagnosis), hepatosplenomegaly, and cytopenias [51,52]. Neurologic symptoms are often prominent features with symptoms of irritability, ataxia, hypo- or hypertonia, evidence of increased intracranial pressure, meningismus, depressed mental status, cranial nerve palsies, and seizures [53]. The most common neurologic features in one large pediatric study were irritability and seizures [54]. Other, less frequently observed symptoms include lymphadenopathy, rash, jaundice, diarrhea, and edema. The rashes are polymorphous and vary from diffuse erythematous maculopapular to scattered petechial rashes.

Biochemical and cellular abnormalities noted on clinical laboratory assessment include anemia, thrombocytopenia, neutropenia, elevated liver transaminases, hyperbilirubinemia, hypofibrinogenemia, coagulation abnormalities, hypoalbuminemia, hyponatremia, hypertriglyceridemia, and hyperferritinemia. Cerebrospinal fluid (CSF) pleocytosis is often seen on lumbar puncture in patients with significant neurologic involvement. Occasional inflammatory hemophagocytic cells may even be present in the CSF.

The onset of disease in the primary (familial) form is typically during infancy or early childhood, but can present at any age [55]. There are even reports of intrauterine cases of familial HLH manifesting as hydrops fetalis [56,57]. Infectious triggers can often be identified in primary HLH. Secondary HLH is clinically indistinguishable from primary disease and can occur at any age.

In the early days to months of illness, symptoms may exhibit a relapsing-remitting course with spontaneous improvement, but subsequent recrudescence [58]. In time, the clinical trajectory becomes more severe as significant tissue injury accumulates and organ failure sets in. Patients can also present acutely with an abrupt cardiopulmonary decompensation and a clinical picture that appears very similar to septic shock and ARDS [59,60]. In this scenario, respiratory distress is usually the first symptom noted by care providers with the rapid development of tachycardia and hypotension. Children often display agitation progressing to depressed mental status. Multiorgan system failure ensues with oliguria and liver failure characterized by jaundice and coagulopathy.

Radiologic abnormalities frequently observed in HLH are consistent with the involved organ systems. On chest x-ray, alveolar-interstitial opacities are often visualized in patients with respiratory distress, and are occasionally associated with pleural effusions. Abdominal imaging (ultrasound and computerized tomography) frequently reveals hepatosplenomegaly with gallbladder wall thickening and diffuse adenopathy. Cranial imaging often demonstrates periventricular white matter signal abnormalities with cerebral volume loss and enlargement of ventricles and extra-axial fluid spaces.

Subcortical, enhancing white matter lesions and cerebral edema may occasionally be observed [61].

Children with primary HLH who survive an episode invariably have repeat events until they succumb to the disease, if not treated. Those with secondary forms of HLH may expect disease free survival if the underlying trigger of their illness is completely eradicated.

Diagnosis

Because of the severe nature of this disorder and the existence of disease altering therapies, it is crucial to identify patients early in their course and provide them treatment in order to decrease morbidity and mortality. To facilitate the recognition of HLH and to assist with its timely diagnosis, the International Histiocyte Society has established diagnostic criteria employing both clinical features and laboratory findings (Table 26.1) [10,13]. Laboratory verification of a known genetic defect confirms the diagnosis independent of the presence or absence of any clinical signs or symptoms. Otherwise, five of the eight clinical criteria must be met. It is important to note that NK cell dysfunction is only identified in about 50 % of patients with HLH. Additionally, hemophagocytosis may not be detected early in the HLH disease process. Therefore, serial assessments may be required if that diagnostic criterion is to be met [62]. Finally, the interpretation of soluble IL-2 receptor levels must be undertaken with care as normal levels change with age and method of analysis.

Many of the criteria used for these diagnostic guidelines are found in other infectious or inflammatory disorders including hemophagocytosis. In the arena of pediatric critical care, there is a high degree of overlap between the more severe presentations of HLH and the characteristic features and biochemical abnormalities of sepsis and septic shock with multisystem organ failure [63]. The manner in which clinicians distinguish the two diagnostically is important. The clinical history and specific constellation of symptoms must be taken into account and, in and of themselves, can provide guidance. Although children with septic shock can manifest each one of the HLH criteria in isolation and occasionally in combination, the specific constellation seen with HLH is quite characteristic. Despite a few small reports of increased soluble IL-2 receptor levels in sepsis, [64–66] significant elevations of this marker are rarely observed outside the context of HLH. The rapid availability of such results, however, is often compromised by the fact that most institutions must send patient samples to referral laboratories.

In contrast, because of its ready availability in most hospitals, the serum ferritin level can serve as an important adjunct to the decision-making process. The HLH diagnostic guidelines define a cutoff at greater than 500 μg/L, which may be observed in sepsis or other hyperinflammatory conditions. Ferritin levels in HLH are usually dramatically higher with some series finding mean levels near 45,000 μg/L [67,68]. A recent review of elevated ferritin values at a large pediatric academic tertiary care hospital demonstrated that a ferritin level greater than 10,000 was 90 % sensitive and 96 % specific for HLH [69]. Due to the fact that studies of NK cell function and soluble IL-2 receptor levels may take some time to result, a diagnostic algorithm to facilitate the differentiation of HLH from sepsis has been proposed that is based on early evaluation of serum ferritin levels (Fig. 26.3) [70].

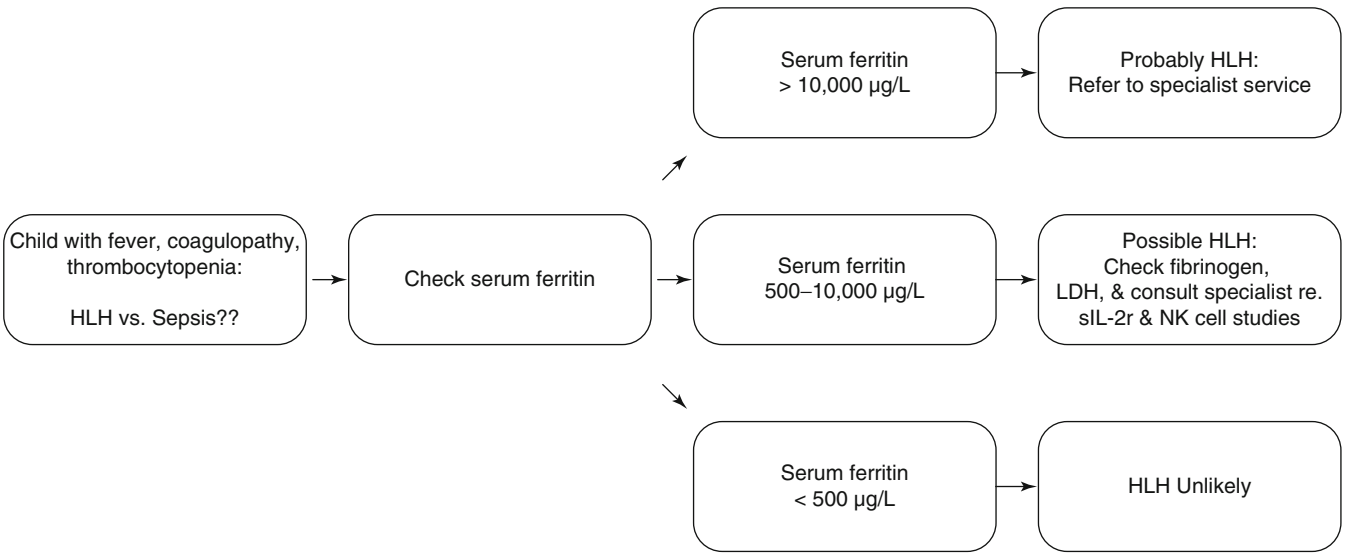

Fig. 26.3 Suggested algorithm for using serum ferritin in the evaluation of suspected HLH (Adapted from [70] With permission from BMJ Publishing Group LTD)

Treatment

Without treatment, HLH can be rapidly fatal. An early review of familial HLH described a mean survival from onset of symptoms of less than 1 month and an overall 1 year survival from diagnosis of 5 % [71]. Reported mortality for untreated secondary HLH is 50 % [4]. However, with current therapies, survival rates ranging from 50 to 70 % are now being reported [72]. Therefore, it is recommended that specific therapy be initiated as soon as there is a high clinical suspicion for HLH even if confirmatory diagnostic or genetic studies are still pending. Specific protocols to standardize the rational treatment of HLH were established first in 1994 and then revised in 2004 [13,73].

In the critically ill child, excellent provision of supportive care must undergird any HLH specific intervention. Children manifesting with ARDS or severe neurologic decompensation often require intubation and mechanical ventilation. Shock should be treated with appropriate fluid resuscitation and inotropic support. Individuals with significant kidney injury may need renal replacement therapy. Antimicrobial therapy must be provided to eradicate comorbid infections or infections that may have triggered a secondary form of HLH. In this regard, broad spectrum antibiotics are essential early in the course of disease that should be appropriately narrowed once an organism has been identified. Prophylactic trimethoprim-sulfamethoxazole and fluconazole are commonly given. Rituximab can be helpful in the setting of EBV driven HLH by depleting EBV-laden B cells.

The objectives of HLH specific therapy are to counteract the pathophysiologic processes driving the symptomatology and organ failure [10,14,70,74]. Corticosteroids are used for their nonspecific anti-inflammatory properties to suppress hypercytokinemia and promote lymphocyte apoptosis. Dexamethasone is the preferred agent because of its ability to cross the blood brain barrier and quench inflammation in the central nervous system. Etoposide induces cell cycle arrest, and therefore, interferes with lymphocyte proliferation. Cyclosporin disrupts intracellular signal transduction pathways preventing T cell activation and cytokine elaboration. Children with persistent or progressive central nervous system involvement are given intrathecal methotrexate which is toxic to the rapidly dividing immune cells. In addition, efficacy has been reported anecdotally with non-protocol therapies. For example, antithymocyte globulin (ATG) selectively depletes T cells, [75] while alemtuzumab (Campath®, humanized anti-CD52) targets both antigen presenting cells and T cells for elimination [76,77]. Abatacept (Orencia®), a fusion protein capable of blocking the B7 co-stimulatory signals necessary for T cell activation, has also been reported to improve symptoms [74]. Consultation with subspecialists experienced in the treatment of HLH is essential to appropriately navigate the application of these nuanced interventions.

Children who have no identified genetic defect and whose symptoms resolve may discontinue therapy after 8 weeks [13]. However, some require longer courses before remission is achieved. In all cases, ferritin and soluble IL-2 receptor levels are followed to monitor response to therapy. Indeed, the rate of decline in ferritin has recently been reported as an important prognostic indicator [78]. All patients with primary HLH require hematopoietic stem cell transplant (HSCT) and those with secondary forms who experience persistent disease or relapse should seriously be considered for HSCT as well [14,70,72,74,79]. Active disease at the time of HSCT is a poor prognostic indicator, and thus, considerable effort to induce remission should be undertaken [72,79].

Prognosis

As noted above, significant strides have been made in the treatment of HLH with survival now generally ranging from 50 to 70 % [72]. In children with non-familial HLH overall survival was 72 %, but only 20 % of them did not require HSCT [80]. Survival is increased in children, irrespective of genetic status, who receive HSCT from matched rather than unmatched donors [72]. Reduced-intensity pre-transplant conditioning regimens which are less inflammatory than myeloablative protocols appear to further decrease mortality [81]. The best outcomes in HSCT are seen in children who have a rapid and complete response to pre-transplant therapies and who do not exhibit significant neurologic involvement [54]. Patients with significant neurologic involvement can suffer severe and permanent sequelae even if they survive [53,82].

Conclusion

HLH is a severe, life-threatening, hyper-inflammatory disorder caused by dysregulation of the immune response that leads to critical multisystem organ dysfunction and death if untreated. Primary (familial) and secondary (acquired) forms exist, but all identified defects have in common the feature of immune effector cell cytotoxic impotence. Many isolated clinical characteristics are shared with other disease processes, including septic shock, but specific criteria have been established to facilitate the appropriate diagnosis. Disease specific treatment should be started as soon as possible to prevent progression of morbidity and mortality. HLH cannot be reversed by critical care interventions alone. Dexamethasone, etoposide, and cyclosporin form the mainstay of pre-transplant therapy. All children with primary HLH and many children with secondary HLH require HSCT to eradicate their disease. Current overall survival rates have improved to approximately 60–70 %. In the future, as the molecular mechanisms of HLH are more clearly elucidated, targeted interventions may provide even better outcomes for this life-threatening disease.

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Hematopoietic Stem Cell Transplantation in the PICU

27

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Abstract

Hematopoietic stem cell transplantation (SCT) is a therapeutic option for patients with bone marrow failure, certain malignancies and inborn errors of metabolism. Complications requiring intensive care are frequent, and intensivists need to be familiar with the transplantation process and the disorders that are unique to these patients. The transplant process involves the use of high dose chemotherapy or radiation, followed by intravenous infusion of stem cells matched with the recipient at the human leukocyte antigen (HLA) loci. Full recovery of a normal immune system can take a year or more, so following transplantation, patients are exquisitely susceptible to infections. Moreover, complications such as graft versus host disease, idiopathic pneumonia syndrome, sinusoidal obstruction syndrome and transplant associated thrombotic microangiopathy are common in the first hundred days after stem cell infusion. Respiratory failure is a common presentation necessitating intensive care admission and may be due to infectious or non-infectious causes. Mechanical ventilation may be needed along with broad spectrum anti-microbial coverage; corticosteroids are commonly used if graft versus host disease is present. Acute graft versus host disease is most frequent in children receiving grafts from unrelated donors and results in significant morbidity. Increased immunosuppression is the cornerstone of therapy for graft versus host disease, and protection of the children from infection is essential to survival. Sinusoidal obstruction syndrome and transplant associated thrombotic microangiopathy may lead to multiple organ failure with limited therapeutic options, but both disorders can resolve with good supportive care during the period of organ failure. Outcomes for patients who develop multiple organ failure following SCT remain poor despite aggressive supportive care, however, children with failure of a single organ can do well. Integrated multi-disciplinary care between intensivists and transplant physicians, and other specialists such as nephrologists and pulmonologists leads to improved outcomes.

Keywords

Stem cell transplantation • Idiopathic pneumonia syndrome • Respiratory failure • Graft versus host disease • Sinusoidal obstruction syndrome • Transplant associated thrombotic microangiopathy (TMA)

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Introduction

Hematopoietic stem cell transplantation (SCT) is becoming an increasingly common treatment for a variety of malignant and non-malignant disorders in children. Children undergoing SCT may require intensive care for multiple reasons. Life threatening infections, septic shock, respiratory failure, renal failure, seizures, hypertension, bleeding and multiple organ failure are common reasons for these patients to need intensive care services. The number of patients requiring admission to a pediatric intensive care unit (ICU) following SCT is variable, but recent analyses have suggested that up to 40 % of patients undergoing SCT may need ICU admission [1]. Many of the complications following SCT are unique to these patients, such as graft versus host disease (GVHD), sinusoidal obstruction syndrome (SOS), transplant associated thrombotic microangiopathy (TA-TMA), and the idiopathic pneumonia syndrome (IPS), while others such as septic shock and seizures are common to all patients. It is very important that intensivists caring for children following SCT are familiar with the transplantation process and collaborate closely with the transplant physicians. This chapter will focus on complications specific to the SCT population that may necessitate intensive care.

Indications

Indications for SCT have expanded since the first successful allogeneic stem cell transplants in 1968 (see Table 27.1) [2]. The intended therapeutic effect of SCT can be divided into three broad categories. The first category is most intuitive: to correct a defect in blood cell production or function, as used for hemoglobinopathies, bone marrow failure syndromes, immunodeficiencies and disorders of immune regulation. The second category is malignancy, wherein stem cells are used to replace cancerous bone marrow or to "rescue" the bone marrow after marrow ablative doses of chemotherapy and radiation aimed at a solid tumor outside of the bone marrow. Additional control of the malignancy can be obtained from a graft versus tumor effect in allogeneic transplantation. The third category is transplant as a method of gene therapy for the treatment of inborn errors of metabolism.

Hematopoietic Stem Cell Sources

Hematopoietic stem cell donors are most commonly allogeneic (a related or unrelated person) who is HLA-matched with the recipient. In other cases, the stem cell donor can be the recipient themselves (autologous), or rarely, a genetically identical twin (syngeneic donor). Hematopoietic stem cells can be collected from bone marrow, peripheral blood or cord blood (see Table 27.2) [3].

Table 27.1 Pediatric diseases treated with hematopoietic stem cell transplantation

Malignant diseases	Non malignant diseases
Leukemias/lymphomas	Severe aplastic anemia (acquired)
Solid tumors	Hemoglobinopathies
Neuroblastoma	Thalassemia major
Brain tumors	Sickle cell disease
Sarcomas	Congenital disorders of hematopoiesis
Wilms tumor	Fanconi anemia
Retinoblastoma	Diamond Blackfan syndrome
	Dyskeratosis congenita
	Schwachman diamond syndrome
	Immunodeficiency
	Severe combined immunodeficiency disease
	Chronic granulomatous disease
	Wiskott-Aldrich syndrome
	Hemophagocytic lymphohistiocytosis
	Common variable immune deficiency
	Inborn errors of metabolism
	Hurler syndrome
	Leukodystrophies (e.g., Krabbe disease)
	Osteopetrosis
	Acquired autoimmune disorders[a]

[a]Experimental therapy for disorders such as scleroderma

Table 27.2 Comparison of hematopoietic cell sources

Characteristic	Bone marrow	Peripheral blood stem cells (PBSC)	Cord blood
HLA matching	Close match required	Close match required	Less matching required for equivalent outcome
Neutrophil engraftment	Faster than cord blood	Fastest	Slowest
Stem cell dose	Usually adequate; can be challenging if donor is significantly smaller than recipient	High dose easily obtained; survival inferior in pediatrics due to increased chronic GVHD	May be inadequate; limited by unit size; immature cells proliferate very effectively
GVHD risk	Higher than cord blood	Highest[a]	Lowest
Second donation[b]	Possible	Possible	Not possible[c]

[a]PBSC not preferred in pediatrics given the GVHD risk
[b]If additional cells are needed from same donor
[c]May use second unit from another donor

Autologous cells and umbilical cord blood cells are collected prior to the transplant and frozen, using dimethyl sulfoxide (DMSO) as a preservative. The infusion of DMSO with the thawed product can cause hypertension and bradycardia, which are usually self-resolving. Late renal injury can also occur, so aggressive hydration is usually given with the infusion. Allogeneic cells are usually collected on the day of transplant and infused fresh, but may require processing, including red blood cell depletion if the donor is ABO incompatible with the recipient. In vivo (using antibodies given to the recipient) or ex vivo (performed using a selection column in the cell processing laboratory) T-cell depletion can also be performed to reduce the risk of GVHD [4, 5].

Donor Selection

Selection of an allogeneic donor is based on human leukocyte antigen (HLA) matching between the donor and the recipient. The HLA genes reside in the major histocompatibility complex, and are located in close proximity on chromosome 6. Therefore, they are generally transmitted as a single haplotype with Mendelian inheritance. The genes are co-dominant, such that proteins inherited from the mother and father are equally expressed. These highly polymorphic genes code for many immune related functions, most importantly, antigen processing and presentation. HLA class I (A, B, C) and II (DR, DQ, DP) molecules are important in T-cell recognition, and are considered major transplant antigens. Initially, loci A, B and DRB1 were recognized to be of key importance for matching, and in the earlier years of transplantation, donor and recipients were matched for six antigens. However, the locus HLA-C is now recognized as having equal importance and typically donor and recipient are matched at 8 loci (A,B,C and DRB1). Early data, not well supported in more recent studies, suggested that DQB1 was an important locus, and some literature refers to 10 of 10 allele matching by including DQB1 in the matching algorithm [6]. The use of molecular techniques for HLA-typing and the availability of larger registries of unrelated donors to select from have had significant impact on improving transplant outcomes [6, 7]. The ideal donor, a sibling with genetically identical alleles at all 4 loci (8/8 match) is available to only 15–30 % of recipients (as HLA is transmitted in a Mendelian fashion 25 % of siblings will be genotypically matched to each other). The majority of recipients need to find a match from an unrelated donor, and large registries of volunteer adult donors, and banks of frozen cord blood have been developed for this purpose. The largest registry is the Be The Match Registry® operated by the National Marrow Donor Program (NMDP) in the United States. Recipients who receive fully matched unrelated donor transplants have higher rates of graft failure and GVHD than with a matched related donor. However, outcomes of unrelated donor transplants have improved significantly in the last 10 years, particularly in children. Higher resolution DNA typing, larger donor pools and improved supportive care, including aggressive intensive care support during organ failure have resulted in outcomes of unrelated donor transplants that now approach those of matched related transplants [8–12].

Transplant Conditioning Regimens

Recipients generally require pre-transplant conditioning in the form of chemotherapy and/or radiation prior to SCT. Conditioning is used to "make space" in the marrow (myeloablation) and destroy cancerous marrow in malignancies. Additionally, it provides immunosuppression to prevent residual recipient lymphocytes from rejecting the donor stem cells. Myeloablative conditioning regimens are mainly utilized for malignancies where complete elimination of the native bone marrow is necessary. Myeloablative regimens use high dose chemotherapy and sometimes total body radiation, and may be associated with significant transplant-related morbidity and mortality related to tissue injury. Reduced intensity conditioning regimens (RIC) employ medications with significant immunosuppressive properties, but less myeloablative effects. Such regimens are becoming increasingly common in the treatment of immunologic and metabolic disorders where full donor chimerism may not be required to achieve desired effects in reconstituting missing bone marrow function [13]. RIC causes less immediate organ toxicity, but is associated with a higher incidence of mixed donor chimerism and early and late viral infections. Patient undergoing autologous stem cell transplantation for solid tumors such as neuroblastoma or high-risk brain tumors may receive single or multiple high dose myeloablative chemotherapy courses targeted at their primary tumor. Permanent, or at least very prolonged bone marrow ablation occurs as a side effect of this high dose chemotherapy, and therefore, autologous stem transplant (infusion of previously frozen stem cells) is necessary after each high dose chemotherapy cycle to reconstitute the blood-forming capacity of the bone marrow [14, 15].

Graft Versus Host Disease (GVHD) Prophylaxis

GVHD mainly occurs after allogeneic SCT, but it is occasionally reported in patients with autologous SCT. Multiple factors including stem cell source, degree of HLA match, conditioning regimen, donor and recipient age and associated co-morbidities influence the risk and severity of GVHD. The highest risk of GVHD occurs in mismatched unrelated donor transplants, and the least incidence of GVHD is

observed in fully matched, related transplants. Stem cells from cord blood are less likely to trigger GVHD than other stem cell sources, while transplants using peripheral blood stem cells (PBSC) are associated with higher risk of chronic GVHD [16, 17]. GVHD prophylaxis with immunosuppressive agents is standard practice for SCT recipients. The most common prophylactic regimens are calcineurin inhibitors (cyclosporine (CSA) or tacrolimus), commonly in combination with a second agent such as methotrexate, mycophenolate mofetil (MMF, Cellcept®) or corticosteroids. Calcineurin inhibitors are usually started several days prior to the stem cell infusion to achieve therapeutic levels by the time the new graft is infused. Medications such as antithymocyte globulin (ATG) or alemtuzumab (Campath-1H) that remove T-cells and antigen-presenting cells from the recipient are also used for GVHD prophylaxis in certain transplant regimens. These medications not only remove antigen presenting cells from the recipient, but may also remove some mature lymphocytes from the infused stem cell product. T-cell depletion of the donor graft is used for certain disorders (e.g., Fanconi anemia) that are at higher risk of severe GVHD-related complications, or as standard of care in some transplant centers [15]. The length of GVHD prophylaxis varies based on underlying condition and the risk for GVHD. This prophylaxis may last from 100 days to 6–9 months post transplantation. In contrast to solid organ transplants, where recipients take immunosuppressive medications to prevent graft rejection for their lifetime, recipients of hematopoietic stem cell transplants are expected to be free of immunosuppressive therapy at some point due to the ability of the new graft to adapt and learn to live in the recipient body (tolerize). It is important to note that any GVHD prophylaxis by immunomodulatory agents for T-cell depletion or immune suppression increases the risk of opportunistic infection [18]. It should be recognized that uncontrolled GVHD is profoundly immune suppressive and aggressive effective treatment of GVHD is essential for recovery from infections and recovery of immune competence.

Infection Prophylaxis

Routine infection prophylactic measures have been established that significantly reduce transplant-related mortality. Transplant patients are typically kept in HEPA (High-Efficiency Particulate Air)-filtered and positive pressure rooms, with appropriate isolation restrictions based on the degree of immunosuppression. Good hand hygiene plays a very important role in horizontal infection transmission, especially with enteric pathogens such as *Clostridium difficile* and norovirus (the official genus name for the group of viruses previously described as Norwalk-like viruses). Good skin, oral and dental hygiene is also very important. Mucosal integrity is disrupted by the conditioning regimen, with oral and gastrointestinal mucositis, and plays a significant role in post-transplant infectious complications. Patients with mucositis (mucosal integrity breakdown due to chemotherapy or radiation) are at a very high risk of seeding oral and enteric pathogens into the blood stream, and therefore, regular mouth care is needed. Mouth and gut prophylaxis varies based on institutional guidelines and transplant-associated risk factors [19]. Rectal instrumentation (e.g., thermometers, enemas, digital exams) is contraindicated in SCT patients [20, 21]. All SCT patients receive antiviral prophylaxis based on their prior viral exposure. Patients who are seropositive for herpes simplex virus (HSV) or cytomegalovirus (CMV), or who receive stem cells from HSV or CMV seropositive donors, are screened by blood polymerase chain reaction (PCR) once or twice weekly for viral reactivation, and treated pre-emptively with antiviral agents for any rise in PCR copies. Improved technology now allows screening for an increased number of viruses, and screening and pre-emptive treatment of adenovirus infection and Epstein Barr virus (EBV) reactivation is common. Intravenous immunoglobulin supplementation is often used to maintain immunoglobulin G levels within normal limits for age [21, 22]. All transplant patients should receive CMV-safe blood products, commonly depleted of leukocytes at the point of collection. *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) prophylaxis is provided for approximately 1 year post transplantation using pentamidine or trimethoprim/sulfamethoxazole. Trimethoprim/sulfamethoxazole is commonly started after stem cell engraftment due to its myelosuppressive properties [21]. Antifungal prophylaxis is vital after SCT and should be directed against yeast (e.g., *Candida* species) and molds (e.g., Aspergillus). The most common antifungal medications used are amphotericin B, voriconazole, caspofungin, or micafungin [23]. Environmental measures such as using face masks as well as avoiding gardening, construction and moldy areas after discharge from the hospital also helps avoid inhaling fungal spores.

Complications Following Hematopoietic Stem Cell Transplantation

Infections

SCT recipients are at increased risk for infections given their state of immune deficiency: the susceptibility to particular infections differs based on the phase of immune recovery after transplant [24]. Most of the infecting organisms arise from the patient's endogenous flora or reactivation of a latent infection. The first phase, the *pre-engraftment period* (day 0 to day approximately +30 following transplant) is remarkable for both neutropenia and breakdown of mucosal barriers

Table 27.3 Prominent infectious agents following HSCT

Pre-engraftment	Early engraftment	Late engraftment
Bacterial	**Viral**	**Bacterial**
Staphylococcus epidermis, *Staphylococcus aureus*, Viridians streptococci	Cytomegalovirus (CMV) Adenovirus	*Strepotoccus pneumoniae*
Escherichia coli, *Klebsiella spp*., *Pseudomonas*		*Haemophilus influenza*
Viral	Respiratory viruses– respiratory syncytial virus, parainfluenza, influenza, human metapneumovirus	**Viral**
Herpes simplex virus (HSV)	Adenovirus	Varicella-zoster virus
Respiratory viruses respiratory syncytial virus, parainfluenza, influenza, human metapneumovirus	Epstein-Barr virus (EBV) Human herpes virus 6 (HHV 6) Polyoma viruses (BK virus and JC virus)	Cytomegalovirus (CMV)
Adenovirus		
Enteric viruses – rotavirus, enterovirus		
Fungal	**Fungal**	
Candida spp.	*Pneumocystis jiroveci*	
Aspergillus spp.	**Parasitic**	
Mucor spp.	*Toxoplasma gondii*	

from conditioning regimens. In this phase, recipients are particularly susceptible to bacterial and fungal infections. Common bacterial infections include catheter associated bloodstream infections (CA-BSI) and bloodstream infections (BSI) secondary to bacterial translocation from damaged mucosal surfaces commonly in the gastrointestinal tract. Viral infections that affect mucosal surfaces are also prevalent in this phase [24–26]. The next phase, *early engraftment* (approximately day +30 to +100) is remarkable for granulocyte recovery, but significantly impaired cell mediated immunity [24, 25]. During *late engraftment* (after 100 days), there is continued immune reconstitution, but patients still have significant impairment in cell-mediated and humoral immunity, and may have defects in reticuloendothelial function especially in conjunction with GVHD. Hypogammaglobulinemia can be a finding during this period [24, 25]. Prominent infections following SCT are presented in Table 27.3.

Management of bacterial infections includes supportive care and broad spectrum, empiric antibiotic therapy that is tailored to culture results. Administration of broad spectrum antibiotics, selected by careful study of the flora prominent in each institution, at the onset of fever is essential. It is not acceptable to delay the use of antibiotics until a positive culture is obtained. In patients that are persistently febrile despite negative bacterial cultures, imaging such as CT scans looking for invasive fungal infections may be indicated. Additionally, broad spectrum fungal coverage (e.g., amphotericin B) should be added. Azoles and caspofungin are appropriate treatment for invasive aspergillosis infections and candidal infections [27]. Treatment for viruses, if available, is variably effective (see Table 27.4) [24, 28].

Table 27.4 Viral infections and therapy

Viral pathogen	Therapy
Cytomegalovirus (CMV)	Ganciclovir[a], foscarnet, cidofovir
	CMV immune globulin (CMVIg)[b]
Adenovirus	Cidofovir
Herpes simplex virus (HSV)	Acyclovir, valacyclovir, famciclovir
	Foscarnet (acyclovir resistant HSV)
	Cidofovir (acyclovir/foscarnet resistant HSV)
Polyoma virus (BK)	Cidofovir, leflunomide
Ebstein-Barr virus (EBV)	Rituximab
Human Herpes Virus Type 6 (HHV6)	Ganciclovir, foscarnet, cidofovir
Varicella-Zoster virus infection (VZV)	Acyclovir, valacyclovir (low risk patients)
	Famciclovir (low risk patients)
Respiratory Syncytial virus (RSV)	Ribavirin[c], RSV immunoglobulin
Parvovirus B19	Intravenous immunoglobulin

[a]Myelosuppressive, needs to be used with caution in the early phase post SCT, especially prior to engraftment
[b]Along with anti-viral medication
[c]Aerosolized, data mixed on efficacy

Respiratory Failure Following Hematopoietic Stem Cell Transplantation

Respiratory failure following SCT is among the most common reasons for these patients to require intensive care. The proportion of children undergoing SCT that require mechanical ventilation is variable with studies reporting up to 30 % needing mechanical ventilation [1]. It is important for clinicians to ascertain the presence of pre-transplant pulmonary

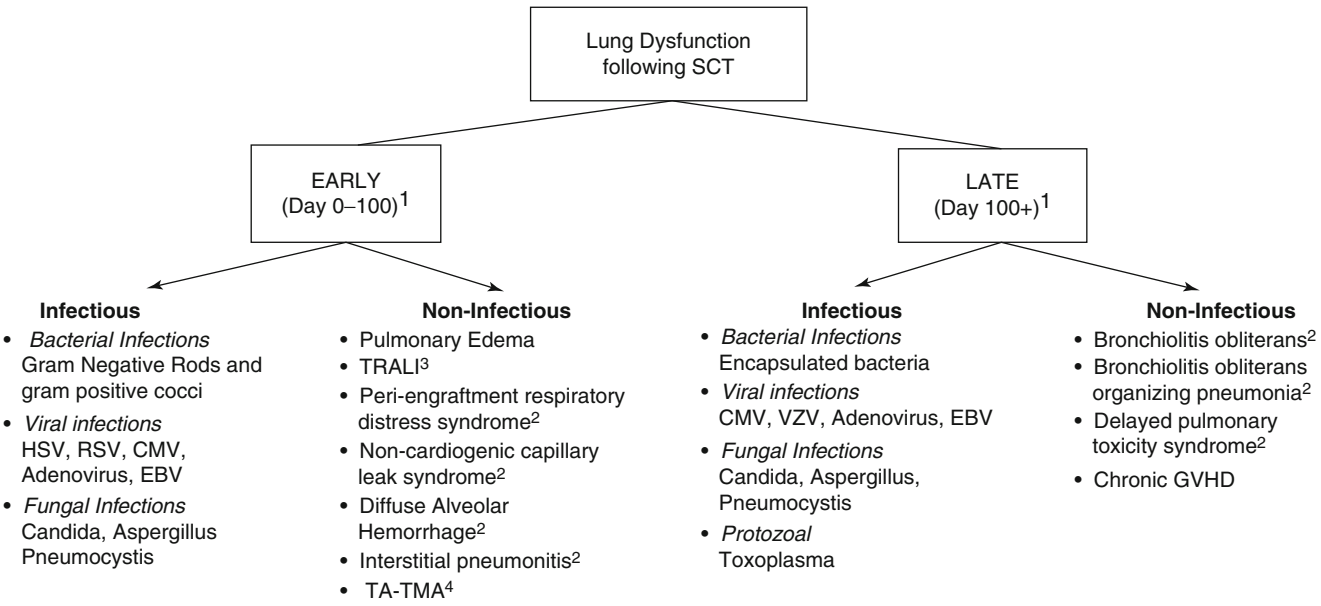

Fig. 27.1 Causes of lung dysfunction following hematopoietic stem cell transplant

morbidity such as lung damage from chemotherapy (bleomycin, busulfan and cyclophosphamide), a history of respiratory infections, any prior surgical procedures involving the lung and the use of radiotherapy. The presence of these conditions may impact the course of respiratory illness following transplant. A wide variety of processes may involve the lung following SCT leading to the development of respiratory failure. Some processes may be intrinsic to the lung such as pneumonitis or may be extrinsic such as fluid overload. Generally, respiratory failure in the post-transplant setting is divided into infectious and non-infectious categories, and like other processes following SCT, follows a temporal profile paralleling immune recovery (see Fig. 27.1). Clinically, it is important to note that this distinction may be difficult to discern as multiple processes may contribute to lung dysfunction resulting in respiratory failure.

Non-Infectious Causes of Lung Injury

This is becoming a proportionately larger contributor to post-transplant pulmonary-related morbidity and mortality, as prompt use of anti-microbials is now standard of care for febrile patients, and some potentially severe infections may be aborted. Non-infectious lung injury post-transplant can occur early (within 100 days of SCT) or late (after 100 days of SCT). A variety of non-infectious lung processes that occur following SCT constitute the idiopathic pneumonia syndrome (IPS). IPS is a distinct constellation of lung diseases characterized by non-infectious widespread lung injury after SCT that may affect the pulmonary parenchyma, the vascular endothelium or the airway epithelium. By definition, this injury cannot be attributable to active infection, cardiogenic causes, or renal failure/fluid overload [29]. The reported incidence of acute IPS ranges from 5 to 23 % after allogeneic stem cell transplantation with onset occurring within a 100 days of transplant [29–37]. Two separate pediatric studies reported the incidence to be 11 and 23 % respectively [33, 34]. The risk factors for the development of IPS underscore the potential mechanisms of injury: direct injury (myeloablative conditioning, including total body irradiation) and immune-mediated injury (allogeneic transplant, presence of GVHD, HLA disparity of donor and recipient). Although IPS can occur in autologous transplants, this is rare, and outcomes are better. Other risk factors for IPS include older recipient age and worse pre-transplant lung function [29–34, 36–38]. The mechanisms leading to the development of the disease processes that make up this syndrome remain unclear. However, the clinical spectrum of IPS has been replicated in animal models by varying combinations of antigen mismatching, high dose chemotherapy, and injection of lipopolysaccharide (LPS) in murine models of GVHD [39–46]. The triggers of the inflammatory cascade and lung injury are still unknown. Much recent attention has been focused on a proposed "gut-lung-liver" axis of inflammation. This model is supported by the association of GVHD and hepatic injury with IPS. The model proposes that LPS translocation across damaged mucosa in the gut plays an important role in triggering a systemic inflammatory cascade, inducing lung injury [46]. Tumor necrosis factor

(TNF)-α may have an important role in the pathogenesis of IPS, as blocking TNF-α decreases severity of IPS in animal models, and potentially in patients [36, 45, 47]. Although GVHD is not classically described in the lungs, the interactions between donor alloreactive T-cells, recipient antigen presenting cells, donor accessory cells and pulmonary parenchymal cells in the development of IPS is of great interest [48]. In experimental models, the importance of these interactions in development of lung injury following hematopoietic SCT has been demonstrated. In all likelihood the pathogenesis of IPS likely involves complex interactions of all of these factors [29].

Peri-engraftment respiratory distress syndrome (*PERDS*) occurs around the time of stem cell recovery, typically 2–3 weeks after the transplant infusion. As the name suggests, symptoms (fever, shortness of breath, hypoxemia, weight gain, pulmonary edema) begin within 5 days of neutrophil engraftment [29]. Although reported in recipients of both allogeneic and autologous transplants, response to steroids and survival is better in the autologous group [29, 49, 50]. Patients who undergo non-myeloablative conditioning regimens also have better outcomes [29, 51]. PERDS refers to the pulmonary manifestations of a broader engraftment syndrome, characterized by fever, rash, non-cardiogenic pulmonary edema, and weight gain. The symptoms of engraftment syndrome may also include hepatic dysfunction, renal insufficiency and encephalopathy. The engraftment syndrome itself may not portend a poor outcome: many patients with engraftment syndrome do not require pulmonary support [50, 52–54]. A similar entity, *noncardiogenic capillary leak syndrome* is also characterized by respiratory symptoms, weight gain, and edema, and typically occurs within the first 30 days post-transplant [55, 56]. The chest radiographs are remarkable for bilateral pulmonary infiltrates, pleural effusions and pulmonary edema in both categories, and it is unclear if these are distinct entities [29].

Diffuse alveolar hemorrhage (*DAH*) is another distinct entity that occurs soon after transplant. Allogeneic transplant is associated with a higher incidence, and unlike some forms of IPS, reduced intensity conditioning does not appear to be protective. The reported time to onset for early onset DAH is up to 50 days post-transplant, although there are reports of late alveolar hemorrhage. DAH is characterized by progressive shortness of breath, cough, and hypoxemia, and rarely, frank hemoptysis. Bronchoalveolar lavage reveals progressively bloodier returns of fluid with repeated lavages. Hemosiderin laden macrophages may be present, but this finding is non-specific. Chest radiographs are remarkable for bilateral, initially central infiltrates. Treatment is typically high dose steroids and supportive care in the form of mechanical ventilation with high mean airway pressures. One retrospective study did demonstrate a lower mortality in a cohort of their patients receiving aminocaproic acid, although this has not been demonstrated prospectively [57]. Despite therapy, the mortality for DAH is high and is reported to range between 48 and 100 % [29, 54, 57–65].

Thrombotic microangiopathy is another distinct pathology being increasingly noted to affect the pulmonary vasculature of a subset of SCT recipients. This disorder can present as hypoxemic respiratory failure with or without pulmonary hypertension. In a patient with unexplained hypoxemia, the presence of pulmonary hypertension is suggestive of the diagnosis; however, it is difficult to make the diagnosis in the absence of a lung biopsy, and it may only be apparent on autopsy [66].

IPS can also present as a non-infectious *acute interstitial pneumonitis*. This condition presents with fever, cough, dyspnea, and hypoxemia and usually occurs 2–6 months after transplant. As the name suggests, the chest radiograph is remarkable for bilateral interstitial infiltrates [29]. One form of IPS that appears to result as direct injury from radiation and chemotherapy is the *delayed pulmonary toxicity syndrome* (*DPTS*). DPTS, while traditionally grouped with IPS, is infrequent, and is characterized by lung dysfunction that is associated with chemotherapeutic agents, particularly 1,2-*bis*(2-choloroethyl)-1-nitrosurea (BCNU), cyclophosphamide and cisplatin. Unlike other forms of IPS, it is quite responsive to corticosteroid treatment [29]. DPTS was first described with autologous transplant recipients for the treatment of breast cancer, and is remarkable for its late onset (months to years after the transplant) [67].

Late onset non-infectious pulmonary complications have a reported incidence of 8–26 % among recipients who survive more than 3 months [35, 68–72]. Some degree of pulmonary dysfunction (especially impaired diffusion capacity and restrictive lung disease) has been reported in 25–85 % of children who survive hematopoietic stem cell transplantation, although not all are symptomatic and many experience improvement [73]. Chronic restrictive lung disease may result from radiation, chemotherapy, or infection; the etiology is not clearly understood, and may be multi-factorial.

Bronchiolitis obliterans organizing pneumonia (*BOOP*), is a distinct category of chronic restrictive lung disease, and is rare, perhaps because the diagnosis is difficult to secure, or one of exclusion, in the absence of a lung biopsy. Risk factors for BOOP include chronic and acute GVHD, and it occurs almost exclusively after allogeneic transplant suggesting that immune dysregulation is the mechanism of pulmonary injury [74, 75]. Clinical symptoms include dry cough, dyspnea, fever, and a restrictive pattern on spirometry. The onset has been reported to range from 1 month to 2 years after transplant. The chest radiograph demonstrates patchy airspace disease and nodular opacities, and may have a "ground glass" appearance. Response to increased immunosuppression, typically steroids, is good. Some reports have successfully used lower dose of steroids in conjunction with macrolides [29, 35, 69, 72, 76–80].

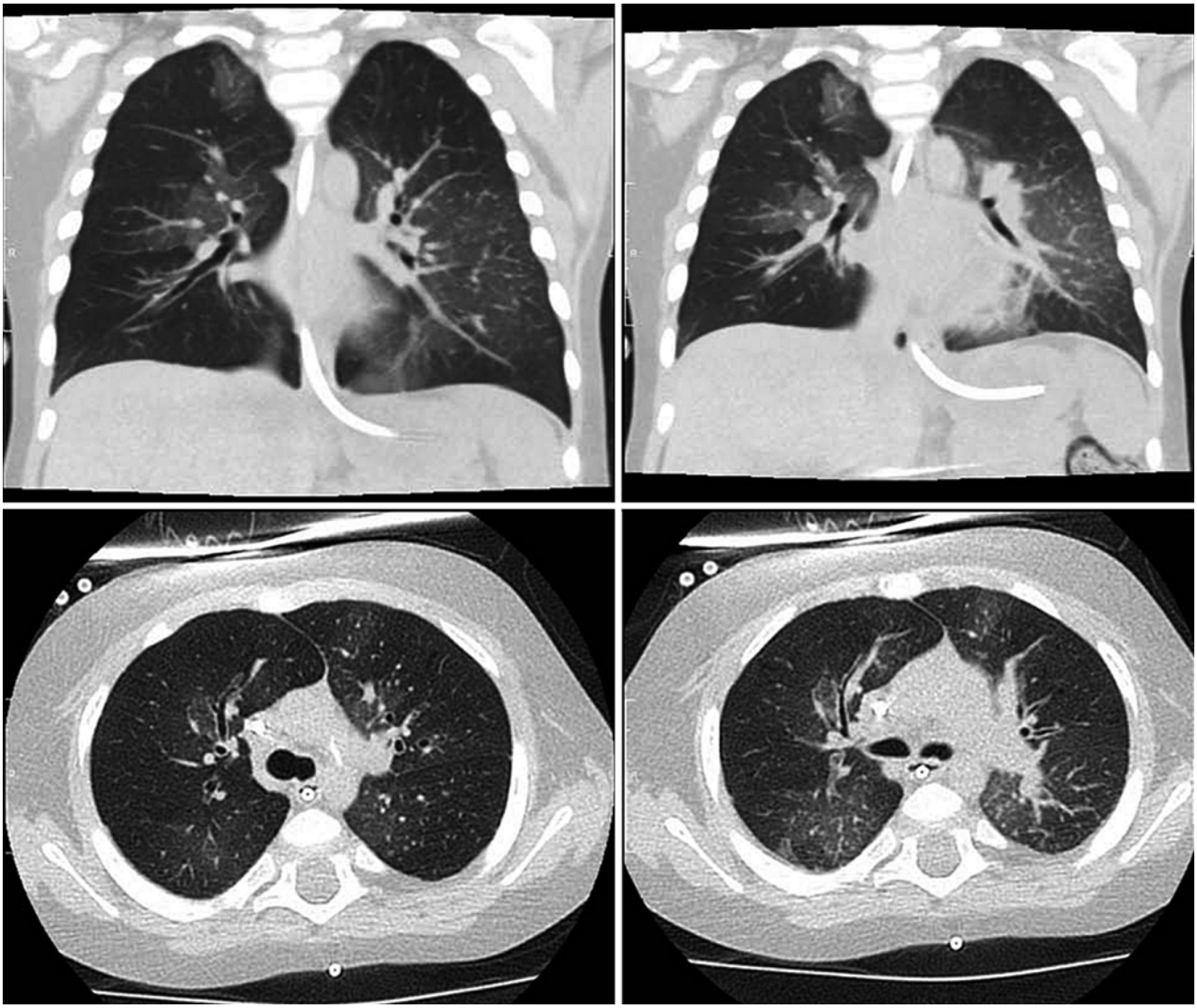

Fig. 27.2 Lung High Resolution Computed tomography (HRCT) in a stem cell transplant recipient demonstrating bronchiolitis obliterans. Inspiratory (*left*) and expiratory (*right*) images in coronal (*top*) and axial (*bottom*) planes demonstrating mosaic attenuation pattern with patchy ground glass appearance of lung, air trapping and bronchiectasis consistent with bronchiolitis obliterans (Courtesy of Dr. Daniel J Podberesky, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

Bronchiolitis obliterans (*BO*), which is distinct from BOOP, is a manifestation of chronic GVHD of the lung and is likely an immune-mediated process. Risk factors include the presence of GVHD in another organ, previous viral respiratory infections and poor pre-transplant lung function [81–88]. The incidence is lower with T-cell depletion of donor cells, and with reduced intensity conditioning [75, 89]. BO has a more severe clinical course than restrictive lung disease, and is associated with 60 % mortality. BO can occur years after SCT, but the typical onset is 7–15 months post-transplant. BO is characterized by respiratory symptoms, including wheezing, in the absence of fever [29, 90]. Radiographs demonstrate hyperinflation of the lungs, as this is an obstructive process, with CT scans demonstrating bronchiectasis, septal lines and a ground glass appearance (see Fig. 27.2) [91]. The treatment is immunosuppression with systemic and inhaled steroids, calcineurin inhibitors, and antithymocyte globulin (ATG) [88, 92, 93]. Newer therapies, including azithromycin, infliximab, etanercept, statins, and extracorporeal photopheresis have all shown some efficacy in small trials and case reports [28, 29, 87, 94–99]. Although very rare, successful lung transplantation has been reported [100, 101].

Infectious Causes of Lung Injury

Lung injury and respiratory failure from infectious agents is a significant cause of post-transplant related morbidity and mortality. As described above, the pattern of susceptibility to particular infectious agents/organisms changes with immune

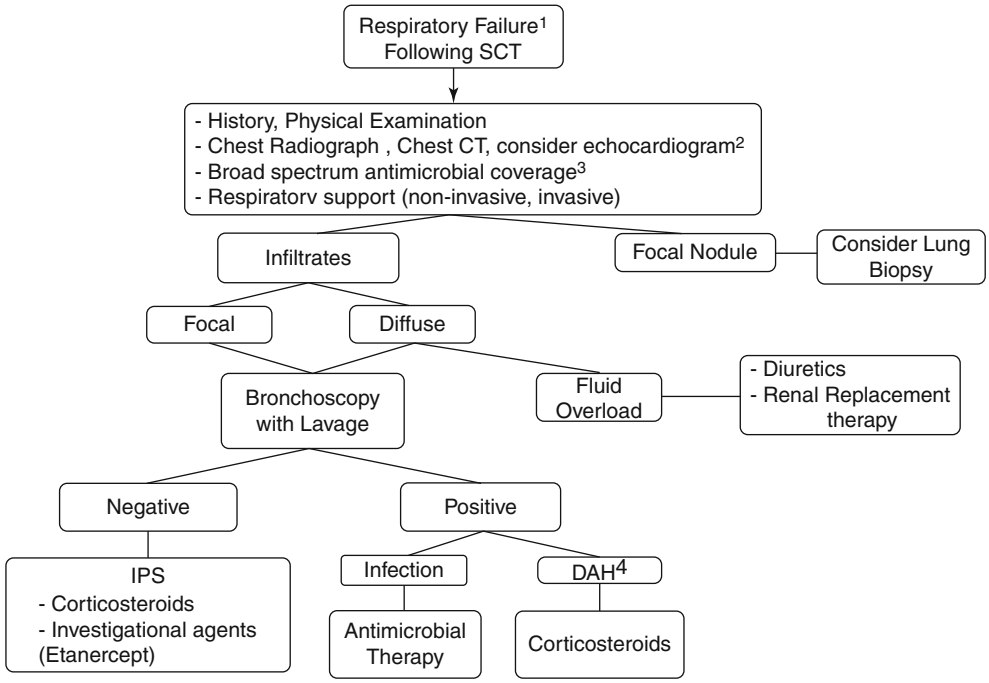

Fig. 27.3 Clinical approach to respiratory failure following hematopoietic stem cell transplant

[1]Include patients with respiratory distress and/or hypoxemia; [2]Echocardiogram to assess ventricular function and presence of pulmonary hypertension; [3]Includes appropriate antiviral and antifungal coverage; [4]diffuse alveolar hemorrhage

recovery and the common causes of infectious pneumonitis are listed (see Fig. 27.1).

Management

SCT patients requiring intensive care for respiratory failure need a thoughtful and detailed workup to delineate the proximate cause of their lung dysfunction. Our suggested approach to a patient with respiratory failure requiring intensive care is presented in Fig. 27.3. All SCT patients admitted to the ICU for respiratory distress should be assessed clinically for signs and symptoms of infection and fluid overload. The latter may occur in the setting of renal dysfunction and/or heart failure. Bacterial and fungal cultures as well as viral PCR testing should be performed to identify infectious agents. Importantly, a bronchoscopy with a lavage should be considered early. In addition to a routine chest radiograph, further imaging in the form of a CT scan and echocardiography should be performed. A lung biopsy may be considered especially in patients who have focal processes. In the absence of positive microbiologic studies, a diagnosis of IPS may be considered.

The treatment of respiratory failure from the ICU standpoint is supportive, until the underlying disease process can be addressed. Fluid overload may play a significant role in lung dysfunction, and aggressive fluid management is often helpful in these patients. Ventilatory support in the form noninvasive ventilation (CPAP, BiPAP and high flow nasal cannula) may be helpful in the early stages; however, body habitus, skin breakdown and the presence of mucositis may make the interface for non-invasive support tenuous. Invasive mechanical ventilation should be initiated as needed using a lung protective strategy with the utilization of a low tidal volume and an open lung strategy. Being cognizant of ventilator-induced lung injury is extremely important and it is not uncommon in the sickest patients to tolerate oxygen saturations of >80–85 % and allow for moderate respiratory acidosis (pH >7.2–7.25), irrespective of PCO_2. Sometimes, it is preferable to switch early to high frequency oscillatory ventilation, especially in patients needing high mean airway pressures to attain oxygenation and ventilation goals. Other supportive strategies that may be beneficial in individual patients include prone positioning, inhaled nitric oxide and surfactant. The value of these therapies in this patient population remains largely unproven. For example, the largest prone positioning trial in children with acute lung injury excluded SCT patients [102]. However, in certain patients, the selective use of these therapies may be helpful. For instance, patients transplanted for malignant infantile osteopetrosis appear to have a particular predilection for pulmonary hypertension that may be responsive to inhaled nitric oxide [102, 103]. Moreover, the largest pediatric trial of calfactant did include SCT patients, and although those children accounted for the less 20 % of the total study population, SCT patients treated with calfactant (n = 10) experienced an 11 % absolute reduction in mortality when compared to SCT patients who received air control (n = 17) [104, 105]. Moreover, 60 % of the

SCT patients who received calfactant experienced a 25 % or greater decrease in their oxygenation index [105]. The ultimate supportive therapy for respiratory failure, extracorporeal support, may be considered for this patient population. Extracorporeal membrane oxygenation (ECMO) may be considered for specific patients including those who have engrafted and have normal platelet counts. Isolated reports of the use of ECMO in this patient population have been published [106, 107]. However, most centers exclude SCT patients on the basis of several factors including the reversibility of the lung disease. Early renal replacement therapy, especially in individuals with kidney injury, may be helpful, particularly in children with fluid overload. Small studies in children have suggested both short term oxygenation and survival benefits, however, the mechanisms by which renal replacement therapy may alter the course of respiratory failure in following SCT remain unclear [108, 109].

The mainstay of therapy to address the lung disease in these patients focuses on the etiology. Aggressive and immediate broad spectrum antimicrobial coverage, including antiviral coverage is important. Therapy can be later tailored on the basis of microbiologic testing. In the absence of an infective etiology, corticosteroids are the drugs most commonly utilized to blunt the inflammatory response. The dose is variable (often 2–5 mg/kg/day), and in certain conditions such as DAH patients may require higher pulse doses (e.g., 10 mg/kg) [29, 31, 59, 60]. The risks and benefits for starting corticosteroids must be weighed on a case to case basis, especially in the presence of active infections. Once initiated, corticosteroids are tapered slowly. Another potential therapy for IPS is etanercept, a dimeric fusion protein consisting of two soluble TNF receptors that binds TNF-α(alpha) thereby serving as a TNF-α(alpha) inhibitor. In a small study involving 15 patients with IPS, the addition of etanercept to corticosteroids resulted in improved response rates as defined by the ability to discontinue supplemental oxygen within 28 days of the initiation of therapy [47]. Further trials of etanercept in the treatment of IPS are currently ongoing [110]. Early renal replacement therapy may be helpful, however the mechanisms and the ideal timing of initiation remain unclear [108, 109]. In summary, the management of respiratory failure following SCT is supportive with diligent fluid management and respiratory support, while broad spectrum antimicrobials and corticosteroids can be used to address the underlying cause of disease.

Outcomes

Outcomes following respiratory failure in SCT patients who require mechanical ventilation appear to have improved over time; however, they remain very poor when compared to other populations. In a recent meta-regression analysis, ICU mortality for mechanically ventilated children following SCT was highly variable ranging between 25 and 91 %. More recent studies appear to show a more promising trend [1, 111–113]. In patients with IPS, mortality is reported between 56 and 94 %.

Graft Versus Host Disease

Graft versus host disease (GVHD) is a significant cause of transplant-related morbidity and mortality. The incidence of acute GVHD in children has been reported to be between 19 and 85 % and varies according to degree of HLA matching and type of donor [114]. GVHD can present as acute or chronic. Chronic GVHD is a distinct entity from acute GVHD. Historically, acute and chronic GVHD have been differentiated by the time of onset (chronic >100 days), but it is now recognized that there may be overlap in the time of onset of the disease. Clinical features, pathophysiology and histology of acute and chronic GVHD are distinctly different [115]. The median time of onset for acute GVHD in one large multicenter study was reported to be 3 weeks after the stem cell infusion [116]. The risk of acute GVHD is increased in unrelated transplants (although as matching improves, risk is reducing) and transplants with more HLA disparity [117]. Other risk factors reported in some, but not all studies, include older donor and recipient age, female (especially multiparous) donors for male recipients, a history of infections (including CMV), the intensity of the conditioning regimen (especially radiation, which increases risk), and the type of GVHD prophylaxis received [114].

Mechanism of Disease

Acute GVHD can develop when an allogeneic graft contains immunologically competent cells with differing antigens between the graft and host and the immune system of the host is unable to reject the graft [118]. Mechanistically, acute GVHD is thought to develop as a consequence of 3 interrelated phases. In phase 1, there is damage to the mucosal surfaces of the host from the chemotherapy and radiation preparative regimen, especially the gastrointestinal tract. The disruption of the mucosal barrier allows translocation of LPS produced by endogenous bacteria, leading to stimulation of inflammatory cytokines in the host, characterized by activation of the host antigen presenting cells [119, 120]. Phase 2 involves the presentation of these alloantigens to donor T-cells. Subsequently, activation of the donor T-cells leads to further proliferation, and a resulting inflammatory cascade and recruitment of further immune response by donor effector cells. Phase 3 is characterized by damage to host tissues caused by effector cells (including donor mononuclear cells, including cytotoxic T cells, phagocytes, and neutrophils among others). Soluble mediators believed to be particular important include IL-2, LPS, IL-12, interferon-γ, and TNF [119]. The pathophysiology of chronic GVHD is less well understood, and is thought to involve dysregulation of both the T and B cell systems as well as an autoimmune component

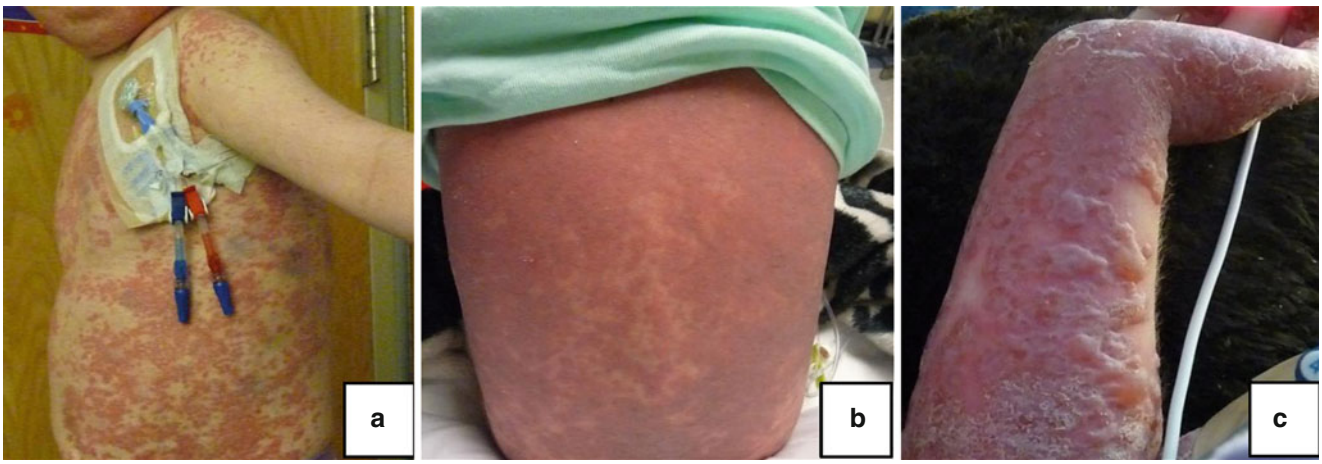

Fig. 27.4 Skin manifestations of acute graft versus host disease. (**a**) Erythematous morbilliform maculopapular rash involving the trunk suggestive of Stage 1 and 2 skin involvement. (**b**) Generalized erythroderma suggestive of Stage 3 skin involvement. (**c**) Bullae involving the extremities suggestive of Stage 4 skin involvement

Table 27.5 Consensus grading of acute graft versus host disease

Organ/extent of involvement			
	Skin	Liver	Intestinal tract
Stage			
1	Rash <25 % of skin[a]	Bilirubin 2–3 mg/dL[b]	Diarrhea >500 mL/day[c] or persistent nausea[d]
2	Rash 25–50 % of skin	Bilirubin 3–6 mg/dL	Diarrhea >1,000 mL/day
3	Rash >50 % of skin	Bilirubin 6–15 mg/dL	Diarrhea >1,500 mL/day
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade			
0	None	None	None
I	Stage 1–2	None	None
II	Stage 3	or Stage 1	or Stage 1
III	–	Stage 2–3	or Stage 2–4
IV[e]	Stage 4	or Stage 4	–

Adapted from Przepiorka et al. [124]. With permission from Nature Publishing Group
[a]Use of rule of nines to determine body surface area involvement
[b]Total bilirubin, downgrade one stage if an additional cause of elevated bilirubin is documented
[c]The volume of diarrhea applies to adults. For pediatric patients, volume of diarrhea should be based on body surface area
[d]Persistent nausea with histologic evidence of GVHD in the stomach or duodenum
[e]Grade IV may also include lesser organ involvement, but with extreme decrease in performance status

[121]. Hereafter, we will focus on acute GVHD as it is responsible for the majority of ICU admissions from GVHD.

Clinical Features

Acute GVHD primarily involves three organ systems: the skin, the liver and the gastrointestinal tract. The skin is the most common site of disease. Typically, skin involvement starts as a morbilliform, maculopapular eruption, usually involving the sun-exposed areas (face, arms, behind the ears, shoulders) and the palms and soles (see Fig. 27.4a). Depending on the severity, it may progress to generalized erythroderma with bullae formation (see Fig. 27.4b, c). In addition to problems secondary to loss of mucosal integrity (electrolyte abnormalities, fluid loss, and risk of infection), these patients can experience severe pain [18]. Hepatic GVHD is marked by cholestasis, hepatitis, and, depending on the severity, progressive hepatic insufficiency and failure [122]. Gastrointestinal GVHD is remarkable for secretory, sometimes bloody diarrhea, abdominal pain, nausea, vomiting and anorexia. Patients may have severe fluid losses, electrolyte abnormalities, anemia and protein losing enteropathy. Other organ systems may also be involved including the eyes [18, 114, 123].

Diagnosis

The diagnosis of acute GVHD is a clinical one and the severity is graded according to the degree of involvement of the skin, liver and gastrointestinal tract (see Table 27.5) [124]. The skin is staged by character and percent body

surface area involved. The liver involvement is staged by the total bilirubin level, and the gastrointestinal tract is staged by the volume of diarrhea. The grading depends on the combined severity of involvement of the skin, liver and gastrointestinal tract (see Table 27.5). A biopsy of the skin and gastrointestinal tract may be performed to establish a pathological diagnosis of GVHD [114]. The differential diagnosis for acute GVHD is broad, and includes skin reactions, conditioning toxicity to the skin, liver or gut, sinusoidal obstruction syndrome and infection. It is important to appreciate that most of the mortality associated with acute GVHD is due to infection as a consequence of the profound immune incompetence associated with active GVHD including its treatment, and not to the clinical features described above.

Treatment

Therapy for acute GVHD is immune suppression to interrupt the cycle of cell proliferation, the generation of pro-inflammatory proteins and tissue injury. Therefore, first line therapy is the initiation of steroids. The reported response rates to steroids vary from 35 to 80 %, depending on the grade and degree of response assessed [125–128]. Once a response is achieved, steroids are slowly weaned. Some patients will have steroid resistant GVHD, typically defined as any worsening after 3 days of therapy, or the lack of improvement in 5 days of therapy. Steroid refractory GVHD is difficult to treat, and morbidity and mortality are high. Additional immune suppressive agents are used, and while response can be seen to any of these, all are generally unsatisfactory [129]. The most common agents used are monoclonal and polyclonal antibodies such as alemtuzumab (Campath-1H) and ATG, IL-2 receptor antagonists (e.g., basiliximab), and anti-TNF-α agents (e.g. infliximab, etanercept). Immunosuppressants including MMF, calcineurin inhibitors, and sirolimus may also be used [114, 129]. Other strategies attempted include pentostatin, infusion of mesenchymal stem cells and extracorporeal photopheresis [130–132]. Of note, all of these strategies are immune suppressive, and increase the risk of infection, but are necessary for control of disease and ultimate return to immune competence. Aggressive supportive care is also necessary for successful treatment and may require an intensive effort. Antibacterial, antiviral and antifungal surveillance and prophylaxis are required, and essential for success, with appropriate escalation of agents with documented or suspected infection [114, 129, 133]. Meticulous skin care with topical emollient therapy and wound care is required to prevent against infection. Ophthalmological examination for evaluation, and subsequent lubrication, is indicated as well as antimicrobial protection of the eyes. Gut rest and hyperalimentation are needed for gastrointestinal GVHD. Gastrointestinal bleeding may require transfusion support, and octreotide may be effective in controlling secretory diarrhea and gastrointestinal bleeding. Pain control is important and can be challenging; rarely, patients may require mechanical ventilation for adequate doses of pain medication.

Outcome

Long term survival rates correlate with the grade of severity of the GVHD. In a recent, large, multicenter study of adults and children, 5 year survival for those with Grade I-II GVHD was between 80 and 85 %, while those with Grade III GVHD had a 5 year survival of 25 %, and those with Grade IV GVHD had a survival of only 5 % [116].

Sinusoidal Obstruction Syndrome (Veno-Occlusive Disease of the Liver)

Previously termed veno-occlusive disease of the liver, sinusoidal obstruction syndrome (SOS) is a complication of SCT secondary to chemotherapy and radiation toxicity. The term veno-occlusive disease is a misnomer, as the site of initial injury is the sinusoids of the liver. SOS is characterized by liver injury and manifests as a triad of tender hepatomegaly, elevated serum bilirubin with fluid retention and weight gain (see Table 27.5) [134]. The incidence of SOS in children has been reported to be between 11 and 31 % [135–141]. Typically, SOS occurs within 20 days after transplant and generally does not occur beyond 30 days post stem cell infusion although cases have been reported later. Risk factors for the development of SOS include conditioning with certain chemotherapeutic drugs, including busulfan, cyclophosphamide, and melphalan, among others. The availability of an intravenous formulation of busulfan, and reliable, individualized, dosing guided by pharmacokinetics has been helpful in reducing the incidence of SOS secondary to busulfan exposure [142]. Additional risk factors for SOS include high doses of radiation, pre-existing liver disease, younger age, unrelated donor, positive CMV serology in the recipient, and receipt of total parenteral nutrition (TPN) within the 30 days before transplant [135, 137, 138].

Mechanism of Disease

SOS is characterized by injury to the sinusoidal endothelium in the liver followed by subendothelial edema with extravasation of red blood cells and fibrin deposition, with ensuing hepatocyte damage and deposition of collagen. This sequence of events leads to sinusoidal obstruction, the development of portal hypertension, and in advanced cases, to hepatocyte necrosis and liver failure [143]. More recently, disruption in the coagulation cascade related to endothelial activation and injury leading to thrombosis has been thought to play a role in the pathogenesis of SOS [144, 145].

Table 27.6 Diagnostic criteria for sinusoidal obstruction syndrome

Baltimore criteria	Seattle criteria[a]
Prior to day 21 post-SCT,	Prior to day 30 post-SCT,
1. Serum bilirubin level ≥2 mg/dL and	1. Two or more of the following:
2. Two or more of the following:	Serum bilirubin level ≥2 mg/dL
Ascites	Hepatomegaly and right upper quadrant pain
Hepatomegaly (usually painful)	Ascites and/or unexplained weight gain >2 % over baseline
Weight gain >5 % over baseline	

[a]Modified Seattle criteria require clinical presentation prior to day 20 post-SCT

Clinical Features

The clinical presentation of SOS begins with the onset of tender hepatomegaly and weight gain, with hyperbilirubinemia following shortly thereafter. Sodium retention is common and ascites is often present. Other clinical findings may include peripheral edema including anasarca, pleural effusions, jaundice, thrombocytopenia, liver and renal failure. SOS severity is classified on the basis of clinical outcome. Mild disease resolves spontaneously while moderate disease resolves with treatment. The majority (70–85 %) of patients have mild or moderate disease. Severe disease is characterized by rapid progression to multiorgan failure (MOF) and death or symptoms that continue beyond day +100 [135]. The risk of development of severe disease can be estimated utilizing percent weight gain and total bilirubin in conjunction with the number of days post-transplant. As might be anticipated, severe disease is associated with higher bilirubin values occurring early after transplant [146].

Diagnosis

The diagnosis of SOS is based on the presence of the clinical criteria, however, these findings can be quite non-specific (see Table 27.6) [147–149]. Common laboratory findings include an increased serum bilirubin level and elevations of liver enzyme levels (which may occur later). Thrombocytopenia is common, as are decreased levels of protein C and antithrombin III [144]. Abdominal ultrasound is a commonly used tool to identify findings that will assist in securing the diagnosis. In addition to excluding other liver lesions that may result in similar symptoms, ultrasound may demonstrate hepatomegaly, ascites and gallbladder wall edema. Doppler evaluation may reveal attenuation of hepatic vein flow, slowing or reversal (late finding) of portal vein flow, and an increased resistive index in the hepatic artery (see Fig. 27.5). Ultrasound, however, may not provide reliable markers for early diagnosis, and should be repeated when the diagnosis is unclear [150–152]. Liver biopsy is diagnostic, but is rarely performed given the significant risk of bleeding, especially in the setting of thrombocytopenia. Transvenous liver biopsy has been suggested as an alternative to percutaneous biopsy, and allows for the measurement of a hepatic venous pressure gradient (elevation >10 mmHg is highly specific for SOS) [145]. However, this strategy may yield small, non-diagnostic samples for histology. In addition, infrequent use of the technique may lead to limited operator expertise. Consequently, the use of this approach has not gained widespread acceptance.

The differential diagnosis for SOS is broad, and includes sepsis with renal insufficiency and cholestasis, TPN-related cholestatic liver disease, and hyperacute GVHD. These disorders may co-exist with SOS and may complicate establishing the diagnosis [145].

Management

The management of SOS is mainly supportive and is dependent on disease severity. The close monitoring of fluid balance and electrolyte levels, in conjunction with sodium restriction and the use of diuretics, is important to avoid the need for ventilation secondary to fluid overload [135, 145, 153]. The early institution of renal replacement therapy may be helpful for patients with associated renal insufficiency and fluid overload or electrolyte abnormalities. Many therapies have been attempted for severe SOS with organ failure, including thrombolytic therapy and transhepatic shunts [144, 154–158]. Perhaps the most promising new therapy is defibrotide, a polydisperse oligonucleotide with antithrombotic and profibrinolytic effects, that is currently undergoing clinical trials. The response to defibrotide is encouraging and patients receiving this therapy have been found to have up to a 76 % response rate in reversal of disease [159]. The drug is not licensed by the FDA pending efficacy studies, but is available for compassionate use in the United States. Additionally, high dose corticosteroids may be effective for patients with earlier stages of disease, especially in those that do not meet the criteria for defibrotide [160]. Finally, in patients with hepatic failure liver, transplantation may be considered an option for a very small number of patients with end stage liver disease, but no irreversible dysfunction in other organs.

Prevention of SOS is important since therapeutic options are limited. Various prophylactic agents have been explored, especially in patients with previous hepatic injury, but with equivocal results. Antithrombin III demonstrated no protective effect in a large pediatric study [161]. Heparin may have some benefit, but has an increased risk of hemorrhage; low molecular weight heparin appears to be safer and may have some preventative

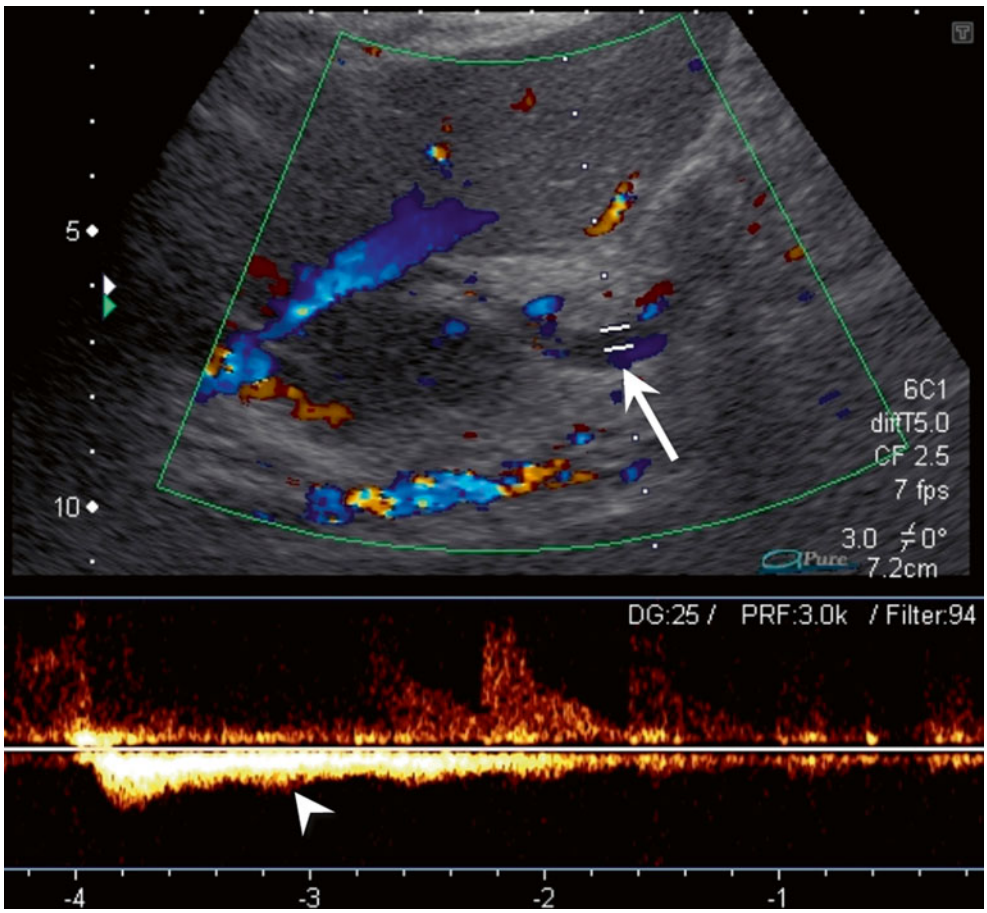

Fig. 27.5 Liver ultrasound with Doppler at the level of the main portal vein (*arrow*) in a stem cell transplant patient with sinusoidal obstruction syndrome demonstrating doppler waveform (*arrowhead*) below the baseline consistent with reversal of flow (Image courtesy of Dr. Alexander J Towbin, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

effect [162–166]. Prostaglandin E1 therapy has yielded mixed results with clear risk for toxicity [167, 168]. Ursodiol, is commonly used as supportive therapy and is generally safe, but has provided mixed results for the prevention of SOS [169]. Defibrotide has also been studied as a prophylactic therapy in high-risk children with promising results [170–173].

Outcomes

Mortality from SOS typically does not occur from fulminant liver failure, but rather, from respiratory and renal failure in the setting of fluid overload [153]. Outcomes appear related to the severity of the disease. Mild and moderate disease generally resolves with good outcomes; 100 day mortality rates for moderate disease are considered to be 20 %. However, individuals with severe disease and multiple organ failure have a dismal prognosis with a 100 day mortality approaching 98 %.

Transplant-Associated Thrombotic Microangiopathy

Transplant-associated thrombotic microangiopathy (TA-TMA) is a significant and relatively common complication of the SCT process. Most large retrospective studies report a TA-TMA prevalence of 20–25 % [174]. TA-TMA belongs to the family of thrombotic microangiopathies (TMAs) including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Mechanism of Disease

TA-TMA occurs when endothelial injury, in the context of SCT, causes microangiopathic hemolytic anemia and platelet consumption resulting in thrombosis and fibrin deposition in the microcirculation [175, 176]. High dose chemotherapy, radiation, calcineurin inhibitors (e.g., cyclosporine), graft versus host disease (GVHD) and infections such as adenoviremia and BK viremia have been implicated as causative factors for TA-TMA [174, 177–179]. TA-TMA usually occurs in allogeneic transplant recipients within the first 100 days post HSCT, but can also occur in patients after autologous transplant [174, 180]. While endothelial injury represents the final common pathway of disease, the exact pathophysiology of TA-TMA remains unclear, limiting the development and evaluation of targeted therapies. The kidney is the most commonly affected organ, although injury has been reported in the lungs and the gastrointestinal tract [178, 181, 182]. The histological features of TA-TMA in the kidney include thickened capillary walls, fragmented erythrocytes, occluded

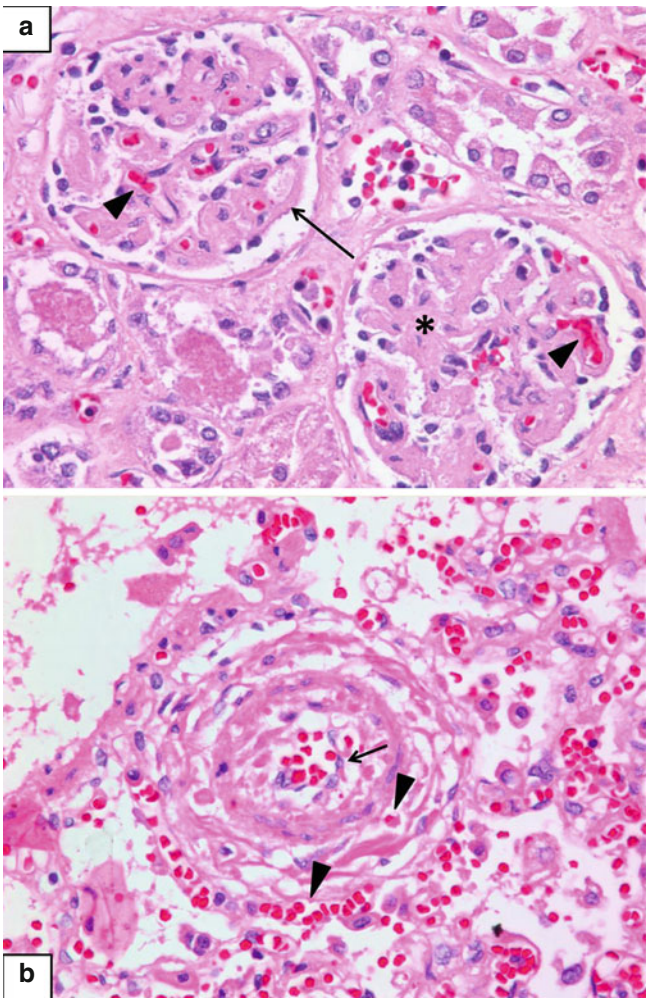

Fig. 27.6 Histologic changes of transplant-associated thrombotic microangiopathy (TA-TMA) in the kidney and lung. (**a**) Renal glomeruli demonstrating thickened capillary walls (*arrows*) with vessel occlusion. Red blood cell fragments can be seen (*arrow heads*) with mesangial expansion (*asterisk*) (H&E stain; magnification ×200). (**b**) Pulmonary arterioles demonstrating endothelial separation from underlying basement membrane (*arrow*) with red blood cell extravasation (*arrow heads*) into the intima and into the lung tissue with red cell fragments (H&E stain; magnification ×200)

vascular lumens, and endothelial separation with swelling, fibrin deposition, and necrosis (see Fig. 27.6a). Similar changes may also be seen in the pulmonary and mesenteric vascular beds (see Fig. 27.6b).

Clinical Features and Diagnosis

The diagnosis of TA-TMA remains challenging and requires a high index of suspicion. The acute presentation of TA-TMA may mimic acute multiorgan failure, sepsis, and/or polyserositis, and therefore, the diagnosis is easily overlooked or attributed to another process [175, 183]. Current clinical consensus diagnostic criteria for TA-TMA include hematologic and renal markers such as *de novo* anemia and thrombocytopenia, elevation of lactate dehydrogenase levels (LDH) levels, low haptoglobin levels, the presence of schistocytes on blood smear, and the doubling of serum creatinine level [184, 185]. These criteria are inadequate for the early diagnosis of TA-TMA, and pose significant challenges in SCT patients, who have multiple potential reasons for these laboratory abnormalities, and in whom anemia and thrombocytopenia are almost universal [174, 186]. Serum creatinine is a poor marker of renal function in chronically ill SCT patients as it is strongly depends on muscle mass, and can remain relatively normal even with significant renal dysfunction [175, 180, 187]. Several autopsy studies have demonstrated that these criteria significantly under diagnose TA-TMA [175]. Current guidelines do not include other kidney injury markers such as elevation of blood pressure or proteinuria; more recently, a "renal-centric" approach to diagnosing TA-TMA has been suggested [174]. Renal biopsy, while very useful for the diagnosis of TA-TMA, remains a challenging procedure in SCT patients at risk for bleeding. Since the pulmonary vasculature maybe involved in TA-TMA, clinicians caring for these patients need to be aware of pulmonary TMA as a diagnosis in the setting of SCT patients presenting with respiratory failure and pulmonary hypertension [188, 189]. In summary, TA-TMA has to be included in the differential diagnosis of acutely ill SCT patients treated in the PICU. A high index of suspicion for TA-TMA is needed in patients with other endothelial disorders such as SOS, especially in patients with multiorgan failure, severe hypertension, posterior reversible encephalopathy syndrome (PRES), acute hemolysis and thrombocytopenia, pulmonary hypertension and polyserositis [183, 188, 190].

Management

In large part due to the lack of understanding of the TA-TMA pathogenesis, therapeutic options are limited. Patients treated for "probable-TMA" or prior to irreversible organ damage have a better response to clinical interventions [191]. The discontinuation of calcineurin inhibitors (e.g. cyclosporine) is the most accepted intervention in the management of TA-TMA. However, the discontinuation of this therapy must be supervised by a skilled transplant physician in order to minimize the risk of provoking or exacerbating GVHD. Several case reports demonstrate the benefit of using rituximab and defibrotide as single agents or in combination with therapeutic plasma exchange (TPE) [183, 192–194]. The effectiveness of TPE in the treatment of TA-TMA remains uncertain due to variable outcome measurements and an incomplete understanding of its exact therapeutic mechanism. The success of TPE may be influenced by the timing of the clinical interventions. TPE has been found to be most effective when initiated early after the TA-TMA presentation [183, 195]. The successful treatment of the underlying triggers of TA-TMA such as infections and GVHD is also important for success.

Outcomes

In its most severe form, mortality rates for TA-TMA are very high (60–90 %), while milder cases have an increased risk of later chronic kidney disease (CKD) [175, 196]. Patients surviving acute TA-TMA are left with severely affected renal function, and many later progress to CKD [187]. SCT patients diagnosed with TA-TMA are four times more likely to develop CKD, and nine times more likely to have long term hypertension than SCT patients without TA-TMA. TA-TMA-associated renal complications such as hypertension result in significant subsequent heart disease, a major cause of morbidity and mortality in childhood SCT survivors [197, 198].

Kidney Injury Following Hematopoietic Stem Cell Transplantation

Both acute and chronic kidney disease are common complications in SCT recipients. The reported incidence of acute kidney injury ranges from 20 to 50 % and 5 to 28 % for chronic kidney disease. Up to 10 % of patients who have acute kidney injury require renal replacement therapy [199–209]. The cause of renal injury in this patient population is often multifactorial; etiologies include drug and radiation toxicity, infusion reactions, septic shock, SOS, TA-TMA, and renal infection secondary to immunosuppression (e.g. BK nephropathy). Risk factors for renal insufficiency include allogeneic transplant, drug toxicity (particularly cyclosporine, amphotericin B, and cyclophosphamide), total body irradiation, sepsis, hepatic impairment (including hyperbilirubinemia, weight gain, and SOS), and pre-transplant renal impairment. Interestingly, the incidence of pre-transplant renal impairment is relatively low. The clinical consequences of renal impairment are often fluid overload, as SCT recipients require substantial volume of fluid for blood product replacement, medications, and nutritional support. Mortality in transplant recipients with renal failure is usually secondary to other organ system dysfunction, including respiratory failure, hepatic disease, septic shock and multiorgan failure [201–205, 207].

Diagnosis

The diagnosis of acute kidney injury has typically relied on changes in serum creatinine levels and urine output. However, criteria such as pRIFLE (pediatric risk, injury, failure, loss and end-stage renal disease) may afford greater sensitivity in diagnosing acute kidney injury, while markers like cystatin C that are unaffected by age, muscle mass and weight may be superior to creatinine clearance in estimating glomerular filtration rate (GFR) [210–215]. Though not validated SCT recipients, studies have demonstrated that cystatin C is a better estimator of GFR than creatinine clearance in pediatric oncology and SCT patients [216–218].

Management

The treatment of kidney injury is largely supportive and includes aggressive monitoring of renal function, overall fluid status, and urine output, as well as the prevention of further injury by avoidance of nephrotoxic drugs if possible (e.g., using liposomal amphotericin B). Increasingly, there has been an emphasis on prevention of fluid overload in critically ill children in the critical care literature, and this extends to the SCT recipient where fluid restriction may be even more challenging given the need for blood products and medications. Several studies have demonstrated increased morbidity and mortality in children who had greater fluid overload at the initiation of renal replacement therapy [219–224]. In a study of SCT recipients with renal failure who received renal replacement therapy, patients who either started at, or attained less than 10 % fluid overload survived, while all those who remained fluid overloaded beyond this degree died [209]. Thus, the aggressive use of diuretics and renal replacement therapy are warranted in these patients to treat fluid overload. Diuretics remain the first choice of therapy to address fluid overload. It is not uncommon for SCT patients to need higher than usual doses of diuretics given their underlying kidney injury. The indications for the initiation of renal replacement therapy in SCT patients are similar to other patients in the ICU and modalities include continuous renal replacement therapy (CRRT) and intermittent hemodialysis. Peritoneal dialysis, given the risk of infection, is rarely used. In addition to removing fluid, CRRT may offer immune benefit as demonstrated in a small study in children [109]. However, the optimal timing of the initiation and the dose of renal replacement therapy for these patients remains unclear.

Outcomes

The outcome for SCT patients developing kidney injury and requiring renal replacement therapy is poor. Data from the pediatric renal replacement therapy registry suggested a 45 % survival rate to intensive care discharge for these children; however, survival was markedly lower for patients requiring mechanical ventilation and those with multiple organ failure [208]. In an another recent report, the need for continuous renal replacement therapy was associated with a poor long-term survival as only a single patient survived more than 6 months [225].

Neurologic Complications Following Hematopoietic Stem Cell Transplantation

Neurologic complications following SCT occur in up to 15 % of children [226–228]. Clinically, patients may present with seizures, altered mental status, visual abnormalities, ataxia, cranial nerve palsies, parasthesias, and paresis. A thorough approach including a detailed history and physical exam

assessing the state of immune reconstitution (for both bleeding and infection risk), the history of the primary disease including the risk of central nervous system (CNS) relapse, and the use of neurotoxic medications is necessary when evaluating these patients. The common causes of neurologic complications are toxicity from medications to prevent graft versus host disease (specifically calcineurin inhibitors), metabolic toxicity (including electrolyte abnormalities such as hypomagnesemia), irradiation and chemotherapy toxicity, CNS infections, cerebrovascular accidents (especially hemorrhage related to coagulation abnormalities including thrombocytopenia), hypertension, and rarely, immune-mediated encephalopathy. Risk factors for neurotoxicity include total body irradiation, GVHD >Grade 2, and GVHD prophylaxis with cyclosporine [226]. The most common complication reported with allogeneic transplantation is drug toxicity especially related to cyclosporine, although other drugs including tacrolimus have been implicated [226, 227, 229–234]. Of note, patients with CNS toxicity from calcineurin inhibitors may not have drug levels in the toxic range [231].

In addition to the appropriate laboratory evaluation and discontinuation of neurotoxic medications, CNS imaging in the form of a computerized tomogram is indicated. Magnetic resonance imaging (MRI) may be preferred; however, it may not always be available in a timely manner. While imaging may reveal a focal finding such as a CNS hemorrhage, imaging findings may be completely normal in the setting of metabolic and drug toxicity. However, in a substantial percentage of patients with drug toxicity, especially secondary to cyclosporine, imaging findings are consistent with posterior reversible encephalopathy syndrome (PRES). PRES is a clinical syndrome characterized by headache, seizures, visual abnormalities, encephalopathy, and less frequently, focal neurologic deficits. As the name suggests, this disorder is most often reversible with discontinuation of the offending drug; however, this recovery may take weeks. Classic findings on MRI include hyperintensity of the subcortical and cortical regions in the parieto-occipital regions on T2-weighted and FLAIR images (see Fig. 27.7) [235]. Paramount in the treatment of PRES is the discontinuation of the offending agent; an alternate agent may be used including a different calcineurin inhibitor. Although hypertension is not present in all patients, calcineurin inhibitors themselves can cause hypertension, and aggressive blood pressure control is indicated in the supportive care of PRES [235–237].

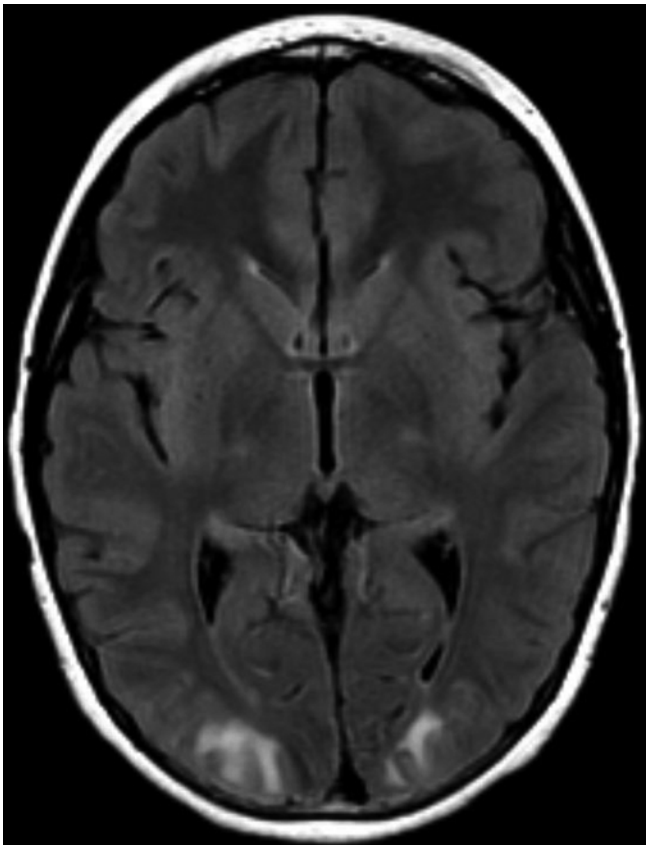

Fig. 27.7 Brain MRI from stem cell transplant recipient with posterior reversible encephalopathy syndrome (PRES). Axial FLAIR image with bilateral symmetric abnormal signal in the occipital subcortical white matter and cortex demonstrating characteristic changes for PRES (Courtesy of Dr. Marcia K Kukreja, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

Conclusion

The field of hematopoietic stem cell transplantation continues to move forward with expanding indications, utilization of better matching techniques and newer drug therapies to treat complications associated with SCT. Despite this, a proportion of SCT patients develop complications and need critical care. Notably, organ failure in these patients is associated with an immune system that is dysfunctional, making the clinical course of an otherwise uncomplicated disease processes tenuous. Although critical care outcomes for these patients are improving, this cohort of patients continues to have an unacceptably high morbidity and mortality. Hence, it is important for critical care physicians to familiarize themselves with the unique complications and care needs of these patients and manage them closely in conjunction with the transplant service. Given the complexity of the disease processes and the ever increasing arsenal of therapeutic strategies, a multidisciplinary approach to their care is essential.

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Part VI

The Immune System in Critical Illness and Injury

Derek S. Wheeler

The Immune System in Critical Illness and Injury

28

Jessica G. Moreland

Abstract

During the onset of critical illness or injury, initial attention is focused on supporting vital parameters for patient survival including oxygenation and tissue perfusion. Successful navigation past the primary insult often results in the patient with massive systemic inflammation and multi-organ dysfunction, thus at high risk for progression to organ failure, or secondary infection. It has become increasingly evident that the activation (or deactivation) state of the immune system is highly relevant to the prognosis of every critically ill or injured patient, not just those patients initially presenting with bacterial sepsis. Both the innate immune system, first described by Metchnikov in 1884 with his observations of phagocytosis, and the adaptive immune system are interconnected to sense and respond to invasion of the host by any pathogen. The outcome of these integrated the cellular and humoral responses can range from immediate termination of the microbe at site of invasion, with minimal systemic insult, to profound uncontrolled inflammation and organ damage, to systemic immunoparalysis and death from nosocomial sepsis. A broad overview of host defense is provided below with some discussion of how dysregulation of immune function impacts outcome in the critically ill patient.

Keywords

Innate immunity • Pattern recognition receptors • Systemic inflammatory response • Immunoparalysis • Sepsis

Introduction

There is no question that the patient presenting to the pediatric intensive care unit (PICU) with septic shock and purpura fulminans requires an intact, high-functioning innate immune system for host survival. The initial phase of sepsis is characterized by the rapid onset of the Systemic Inflammatory Response Syndrome (SIRS) directed at elimination of the pathogen. Under ideal conditions, the microbe is eradicated and the Compensatory Anti-inflammatory Response Syndrome (CARS) is subsequently mobilized, that restores the host homeostatic balance. The intensivist's repertoire for rapid evaluation of an individual patient's immune response, and subsequent modulation of therapeutic decisions based on this information is rapidly expanding. Thus a broad basic understanding of normal immune system function is critical to the practice of intensive care.

The immune system is made up of three integrated lines of protection. The first and most primitive level involves anatomical barriers to host invasion by microbes, i.e. skin and mucosal surfaces, including airway mucociliary clearance. Compromise of this first level of defense can result from injury (burn, trauma), genetic mutations (ciliary dyskinesias, epidermolysis bullosa), or iatrogenic requirements of intensive care (intubation, central line placement, antibiotic

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therapy, and neuromuscular blockade). The next level is the rapidly acting innate immune system, that responds to conserved patterns and danger signals in order to eradicate invading pathogens, but often non-specifically and with associated inflammation. The third line of defense is the more specific, but much slower-acting adaptive immune response. These three systems of host defense do not function sequentially or in isolation, but rather through complex, integrated crosstalk.

Innate Immune System

The evolutionarily more "ancient" arm of the immune system can be broadly categorized into sensing components and responding or effector components. These two arms of the innate immune system function to accomplish three basic goals: (1) recognition of an invading pathogen or dangerous material, (2) containment of the danger signal and elimination of the threat, and (3) limitation of the host tissue damage/initiation of host tissue repair.

Innate Immune Sensing

The general approach of innate immune system sensing is the recognition of conserved molecular patterns that are broadly repeated across a wide variety of microbial pathogens, but are distinct from the host, such that the distinction between "self" and "non-self" is readily apparent. Charles Janeway used the term pattern recognition receptors (PRRs) to broadly denote these innate immune receptors and the term pathogen-associated molecular patterns (PAMPs) to define the microbial molecules identified by these receptors [1]. Another component of innate immune detection includes the recognition of damage-associated molecular patterns (DAMPs) which are host molecules upregulated or released during infection or inflammation and provide evidence of the host stress response.

Pattern Recognitions Receptors (PRRs)

Toll-like receptors (TLRs): TLRs were the first PRRs to be described and are the best characterized. At this time, there are ten known functional human TLRs (12 in mice) and each receptor detects distinct PAMPs arising from bacteria, mycobacteria, viruses, parasites, or fungi. TLRs are membrane bound and thus recognize extracellular and phagocytosed PAMPs. Molecules recognized by TLRs include single and double-stranded RNA, lipoproteins, DNA, lipopolysaccharide, and flagellin. Innate immune sensing is made more specific by the subcellular localization of the TLRs. Certain receptors are predominantly found on the plasma membrane and recognize chiefly membrane components of microbial pathogens (TLR1, TLR2, TLR4, TLR5, and TLR6). Conversely, a separate group of TLRs, which detect microbial nucleic acids, are located principally within the membranes of intracellular compartments, including endosomes, lysosomes, endoplasmic reticulum (TLR3, TLR7, TLR8, TLR9) [2].

The general paradigm of TLR function involves binding of the PAMP by the TLR (sometimes requiring co-receptors), with subsequent recruitment of additional signaling proteins and activation of a variety of signaling pathways. The signaling cascade activated under these conditions is specific to the TLR that has been activated, but many TLRs (TLR1, 2, 4, 6, 7, and 9) require recruitment of the adaptor protein MyD88 and subsequent activation of NF-κB, leading to downstream generation of inflammatory cytokines. For other TLRs, the "TRIF-dependent" signaling cascade is activated, culminating in induction of Type I interferon (IFN). An overview of both trafficking and signaling induced by the TLRs is shown in Fig. 28.1 [3].

The requirement for TLRs in innate immunity was initially defined using knock-out mice. Numerous infection models dependent on the TLR signaling pathways have been reported: MyD88-deficient mice are highly susceptible to infection; immunity to *Staphylococcus aureus* requires TLR2-TLR6 recognition of lipoteichoic acid; and TLR2-deficient mice display enhanced mortality after system infection [4]. In contrast, *Salmonella typhimurium*, a Gram-negative intracellular bacteria, contains PAMPs recognized by four distinct TLRs (TLR2, -4, -5, and -9) and response to challenge is dependent not only upon which TLR is absent, but also the route of infection [5]. TLRs are not solely involved in recognition of bacterial pathogens. Many TLRs respond to viral nucleic acids and sense viral infections. Impaired sensing of viral nucleic acids by intracellular TLRs often leads to diminished production of type I IFN and subsequently altered anti-viral immunity [2]. In addition, fungal PAMPs are recognized by several TLRs, with increased susceptibility to Candidal disease in TLR2-deficient mice, and more complicated alterations in fungal host defense in the absence of TLR4 [6].

More recently, human genetic mutations in TLR signaling pathways have been reported that provide critical information about global immune function. Monogenic deficiencies of both IRAK4 [7] and MyD88 [8] have been associated with identical phenotypes, as expected based on their location as binding partners in the same signaling cascade. Surprisingly, despite a broad impairment in TLR sensing in the absence of this pathway, these patients were susceptible to a fairly narrow range of pathogens. The majority of infections were associated with extracellular pyogenic Gram-positive bacteria: *Streptococcus pneumoniae* and *Staphylococcus aureus*. The fact that viral immunity is not impaired in this setting suggests significant redundancy [9]. The profound difference in the spectrum of immune defects in humans lacking MyD88 as compared to the knockout mice is a powerful lesson for all basic researchers who rely on murine models!

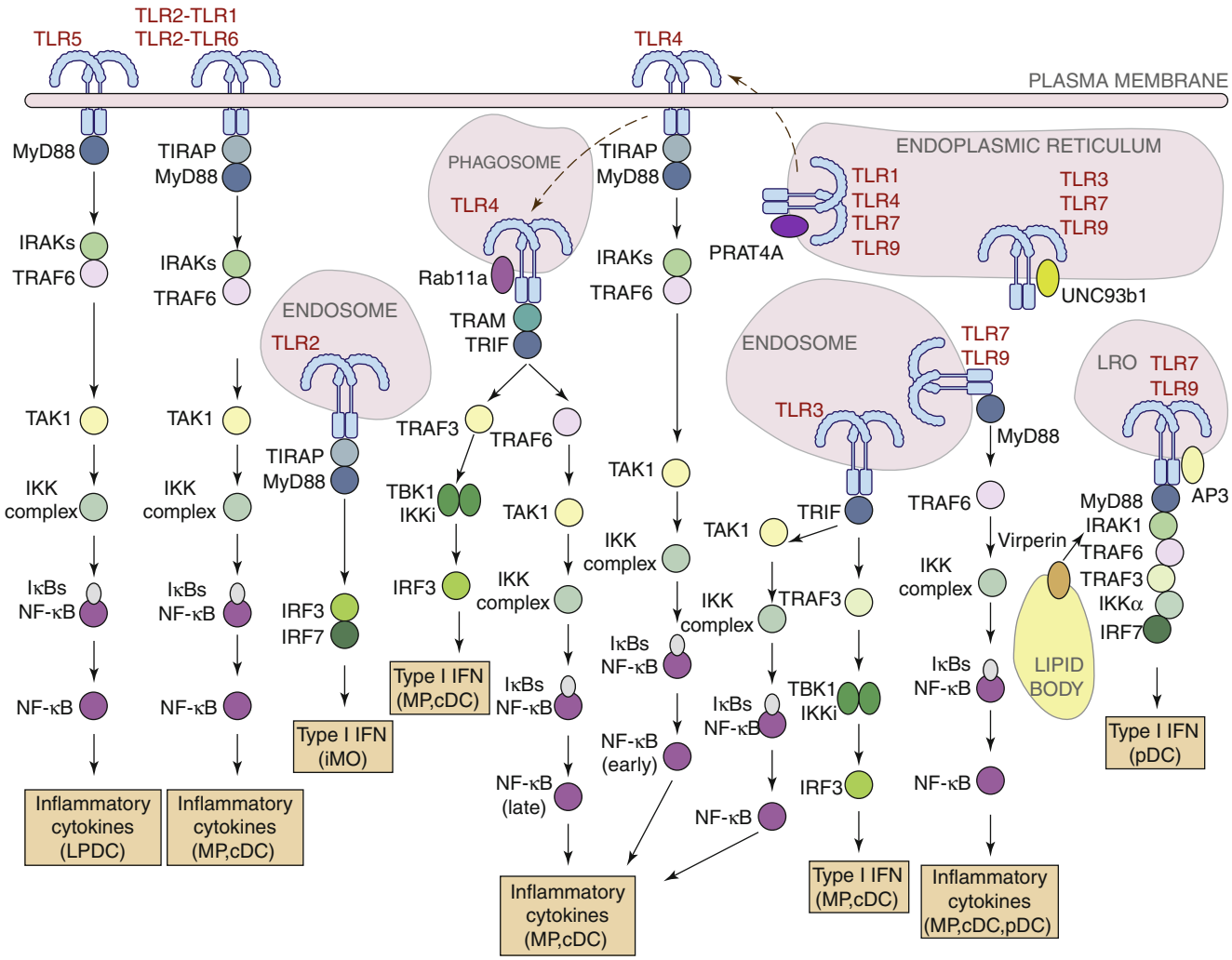

Fig. 28.1 Intracellular trafficking and signaling by TLR family. Following engagement by PAMPs, TLR receptors undergo conformational changes and recruit adaptor proteins to the cytoplasmic face of the receptor. Following this initial activation step, individual TLR receptors at either the plasma membrane or within intracellular membrane bound compartments initiate defined signaling pathways. Although each TLR has at least one distinct signaling pathway, many of these pathways are overlapping. TLR signaling culminates in either NF-κB mediated inflammatory cytokine production or Type I IFN response, depending on the stimulating PAMP, the receptor activated, and the cell type (Reprinted from Kawai [3]. With permission from Elsevier)

Nucleotide oligomerization domain (NOD)-like receptors (NLRs) and the inflammasome: The NLR family of innate immune sensors recognize microbial products (PAMPS) or host danger signals (DAMPs) within the intracellular or cytoplasmic environment. Activation of some of these receptors leads to the formation of an inflammasome, a multi-component cytoplasmic complex that induces inflammatory caspase activation and production of certain cytokines [10]. At this time, three distinct prototypic inflammasomes have been characterized which include the NLRP3, NLRP1, and the NLRC4 inflammasomes. There are four families of NLRs that response to distinct signals including a variety of pathogen-associated products (flagellin, pore-forming toxins, cytolysins, MDP, viral nucleic acids, hyphae) and also metabolic stress signals suggesting host cell injury (extracellular ATP, crystals, particulates, hyaluron, necrotic cell debris) [11, 12]. These host- and pathogen-derived signals elicit inflammasome assembly and activation through mechanisms that are not yet fully understood. However, the critical role of NLR family members in the host response to inflammation is underscored by the reports of human diseases caused by mutations in these proteins. Gain-of-function mutations in *NLRP3,* which lead to enhanced IL-1β production, underlie the cryopyrinopathies: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (or CINCA) [13]. In addition,

the broad clinical importance of NLR family members was further demonstrated by the recognition of frequent *NOD2* mutations in patients with Crohn's disease. The role of NLRs in the host immune response is not isolated to innate immune recognition, but also plays a role in T and B cell activation, thus functioning in the innate immune system's instruction of adaptive immunity [12]. A third family of PRRs are the RIG-I-like receptors (RLRs) which are cytosolic proteins containing RNA helicases involved in viral nucleic acid sensing. Mice deficient in specific RLRs have altered immunity to specific viruses, and viral evasion of these innate immune sensing mechanisms is actively under investigation by many laboratories [14].

Humoral Elements of Innate Immune Sensing

Host recognition of microbial invasion also occurs in the extracellular fluidic compartment with contact made by a number of diverse families of proteins which function as soluble pattern recognition molecules [15]. The human collectin family includes the mannan-binding protein (MBL) and the surfactant proteins A and D (SP-A and SP-D). SP-A and SP-D are predominantly synthesized in the lung and secreted by alveolar type II cells, where they participate in innate immune recognition by enhancing microbial uptake by phagocytic cells [16]. MBL and the more recently discovered family of collagen-like proteins, ficolins, bind microbial carbohydrate motifs as well as some molecules expressed by dying host cells. This interaction leads to activation of the lectin pathway of the complement system via MBL-associated serine protease (MASP) activation [17]. In addition, the C-reactive protein and other members of the pentraxin family function in "non-self" recognition, by binding to a number of microbial molecules [18]. Finally, there are several soluble proteins found in the serum that participate in microbial sensing: lipopolysaccharide-binding protein (LBP) and the soluble form of CD14 bind endotoxin from Gram-negative bacteria. Both soluble proteins are involved in recognition and presentation of endotoxin for TLR4 activation.

Effectors of the Innate Immune System: Cellular Mechanisms

Professional Phagocytes

The ability to rapidly sense microbial "non-self" is necessary, but not adequate for host protection. Rather, the innate immune system must move swiftly from detection to eradication of invading pathogens. A number of hematopoietic cells participate in the effector arm of innate immunity including polymorphonuclear leukocytes (PMNs or neutrophils), eosinophils, monocytes, macrophages, dendritic cells, and mast cells. Many of these innate immune effector cells also provide a direct link to activation of the adaptive immune system. In addition, natural killer (NK) cells function in both innate and adaptive immunity, as will be discussed at the end of this subsection.

The neutrophil is the most abundant leukocyte in humans and provides the critical first line of defense for killing invading microorganisms. Neutrophils circulating in the bloodstream are generally in a quiescent or non-activated state. In the setting of innate immune activation by a microbial pathogen, rapid neutrophil recruitment to the site of infection can be elicited by: (1) interactions with activated endothelial cells in the post capillary venules leading to firm adhesion and diapedesis; or (2) exposure to elevated circulating chemokines, cytokines, or bacterial products leading to neutrophil priming, increased adhesiveness and subsequent migration. Following transmigration across the vascular endothelium, PMN are spatially directed to the site of microbial invasion by chemokines (IL-8), leukotrienes, and activated complement components (C5a), many of which are produced by monocytes, mast cells and other non-hematopoeitic cells. Following phagocytosis of microbial pathogens, neutrophils possess both oxygen-dependent and -independent killing mechanisms that can be activated to terminate pathogens.

The unequivocal requirement for the neutrophil in innate immunity has been demonstrated by the numerous immune defects stemming from genetic deficiency/absence of specific neutrophils proteins. A few examples include: chronic granulomatous disease with deficiency of one of the components of the PMN NADPH oxidase leading to recurrent serious infections with specific bacteria and fungi; leukocyte adhesion deficiency, stemming from an absence of various integrin subunits causing profound impairment in neutrophil migration from the vascular space, with resultant severe, life-threatening infections; and Chediak –Higashi syndrome characterized by impaired delivery of lysosomal proteins to the phagosome, thus diminishing bacterial killing [19, 20]. Moreover, neutropenia, from any cause, is a major risk factor for the development of serious infections. Despite the absolute requirement for neutrophils in the initial response, regulated neutrophils apoptosis is critical to the termination of the host inflammatory response, and macrophages are required to dispose of the debris. In fact, progression of neutrophil apoptotic programs are temporally associated with a decrease in other pro-inflammatory mediators [21], and represent one of the signals that elicit the shift from the SIRs phase to the CARs phase during critical illness.

Monocytes are circulating leukocytes that do not proliferate under resting conditions. In response to specific signals, monocytes can migrate into tissues spaces, produce and secrete inflammatory cytokines, and mature into tissue-specific macrophages and inflammatory dendritic cells. The critical role of the monocyte in the host inflammatory balance

has become increasingly evident as the literature on immunoparalysis and monocyte dysfunction expands. Macrophages function in specific tissues as resident phagocytes and maintain tissue homeostasis by clearing debris under non-inflammatory conditions. In the setting of infection or inflammation, macrophages are equipped with numerous PRRs allowing both production of inflammatory cytokines and phagocytosis of pathogens.

Dendritic cells (DCs) function as a bridge between innate and adaptive immunity, based on their ability to sample the environment, generate inflammatory mediators, and subsequently process antigens and serve as antigen-presenting cells. DCs are classified into several different subgroups based on origin and function. Inflammatory dendritic cells are derived from circulating monocytes and function at foci of infection or inflammation [22]. Other subgroups of dendritic cells not derived from circulating monocytes include classical DCs and plasmacytoid DCs. The former are relatively short-lived phagocytic cells that participate in cytokine generation, and can move from the circulation into lymphoid organs to interact with T-cells and B-cells to regulate adaptive immune responses. Plasmacytoid DCs are a distinct subpopulation which respond to viral pathogens by production of type I interferons, and also have antigen presenting capabilities [23].

NK Cells

NK cells were first identified more than 30 years ago and initially categorized as lymphocytes due to origin, cell morphology, and surface marker expression. However, their functional classification primarily within the innate immune system is secondary to a lack of antigen-specificity. NK cells can recognize cell-damage or stress signals, as well as microbe-infected cells. As their name implies, they possess cytolytic capabilities, and have been demonstrated to produce and secrete many chemokines in addition to both pro- and anti-inflammatory cytokines. NK cells also have a regulatory role in adaptive immune responses; production of IFN-γ and other cytokines can promote differential T helper cell subset development in lymph nodes, and targeted cell killing alters antigen presentation and CD8 cell function. Moreover, within the innate immune system, NK cells have a bidirectional interaction with DC: promotion of DC maturation by NK cytokine production, and enhancement or priming NK cell function by DC (and macrophage)-generated cytokines [24].

Humoral Innate Immune Effectors: The Complement System

Not all effector components of the innate immune system are cellular, or cell based; the complement proteins include an array of 25 soluble proteins that are critical for innate and adaptive immunity. The complement system can be activated by three distinct pathways: classical, alternative, and lectin, all of which converge at the cleavage of C3 and subsequently generate the membrane attack complex. Activation of complement by the classical pathway is necessary for the innate immune response to encapsulated, pyogenic bacteria, and also in response to viral envelopes. Classical activation is initiated by C1q binding to antibodies bound to pathogenic bacteria or in immune complexes. Lectin pathway activation as previously mentioned is initiated by MBL and/or ficolin family member binding to microbial carbohydrate motifs, and thus activating the associated MASP esterase activity. Classical and lectin pathway activation converge with generation of the C3 convertase (C4bC2a). Alternative activation of the complement system occurs as an amplification mechanism following activation by either of the first two described pathways, or can also occur independently in response to activation of the serine protease, factor D, by certain microbial fragments.

Following activation of the complement system by any pathway, elimination of invading pathogens is enhanced by (1) activation and deposition of the complement opsonins (C3b and C3bi) on the surface of microbes promoting phagocytosis, (2) activation of the MAC that can induce bacterial cell lysis, and (3) generation of C5a, an inflammatory chemokine that propagates the activation and migration of leukocytes to the site of infection [25]. The requirement for complement in innate immunity is demonstrated by disease-causing genetic mutations. Deficiency of any of the terminal MAC components leads to enhanced susceptibility to meningococcal disease and is investigated frequently in the ICU patient. C3 deficiency, although rare, predisposes to serious infections with encapsulated bacteria. Many other mutations are also associated with inflammatory and autoimmune conditions and some association with bacterial infections [26].

Additional humoral effectors of the innate immune system include the antimicrobial peptides (AMPs), small cationic peptides that are evolutionarily conserved in host defense. There are two families of AMPs in mammals: the defensins and the cathelicidins. These peptides are produced by epithelial cells and some hematopoietic cells and function by two mechanisms in innate defense: direct antimicrobial activity and immunomodulatory properties including direct chemoattractant properties, as well as induction of host cytokine and chemokine production [27].

Adaptive Immune System

Whereas the innate immune system has developed to sense and rapidly respond to a wide range of common patterns, the adaptive immune system evolved more recently (~500 million years ago) to recognize a vast repertoire of antigens and maintain immunologic memory. Adaptive immune responses

are initiated following processing of non-native antigens by antigen-presenting cells, including dendritic cells as described above. The adaptive immune system contains both cellular and humoral elements which will be described, followed by a discussion of the interactions between adaptive and innate immunity in relation to critical illness.

Cellular Immunity: T Cells

Early T cell development occurs in the thymus after entry of lymphoid progenitor cells. Development of T cells in the thymus is a complex multi-step process requiring expansion of the population and multiple levels of selection prior to export from the thymus, with only 1–3 % of thymocytes succeeding to reach this step [28]. Mutations in the common gamma chain for numerous cytokine receptors involved in T-cell development underlies X-linked severe combined immunodeficiency (SCID) characterized by an absence of T cells and non-function of the adaptive immune system [29]. Following thymic development, both CD4 and CD8 positive T cells exit to the circulation in an antigenically naïve state.

T cell activation occurs when T-cell receptors (TCRs) interact with MHC molecules in combination with antigenic peptides, based on the type of T cell. $CD8^+$ T cells (or cytotoxic T cells) recognize antigens associated with MHC class I, which are present on a wide variety of cell types. In contrast, $CD4^+$ T cells respond to MHC class II molecules present on a select group of APCs. Activation of T cells in this manner leads to clustering of the TCRs and the development of an immunologic synapse between the T cell and the APC. This interaction is further stabilized by integrins and a complex signaling process is initiated eventually inducing gene expression by the activated T cell.

Within this paradigm generally applicable to all T cells, there are diverse effector functions served by a variety of T cell subsets including direct killing of targeted cells containing pathogens, productions of cytokines, activation of other immune cells, and regulation of inflammatory responses to limit host damage. $CD4^+$, helper T cells make up the largest group of T cells. Almost two decades ago it was recognized that in response to interaction with APCs and surrounding cytokines naïve T_H0 cells differentiated into two groups of T helper subsets that produced distinct cytokines, termed T_H1 and T_H2 cells [30]. T_H1 cells were generated in the presence of IL-12 and produce IFN-γ and IL-2, eliciting activation of monocytes, NK cells and cytolytic T cells to kill intracellular pathogens. In contrast, T_H2 cells were produced in response to IL-4 stimulation and are generators of IL-4, IL-5, IL-10, and IL-13, leading to enhanced antibody production and hypersensitivity responses. In the last few years, it has been recognized that there were additional T helper subsets at work in the adaptive immune response. T_H17 cells are a pro-inflammatory T helper subset induced in response to TGF-β and IL-6. They subsequently produce IL-17, TNF-α, IL-22 and elicit neutrophil recruitment as well as causing host tissue damage, likely critical in autoimmunity. Conversely, T regulatory cells also arise from $CD4^+$ T cells and generate IL-10 and TGF-β, functioning to downregulate immune activation [31].

$CD8^+$ T cells recognize primarily antigenic cytosolic peptides and function to kill cells which contain intracellular pathogens. The cytolytic T cell recognizes the antigenic peptide in conjunction with MHC class I, generates an immunologic synapse, and mobilizes granules containing perforin and granzymes by exocytosis into the target cell to initiate an apoptotic death. One additional T cell subset should be mentioned, generally CD4 and CD8 double negative, expressing a distinct TCR, the γδ TCR. These cells recognize antigens from mycobacterial presented by non-classical MHC and function in immunity to tuberculosis [32].

Cellular and Humoral Immunity: B Cells

B cells develop from hematopoietic stem cells in the bone marrow under the control of a number of transcription factors. At the immature B cell stage, they exit the bone marrow and complete development in the periphery to become mature B cells, demonstrated by the presence of both IgD and IgM on the cell surface. These early stages of development are antigen-independent, and genetic mutations during this phase of B-cell development present with absence of B cells and agammaglobulinemia [33].

The next phase of B-cell development occurs when the B-cell encounters antigen in the spleen, lymph nodes or other lymphoid associated tissues. In most cases, B-cell activation and antibody secretion is T-cell dependent. Mature B cells come in contact with antigens by several mechanisms and immunoglobulin receptor crosslinking occurs on the B-cell surface, initiating intracellular signaling that promotes subsequent interaction with T cells. T cells and B cells then interact and the B cell activation process proceeds down one of two pathways: short-lived, antibody-secreting plasma cell, or a long-lived memory cell. Memory cells enter a follicle to establish a germinal center, where the B cell may remain and produce IgM and IgD, or can undergo class switching to produce other isotypes (IgG, IgA, IgE) of higher affinity immunoglobulin [31]. These secreted immunoglobulins represent the humoral component of the adaptive immune system. During the primary exposure to any antigen, production of antibody is slow and low affinity IgM is the major isotype produced. Higher affinity antibodies are produced after a period of weeks following the initial exposure, but because of the immunologic

memory developed, subsequent exposure to the same antigen leads to much more rapid production of high affinity immunoglobulin, known as the secondary response.

Interplay Between the Innate and Adaptive Immune Systems

There has been extensive discussion and analysis of innate instruction of adaptive immune responses, including antigen presentation to lymphocytes by dendritic cells and macrophages, as well as cytokine production by many innate immune cells, inducing development of T helper cell subsets. More recently, it has become clear that the crosstalk is bidirectional with both adaptive suppression and activation of innate immunity under certain conditions. Both $CD4^+$ and $CD8^+$ T cells have been demonstrated to have roles in dampening of innate inflammatory responses by suppression of inflammasome activation [34], inhibition of inflammatory cytokine production, and downregulation of NK activity [35]. Under other circumstances, both T-cells and B-cells function to activate or amplify innate immune responses by activation of macrophages, mast cells, eosinophils and complement proteins to control specific pathogens [35].

The Immunologic Balance in Critical Illness

Much of this chapter has focused on the role of the immune system in recognition of pathogens, and initiation of the host inflammatory response, thus providing a framework to understand how this inflammatory response can be regulated or dysregulated under different pathologic conditions. However, there is a growing understanding of the importance of the Compensatory Anti-inflammatory Response Syndrome (CARS) [36]. Although the initial phase of many critical illnesses, including sepsis and trauma, are characterized by hyperinflammation, most patients move from the pro-inflammatory SIRS phase to the anti-inflammatory or immunosuppressive CARS, with the net "goal" to achieve return to homeostasis. However, just as the SIRS response can be pathologically activated, and therefore detrimental to the patient, the phenomenon of immunoparalysis, which represents a prolonged and inappropriate CARS, can be similarly injurious [37].

Immunoparalysis

The concept of pathologic suppression of the immune system during critical illness is not new, but rather was first described and characterized over 20 years ago based on concurrent observations in both trauma patients and organ transplant recipients. Polk, et al., systematically studied elements of immune system function in severely injured trauma patients, and recognized that persistent suppression of antigen presenting capacity in monocytes predisposed patients to secondary infection [38]. The association between prolonged monocyte dysfunction and nosocomial sepsis in trauma victims was further strengthened and linked to outcome in subsequent studies [39, 40]. Concurrently, monocyte dysfunction was recognized to be predictive of sepsis outcomes in transplant recipients [41, 42]. During the decade following the initial recognition of this concept of pathologic immunosuppression during critical illness, a number of large scale clinical trials in sepsis examined the ability of anti-endotoxin [43], or anti-inflammatory cytokine antibodies [44–46] to improve mortality. The serial failure of these clinical trials which focused specifically on dampening elements of the SIRS response, led to a general recognition that the model of unopposed inflammation in sepsis needed reexamination [47, 48]. A major paradigm shift occurred with the recognition that the immune response in sepsis was biphasic in character, with a delayed immunosuppressive phase that may be just as critical to the way we practice and treat our patients as the initial hyperinflammatory response.

Pathologic persistence of the anti-inflammatory phase or CARS response in sepsis and other critically illness has been coined "immunoparalysis." The definition of the clinical syndrome of immunoparalysis relies on two assays of innate immune function: first, diminished monocyte HLA-DR expression (<30 % of normal levels) or, second, impaired whole blood ex vivo TNF-α production in response to stimulation with endotoxin. The first criterion is relatively easy to standardize in a quantitative fashion and is now routinely performed on adult and pediatric samples. The second measurement is much more difficult to standardize across laboratories. Although monocytes produce massive quantities of TNF-α in response to stimulation with endotoxin, there is significant variation even between different healthy donors assayed in the same laboratory setting, and the dose and species of endotoxin used for stimulation can profoundly alter the amount of TNF-α generated [49]. That being said, patients samples studied within a single laboratory using the same technique for every patient should be comparable and thresholds for "immunoparalysis" can be set by individual laboratories. The link between immunoparalysis and adverse patient outcomes has been reported in both adult and pediatric patients [50, 51], and is extensively reviewed by Frazier and Hall [49].

In view of the extensive data linking immunoparalysis to nosocomial infections and other poor outcomes, investigators have initiated efforts to therapeutically target the immunosuppressive phase of sepsis and other critical illnesses. Initially, using murine models, the cytokine profiles during each phase of illness were detailed by repetitive blood sampling [52], followed by the demonstration of improved mortality with IL-10 and IL-15 blockade using a cecal ligation and puncture model [53, 54]. Most recently, initial human

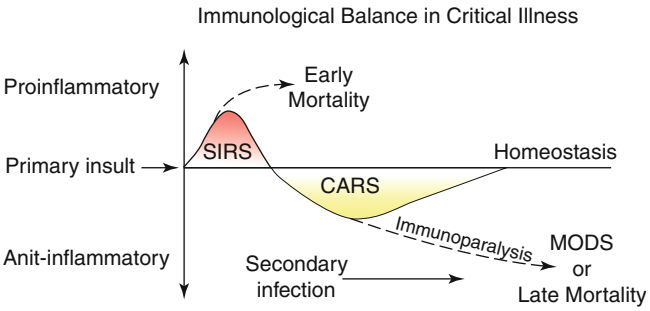

Fig. 28.2 The immunologic balance in critical illness. Following a wide variety of severe primary inflammatory insults (infection, trauma, burn, hemorrhage, pancreatitis, allergic reactions); the Systemic Inflammatory Response Syndrome (*SIRS*) is activated in the initial hours to days. This intense proinflammatory immune response can lead to early mortality in some cases. Subsequently, the host initiates the Compensatory Anti-inflammatory Syndrome (*CARS*) a counter regulatory immune mechanism designed to restore immune homeostasis. However, the CARS phase can also be uncontrolled leading to a state termed "immunoparalysis" during which the host is intensely susceptible to secondary or nosocomial infection. Uncontrolled CARS can lead to MODS and late mortality

trials demonstrate promising results with the use of GM-CSF therapy to modulate immunoparalysis both in adult [55, 56] and pediatric patients [57]. These trials represent the next phase in the evolution of our understanding of the host immune response during critical illness (Fig. 28.2).

Conclusions

The immune response has evolved over more than a billion years to provide the host a vast array of active mechanisms to combat pathogenic invaders. In the setting of critical illness or injury, activation of various cellular and humoral elements of immunity may protect us from life-threatening infection, but may also lead to uncontrolled host tissue damage. Impairment of immune system function in the critically ill patient, whether due to genetic alteration or transient suppression, may profoundly alter the course of sepsis and ultimately impact outcome.

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Primary and Secondary Immunodeficiencies

29

Rajesh K. Aneja and Alexandre T. Rotta

Abstract

Primary immunodeficiencies are rare disorders that are frequently considered in critically-ill children that are admitted to the intensive care unit with recurrent life-threatening infections. In this chapter, we have briefly reviewed the primary and secondary immunodeficiencies that an intensivist is likely to encounter in the PICU. The immunodeficiencies have been categorized as primary defects of antibody production, combined Immunodeficiencies, primary defects of cellular immunity, complement deficiencies and phagocytic Disorders.

Keywords

Primary defects of antibody production • Combined immunodeficiencies • Primary defects of cellular immunity • Phagocytic disorders • Complement deficiencies

Introduction

Children with recurrent infections admitted to the pediatric intensive care unit (PICU) are frequently worked up for immunodeficiencies. While immunodeficiencies are certainly plausible, they are rare disorders, and other disorders that potentially cause recurrent infections i.e., malnutrition, malignancy should be considered. In most cases, a thorough history and physical examination will help in identification of the underlying cause of recurrent infections. The initial work-up of these children presenting with recurrent infections is outlined in Table 29.1.

Since Dr. Bruton's first case report in 1952, the field of immunology has witnessed a tremendous growth. This advancement was partly fueled by the advent of sophisticated molecular biologic techniques aimed at identifying underlying genetic defects of these disorders. New therapeutic approaches were subsequently designed to target these defects. Rather than, focus on the therapeutic approaches and techniques, we have briefly reviewed the primary and secondary immunodeficiencies that an intensivist is likely to encounter in the PICU.

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Part I Primary Immunodeficiency Syndromes

Primary Defects of Antibody Production

As a general rule, primary defects of antibody production involve a single class of immunoglobulin—although some disorders in this group affect all classes of immunoglobulin. The characteristic features and underlying genetic defects for many of the primary antibody deficiency diseases are summarized in Table 29.2.

X-Linked (XLA or Bruton's) Agammaglobulinemia

XLA was first described by Colonel Ogden Bruton in 1952 [1]. XLA represents the prototypic genetic immunodeficiency

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Table 29.1 Initial workup of patient with recurrent infections

Type of infection	Laboratory studies
Recurrent sepsis with encapsulated organisms	Serum immunoglobulin levels Specific antibody titer (natural antibodies, vaccines)
Recurrent meningococcal infections	CH50
Opportunistic infections	T cell enumeration in peripheral blood, delayed hypersensitivity skin testing Assess in vitro T cell function Antibodies to T cell markers
Recurrent pulmonary infections (Aspergillus or Staphylococcus aureus), subcutaneous abscesses (Staphylococcus aureus), liver abscesses (Staphylococcus aureus)	Neutrophil count Nitroblue tetrazolium test Dihydrorhodamine 123 (DHR) test

Table 29.2 Characteristic features of main antibody deficiency syndromes

Characteristic	Age of onset	Molecular defect	Immunoglobulin	Characteristic features
X linked agammaglobulinemia	After 6 months of life	Bruton's tyrosine kinase gene	IgM decreased IgG decreased IgA decreased	*Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus and Pseudomonas species*
Common variable immunodeficiency	Any age (generally after 18 months)	Unknown so far	IgM normal IgG low IgA normal	Respiratory infections—*H. influenzae, Moraxella catarrhalis and S. pneumoniae* gastrointestinal tract infections—*Giardia. lamblia and Campylobacter jejuni*
Hyper IgM Type 1	Infancy	CD40 ligand gene	IgM very high IgG low IgA low	*Pneumocystis carinii* pneumonia, protracted diarrhea (*Giardia lamblia*), neutropenia, autoimmune disorders

for this group of disorders; it is characterized by a profound defect in B lymphocyte development—resulting in severe hypogammaglobulinemia, as well as absent mature B cells and plasma cells. The underlying genetic mutation in XLA was mapped to the long arm of the X chromosome at Xq 21.2–22.2 [2, 3], that encodes for *Bruton's tyrosine kinase* (Btk)—a member of the Tec family of non-receptor tyrosine kinases [4, 5]. Btk plays a predominant role in signal transduction in numerous hematopoietic cells, and B cell differentiation. Patients with XLA demonstrate reduced levels of Btk messenger ribonucleic acid (mRNA) and protein in B-cell lines derived from blood or bone marrow [6]. Btk-dependent inositol 1,4,5-trisphosphate (IP3) production is crucial for calcium signaling in B cell receptor engagement and regulates a subset of transcriptional events essential for B lineage growth [7].

Male children afflicted with XLA are protected from infections in the first 6 months of life by maternally transmitted IgG antibodies. During the first year of life as serum IgG levels wane, these children become more susceptible to develop infections [8]. In a multi-center review of 96 XLA patients, almost a fifth of these patients are symptomatic by 12 months of age, and an additional 10 % experience clinical symptoms by 18 months of age [8]. Patients commonly present with infections of upper (75 %) and lower (65 %) respiratory tract, gastrointestinal tract (35 %), skin (28 %), and central nervous system (16 %) [8]. Bacterial infections are usually caused by pyogenic encapsulated bacteria including *Streptococcus pneumoniae*, *Haemophilus influenza*, *Staphylococcus aureus*, and *Pseudomonas* species [8, 9]. As T cell dependent immunity is intact in these patients, fungal and viral infections do not cause a significant problem. However, certain viruses (hepatitis C virus and enterovirus) can cause overwhelming infections [10–12]. Patients with enteroviral infections can present with progressive myelopathy, encephalopathy, or myelopathy progressing to an encephalopathy [13]. These observations suggest a primary role of antibodies in neutralizing these viruses during the initial infection in the gastrointestinal system or during the viremic phase of the infection [14–16].

Patients with XLA often present with gastro-enteritis or chronic intestinal inflammation [17]. Over 20 % of patients with XLA develop arthritis. The physical examination is significant for markedly hypoplastic tonsils, adenoids, and lymph nodes. The diagnosis of XLA is suspected when all major classes of immunoglobulins are significantly low [18, 19]. The serum concentrations of IgG are usually less than 200 mg/dL. The levels of IgM and IgA are less than 20 mg/dL. The definitive diagnosis is established in male patients with *less than 2 % mature B cells* and *proof of a Btk abnormality*. Since T cells are normal, tests for cell mediated immune functions and delayed hypersensitivity are

preserved. The response to antigenic challenge in the form of childhood vaccinations is markedly reduced in children with XLA, but is preserved in children with transient hypogammaglobulinemia [18, 19]. Prenatal diagnosis of affected male fetuses is possible by examining Btk expression in amniotic fluid cells and B lymphocytes of fetal cord blood.

Common Variable Immunodeficiency (CVID)

CVID is a heterogenous disease characterized by hypogammaglobulinemia—impaired antibody production, despite phenotypically normal B cells and an increased susceptibility to recurrent bacterial infections. Patients with CVID present after 18 months of age with respiratory and gastrointestinal tract infections caused by encapsulated bacteria; CVID has a bimodal age distribution i.e., between1–5 and 16–20 years [20]. In a study of 248 consecutively referred CVID patients, the median age at the time of onset of symptoms was 23 years for males and 28 years for females [21]. Both sexes are affected with CVID.

The precise molecular defect is still unknown although it has been suggested that there may be more than one genetic defect. Patients with CVID demonstrate decreased T cell activation and proliferation [22], defective antigen driven response [23] and reduced production of cytokines [24, 25]. Whether the T-cell defects and agammaglobulinemia in CVID are primary or secondary to the dysfunction of dendritic cells continues to be a subject of debate [26]. Recent evidence suggests that in addition to the role of T-cell dysfunction, there is a primary defect in the function of myeloid dendritic cells and B-cells [27, 28]. B cell defects in CVID include an increased proportion of phenotypically immature B cells, as well as a variable block in B-cell differentiation resulting in deficient immunoglobulins and antibodies [29, 30]. Family members of patients with CVID often have IgA deficiency suggesting a shared genetic basis.

CVID patients commonly present with respiratory tract and gastrointestinal tract infections [31]. The pathogenic organisms causing sino-pulmonary infections include *Haemophilus influenzae*, *Moraxella catarrhalis*, *and Streptococcal pneumoniae*, while the gastrointestinal tract infections are caused by *Giardia lamblia* and *Campylobacter jejuni*. Undiagnosed CVID patients with recurrent respiratory infections progress on to develop bronchiectasis. In a series of 240 patients with CVID, 18 % patients had developed bronchiectasis at the time of diagnosis [20]. In contrast to XLA, patients with CVID have normal-sized or enlarged tonsils and lymph nodes. Prolonged infections with *Mycoplasma pneumoniae* and recurrent attacks of Herpes Simplex virus (HSV) are commonly observed. A higher incidence of hepatitis C infection has been reported in CVID patients. Approximately 25 % of patients with CVID have splenomegaly. Older patients with CVID can present with autoimmune disorders like idiopathic thrombocytopenia, autoimmune hemolytic anemia, rheumatoid arthritis, and systemic lupus erythematosus. Patients with CVID also demonstrate an increased propensity to develop malignancies—gastric carcinoma and lymphomas [32, 33].

The presenting signs and symptoms of CVID are nonspecific and overlap with many other diseases. Hence, a careful family history and work up is essential before the diagnosis is established. Differential diagnoses include transient hypogammaglobulinemia of infancy, XLA, severe combined immunodeficiencies, and secondary causes of hypogammaglobulinemia. The serum immunoglobulin levels, although higher than patients with XLA, are still depressed. Most patients have reduced levels of IgA and IgM, and IgG levels rarely exceed 300 mg/dL. The majority of patients have normal numbers of circulating B lymphocytes. Few CVID patients demonstrate a diminished response to T-cell receptor stimulation, decreased lymphocyte proliferation, and reduction in production and/or expression of IL-2, IL-4, and IL-5 [24, 34, 35]. Reduction in the absolute numbers of circulating CD4+ T cells, particularly those of the CD4+, CD45RA+ subset have also been reported [36].

Hyper-IgM Syndrome

X-linked hyper-IgM syndrome is characterized by neutropenia, defective B cell isotype switching; this results in normal to increased levels of IgM and very low serum concentrations of IgG and IgA [37]. The interaction between CD40 (B cell) and the CD40 ligand (CD154) on the activated T cell is essential for switching the production from IgM to IgG [38, 39]. A mutation in the CD40 ligand gene on the Xq26 chromosome results in the inability of B cells to switch over to IgG production; consequently, there is increased IgM and deficient IgG production.

An autosomal recessive form of hyper IgM (Hyper IgM type 2) has also been described in older patients. This form is characterized by a deficiency of activation induced cytidine deaminase (AID)—enzyme critical for immunoglobulin isotype switching. AID plays a predominant role in the terminal maturation and proliferation of B cells in germinal centers; therefore, deficiency of AID results in impaired differentiation and proliferation of B cells.

Boys with CD40 ligand defect have small tonsils, palpable lymph nodes, and neutropenia and frequently present in infancy with recurrent pyogenic and gastrointestinal infections. These patients exhibit normal numbers of circulating B lymphocytes, low serum IgG, IgA, IgE, and normal to elevated IgM concentrations [40]; these patients have a marked propensity to develop *Pneumocystis carinii* pneumonia [40–42]. Gastro-intestinal infections with *Cryptosporidium* and *Giardia lamblia* are frequent in patients with Hyper IgM syndrome [40]. Sclerosing cholangitis as a result of *Cryptosporidium* infections can further worsen the liver disease in patients with hyper IgM syndrome. Patients with

Hyper IgM syndrome are prone to autoimmune diseases e.g., thrombocytopenia, hemolytic anemia, and hypothyroidism. Very few patients present with neutropenia and demonstrate oral ulcers, persistent stomatitis, and proctitis [40]. CD40 ligand gene analysis is required for confirmation of the diagnosis.

Selective IGA Deficiency

With a chemical structure similar to IgG, IgA is the second most abundant immunoglobulin in the serum. IgA is primarily secreted in the mucosa of the sino-pulmonary, urogenital, or gastrointestinal tracts. It provides local immunity by neutralizing viruses, binding toxins, agglutinating bacteria, and preventing epithelial binding of bacteria. The function of serum IgA is not clear at present. IgA deficiency is the most commonly reported immunodeficiency [43–45] with a prevalence ranging from 1:396 to 1:1,000 in healthy blood donors. A reliable diagnosis of IgA can only be made in patients older than 4 years of age as normal, healthy children less than 4 years have low IgA concentrations [46]. Lack of uniform serum IgA cut-off levels in the published literature make it difficult to determine IgA deficiency [47].

The majority of cases of IgA deficiency appear to be inherited in a sporadic fashion, though familial cases have been described [48–50]. IgA deficiency is relatively common in family members of patients of patients with CVID [48]. Although the genes responsible for increased susceptibility to IgA deficiency are not known, IgA deficiency is associated with HLA DR1, DR3, and DR7 MHC haplotypes. This implies inheritance of a gene in the MHC area of chromosome 6.

Most individuals with IgA deficiency are asymptomatic, however, IgA deficient patients can present with recurrent infections, allergies, celiac-like enteropathy, and autoimmune disease. Infections occur predominantly in the respiratory, gastrointestinal, and urogenital tracts—most common infections being recurrent sino-pulmonary infections. The gastrointestinal manifestations of IgA deficiency are frequent giardiasis, nodular lymphoid hyperplasia, and malabsorption [51, 52]. IgA deficient patients have a higher incidence of autoimmune diseases (juvenile rheumatoid arthritis, systemic lupus erythematosus, hemolytic anemia, and thyroiditis) and malignancy (gastrointestinal carcinomas and lymphomas). Classically, these patients have low serum IgA levels (<7 mg/dL) with normal serum IgG and IgM levels. Almost half of these patients have a co-existing IgE deficiency.

Children with selective IgA deficiency are at higher risk to develop anti-IgA antibodies, often with severe, potentially life-threatening consequences following transfusion of blood products, as there is no tolerance to the IgA protein. As other immunoglobulins levels are normal, these children do not need replacement of immunoglobulins with IVIG administration.

IgG Subclass Deficiencies

Each of the lgG subclass molecules is composed of two heavy and two light chains (kappa and lambda) covalently bound to each other by disulfide bonds. Different amino acid sequences in the constant heavy-chain domains confer distinction on the IgG subclasses [53]. Human IgG can be subdivided in to four subclasses—IgG1, IgG2, IgG3, and IgG4. IgG1 is the preponderant immunoglobulin subtype (66 %), followed by IgG2 (24 %), IgG3 (7 %), and IgG4 (3 %) [54, 55]. Significant IgG1 and IgG3 synthesis occurs during the first year of life, reaching nearly normal adult levels by age 3–4 years; IgG2 and IgG4 levels, however, rise slowly during infancy, reaching adult levels at age 12 years or later [53]. IgG subclass deficiencies can present as isolated abnormalities or in consort with other immunodeficiency syndromes such as ataxia telangiectasia or IgA deficiency. Deficiency of one or more subclasses of IgG is possible despite normal or elevated total IgG serum concentrations. The true biologic significance of many reported IgG subclass deficiencies is not completely understood at the present time. Completely asymptomatic individuals who lack IgG1, IgG2, IgG4, or IgA1 because of heavy-chain gene deletions have been known to produce antibodies normally [56].

Since IgG1 is the predominant component of total IgG, its deficiency leads to low total IgG levels and often an increased susceptibility to infections. Patients with IgG2 deficiency present with recurrent respiratory infections, allergy, and asthma. Due to the significant contribution of IgG2 in antibodies to polysaccharide antigens, IgG2 deficient patients present with *Hemophillus influenza* or *Pneumococcal* pneumonias. Moreover, IgG2 deficiency is often accompanied by another IgG subclass deficiency or an IgA deficiency.

IgG3 has the shortest half life of all subclasses [57]. Studies in 12 subjects with normal IgG serum concentration demonstrated the average biologic half-life of IgG1, IgG2, and IgG4 to be 21 days, while that of IgG3 was only 7.1 days [57]. IgG3 deficiency was reported in 313 (4.7 %) patients after measuring IgG concentrations in 6,580 patients with recurrent infections. Most of the patients with IgG3 deficiency experience upper respiratory tract infections, but many also suffer from recurrent bronchitis, bronchopneumonia and asthma [58]. Isolated IgG3 deficiency was noted in almost half of the IgG3 deficient patients [58]. IgG4 often accompanies IgG2 deficiency [59], and patients present with recurrent infections and poor antibody responses to polysaccharide antigens [59].

Transient Hypogammaglobulinemia of Infancy (THI)

At birth neonates have IgG concentrations comparable to maternal serum levels. The total immunoglobulin level in the normal infant usually reaches a nadir at approximately 4–5 months of postnatal life. The rate of IgG synthesis

increases during the first year of life and reaches adult concentrations of total IgG by 7–8 year of age.

THI is defined as persistently low immunoglobulin in an infant beyond 6 months of age, after other causes of hypogammaglobulinemia have been excluded. It has been suggested that THI may be an extension of the physiologic nadir of hypogammaglobulinemia. There is considerable debate if low IgA levels should be included in defining THI. Due to considerable variability in IgA levels in infants, many authors recommend that diagnosis of THI be based on an IgG level at least two SDs below the normal mean for age, with or without low levels of other Ig isotypes [60]. The molecular basis for THI is conjectural at best. Suggested hypotheses in the pathogenesis of THI include a possible defect in maturation of T-helper cells [61] and cytokine abnormalities (TNF and IL-10) [62].

Treatment of Antibody Deficiency Diseases

The initial approach to patients with antibody deficiency diseases includes the early recognition of any acute or chronic active infection, followed by identifying the offending organism. Aggressive treatment with appropriate antibiotics is warranted. If the workup fails to demonstrate an etiologic agent, empirical treatment with broad spectrum antibiotics must be considered. The definitive treatment of antibody deficiency states is administration of intravenous immunoglobulins (IVIG). Broad antibody deficiency should be carefully documented before IVIG therapy is initiated. The IVIG therapy is intended to provide the missing antibodies. The minimum starting dose for IVIG is approximately 200 mg/kg/month. IVIG administration (400 mg/kg/month) has allowed XLA patients to achieve normal or near normal serum IgG levels and has significantly improved their clinical course [63]. Treatment of patients with CVID and Hyper IgM is similar to those with XLA patients. Patients with Hyper IgM syndrome should receive trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia [40].

Major adverse reactions to IVIG administration are uncommon. The most common adverse reactions associated with IVIG administration include myalgias, fever, rigors, nausea and vomiting. Systemic reactions are rare, and patients with absolute absence of IgA or panhypogammaglobulinemia have a small risk for anaphylaxis, particularly if the administered IVIG has a high concentration of IgA. Patients with CVID should be screened for anti-IgA antibodies and if they are detected, IVIG without IgA should be administered. Patients should be monitored while being administered IVIG as many adverse reactions may be related to the rate of flow of the administered IVIG. Most institutions have protocols for IVIG administration in which patients are premedicated with antihistamines and/or nonsteroidal anti inflammatory agents; the IVIG is initiated at a slow rate, and then the rate of IVIG administration is quickly increased as tolerated. There have been no documented cases of transmission of HIV by any IVIG preparation. Bone marrow transplantation is recommended in patients with CD40 ligand defect. Most patients with THI demonstrate a clinical recovery by 12–15 months of age although the immunoglobulin levels may not normalize until 5 years of age [64–66].

Combined Immunodeficiencies

This profound group of immunodeficiencies is broadly characterized by defects in T-cell function and/or development; it is variably associated with deficiencies of other lymphocyte lineages (B-cell, natural killer (NK) cell). Common clinical manifestations include chronic diarrhea, recurrent respiratory and opportunistic infections, consequently leading to failure to thrive.

Severe Combined Immunodeficiency (SCID)

The overall frequency of these disorders is estimated to be 1 in 50,000–100,000 live births. SCID is associated with mutations of at least nine different genes [67]; it represents a heterogenous group of disorders characterized by defective or absent T and B-cell function, and inadequate NK cell function. Simply put, the underlying defect is a complete block in T-cell development or defective T-cell function and is associated with impaired B cell immunity [68]. These disorders, if untreated are highly fatal in the first year of life. Affected infants present with life-threatening bacterial, fungal, and viral infections. Children with SCID frequently present with sepsis, diarrhea, pneumonia, otitis media, and cutaneous infections. Recurrent infections along with diarrhea and malabsorption often lead to failure to thrive. Common bacterial and fungal organisms include gram-negative rods, candida, aspergillus, and *Pneumocystis carinii*; pathogenic viruses include cytomegalovirus, parainfluenza, adenovirus and respiratory syncytial virus. Infants with SCID lack the ability to reject foreign tissue, therefore are at risk for graft versus host disease (GVHD) from maternal immunocompetent T-cells crossing the placenta [69], or from T lymphocytes in non-irradiated blood products or allogeneic bone marrow. Other features include thymic hypoplasia, small lymph nodes, hepatosplenomegaly, and occasionally erythematosus maculopapular rash shortly after birth.

The suggested diagnostic criteria for SCID syndromes include a lymphopenic infant (<3,000 cells/mm^3), with less than 20 % CD3$^+$ T lymphocytes, and severe hypogammaglobulinemia (IgG <150 mg/dL) [46, 70]. The various lymphocyte phenotypes for different mutations for SCID are classified based on the number of the T, B and NK cells. These include (i) No T cells, B and NK cells present ($T^-B^+NK^+$SCID); (ii) No T and NK cells, B cells present ($T^-B^+NK^-$SCID); and (iii) all three types of lymphocytes

decreased ($T^-B^-NK^-$SCID). Some of the genetic mutations that cause SCID are discussed below.

X-linked Severe Combined Immunodeficiency (X-SCID)

X-SCID represents almost 40 % of all SCID patients. The abnormal gene has been mapped to Xq13 and codes for the common gamma chain (γc). The γc-chain is constitutively expressed by T, B, and NK cells, and is a component of six different cytokine receptors (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), all of which are necessary for the development of T and NK cells [71–73]. The binding of these cytokines to their specific receptor results in receptor dimerization, subsequent activation of Janus kinase 1 (Jak1) and Janus kinase 3 (Jak3) that are associated with the intra-cytoplasmic tails of the cytokine receptors. Activation and cross-phosphorylation of Jak1 and Jak3 leads to activation of STAT (*s*ignal *t*ransducer and *a*ctivators of *t*ranscription) proteins that mediate the transcription of the cytokine inducible genes [74]. In lymphocytes, these interactions are required for the proliferation and maturation of the lymphocytes. Absence of the γc molecule results in an early arrest of T and NK cell development, and absent immunoglobulin synthesis. The suggested diagnostic criteria for patients with X-SCID include (i) absolute lymphocyte count of <2,000/mm^3 with less than 200 cells/mm^3 CD3+ T cells; (ii) less than 100 cells/mm^3 NK cells; and (iii) increased percentages of B lymphocytes. Serum IgG and IgA levels are extremely low, as B cells do not undergo class switch recombination. X-SCID is diagnosed by examining the expression of γc molecule on the surface of lymphocytes and monocytes by immunofluorescence.

Jak3 Deficiency

Patients with SCID due to Jak3 deficiency are similar to patients with X-SCID. As mentioned above, Jak3 is a member of the *J*anus *a*ssociated family of protein *k*inases and plays a crucial role in hematopoietic cytokine signaling [75]. Therefore, mutations of JAK3 are very similar to X-SCID patients [76]. These include chronic diarrhea, severe respiratory infections, and failure to thrive. Similar to X-SCID, these patients have a virtual absence of T and NK cells but normal or elevated numbers of non functional B cells [77, 78]. Jak3 deficiency is diagnosed by Western blot analysis of Jak3 expression in patient's fresh lymphocytes or lymphoid cell lines.

Omenn Syndrome

Lymphocytes respond to a variety of viral and bacterial due to presence of different antigen receptors on its surface, thereby demonstrating their exceptional diversity. V(D)J recombination or recombination of variable (V), diversity (D), and joining (J) gene segments is the DNA rearrangement process that drives this diversity. Recombination activating gene (RAG)-1 and RAG-2 endonuclease proteins initiate the formation of immunoglobulin (Ig) and T-cell receptors, which are essential for B- and T-cell development, respectively. Most mutations in RAG-1 or RAG-2 genes result in a functional impairment of antigen receptor recombination, which causes T^-B^-SCID [79]. On the other hand, some RAG mutations with partial VDJ recombination activity present as Omenn Syndrome—T cells with T-helper 2 phenotype, absence of B lymphocytes and high serum IgE levels. Villa et al. reported mutations in the RAG1 and RAG2 in seven children with Omenn syndrome [80–82]. Omenn syndrome is an autosomal recessive SCID characterized by early onset of papular rash, scaly erythroderma, lymphadenopathy, hepatosplenomegaly, and severe respiratory infections and diarrhea. The diagnosis of Omenn syndrome is based on the typical clinical features described above. A characteristic feature of Omenn syndrome is marked eosinophilia. The identification of RAG1 and RAG2 mutation serves as confirmatory diagnosis.

Other defects that are not being discussed here include reticular dysgenesis, IL-7Rα deficiency, CD45 deficiency and Artemis deficiency.

Adenosine Deaminase (ADA) Deficiency

ADA is a 41 kDa protein encoded by a 32 kb gene located on chromosome 20q13.11 [83] and catalyzes the deamination of adenosine and deoxyadenosine to inosine and deoxyinosine. Deficiency of this enzyme leads to marked accumulations of adenosine, 2′-deoxyadenosine, and 2′-*O*-methyladenosine, leading directly or indirectly to T-cell apoptosis. This results in defective lymphocyte function, profound lymphopenia (mean absolute lymphocyte counts of <500/mm^3) and low absolute numbers of T, B and NK cells. Patients with ADA deficiency have variable B-cell function. The clinical presentation is similar to other forms of SCID but patients with ADA tend to present early with highly morbid infections and are likely to die before stem cell transplantation [84]. ADA patients can have associated skeletal, hepatic, and/or neurological abnormalities. The diagnosis is established by demonstrating <1 % of normal catalytic activity in hemolysates prepared from fresh or frozen packed erythrocytes. The precise diagnosis of ADA deficiency is important, as enzyme replacement is available for patients who are not candidates for stem cell transplant.

Purine Nucleoside Phosphorylase (PNP) Deficiency

PNP reversibly catalyzes the degradation of the purine nucleosides (inosine and deoxyinosine) to hypoxanthine, and guanosine/deoxyguanosine to guanine. PNP deficiency leads to the accumulation of excess intracellular levels of deoxyguanosine triphosphate and reduced levels of uric acid (≤1 mg/dl). Point mutations in the PNP gene on chromosome

14q13.1 account for these deficiencies; the exact mechanism is still unclear, however, accumulation of deoxyguanosine in lymphocytes may accelerate T cell apoptosis [85]. This rare autosomal recessive immunodeficiency is associated with immune and neurologic defects, lymphopenia, and decreased lymphoproliferative responses to mitogens. B cell defects are mild in infancy and the IgG and IgA levels abrogate over time. Patients with PNP deficiency develop autoimmune disease, vasculitis, hemolytic anemia and thrombocytopenic purpura. These patients are diagnosed by measuring erythrocyte PNP activity. Bone marrow transplant has been tried with mixed results, and the overall prognosis for PNP deficiency remains extremely poor.

Cartilage Hair Hypoplasia (CHH)

CHH is an autosomal recessive T cell deficiency associated with metaphyseal chondroplasia. Mutations in *RMRP*, a gene encoding an RNA component of the mitochondrial RNA processing ribonuclease (RNase MRP) [86] is responsible for CHH [87, 88]. This nuclear protein plays a role in DNA replication in mitochondria. It has primarily been reported among the Pennsylvania Amish community, although non-Amish cases have since been described. Patients with CHH demonstrate short stature, sternal defects, short and pudgy hands; hyperextensible joints of hands and feet but an inability to extend the elbows. The hair, eyebrows and eyelashes are sparse, silky white or yellow in color.

Primary Defects of Cellular Immunity

Primary T cell immunodeficiencies are rare inherited disorders that affect T cell development and function. These disorders usually manifest in childhood, but the presentation may vary depending upon the intensity of the gene defect. This section will discuss DiGeorge Syndrome and defective expression of the T-cell receptor-CD3 complex.

DiGeorge Syndrome

The constellations of symptoms defining this syndrome include, congenital T cell immunodeficiency, conotruncal cardiac anomaly, hypocalcemic tetany, unusual facies, and hypoplastic thymus gland [89]. The association of DiGeorge syndrome with chromosome 22 defect was first defined in 1981 [90]; however, all patients with chromosome 22q11.2 deletion do not have the clinical features of DiGeorge syndrome. The hemizygous chromosome 22q11.2 microdeletion is responsible for many, but not all of the manifestations in afflicted children [90, 91]. Several candidate genes have been identified in this region. Differential diagnosis includes velocardiofacial syndrome (VCFS), and the conotruncal anomaly face syndrome (CTAFS). It has been postulated that there is failure of thymus descent in many cases of partial or incomplete DiGeorge syndrome; the undescended thymi are present in other sites like the tongue, thyroid and middle ear. The word *CATCH22* has been used describe the syndrome of *C*ardiac anomalies, *A*bnormal facies, *T*hymic aplasia, *C*left palate, and *H*ypocalcemia associated with chromosome *22* deletions. The cardiac anomalies frequently associated with DiGeorge syndrome are interrupted aortic arch, tetralogy of Fallot, and truncus arteriosus. The cardiac defects occur in about 75–90 % of patients with the deletion, and hypocalcemia is present in about half of the patients. The characteristic facial features include hypertelorism, down-turned eyes, low set ears, and micrognathia. Other features include short philtrum of the upper lip, bifid uvula, and cleft palate. DiGeorge syndrome occurs in both males and females. Absolute lymphocyte counts are moderately low for age. The CD3 T cell counts are proportional to the degree of thymic hypoplasia [92]. T cell numbers and lymphoproliferative responses in these patients range from normal to completely absent. Almost all serum immunoglobulins are normal except reduced IgA levels [93]. Positive FISH test for a chromosome 22q11.2 deletion establishes the diagnosis. Hypocalcemia and heart disease are the exigent symptoms after birth and need to be addressed. The definitive therapy is a thymic transplant from an HLA identical donor [94].

Defective Expression of the T-Cell Receptor-CD3 Complex

The T cell receptor is assembled and expressed on the surface of T cells in association with CD3, which is a complex of six subunits (εγ,εδ,ζζ). Mutations of CD3 protein can lead to defective TCR expression. Affected patients have decreased T cell numbers and function.

Other Immunodeficiency Syndromes Associated with T Lymphocytes

Wiskott-Aldrich Syndrome (WAS)

WAS is an X linked inherited immunodeficiency characterized by eczema, atopic dermatitis, thrombocytopenic purpura, recurrent infections along with increased risk of autoimmune and neoplastic disorders [95, 96]. The affected gene WASP encodes for the WAS protein (WASP) and is located at Xp11.23 [97]. WASP is an intracellular signaling molecule involved in hematopoietic cell signaling, and plays an important role in cytoskeletal organization by regulating actin polymerization [98]. WASP interacts directly with two proteins Arp2 and Arp3, which form the Arp2/3 complex, and form actin filaments [99]. WASP is also a participant in the cytoplasmic tyrosine kinase pathway in B-lineage cells, and may serve as the substrate of Btk in vivo [100].

The average age of diagnosis is 21 months and most cases present with petechiae, eczema, thrombocytopenia, and bleeding. Patients with WAS have reduced platelets count (<70,000/mm^3), decreased mean platelet volume, and

functionally abnormal platelets. Ineffective thrombocytopoiesis, [101] and reduced survival of the defective platelets [102] leads to thrombocytopenia—consequently, patients with WAS can manifest early with intracranial hemorrhage after delivery, or excessive bleeding from a circumcision [95] or the umbilical stump [96]. Eczema customarily develops during the first year of life [96]. Patients with WAS present with recurrent childhood infections (otitis media, sinusitis, meningitis, sepsis, and pneumonia). Viral and fungal infections are severe and prolonged in WAS patients.

The natural course of the disease is further complicated by the development of malignancies such as leukemia and lymphoma. Approximately 40 % of the patients experience autoimmune diseases including hemolytic anemia, arthritis, vasculitis and inflammatory bowel. Both cellular and humoral immune dysfunction are present in these patients. Older children have lower lymphocyte counts as compared to normal lymphocyte counts in younger children. The immunoglobulin levels are characterized by a low serum IgM, and low to normal IgG levels; serum IgA and IgE levels are usually elevated. WAS patients are unable to generate antibody titers against polysaccharide antigens. Identification of WASP gene mutation serves as the confirmatory test for WAS. Flow cytometric analysis of lymphocytes for decreased or absent WASP help in the diagnosis of WAS.

Ataxia-Telangiectasia (A-T)

The prevalence of A-T in the population is estimated to be 1:40,000 live births. A-T is a complex autosomal recessive disorder characterized by cerebellar ataxia, oculocutaneous telangiectasia, combined immunodeficiency, and predisposition to malignancy. Telangiectasias are bright red horizontal torturous streaks across the bulbar conjunctivae and other parts of the face and neck. Ataxia-telangiectasia-mutated (ATM) protein is a member of the phosphoinositide 3-kinase (PI3-kinase) family—a nuclear serine/threonine protein kinase; it is involved in signal transmission through cell-cycle checkpoints, DNA recombination, apoptosis, and other cellular responses to DNA damage. The mutations of the ATM gene, lead to total loss of the ATM protein [103], whereas milder forms of A-T are associated with missense mutations. Hence, ATM deficient cells demonstrate inappropriate cell cycle progression, defective stress response pathways and apoptosis.

The earliest presenting symptom in a majority of patients is an ataxic gait [104, 105]. Most patients have difficulty with chewing and swallowing and experience repeated aspiration pneumonias [106]; these patients are also at risk for recurrent respiratory tract infections. Gradual deterioration of gross and fine motor skills continues until 7 years of life. Other neurological manifestations include choreiform movements of the hands and feet, tremors, and myoclonus. The cutaneous manifestation include telangactasias, atrophic thinning of skin on the hands and feet, premature graying of hair and skin discoloration. The major causes of morbidity and mortality in these patients include pneumonias, chronic lung disease and carcinomas. Patients with A-T predominantly develop non-Hodgkin's lymphoma, leukemia and solid tumors.

Immunodeficiency is variable in patients with A-T. Most A-T patients have deficiency of cell mediated immunity [107]—lymphopenia, reduced CD4 cells, and depressed T cell function [108]. Patients with A-T demonstrate decreased levels of IgA and IgG subclass [109, 110] along with decrease in antibody production.

When the classical signs of A-T are present (progressive ataxia, neurodegeneration and telangiectasia), the diagnosis is relatively straightforward. However, in the absence of these characteristic signs, the diagnosis of A-T can be challenging. An elevation of the serum alpha feto-protein level in children older than 8 months assists in diagnosing these patients. The diagnosis of A-T can be confirmed by identification of both ATM mutations. There is no treatment for A-T at the present time. All patients should receive supportive care and immunoglobulin replacement.

Combined Immunodeficiency (CID or Nezelof Syndrome)

CID is characterized by mild impairment of the T cell function, as compared to its complete absence in SCID patients. Patient with this autosomal recessive disease often have recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, gram-negative sepsis, and urinary tract infections. The serum immunoglobulins are usually normal, although isolated immunoglobulins can be abnormal. The thymuses are small with paucity of thymocytes, and usually no Hassall's corpuscles.

Treatment of Cellular Immunodeficiency

The prognosis of untreated cellular or combined immunodeficiency is poor. As previously mentioned, early identification and aggressive treatment of bacterial, viral, and fungal infections is instrumental in prolonging survival in these patients. Other measures include IVIG (for B cell defects) and co-trimoxazole prophylaxis for *Pnemocystis carinii infection*. The standard treatment of patients with fatal T-cell or combined T- and B-cell defects is transplantation of MHC compatible or haploidentical parental bone marrow [111]. The results of bone marrow transplantation have improved considerably over the last decade. The major risk for the bone marrow transplant recipient is graft-versus-host disease. The development of techniques to eliminate the T cells from the marrow inoculum has enhanced the success of haploidentical (half-matched) bone marrow cells and minimized GVHD [112]. These techniques employ soybean lectin

Table 29.3 Inherited complement deficiencies and clinical associations

Presenting syndrome	Deficient component	Pathway	Clinical associations
Rheumatic disorders	C1q, C1r, C1s, C4, C2, C4	CP	Autoimmune conditions particularly SLE
	Mannose-binding lectin (MBL)	LP	Autoimmune conditions particularly SLE
Infection	C1q, C1r, C1s, C2, C4	CP	Recurrent pyogenic bacterial infections
	C3	Common to CP, AP, LP	Severe, recurrent infections-encapsulated bacteria
	C5, C6, C7 C8, or C9	MAC	Recurrent meningococcal infections
	Factor H	AP inhibitor	Recurrent meningococcal infections, glomerulonephritis and HUS
	Factor I	AP inhibitor	Encapsulated pyogenic bacterial infection
	Properdin	AP	Recurrent meningococcal infections
	Mannose-binding lectin (MBL)	LP	Pyogenic infections sepsis in children and neonates
Hereditary angioedema (HAE)	C1-Inh	CP inhibitor	HAE

incubation, followed by sheep erythrocyte rosette depletion or incubation with monoclonal antibodies to T cells plus complement. Both methods enrich the final cell suspension in stem cells. Patients with less severe forms of cellular immunodeficiency, such as Nezelof syndrome, Wiskott-Aldrich syndrome reject HLA-identical marrow grafts. Hence, these patients are treated with immunosuppressive agents before transplantation.

The treatment for ADA deficient patients is bone marrow or blood stem cell transplantation from an HLA identical sibling. The outcome for patients transplanted with a non HLA-matched sibling donor marrow is generally poor. Alternative therapies for ADA deficient patients include enzyme replacement. Polyethylene glycol–modified bovine ADA (PEG-ADA) is administered intramuscularly once a week. The plasma ADA activity peaks in 24–48 h and declines over the next few days. A retrospective study demonstrated that the lymphocyte counts of all PEG-ADA treated patients were below the normal range at all times [113]. The clinical course of the study patients was far superior to the expected course with recurrent severe, life-threatening infections compared to the group that did not receive any intervention [113]. Bone marrow transplantation remains the effective, mainstream therapy for these inborn errors of the immune system, till newer modalities like gene therapy are perfected.

Complement Deficiencies

The complement pathway is an enzymatic reaction cascade composed of a series of proteins and cellular receptors that are instrumental in host defense, inflammation, and immune complex clearance. Briefly, this pathway can be activated by three different mechanisms—(i) Classic pathway (ii) alternative pathway, and (iii) the mannan-binding lectin pathway. Among the many activators that can potentially activate the classic pathway, activation usually occurs when C1q binds to the Fc portion of an antibody in an immune complex [114, 115]. The alternative and MBP pathways are able to function even in the absence of the antibody. All the three pathways merge at the C3 step and lead to the formation of a membrane attack complex (C5b6789). The common end point is promoting inflammation, eliminating pathogens, and enhancing the immune response.

The majority of complement deficiencies are inherited in an autosomal recessive pattern; the exception is properdin deficiency—an X-linked trait. Complement deficiencies can manifest as recurrent infections, autoimmune disorders, hereditary angioedema, and renal damage (Table 29.3, modified from reference [116]). The complement system is tightly regulated by complement inhibitors and inactivating proteins. Deficiency of regulator proteins results in excessive complement consumption, inflammation, destruction of self-tissue, and depletion of C3 or other components downstream of the missing control protein [116].

Rheumatic Diseases in Complement Deficiencies

Rheumatic diseases associated with complement deficiencies include systemic lupus erythematosus (SLE), discoid lupus, dermatomyositis, scleroderma, anaphylactoid purpura, vasculitis, and membranoproliferative glomerulonephritis [117, 118].

There are two hypotheses that have been put forward to explain the causal link between complement deficiency and the development of SLE [119]. First, injured tissue and dying cells serve as auto-antigens and lead to increased autoantibodies promoting tissue inflammation. Secondly, complement deficient individuals demonstrate impaired mechanisms of tolerance induction and maintenance, contributing further to autoantibody production [119]. Homozygous deficiency of the early components of the CP (C1q, C1r, C1s, C4 and C2) pathway predisposes children to develop SLE [119]. The incidence of SLE in patients with C1q, C4, or C2 deficiency is 90, 75, and 15 %, respectively [120]. Association

and severity of SLE co-relates with the deficient complement protein i.e. patients deficient in C4 [120, 121] or one of the C1-complex proteins [120, 122] exhibit a highly prevalent (>80 %) and life threatening disease, as compared to patients that are deficient in C2 [123]. This relationship has not been validated in partial complement deficiencies states; however, a recent report associated decreased serum levels of C1q due to a single nucleotide polymorphism (SNP) in the C1qA gene with increased incidence of sub-acute cutaneous lupus erythematosus [124].

The complement C4 exists in two isoforms and is encoded by separate genes—*C4A* and *C4B* located in the MHC class III region. A relatively high frequency of *C4A* and *C4B* null alleles has been associated with SLE [125, 126]. Homozygous or partial deficiency of C4A is defined as lower expression of C4A relative to C4B in plasma or serum [127, 128]. Cumulative results from more than 35 different studies in all ethnic groups have revealed the presence of C4A heterozygous and homozygous deficiencies in 40–60 % of SLE patients [129].

Infections in Complement Deficiencies

The prevalence of complement deficiency in patients with serious infections, i.e., *Streptococcus pneumoniae* and *Haemophilus influenzae* is extremely low. Hence, screening every patient with first episode of bacterial infection for complement deficiencies is not practical. However, patients with auto-immune disease who present with significant bacterial illness should be evaluated for complement deficiencies. Patients with C2, C3 and C4 deficiencies demonstrate an increased susceptibility to develop severe infections with encapsulated organisms (*Streptococcus pneumoniae* and *Haemophilus influenza type b*) [117, 130]. The presentation of C3 manifests is remarkably similar to hypogammaglobulinemia and manifests as severe, recurrent pyogenic infections beginning shortly after birth [118, 131]. These infections are commonly blood-borne and manifest as sepsis, meningitis, and arthritis. Other complement deficiencies associated with *Streptococcus pneumoniae* infections include C1q, C1r, C1s, and properdin [117, 130].

The prevalence of complement deficiency (C5–C9) in patients with recurrent meningococcal disease is approximately 40 % [132, 133], and patients with this deficiency are unable to form the membrane attack complex [118, 134]. C6 deficiency is a common complement deficiency and is associated with systemic blood-borne meningococcal infections [117, 130]. Similarly, patients with C7, C8 and C9 deficiency have an increased susceptibility to systemic meningococcal infections [117, 130]. Patients with C5 deficiency have absent total hemolytic complement (CH_{50}) activity. In contrast, patients with Factor D (activates alternative pathway) deficiency have normal CH_{50} and C3 levels [135]. Patients with this rare deficiency experience meningococcal and pneumococcal infections. Other factors (I and H) function as control proteins of the alternative pathway. Factor I deficiency is inherited as an autosomal recessive trait, and patients with this deficiency have uncontrolled activation and consequent depletion of C3 via the alternate pathway [136]. C3 dependent activities like the bactericidal, opsonic, and chemotactic activities are impaired in patients with factor I deficiency.

Factor I deficient patients are prone to develop infections caused by encapsulated pyogenic bacteria. Factor H is an inhibitor of the alternative pathway activation, and its deficiency leads to persistent activation of the alternative pathway and subsequent depletion of C3. Common clinical manifestations of Factor H include hemolytic uremic syndrome, glomerulonephritis and meningococcal infections. Properdin enhances the activity of AP by stabilizing the alternative pathway C3 and C5 converting enzymes. The majority of patients with properdin deficiency are affected with meningococcal disease [117].

Hereditary Angioedema (HAE)

HAE is a rare, autosomal-dominant disorder of C1 inhibitor (C1INH) deficiency. C1 INH binds to C1r and C1s leading to dissociation of the C1 macromolecular complex [137]. Hereditary Angioedema is characterized by reduced C1INH functional activity due to either a deficient or dysfunctional C1INH protein [138]. The precise mechanism by which reduction of C1INH activity leads to angioedema is unclear. C1 INH deficiency presents in adolescent or early childhood with recurrent attacks of submucosal or subcutaneous edema; edema worsens for 12–36 h and then subsides over a period of days. Patients can present with life threatening edema of the upper airway [139], abdominal pain, nausea and vomiting. Urticaria is not a presenting feature of C1 INH deficiency, but erythema has been reported in some patients [140].

Serum C4 level has been recommended as a good screening test for C1 INH deficiency, as serum C4 is invariably low in untreated HAE (C4 <30 % of mean normal level) [141]. A recent case report discusses a patient presenting with angioedema and normal C4 concentration [142]. Hence it may be prudent to measure both C4 and C1 inhibitor concentrations. The confirmatory diagnosis of type I HAE (85 % of cases) is by demonstrating low amounts of C1 inhibitor protein by immunochemistry.

Treatment of Complement Deficiencies

Since it is not possible to replace the specific complement, the management of complement deficiencies is limited to supportive care, and managing secondary complications associated with the deficient complement. Studies support the use of vaccination as a preventive measure in terminal complement deficient individuals [143]. As post vaccination

acquired immunity wanes, frequent booster immunizations should be administered [144]. The treatment of rheumatological disorders in complement deficiency entails the use of anti-inflammatory and immunosuppressive agents.

The treatment of acute episodes of hereditary angioedema is largely dictated by the degree of swelling. Episodes of peripheral swelling do not require treatment, but danazol given early in the course of an attack may shorten the duration. If there is suspicion of airway involvement, C1 INH concentrate should be given promptly. Early intervention decreases morbidity and prevents complications. The long term prophylaxis of HAE is androgens that increase serum concentrations of the normal C1 INH by increasing C1 INH gene transcription [145, 146]. Maintenance therapy should be considered in patients with frequent episodes of severe abdominal pain, head, neck swelling and frequent peripheral or genital swelling. The endocrinological side effects of androgens preclude its use in pre-pubertal children. An alternative strategy involves prophylactic administration of antifibrinolytic agents (transexamic acid) [147] or epsilon-aminocaproic acid (EACA). This has proved useful in reducing the frequency or severity of attacks. Short term prophylaxis for dental procedures or surgeries can be achieved by infusion of C1 inhibitor concentrate 24 h prior to the procedure [148].

Phagocytic Disorders

During inflammation, a series of coordinated processes steer the phagocytes to the site of inflammation; predominantly, the increasing gradient of chemo-attractants are instrumental in guiding the leukocytes to the inflammatory sites. Prior to the firm adhesion and diapedesis of phagocytes at sites of tissue injury and inflammation, the selectin family of adhesion molecules mediates the initial attachment of leukocytes to endothelial cells. The selectin family consists of three closely related cell-surface molecules with varying expression by different cells—L-selectin (leukocytes), P-selectin (platelets), and E- and P-selectin (vascular endothelium). The ligands for these selectins are glycans or mucins that possess the Sialyl Lewis moiety. Neutrophils and monocytes must adhere firmly to endothelial cells to migrate to the extravascular tissue. Active β_2 integrins mediate leukocyte adhesion and transmigration across the endothelium through interactions with (intercellular adhesion molecule-1) ICAM-1 on the activated endothelium [149]. The β_2 integrin family is composed of four integrin family members, CD11a/CD18 [lymphocyte function-associated antigen-1 (LFA-1)], CD11b/CD18 (Mac-1), CD11c/CD18 and CD11d/CD18, which are heterodimers composed of a unique α (CD11) subunit complexed to a common β_2 (CD18) subunit [149, 150]. This is followed by diapedesis (migration of neutrophils between the endothelial cell junctions in to the extravascular tissue), and chemotaxis (movement to the center of the inflammation). This culminates in either a full expression of phagocytic activation followed by opsonization and ingestion. After ingestion, the pathogen is engulfed into a closed vacuole called as a phagosome.

The secondary granule of the phagocytes fuses with the phagosome and deposits cytochrome in the membrane. NADPH oxidase is a heterodimeric membrane-bound complex embedded in the walls of secondary granules of the phagocytes that remain dormant till its activation. For the activation to begin, three cytoplasmic components $p67^{phox}$, $p47^{phox}$ and $p40^{phox}$ translocate to the membrane bound cytochrome (composed of $gp91^{phox}$ and $p22^{phox}$). The activation and translocation of *rac*, a member of the low-membrane-weight guanosine triphosphate (GTP)-binding protein to the cytochrome complex is necessary for NADPH oxidase activation [151].

The NADPH complex catalyzes the transfer of electrons from NADPH to molecular oxygen (O_2) resulting in $NADP^+$ and superoxide. The term respiratory burst is used as the conversion of O_2 to O_2^- increases the O_2 consumption of the cell by up to 100-fold [152]. The resulting unstable superoxide is converted to hydrogen peroxide by superoxide desmutase. Myeloperoxidase (MPO) catalyzes hydrogen peroxide to form potent microbicidal oxidants i.e., hypochlorous acid (HOCl) or OH^-. Defects in these pathways lead to poor inflammatory response because of poor recruitment of neutrophils to the inflammatory site.

Leukocyte Adhesion Deficiency Type I (LAD)

LAD type I is a rare autosomal recessive disorder affecting one in ten million individuals. First described almost 25 years ago, patients present with recurrent bacterial infections, delayed separation of the umbilical cord, neutrophilia, and neutrophil defects [153, 154]. Other distinctive features include impaired pus formation and wound healing. LAD-1 results from mutations of gene on chromosome 21q22.3, and leads to impaired expression of CD18, which is required for β2 integrin functioning. Defects in CD18 expression lead to decreased expression or absence of CD11a, Cd11b and CD11c [155, 156]. Deficient CD11/CD18 neutrophils are unable to form adhesions with the endothelium, leading to the impaired migration of neutrophils to the infection site.

Patients with severe LAD (<1 % of the normal CD18 expression) often present with persistent leukocytosis, delayed umbilical separation and omphalitis. Other features include recurrent bacterial infections of the skin, respiratory tract, bowel, and peri-rectal areas. Common infecting organisms include *Staphylococcal aureus*, gram negative organisms, *Candida*, and *Aspergillus*. During infections, these patients have high circulating neutrophil count typically exceeding 25,000/μL. The infected sites have reduced pus

formation, and few neutrophils are identified on histopathology. LAD patients also suffer from severe gingivitis, peridontitis, and loss of teeth [157, 158]. Patients with the moderate phenotype of LAD-1 (1–30 % of normal CD18 expression on neutrophils) are diagnosed later in life.

The diagnosis is made by flow cytometric analysis demonstrating significant reduction or absence of CD18 and other molecules like CD11a, CD11b, and CD11c on neutrophils. Abnormalities of neutrophil, monocyte adherence and chemotaxis in LAD-1 have also been documented [157].

LAD Type 2

LAD type 2 is an extremely *rare* autosomal recessive inherited disease of fucose metabolism [159, 160]. As mentioned previously, the initial rolling of the neutrophils in response to inflammation is dependent on selectins present on the surface of the endothelial cells. The neutrophilic ligands for these selectins are the sialyl Lewis protein. Mutations in the guanosine diphosphate-fucose transporter gene lead to abnormal fucosylation of the Sialyl Lewis protein leading to impaired neutrophilic performance [161, 162]. The clinical features of LAD type 2 patients are similar to LAD type 1, except the infections are less frequent and severe [159, 163]. In addition, these patients have mental retardation, short stature and cranio-facial abnormalities.

Chronic Granulomatous Disease

The incidence of chronic granulomatous disease (CGD), a genetically heterogenous disorder in US is 1 in 200,000 to 1 in 250,000 live births [164]. At least 20 patients are born every year with CGD. The disease is caused by a defect in the NADPH oxidase enzyme system. As discussed above, NADPH is responsible for the *phagocyte respiratory burst an*d the generation of microbicidal oxidant production. Approximately 70 % of the cases of CGD result from mutations in the X chromosome gene (CYBB gene (Xp21)) encoding $gp91^{phox}$. CGD is also caused by disabling mutations in genes encoding $gp47^{phox}$ (25 %), $gp67^{phox}$ (<5 %) $gp22^{phox}$ (<5 %). These mutations disrupt the NADPH oxidase complex and result in impaired production of hydrogen peroxide. There is a single case report of a patient with rac2 gene mutation who presented with recurrent infections and defective neutrophil cellular functions. Recent data from a U.S. registry of 368 CGD patients showed that 259 patients have X-linked recessive form of CGD, 81 have 1 of the autosomal recessive forms, and in 28 patients the mode of inheritance is unknown [164].

CGD patients present with dermatitis, subcutaneous abscesses, and abscess formation in the organs of the mononuclear phagocyte system. The hallmark of CGD is recurrent infections with catalase-producing pathogens. Staphylococcal liver abscesses are almost pathognomonic for CGD [165, 166]. As per the published data from U.S. registry of CGD patients, pneumonia caused was the most prevalent infection, followed by suppurative adenitis, subcutaneous abscess, liver abscess, osteomyelitis, and sepsis [164, 165]. Common organisms responsible for these infections include *Aspergillus*, *Staphylococcus* and *Salmonella*. Aspergillus pneumonia with or without sepsis is the leading cause of death in CGD patients. *Aspergillus fumigatus* was commonly isolated, but *Aspergillus nidulans* was most virulent based on mortality and severity of infections [167].

The sequelae of infections in CGD are abnormally prolonged and are also characterized by tissue granuloma formation. Other manifestations include skin ulceration, excessive inflammation, gingivitis, gastric outlet obstruction [168, 169], systemic lupus erythematosus, and inflammatory bowel disease. The genitourinary manifestations of CGD include bladder granulomata, uretral obstruction, and urinary tract infection [170].

The initial presentation of a CGD patient with life threatening infections may not include fever and leukocytosis. An elevated erythrocyte sedimentation rate may be the only abnormal laboratory test [166]. CGD screening is accomplished by the nitroblue tetrazolium (NBT) dye test, which screens for adequate superoxide anion. Another commonly used test is the Dihydrorhodamine 123 (DHR) test. Neutrophils stimulated by phorbol ester, using metabolic burst can oxidize DHR to form a brightly fluorescent compound rhodamine 123, which is measured fluorometrically. This assay is performed by the flow cytometry method using lysed whole blood.

Chediak-Higashi Syndrome (CHS)

This rare autosomal recessive disorder is characterized by oculocutaneous albinism, bleeding diathesis, peripheral neuropathy, and increased susceptibility to infection. Patients with CHS demonstrate hypopigmentation of the skin, iris, and hair, along with recurrent infections and neuropathy. Neurological manifestations include ataxia, seizures, progressive neuropathy, and cranial nerve palsies [171, 172]. The hallmark of CHS is the presence of giant abnormal granules in all granule-containing cells i.e., melanocytes, neutrophil, lymphocytes, central and peripheral nerve tissue, pancreatic cells, fibroblast and hair. CHS has been associated with mutations in the lysosomal trafficking regulator (LYST) gene located on chromosome 1q42.1–42.2, however, the precise mechanism linking LYST abnormalities to CHS is unclear at the present time.

The clinical course is characterized by recurrent severe infections, culminating in the *accelerated phase* of lymphoproliferation and hemophagocytosis. The deposition of lymphohistiocytes in the liver, spleen, lymph nodes, and bone marrow leads to hepatosplenomegaly, bone marrow infiltration, and hemophagocytosis [173]. Other characteristics of this syndrome include hypertriglyceridemia, hypofibrinogenemia. These patients have defective cytotoxic T-cell and natural killer-cell function, decreased chemotaxis of macrophages and polymorphonuclear leukocytes, and delayed

intracellular killing. Morphological examination of peripheral blood and bone marrow demonstrates giant primary granules are seen in neutrophils, eosinophils and basophils and lymphocytes. The confirmatory test is the presence of a mutated LYST gene.

Treatment of Phagocytic Disorders

The curative therapy for patients with LAD1 and 2 is bone marrow transplantation [174, 175]. Gene therapy for LAD-1 is in pre-clinical trials, and not yet ready for therapeutic trials. Treatment of LAD-2 patients with fucose has been tried, and the results have not been successful. Early recognition and aggressive treatment of infections with appropriate antibiotics can be lifesaving.

Prophylactic therapy with long-term trimethoprim-sulfamethoxasole (TMP-SMZ) in CGD patients has been shown to reduce the frequency of infections and also increase the duration of infection-free periods [176, 177]. Itraconazole prophylaxis has been shown to reduce the rate of fungal infections in CGD patients [178]. Hepatic abscesses often need to be surgically drained. Interferon-γ (IFN-γ) has been shown to increase H_2O_2 generation in circulating monocytes, and hence was tried in patients with CGD [179]. In a large multi-center placebo controlled study, CGD patients that received prophylactic IFN-γ (50 μg/m^2 subcutaneously three times weekly) demonstrated a 70 % decrease in the incidence of infections as compared to patients who did not receive IFN-γ [180]. Gastric outlet obstruction and granulomatous cystitis have been successfully managed with prolonged antimicrobial therapy and prednisone. Bone marrow transplantation has been carried out in several CGD patients with limited success [181, 182]. CHS patients in the accelerated phase have been treated with etoposide (VP 16), steroids and intrathecal methotrexate. Following this regimen, transient remissions have been reported [183]. HLA matched bone marrow transplant is the only curative therapy for CHS patients.

Part II Secondary Immunodeficiency Syndromes

The Acquired Immunodeficiency Syndrome (AIDS) is the prototype for the secondary immunodeficiency syndromes and is reviewed in detail in a subsequent chapter. Other secondary immunodeficiency syndromes that commonly present to the PICU are discussed briefly here.

Treatment with Immunosuppressive Agents

The use of medications that intentionally suppress the immune system (reviewed in the previous chapter) is the cornerstone in managing children with organ transplants, autoimmune and inflammatory disorders. Although the goal of therapy is often to achieve a controlled level of immunosuppression, resultant alterations in host immunity increase vulnerability to infection. Therapy-induced depression of the humoral, cellular and phagocytic systems, even if transient, can lead to infection by newly acquired organisms including opportunistic infections and common pathogenic bacteria, or reactivation of latent infections such as *Herpes simplex* and V*aricella-zoster* [176, 177].

Immunoparalysis and the Immune Response to Trauma, Surgery, Burns, and Anesthesia

The response to tissue injury and trauma is a complex integration of events that act to prevent infection and promote healing. This is marked by the release of proinflammatory cytokines [178], activation of adhesion molecules [179], and increased numbers and activity of circulating granulocytes [86, 178]. What often follows is a significant depression of both acquired [180] and innate immune function [86, 180, 181] with increased risk of sepsis and nosocomial infection [181, 182]. The clinical events that lead to altered immunity after trauma may include tissue injury, ischemia, hypovolemia, blood transfusions, endocrine mediator release, pain and surgery [183]. The stress of surgery, particularly when associated with traumatic injury can result in a similar pattern of immune response that can contribute to end-organ injury, leading to multiple organ system failure and death [103, 184]. Burn injuries are well known to adversely affect host immunity and increase the risk of infection [185]. Loss of tissue integrity following a burn injury disrupts the epithelial barrier, thus making the patient more vulnerable to the invasion of ubiquitous microorganisms. The increased risk of infection is compounded by decreased circulating immunoglobulins [186], as well as inhibited chemotaxis, phagocytosis and bacterial killing [124, 187–189].

Drugs administered for the purpose of anesthesia have been known to affect the immune function. Opioids in particular have been shown depress immunity [181, 190, 191], but the immunologic effects of nonopioid anesthetics are less well documented. Human and animal studies have suggested that some intravenous [192] and inhaled anesthetics [193] can depress neutrophil (PMN) and mononuclear cell (MNC) function, leading to increased experimental mortality from infection and sepsis [194]. In clinical practice, however, the independent impact of anesthesia on the immune system is difficult to separate from the apparently more important surgical stress, tissue injury and potentially the baseline condition that led to the procedure. In the absence of surgery, immune function is only mildly and transiently affected in healthy volunteers [183].

Altered Immunity due to Intercurrent Illness or Insult

Host immunity can be adversely affected by intercurrent infections and insults. Infections by parasites such as *Plasmodium falciparum* or *Trypanosoma* [195] but, more commonly, viruses are well known to impair normal cellular and humoral immune responses leading to an increased susceptibility of secondary bacterial infections [196]. Local organ insults can also impair host immunity and the antibacterial response system. Gastric aspiration has been shown to create an acute pro-inflammatory response and a more persistent anti-inflammatory state that decreases pulmonary bacterial clearance in face of a subsequent bacterial challenge [197]. An injurious mechanical ventilation strategy has also been shown to adversely affect the host antibacterial response in the experimental setting [198]. These factors might contribute to the increase risk of secondary bacterial infection in mechanical ventilated patients following an initial non-infectious pulmonary insult.

Treatment of Phagocytic Disorders

The curative therapy for patients with LAD1 and 2 is bone marrow transplantation [174, 175]. Gene therapy for LAD-1 is in pre-clinical trials, and not yet ready for therapeutic trials. Treatment of LAD-2 patients with fucose has been tried, and the results have not been successful. Early recognition and aggressive treatment of infections with appropriate antibiotics can be lifesaving.

Prophylactic therapy with long-term trimethoprim-sulfamethoxasole (TMP-SMZ) in CGD patients has been shown to reduce the frequency of infections and also increase the duration of infection-free periods [176, 177]. Itraconazole prophylaxis has been shown to reduce the rate of fungal infections in CGD patients [178]. Hepatic abscesses often need to be surgically drained. Interferon-γ (IFN-γ) has been shown to increase H_2O_2 generation in circulating monocytes, and hence was tried in patients with CGD [179]. In a large multi-center placebo controlled study, CGD patients that received prophylactic IFN-γ (50 μg/m^2 subcutaneously three times weekly) demonstrated a 70 % decrease in the incidence of infections as compared to patients who did not receive IFN-γ [180]. Gastric outlet obstruction and granulomatous cystitis have been successfully managed with prolonged antimicrobial therapy and prednisone. Bone marrow transplantation has been carried out in several CGD patients with limited success [181, 182]. CHS patients in the accelerated phase have been treated with etoposide (VP 16), steroids and intrathecal methotrexate. Following this regimen, transient remissions have been reported [183]. HLA matched bone marrow transplant is the only curative therapy for CHS patients.

Part II Secondary Immunodeficiency Syndromes

The Acquired Immunodeficiency Syndrome (AIDS) is the prototype for the secondary immunodeficiency syndromes and is reviewed in detail in a subsequent chapter. Other secondary immunodeficiency syndromes that commonly present to the PICU are discussed briefly here.

Treatment with Immunosuppressive Agents

The use of medications that intentionally suppress the immune system (reviewed in the previous chapter) is the cornerstone in managing children with organ transplants, autoimmune and inflammatory disorders. Although the goal of therapy is often to achieve a controlled level of immunosuppression, resultant alterations in host immunity increase vulnerability to infection. Therapy-induced depression of the humoral, cellular and phagocytic systems, even if transient, can lead to infection by newly acquired organisms including opportunistic infections and common pathogenic bacteria, or reactivation of latent infections such as *Herpes simplex* and V*aricella-zoster* [184, 185].

Immunoparalysis and the Immune Response to Trauma, Surgery, Burns, and Anesthesia

The response to tissue injury and trauma is a complex integration of events that act to prevent infection and promote healing. This is marked by the release of proinflammatory cytokines [186], activation of adhesion molecules [187], and increased numbers and activity of circulating granulocytes [186, 188]. What often follows is a significant depression of both acquired [189] and innate immune function [188–190] with increased risk of sepsis [191] and nosocomial infection [190]. The clinical events that lead to altered immunity after trauma may include tissue injury, ischemia, hypovolemia, blood transfusions, endocrine mediator release, pain and surgery [192]. The stress of surgery, particularly when associated to traumatic injury, can result in a similar pattern of immune response that can contribute to end-organ injury, leading to multiple organ system failure and death [186, 193]. Burn injuries are well known to adversely affect host immunity and increase the risk of infection [194]. Loss of tissue integrity following a burn injury creates a break in the efficient epithelial barrier, thus making the patient more vulnerable to the invasion of ubiquitous microorganisms. The increased risk of infection is compounded by decreased circulating immunoglobulins [195], as well as inhibited chemotaxis, phagocytosis and bacterial killing [130, 196–198].

Drugs administered for the purpose of anesthesia have been known to affect the immune function. Opioids in particular have been shown depress immunity [190, 199, 200], but the immunologic effects of nonopioid anesthetics are less well documented. Human and animal studies have suggested that some intravenous [201] and inhaled anesthetics [202] can depress neutrophil (PMN) and mononuclear cell (MNC) function, leading to increased experimental mortality from infection and sepsis [203]. In clinical practice, however, the independent impact of anesthesia on the immune system is difficult to separate from the apparently more important surgical stress, tissue injury and potentially the baseline condition that led to the procedure. In the absence of surgery, immune function is only mildly and transiently affected in healthy volunteers [192].

Altered Immunity due to Intercurrent Illness or Insult

Host immunity can be adversely affected by intercurrent infections and insults. Infections by parasites such as *Plasmodium falciparum* or *Trypanosoma* [204] but, more commonly, viruses are well known to impair normal cellular and humoral immune responses leading to an increased susceptibility of secondary bacterial infections [205].

Local organ insults can also impair host immunity and the antibacterial response system. Gastric aspiration has been shown to create an acute proinflammatory response and a more persistent anti-inflammatory state that decreases pulmonary bacterial clearance in face of a subsequent bacterial challenge [206]. An injurious mechanical ventilation strategy has also been shown to adversely affect the host antibacterial response in the experimental setting [207]. These factors might contribute to the increase risk of secondary bacterial infection in mechanical ventilated patients following an initial non-infectious pulmonary insult.

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Sepsis

30

James L. Wynn, Jan A. Hazelzet, Thomas P. Shanley, Hector R. Wong, and Derek S. Wheeler

Abstract

The management of the child with sepsis represents the *sine qua non* of pediatric critical care medicine. Overwhelming sepsis and septic shock often manifest with concurrent derangements of cardiovascular function, intravascular volume status, respiratory function, immune regulation, renal function, coagulation, hepatic function, and metabolic function – sepsis literally affects every organ system to some degree. The degree to which any of these derangements are manifest in a given child is highly variable and influenced by multiple host and pathogen factors, including the child's developmental stage, the presence or absence of co-morbidities, the host's immune/inflammatory state, the host's genetic background, and the specific pathogens involved. These factors combine, in turn, to profoundly influence the ultimate outcome. Successful management of critically ill children depends upon early recognition, early treatment with antibiotics, and early reversal of shock.

Keywords

SIRS • CARS • Sepsis • Severe sepsis • Septic shock • MODS • Early goal-directed therapy • Shock

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> Hectic fever (sepsis) at its inception is difficult to recognize but easy to treat; left untended, it becomes easy to recognize but difficult to treat…
>
> Machiavelli, *The Prince*

Introduction

The management of the child with sepsis represents the *sine qua non* of pediatric critical care medicine. Sir William Osler once stated that *to know syphilis is to know medicine*. To a similar extent, it has been said that *to know sepsis is to know critical care medicine* [1]. Overwhelming sepsis and septic shock often manifest with concurrent derangements in cardiovascular function, intravascular volume status, respiratory function, immune/inflammatory regulation, renal function, coagulation, hepatic function, and metabolic function – sepsis literally affects every organ system to some degree. The degree to which any of these derangements are manifest in a given child is highly variable and influenced by

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multiple host and pathogen factors, including the child's developmental stage, the presence or absence of co-morbidities, the host's immune/inflammatory state, the host's genetic background, and the specific pathogens involved. These factors combine, in turn, to profoundly influence the ultimate outcome.

Sepsis is a major cause of morbidity and mortality among children. Modern intensive care and a better understanding of this disease have led to significant improvements in mortality. For example, sepsis associated mortality decreased from a majority of children in 1966 (i.e., close to 100 %) [2] to approximately 10 % among children in developed countries today [3, 4]. Despite the tremendous advances made in the last few decades, the morbidity and mortality attributed to sepsis remain unacceptably high. Severe sepsis is still one of the leading causes of death in children with almost 4,500 deaths reported annually in the United States alone [5]. Worldwide, especially in developing countries, the toll of sepsis in terms of mortality and costs is probably much higher, although exact figures are lacking. However, if all of the pediatric deaths resulting from infectious diseases are considered in aggregate, sepsis is clearly the leading killer of children worldwide (see further discussion below) [4, 6].

Epidemiology of Sepsis

An accurate picture of the epidemiology of sepsis is clouded, unfortunately, by the lack of a reliable case definition [7]. However, the overall incidence of sepsis in both children and adults is now estimated at 750,000 new cases per year in the United States alone, with an overall mortality rate approaching 30 %, making sepsis the 10th leading cause of death [7–9]. Nearly 100,000 children per year present to U.S. emergency departments (EDs) with severe sepsis [10], resulting in approximately 21,000 hospitalizations [11] and 4,500 deaths in the pediatric age group [5] on an annual basis. Sepsis is the most common cause of death in infants and children worldwide – according to data from the World Health Organization (WHO), the United Nations Children's fund (UNICEF), the National Institutes of Health (NIH), and the Bill and Melinda Gates foundation, the leading killers of children during the early childhood years (pneumonia – 1.6 million/year, diarrhea – 1.3 million/year, malaria, dengue fever, influenza, and HIV) account for approximately eight million deaths a year worldwide [12]. These deaths are not officially counted as deaths attributable to sepsis, though all of these infectious diseases undoubtedly share sepsis as a common final pathway.

As noted above, extensive data regarding the epidemiology of severe sepsis during childhood have been provided by Watson and colleagues [5, 13, 14]. However, more recent studies suggest that the pediatric sepsis is becoming more prevalent [9, 15]. For example, the prevalence of severe sepsis increased by more than 80 % between 1995 and 2000. Between 2000 and 2005, the prevalence of severe sepsis increased again by 45 %. The increase in sepsis is likely due in part to the increasing life expectancy of technology-dependent children and children with chronic medical conditions. Current estimates suggest that there are between 75,000 to 100,000 cases of severe sepsis in children in the United States every year, with an associated cost of $4.8 billion [10, 15]. While the overall case fatality rate has decreased (from 1995 to 2000, the case fatality rate decreased from 10.7 to 8.9 %), because there are more children affected now, the absolute number of deaths from sepsis has increased [15].

Infants less than 1 year of age appear to be at the highest risk of sepsis, with an incidence rate that is tenfold higher than that of older children (5 cases per 1,000 in infants less than 1 year of age compared to 0.56 cases per 1,000 in all children) [5, 10, 11, 13, 14]. In this group, neonates (i.e., infants less than 28 days of age) are particularly at risk for sepsis, with prematurity and low-birth weight being significant risk factors. Again, in the series reported by Watson and colleagues, low- (LBW) and very-low birth weight (VLBW) infants accounted for nearly one-fourth of all children with severe sepsis and approximately 70 % of all infants with severe sepsis in 1995 [5]. During infancy, chronic medical conditions – especially chronic lung disease, congenital heart disease, neuromuscular disorders, and malignancies – appear to be significant risk factors. The increase in sepsis cases also reflects the growing numbers of VLBW infants in the United States. The majority of infections causing severe sepsis in children are respiratory infections (accounting for about one third of all cases) and primary bacteremias (which account for approximately one quarter of all cases of sepsis in children). Bacteremia without an apparent focus appears to be more frequent in neonates and children with an underlying malignancy, whereas respiratory infections predominate in older children without underlying illness [5, 13, 14].

Children less than 2 months of age are at significant risk for sepsis caused by group B β-hemolytic streptococcus (GBBS) and *E. coli*. Infections secondary to *Listeria monocytogenes* and the herpes simpex virus (HSV) are also prevalent in this age group. In contrast, children greater than 2 months of age are more susceptible to community-acquired organisms such as pneumococcus, *Staphylococcus aureus*, and *Neisseiria meningitidis*. Coagulase-negative staphylococci account for a significant proportion of sepsis in some series, especially in LBW and VLBW infants [5, 14, 16–18]. Meningococcal infections, by comparison, are relatively uncommon, though the case fatality rate is much higher in children with meningococcal disease (15–20 %) compared to children with pneumococcal disease (12.8–19.1 %), fungal infections (10.8–16.8 %), and sepsis secondary to coagulase-negative staphylococcal species (7.8–8.6 %).

Boys less than 10 years of age appear to be at a greater risk for sepsis [5, 11, 14]. These gender differences in both the incidence and mortality of sepsis occur in the neonatal period as well as in childhood and adolescence [19, 20], suggesting there are sex-related differences in immunity at a young age, as have been described in adults [21]. The origin of these differences in children is probably not sex hormone related, because they are most apparent at a very young age, when the influences of sex hormones are relatively unimportant.

On the basis of studies of identical twins and adoptees, genetic factors are known to be major determinants of susceptibility to death from infectious disease [22]. Some of these factors are single nucleotide polymorphisms in genes controlling the host response to microbes [23–25] and commonly used therapeutic agents [26]. Identified alterations include polymorphisms in TNF receptors, interleukin-1 receptors, Fcγ-receptor, and Toll-like receptors (TLRs). Polymorphisms in cytokine genes may determine the concentrations of inflammatory and anti-inflammatory cytokines produced during sepsis and may influence whether persons have a marked hyper inflammatory or hypo inflammatory response to infection. Combinations of polymorphisms, or haplotypes, may ultimately be used to identify patients at high risk for the development of sepsis and organ dysfunction during infection and might dictate immune based therapy to modulate the response to a given patient. The interested reader is referred to the chapter on gene polymorphisms in critical illness earlier in this textbook.

Finally, data on the long-term outcomes from sepsis are just beginning to emerge. Zimmerman and colleagues reported the long-term outcomes in survivors from pediatric sepsis in Washington state over a 14 year period (1990–2004). In their retrospective review, 7,183 children were admitted with severe sepsis, with a 28-day mortality rate of 6.8 %. An additional 6.3 % of patients died after hospital discharge. Almost half of the children who survived were re-admitted to the hospital at least once after a median of 3 months – two-thirds of these admissions were categorized as emergent [27]. Further studies like this one are desperately needed to further describe and measure the true impact of sepsis in children.

Definition of Sepsis

Bone and colleagues initially formulated a clinical definition of the *sepsis syndrome* in 1989 [28]. The constellation of signs and symptoms associated with this syndrome included elevated temperature, tachycardia, tachypnea, abnormal peripheral white blood cell (WBC) count, and evidence of organ dysfunction. Shortly thereafter, an international group of experts from the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) convened to refine the definition of sepsis and proposed the now familiar definitions for SIRS, sepsis, severe sepsis, and septic shock [29]. The need for a more pediatric-specific definition for SIRS, sepsis, severe sepsis, and septic shock became clear quickly, and the International Pediatric Sepsis Consensus Conference was held in 2002 to develop these definitions (Tables 30.1, 30.2 and 30.3) [31]. Because tachycardia and

Table 30.1 Definitions of systemic inflammatory response syndrome (*SIRS*), infection, sepsis, severe sepsis and septic shock

SIRS
The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count
Core temperature of >38.5 °C or <36 °C (by rectal, bladder, oral or central catheter probe)
Tachycardia defined as mean heart rate >2SD for age[a] or otherwise persistent elevation over a 0.5–4 h time period (see Table 30.2 for age-specific ranges)
Or for children <1 year old: bradycardia, defined as a mean heart rate <10th percentile for age[b] or otherwise persistent depression over a 0.5 h period
Mean respiratory rate >2 SD above normal for age or mechanical ventilation[c]
Infection
A suspected or proven infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging or laboratory tests[d]
Sepsis
SIRS in the presence of or as a result of suspected or proven infection
Severe sepsis
Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more organ dysfunctions (as defined in Table 30.3)
Septic shock
Sepsis and cardiovascular organ dysfunction as defined in Table 30.3

[a]In the absence of external stimulus, chronic drugs, painful stimuli
[b]In the absence of external vagal stimulus, β-blockers or congenital heart disease
[c]Not for underlying neuromuscular disease or receipt of general anesthesia
[d]By positive culture, tissue stain, or polymerase chain reaction

Table 30.2 Age specific vital signs and laboratory variables

Age group	Heart rate (beats/min) tachy	brady	Respirations (breaths/min)	Leukocyte count ($\times 10^3/mm^3$)	Systolic blood pressure (mm Hg)
0 days – 1 week	>180	<100	>50	>34	<65
1 week – 1 month	>180	<100	>40	>19.5 or <5	<75
1 month – 1 year	>180	<90	>34	>17.5 or <5	<100
2–5 year	>140	NA[a]	>22	>15.5 or <6	<94
6–12 year	>130	NA	>18	>13.5 or <4.5	<105
13–18 year	>110	NA	>14	>11 or <4.5	<117

Lower values for heart rate, leukocyte count and systolic blood pressure are for the 5th and upper values for heart rate, respiration rate, and leukocyte count for the 95th percentile
[a]NA = not applicable

Table 30.3 Organ dysfunction criteria

Cardiovascular dysfunction
Despite the administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 h
Decrease in BP ≤5th percentile for age OR
Need for vasoactive drug to maintain BP in the normal range* OR
Two of the following
Unexplained metabolic acidosis: base deficit >5.0 mEq/L
Increased arterial lactate >2 times upper limit of normal
Oliguria: urine output <0.5 ml/kg/h
Prolonged capillary refill: >5 s
Core-peripheral temperature gap >3 °C
Respiratory
$PaO_2/FIO_2 < 300$ in the absence of cyanotic heart disease or preexisting lung disease OR
$PaCO_2 > 20$ mmHg or 2,7 kPa over baseline $PaCO_2$ OR
Proven need for >50 % FIO_2 to maintain saturation >92 % OR
Need for non-elective invasive or noninvasive mechanical ventilation
Neurological
Glasgow coma scale ≤11 OR
Acute change in mental status with decrease in Glasgow coma scale ≥3 points from baseline.
Hematological
Platelet count <100.000/mm³ or a decline of 50 % in platelet count from highest value recorded over the last 3 days OR
International normalized ration >2
Renal
Serum creatinine ≥2 times the upper limit of normal for age or a twofold increase in baseline creatinine
Hepatic
Total bilirubin ≥4 mg/dL (not applicable for the newborn) OR
ALT 2 times the upper limit of normal

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tachypnea are common symptoms in a variety of pediatric conditions, the major difference in the definition of SIRS between children and adults is that the diagnosis of pediatric SIRS requires that temperature or leukocyte abnormalities are also present. In children less than 1 year of age, bradycardia may be a sign of SIRS and subsequently this condition is also included in the definition. Finally, the presence of fever is defined as >38.5 °C, which provides a more specific cut off than 38 °C. The definitions propose six age groups for age-specific vital sign and laboratory parameters: newborn (0–1 week), neonate (1 week to 1 month), infant (1 month to 1 year), toddler and preschool (2–5 years), school age child (6–12 years), and adolescent and young adult (13–18 years). These categories are based on expert opinion, since evidence based values for abnormal vital signs and laboratory markers are lacking [32]. As new insights develop, the definition of sepsis will also need to be re-evaluated.

The validity and usefulness of the consensus sepsis definitions has been widely debated in the literature due to its relative non-specific qualities and the broad range of patients that could be classified as having SIRS [32–35]. For example, Proulx and colleagues analyzed the incidence and outcome of SIRS, sepsis, severe sepsis, and septic shock in a single tertiary care children's hospital [36]. Out of 1,058 admissions

Table 30.4 Factors determining the severity of sepsis according to the PIRO concept: Predisposition, Infection, Response and Organ dysfunction

Predisposing factors
Pre-morbid conditions like cancer, primary or secondary immunodeficiencies, cystic fibrosis sickle cell disease and asplenia
Gender and age of the patient: e.g., children <2 year are more susceptible to encapsulated bacteria
Genetic factors: gene polymorphisms in cytokine genes or other immune effector molecules
Presence of immunity against certain micro-organisms (vaccination status, previous infections)
Medication: immune-suppressive agents, cardiovascular drugs
Nutritional status: malnutrition is a state of immunodeficiency
Trauma or surgery; increased risk of infection
Presence of foreign substances such as intravenous catheters
Infection
Differences in virulence factors of the causative microbe such as production of LPS, causes different pathology
Size of the inoculum
Initial site of infection: influences the chance of generalization of the infection
Antimicrobial resistance of the pathogen: influence on response on initial antibiotic therapy
The time to recognition of infection by clinical judgment and appropriate laboratory and imaging studies affects outcome
Response of the patient
The host response is determined by the predisposing factors: the nature of the host response influences the chances of survival and significant morbidity: diffuse intravascular coagulation, balance between of pro- and anti-inflammatory cytokines
This response is modified by timely interventions of the physician, such as antibiotics and early goal directed therapy, determining the chance of the development of organ dysfunction
Organ dysfunction
Variations in patterns of organ dysfunction like myocardial depression, ARDS, renal failure and liver failure affect outcome. They are the result of the complex interaction between microcirculatory dysregulation, energy depletion and apoptosis. The severity of organ dysfunction is the major determinant of the outcome of sepsis

analyzed over a 1-year period, 82 % of children admitted to the pediatric intensive care unit (PICU) met criteria for SIRS, while 23 % had sepsis, 4 % had severe sepsis, and 2 % had septic shock. The SIRS criteria also lack sufficient sensitivity and specificity outside the PICU environment, where early recognition and diagnosis are critically important. For many of these reasons, the "PIRO" concept [37] was proposed as a staging system for sepsis, modeled after the TNM (**T**umor, **N**odes, **M**etastasis) system [38] for staging malignancies. The PIRO staging system stratifies patients on the basis of their **P**redisposing conditions, the nature and extent of the insult (**I**nfection), the nature and magnitude of the host **R**esponse, and the degree of concomitant **O**rgan dysfunction (Table 30.4). The PIRO staging system has many favorable attributes, but will require thorough validation and testing before it is widely adopted and applied in clinical practice [39–41], particularly in pediatrics [42, 43].

Importantly, although sepsis is defined as a systemic inflammatory response to an inciting infection, an infectious microorganism is isolated in fewer than 50 % of cases [44]. A suspected infection, as shown by positive findings at physical examination (e.g., signs of arthritis or osteomyelitis), petechial rash, or abnormalities on auscultation of the chest can therefore define *sepsis*. Laboratory evidence of infection such as the presence of white blood cells in a normally sterile body fluid or imaging techniques showing pulmonary infiltrates can also validate the suspicion of an infection. It should also be noted that in the definition of *septic shock*, there is no requirement for systemic hypotension, because children are often able to maintain their blood pressure at the expense of peripheral perfusion, even if they are severely ill.

Scoring systems have been developed that attempt to quantify the degree of organ dysfunction or failure in critically ill children, especially in those children with severe sepsis. For example, the number of dysfunctional organs is frequently used as a surrogate marker of disease severity in children with MODS, with the rational that the greater the number of dysfunctional organs the worse the outcome. This score is called the pediatric MODS score and has been used by several investigators [45]. The Pediatric Logistic Organ Dysfunction (PELOD) score has recently been validated as an outcome measure in children with MODS [46]. In addition, Graciano and colleagues recently developed and prospectively evaluated the Pediatric Multiple Organ Dysfunction Score (P-MODS) using a database of 6,456 consecutive admissions to the PICU at their tertiary care institution [47]. Finally, there are a number of disease-specific scoring systems that have been proposed for use in children with meningococcemia and septic shock [48–51]. Scoring systems such as these are important to link the severity of sepsis with measured outcome variables. Further information regarding these types of scores is provided in other chapters of this textbook. In addition, recent work by our group suggests that a pediatric sepsis biomarker risk profile

(PERSEVERE) reliably identifies critically ill children at risk of death from septic shock. PERSEVERE, which is based upon five biomarkers performs better than any of the currently used severity of illness scores [52].

Clinical Manifestations

It cannot be over-emphasized that the early recognition of sepsis is the key to successful management [53, 54]. Pediatricians need to be constantly aware of the possibility of infections and subsequent sepsis in children admitted to the PICU. A possible focus of infection should be elicited by careful history and physical examination. All the major organ systems of the body are adversely affected by inadequate oxygen delivery from perturbations in cardiac and respiratory function. In addition, these organ systems are also injured by the direct cytotoxic effects of bacterial toxins and circulating cytokines (see below).

The onset of sepsis is often insidious and the initial signs and symptoms are therefore relatively non-specific and reflect the body's attempt to compensate for poor oxygen delivery. Children often present with fever, tachypnea (reflecting a compensatory mechanism aimed at counteracting the metabolic acidosis which occurs due to inadequate oxygen delivery to the tissues), tachycardia (reflecting a compensatory mechanism to increase cardiac output and oxygen delivery to the tissues), leukocytosis or leukopenia, thrombocytopenia, and alterations in mental status. Fever is frequently the initial manifestation of infection and is believed to result from the release of a number of the cytokines elicited in response to infection, including tumor necrosis factor (TNF)-α and interleukin (IL)-1β. Children, especially infants, may also present with hypothermia, which appears to be associated with worse outcome in adults with sepsis [55]. The mental status of a child with sepsis is frequently altered, ranging from agitation to obtundation. This depressed mental status can be present even in the absence of meningitis and reflects inadequate oxygen delivery to the central nervous system. The skin is frequently hypoperfused with decreased capillary refill and mottling. Petechiae and purpura are sometimes present and, while helpful in diagnosis, can be ominous signs. For example, petechiae classically points towards meningococcal sepsis, but can also be manifest in several other infections (e.g., *Haemophilus influenzae*, *Streptococcus pneumonia*, *Staphylococcus aureus*, enterovirus, herpes simplex virus, varicella, etc.).

The four major categories of shock proposed in a classification scheme by Hinshaw and Cox [56] in 1972 include: (i) hypovolemic shock (shock as a consequence of inadequate circulating volume), (ii) obstructive shock (shock caused by obstruction of blood flow to and from the heart), (iii) cardiogenic shock (shock caused by primary pump failure), and (iv) distributive shock (shock caused by maldistribution of the circulating volume). Septic shock does not readily fall into any one of these four categories. Rather, septic shock is unique in that several of these forms may be present simultaneously in the same affected child. For example, a child with septic shock may exhibit signs and symptoms consistent with hypovolemic shock secondary to capillary leak, increased insensible losses, and decreased effective blood volume secondary to venodilation; cardiogenic shock secondary to the myocardial-depressant effects of bacterial toxins and inflammatory cytokines; and distributive shock from decreased systemic vascular resistance. The degree to which any one child manifests these physiologic perturbations varies considerably. For example, Ceneviva et al. [57] categorized 50 children with fluid-refractory septic shock based upon hemodynamic data obtained with the pulmonary artery (PA) catheter into one of three possible cardiovascular derangements – (i) a hyperdynamic state characterized by a high cardiac output (>5.5 L/min/m^2 BSA) and low systemic vascular resistance (<800 dyn sec/cm^5) (classically referred to as *warm shock*); (ii) a hypodynamic state characterized by low cardiac output (<3.3 L/min/m^2 BSA) and low systemic vascular resistance (SVR); or (iii) a hypodynamic state characterized by low cardiac output and high SVR (>1,200 dyn sec-cm^5) (classically referred to as *cold shock*). In stark contrast to adults in which the early stage of septic shock is most often (~90 %) characterized by a high cardiac output and low SVR (*warm shock*), most of the studied children (~60 % of cases) were in a hypodynamic state characterized by low cardiac output and high systemic vascular resistance (*cold shock*) and required the addition of inotropes and vasodilators to decrease SVR, increase CI, and improve peripheral perfusion [57]. Children with low cardiac output (as defined by a cardiac index less than 2.0 L/min/m^2 BSA) had the highest risk of mortality. These findings have been confirmed in multiple studies using a variety of methods to measure cardiac output and vascular resistance [58–64]. Collectively, these studies all point to the fact that hypotension in children is a very late sign that portends a poor prognosis. Moreover, children more commonly present with cold shock, as opposed to warm shock.

The Immunopathobiology of Sepsis

Advances in molecular immunology methods and the use of genetically modified animal models have uncovered remarkable complexity in the pathophysiology of sepsis. An in-depth understanding of the dynamic host immune response to sepsis is a critical antecedent for successful clinical intervention. The addition of immune biomarker-based staging of disease to clinical sign staging is highly likely to increase the accuracy of patient classification for future multi-site clinical trials that will test novel interventions. Lastly, the host

immune response to sepsis is strongly determined by developmental age [65, 66]. As we have emphasized repeatedly, children are not small adults and experimental findings from adult studies should not be assumed to apply to children and neonates.

Sepsis is, by definition, a systemic inflammatory response associated with infection in a normally sterile area [67]. An immune response to eradicate any infectious challenge is appropriate and necessary to prevent evolution and spread of the pathogen throughout the host. However, in some cases the inflammation is not limited and becomes generalized, resulting in the constellation of signs and symptoms of SIRS, as described above. SIRS may or may not be associated with infection. If the infection is not contained, the spread of the pathogen through the blood may result in systemic endothelium activation and precipitate severe sepsis and septic shock. Host immunity is grossly divided into innate and adaptive responses, but in reality there is a great deal of cross-talk between the two systems. Innate immunity is rapid, largely non-specific, and is composed of barriers, phagocytic cells, the complement system, and other soluble components of inflammation. Following breech of a barrier, cellular elements of the innate immune response are the first line of defense against the development and progression of infection. Adaptive immunity, which is antigen-specific, long-lived, and takes several days to develop, provides immunologic specificity and memory. Both systems play important roles in the pathophysiology of sepsis.

Barrier Defenses

Barriers, including skin and mucosal surfaces, are the primary immune defense against the development of local infection. Barrier function is critical because these areas represent the first point of contact between the host and potential pathogens. Multiple immune elements are present to prevent attachment and propagation of pathogens, while simultaneously permitting the presence of commensal organisms required for homeostasis. In contrast to the moist mucosal surfaces of the respiratory and gastrointestinal tracts, the skin is arid which reduces the chances for microbial invasion. The outer layer of skin, the *stratum corneum*, is covered with antimicrobial peptides that possess microbicidal activity [68]. Disruption of the cutaneous barrier via trauma or burn allows microorganisms to enter the subcutaneous tissue increasing the likelihood of establishing a local infection.

Mucosal barriers are defended by several components that serve to prevent invasion including mucus, cilia, antimicrobial peptides, soluble opsonins, destructive enzymes, acidic pH, commensal organisms, and sentinel immune cells such as macrophages, dendritic cells (DCs), neutrophil or polymorphonuclear cell (PMNs), and T cells. The respiratory mucosa is defended by epithelial cells, cough, mucociliary clearance, resident professional phagocytes, and the secretion of a number of proteins and peptides with host defense functions. The collectins, surfactant protein A and D, possess valuable immune function by increasing opsonization of inhaled pathogens. Respiratory mucosal function can be disrupted through altered mucus production, intubation and mechanical ventilation (decreased mucociliary clearance, increased mucus production, and airway irritation), surfactant deficiency, and physical damage to lung parenchyma (volutrauma, atelectotrauma, barotrauma, chemical injury, or infection).

Gastrointestinal (GI) barrier homeostasis may be disrupted by infection or chemotherapy that leads to mucositis. GI barrier integrity is also dependent on the interaction between commensal organisms and host epithelium. Alteration of this relationship with antibiotics or stress in the form of hypoxia or remote infection may increase the risk for barrier dysfunction and bacterial translocation. Under these circumstances, the gut may become the "*motor of systemic inflammation*" [69]. Therefore, maintenance of GI barrier integrity is paramount for prevention of spread of microorganisms out of the mucosal compartment.

Molecular Events During Early Infection

Pathogen Recognition

Once the local barrier function has been compromised, pathogen recognition by local immune sentinel cells is the first step towards the development of an immune response (Figs. 30.1 and 30.2). Pattern recognition receptors (PRRs) [71] including Toll-like receptors (TLRs) facilitate recognition of pathogen-associated molecular patterns (PAMPs) [71]. A litany of PAMP-sensing PRR classes exist including the TLRs, Nod-like receptors (NLRs), retinoic-acid-inducible protein I (RIG-I)-like receptors (RLRs), peptidoglycan recognition proteins (PGRPs), β-integrins, and c-type lectin receptors. The discovery that TLR4 was integral for a robust lipopolysaccharide (LPS)-mediated inflammatory response that occurs with gram-negative sepsis may be why TLRs have been more thoroughly investigated in the setting of sepsis than other PRRs.

Each of the ten known TLRs in humans, present on and within multiple cell types, recognizes extracellular and intracellular pathogens via specific PAMPs [72, 73]. Multiple TLRs may be activated in concert by intact or partial microorganisms and activate multiple second messenger pathways simultaneously [73, 74]. LPS in the gram-negative bacterial cell membrane is the archetype PAMP and a key mediator of systemic inflammation, septic shock, and multi-organ failure and death [75]. LPS signals primarily through TLR4 in conjunction with the cell surface adaptor proteins CD14 and

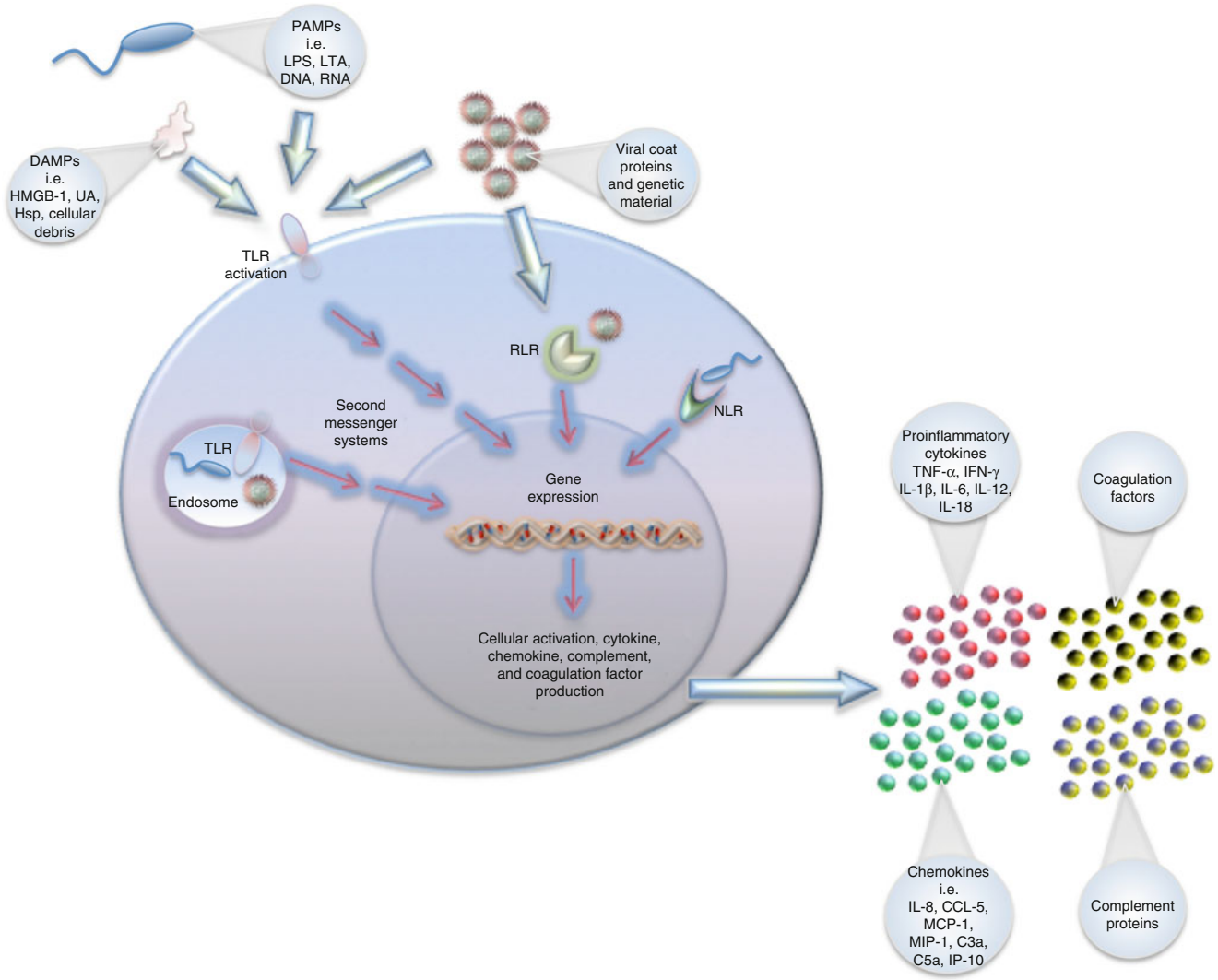

Fig. 30.1 Activation of sentinel immune cells. Sentinel cells (e.g., monocyte, macrophage) sense pathogens via PAMPs or DAMPs binding to PRRs. Pathogen recognition receptors (*PRRs*) include *TLRs* Toll-like receptor, *RLRs* Rig-1-like receptors, and *NLRs* NOD-like receptors. Pathogen associated molecular patterns (*PAMPs*) include *LPS* lipopolysaccharide, *LTA* lipotechoic acid, DNA, and RNA. Damage/Danger associated molecular patterns (*DAMPs*) can also be sensed through TLRs and include uric acid (*UA*), heat shock proteins (*Hsp*), and HMGB-1. Signaling occurs through a series of second messengers and results in transcription and translation of cytokines and chemokines that amplify the immune response (Reprinted with permission from Wynn and Wong [70]. With permission from Elsevier)

MD2 [71]. Bacterial cell wall components (such as lipoteichoic acid) signal primarily through TLR1/2/6, flagellin through TLR5, and CpG double-stranded DNA through TLR9. Common viral PAMPs such as double-stranded RNA or single-stranded RNA signal through TLR3 and TLR7/8 respectively.

Agonist-TLR binding results in a signaling cascade of intracellular second messenger proteins ultimately leading to production of cytokines and chemokines as well as activation of other antimicrobial effector mechanisms [72]. Key intracellular messengers critical for effective TLR signaling include myeloid differentiation factor 88 (MyD88), toll-interleukin (IL)-1 receptor domain containing adaptor protein (TIRAP), Toll/IL-1 receptor homology (TIR) domain containing adapter-inducing interferon B (TRIF), TRIF-related adaptor molecule (TRAM), IL-1 Receptor-Associated Kinase (IRAK)-1 and IRAK-4, and nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (NFKBIA). Signaling through MyD88 typically leads to the production of nuclear factor kappa B (NF-κB)-dependent inflammatory cytokines/chemokines, whereas signaling through TRIF induces production of type I interferons as well as NF-κB-related inflammatory cytokines.

Because TLRs play an essential role in recognition and response to pathogens, alterations in their expression, structure, signaling pathways, and function can have consequences

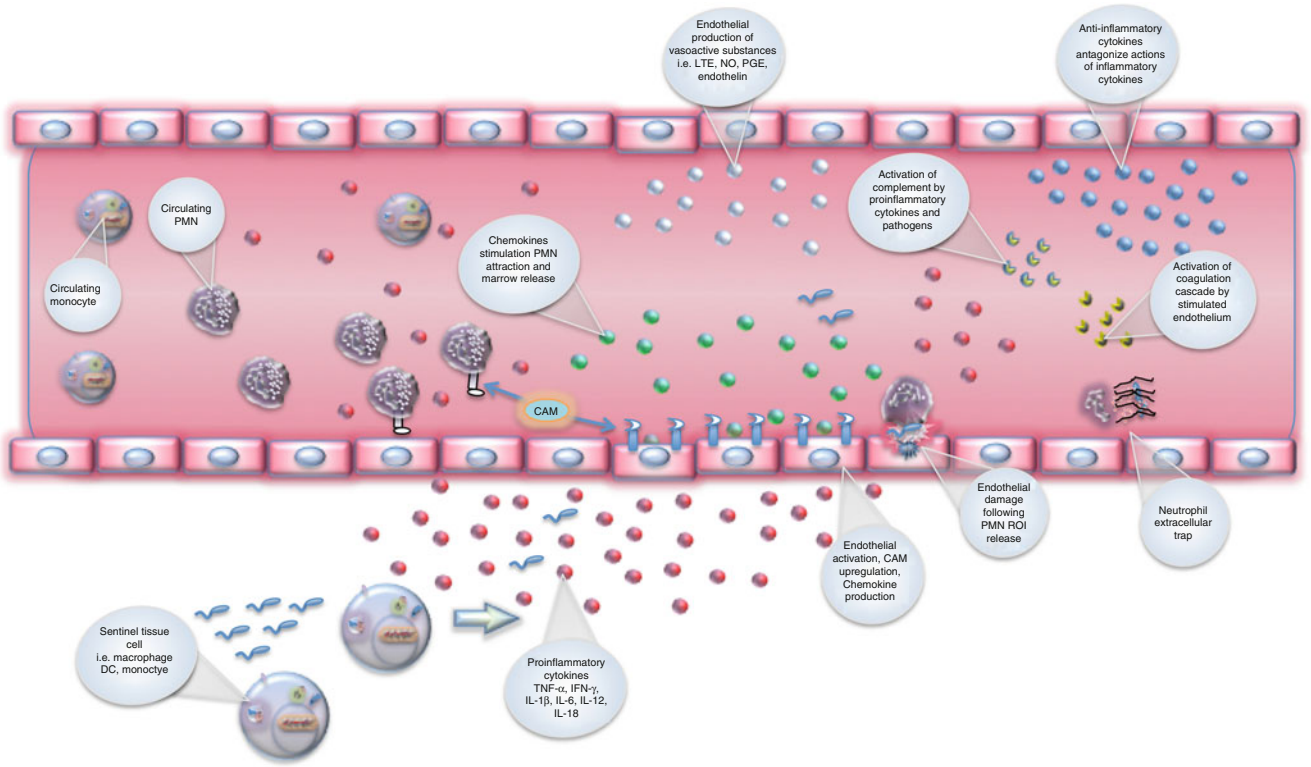

Fig. 30.2 Cellular recruitment and endothelial activation following pathogen detection. Pathogen-stimulated tissue/blood monocytes, dendritic cells (*DC*), and macrophages release proinflammatory cytokines that activate the surrounding endothelium. Endothelial activation results in upregulation of cell adhesion molecules (*CAM*), production of chemokines and vasoactive substances, activation of complement, and development of a procoagulant state. Recruitment of PMNs occurs along the chemokine gradient surrounding the area of inflammation. Anti-inflammatory cytokines counter the actions of proinflammatory cytokines to prevent excessive cellular activation and recruitment that can result in tissue damage and systemic inflammation. Endothelium can be damaged when PMNs release reactive oxygen intermediates (*ROI*) or form NETs. LTE-leukotriene, NO-nitric oxide, PMN-neutrophil. NET-Neutrophil extracellular trap (Reprinted with permission from Wynn and Wong [70]. With permission from Elsevier)

to host defense. Polymorphisms or mutations in TLRs are associated with increased risk for infection in both adults [76–79] and children [80–82]. Modifications in expression or function of co-stimulatory molecules necessary for TLR activation are also associated with an increased risk for infection. Genetic variations in CD14 (LPS co-receptor) and LPS binding protein have been associated with increased risk for sepsis in adults [83–85]. Gene polymorphisms in myeloid differentiation-2 (MD-2), a small protein involved in LPS signaling through TLR4, increase the risk for organ dysfunction and sepsis in adults [86], but the significance in children is unknown. Polymorphisms in select cytokines (IL-6 and IL-10) or their receptors [87] and constituents of their signaling pathways may be associated with increased risk of infection [88–91], though there is not complete agreement on these findings [92–94]. Polymorphisms in downstream (post-TLR activation) intracellular signaling molecules including MyD88 [95], IRAK-4 [96], and NF-κB essential modulator (NEMO) [97] are associated with invasive bacterial infection in older populations.

Damage-associated molecular patterns (DAMPs), such as intracellular proteins or mediators released by dying or damaged cells, may also active PRRs. For example, the DAMP High mobility group box-1 (HMGB-1) is involved in the progression of sepsis to septic shock [75, 98]. HMGB-1 is produced by macrophages or endothelial cells stimulated with LPS or TNF-α and signals through TLR2, TLR4, and receptor for advanced glycation end products (RAGE) [99]. HMGB-1 results in cytokine production, activation of coagulation, and PMN recruitment [98, 100]. HMGB-1 mediates disruption of epithelial junctions within the gut via the induction of reactive nitrogen intermediates (RNI), leading to increased bacterial translocation [101]. Other specific DAMPs, including heat shock proteins (Hsps) and uric acid, may also stimulate TLRs, regulate PMN function, and function as immune adjuvants. Hsp are significantly elevated in septic adults and children [102]. Elevated Hsp60 and Hsp70 measured within 24 h of PICU admission was associated with pediatric septic shock and there was a strong trend towards a significant association with death [103, 104]. Cytokine production, PMN recruitment, and

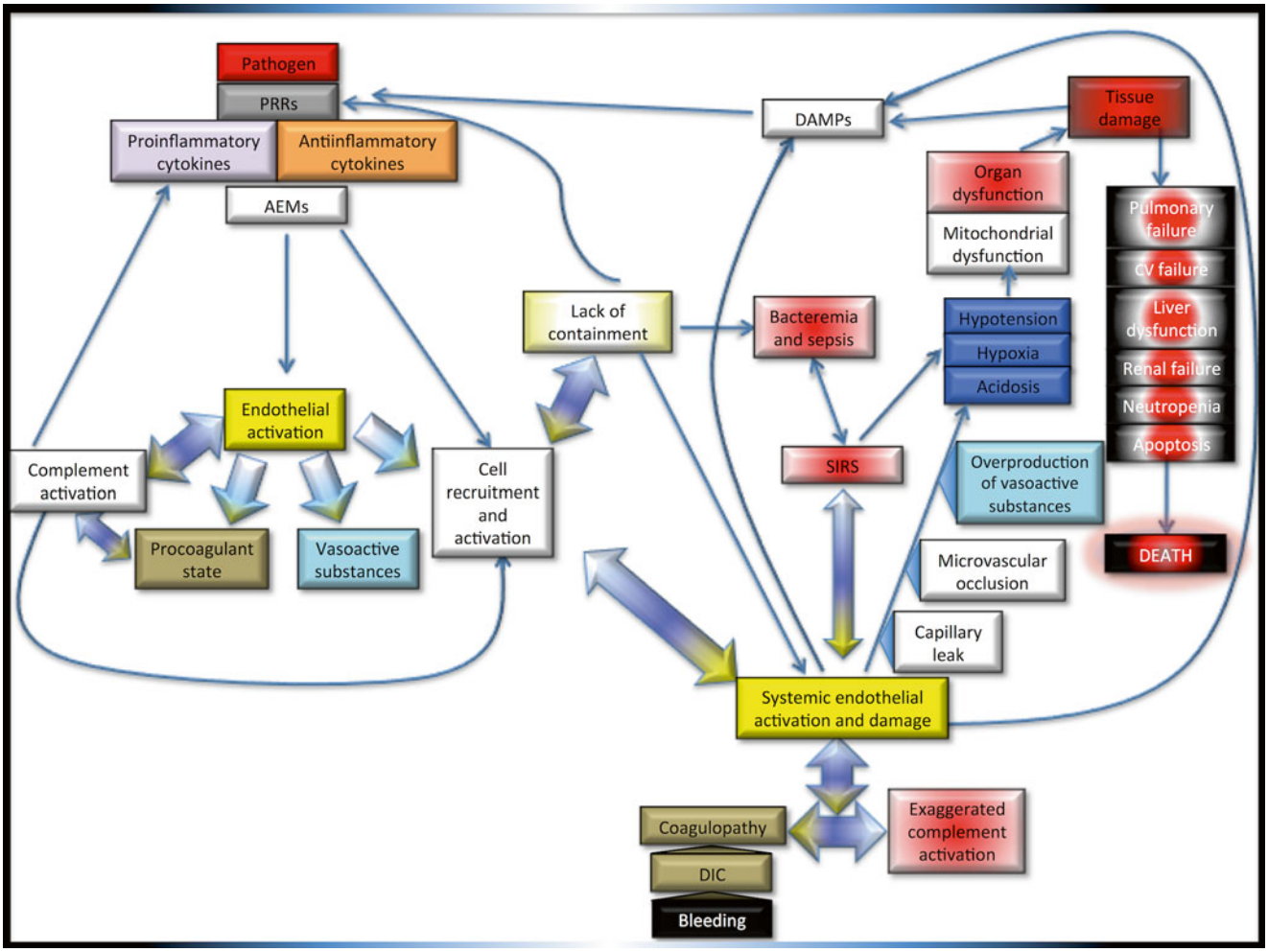

Fig. 30.3 Pathophysiology of sepsis and septic shock. *PRR* Pattern recognition receptors, *AEM* antimicrobial effector mechanisms, *DAMP* Danger/damage-associated molecular patterns, *SIRS* Systemic inflammatory response syndrome, *DIC* disseminated intravascular coagulation, *CV* cardiovascular (Reprinted with permission from Wynn and Wong [70]. With permission from Elsevier)

dendritic cell stimulation [105] are all increased following exposure to uric acid. In addition to its role as a pro-inflammatory DAMP, uric acid may also serve as an potentially beneficial antioxidant [106].

Inflammatory Mediator Production

PRR stimulation results in rapid cytokine and chemokine production alongside amplification of the innate cellular response directed at cellular activation and clearance of pathogenic organisms. Pro-inflammatory cytokines including IL-1β, IL-6, CXCL8 (IL-8), IL-12, IL-18, interferon gamma (IFN-γ), and TNF-α are produced early in the host response and activate innate immune effector cells [107]. Compared to septic adults, septic neonates produce less IL-1β, TNF-α, IFN-γ, and IL-12 [108–113]. A wide variety of chemokines are increased during sepsis, including CXCL10 (IP-10), CCL5 (RANTES), CCL2 (MCP-1), CCL3 (MIP-1a), and CXCL8 (IL-8) [114]. Other chemo-attractive molecules also increase with sepsis, including complement proteins C3a and C5a, antimicrobial proteins or peptides including cathelicidins and defensins, as well as components of invading bacteria themselves [107, 115]. The importance of chemo-attractive substances in the pathogenesis of severe sepsis is highlighted by recent studies showing that CXCL8 can be used a stratifying factor for survival in children [116], and C5a is implicated in sepsis-associated organ dysfunction in adults [75]. Chemokine investigations in septic neonates revealed that CXCL10 is a sensitive early marker of infection [114], and low CCL5 levels may predict development of DIC [117].

Careful interplay between anti- and pro-inflammatory stimuli serves to govern the immune response to allow local pathogen containment but prevent systemic activation leading to excessive inflammatory damage though SIRS associated with multi-organ failure and death (Fig. 30.3) [118]. The previously accepted host-response to sepsis paradigm (an intense pro-inflammatory response, or SIRS temporally

followed by a compensatory anti-inflammatory response syndrome [CARS]) has been challenged by the failure of multiple anti-inflammatory strategies. New data demonstrate a simultaneous pro/anti-inflammatory response where the magnitude may determine outcome [119]. Near simultaneous increases in anti-inflammatory cytokine production (TGF-β, IL-4, IL-10, IL-11, and IL-13) occur during infection countering the actions of pro-inflammatory cytokines [107, 120, 121]. These mediators blunt the activation of phagocytic cells, block fever, modify coagulation factor expression, and decrease production of ROI/RNI, NO, and other vasoactive mediators [122–126].

Soluble cytokine and receptor antagonists produced during sepsis also modulate pro-inflammatory mediator action. Elevation of TNFR2 (which regulates the concentration of TNF-α), sIL-6R, sIL2, and IL-1ra have been documented in neonatal sepsis with resolution following effective treatment [121, 127, 128]. Soluble RAGE (sRAGE) competes with cell-bound RAGE for the binding of HMGB-1 and other RAGE ligands [129]. sRAGE has anti-inflammatory effects, is elevated in adults during sepsis [130], improved survival and reduced inflammation when given to infected adult rodents [131].

Complement

Complement facilitates killing of bacteria through opsonization and direct microbicidal activity. Complement components also possess chemotactic or anaphylactic activity that increases leukocyte aggregation and local vascular permeability at the site of invasion. Furthermore, complement reciprocally activates a number of other important processes such as coagulation, proinflammatory cytokine production, and leukocyte activation [75]. Contrary to its name, the *alternative* pathway is actually the primary mechanism of amplification of complement activation following C3 convertase assembly (which cleaves C3 to C3a and C3b) formation via the classical, lectin, or alternative pathways. Dysregulation of complement activation may participate in the untoward effects with severe sepsis or septic shock. Importantly, neonates, particularly the very premature, exhibit decreased basal levels of complement proteins and function for both the alternative and classic pathways [132, 133].

C3b and C5a facilitate opsonization (primarily C3b), redistribution of blood flow, increased inflammation, platelet aggregation, and release of ROI (primarily C5a) [134, 135]. C5a-mediated local leukocyte activation also results in increased cytokine production with subsequent upregulation of adhesion molecules on vascular endothelium allowing for increased cell recruitment to the site of infection [136]. Deficiencies in C5aR found in term neonates as compared to adults may limit the ability to respond to C5a and therefore increase the likelihood of infection [137].

Complement regulatory proteins (CD55, CD59) modify the effects of complement and prevent potential damage due to over-activation [138]. Dysregulation of complement activation can lead to a vicious activation cycle that results in excessive cellular stimulation, cytokine production, endothelial cell activation, and local tissue damage. Dysregulation likely contributes to the development of SIRS and shock [139]. Elevated C5a levels are associated with the development of DIC, via increased tissue factor expression, cardiomyopathy, increased pro-inflammatory cytokine levels and the development of SIRS, adrenal insufficiency, and PMN dysfunction [75].

In addition to the initial inflammatory response and complement activation following pathogen recognition, infection results in increases in multiple other innate proteins that possess valuable immune function [140]. These components serve to reduce bacterial load and include collectins (e.g., surfactant proteins A and D), lactoferrin, cathelicidin, bactericidal permeability increasing protein (BPI), and phospholipase A_2 [141]. Acute phase reactant proteins including CRP (opsonin), lactoferrin (reduce available iron/antimicrobial peptide-lactoferricin), serum amyloid A (cellular recruitment), procalcitonin (unknown function), haptoglobin, fibronectin (opsonic function), pentraxin 3 (binds C1q and activates classical complement pathway) and others increase significantly during sepsis and provide useful adjuvant immune functions [107]. Natural antibodies (predominantly IgM) produced by circulating B1 lymphocytes augment opsonizing capacity [142–144]. PMNs from term neonates are deficient in BPI, potentially contributing to the increased risk for infection [145]. Polymorphisms in BPI increase the risk for gram-negative sepsis in children [146]. Mannose-binding lectin (MBL) is capable of activating the lectin and alternative complement pathways, and decreased MBL levels are associated with an increased risk of sepsis during the first month of life [147, 148]. Despite increases in acute phase and other innate proteins with infection, neonatal plasma has significantly impaired opsonizing activity compared to adults that increases the likelihood of progression to systemic infection [149].

Coagulation Cascade

An important part of host pathogen containment includes the development of a pro-coagulant state in the microvasculature surrounding a focal site of infection. However, if systemic endothelial activation occurs or proinflammatory cytokine production is high, over-activation of the coagulation system may occur and lead to DIC, resulting in severe tissue and organ damage [150]. In general, the intrinsic pathway amplifies coagulation following initiation by the extrinsic pathway [151]. Important differences exist in children as compared to adults in the coagulation system. Reduced vitamin K-dependent factors (Factor II, VII, IX, X), thrombin generation, consumption of platelets with formation of microthrombi, and counter-regulatory elements (inhibitors) increase the risk for bleeding in pediatric patients [152].

Coagulation cascades during infection may begin with cytokine-activated PMNs, monocytes, or endothelium, which express increased tissue factor apoprotein [153, 154]. Activation of tissue factor leads to increased clotting proteins including thrombin-antithrombin complex (TAT), plasminogen activator inhibitor (PAI), and plasmin-a2-antiplasmin complex [155]. There is also a shift towards inactivation of protein S and depletion of anticoagulant proteins including antithrombin III (ATIII) and protein C [156, 157]. Cytokine production increases expression of endothelial tissue plasminogen activator inhibitor type-1 (PAI-1). PAI-1 inhibits fibrinolysis by inhibiting the conversion of plasminogen to plasmin important for the breakdown of fibrin. Deposition of fibrin in small vessels leads to inadequate tissue perfusion and organ failure [158]. Increased PAI-1 activity levels are associated with increasing IL-6, nitrite and nitrate levels, the development of organ failure (cardiovascular, renal, hepatic, coagulatopathy), and mortality [158].

Clotting can lead to propagation of inflammation via thrombin-induced production of platelet-activating factor (PAF). PAF-activated or platelet TLR4-activated PMNs may then contribute to further endothelial injury and dysfunction leading to the development of a vicious clotting-inflammation-clotting cycle. The protease activated receptor (PAR)-1 also plays a major role in orchestrating the interplay between coagulation and inflammation [159]. PAR-1 may modify the endothelial response during pediatric sepsis and thus represent another target for therapeutic intervention.

Innate Immune Cellular Contributions

PMN

The PMN is the primary effector of innate immune cellular defense. Endothelial cells produce activating cytokines and chemokine gradients that recruit circulating PMNs to the site of infection. Expression of cell adhesion molecules by PMNs and endothelium allows cells to roll and extravasate into surrounding tissues. Activated PMNs phagocytose and kill pathogens via oxygen-dependent and oxygen-independent mechanisms. IL1β is produced by activated PMNs largely via an NLRP3/ASC/CASP1-dependent mechanism that amplifies the recruitment of additional PMNs from the bone marrow to the site of infection [160]. Activated PMNs may release RNI, reactive oxygen intermediates (ROI) and proteolytic enzymes extracellularly via activation of membrane associated-NADPH oxidase. These reactive intermediates and enzymes can lead to destruction of non-phagocytized bacteria but also can cause local tissue destruction [161, 162] and thus play a role in progression from sepsis to multi-organ dysfunction syndrome (MODS). With PMN death, the DNA (chromatin), histone and antimicrobial proteins are expelled into the environment and serve to trap bacteria (neutrophil extracelluar traps, NETs) [163]. The formation of NETs can occur following activation of platelet TLR4 [164] and may lead to excessive local inflammation and tissue damage [165]. High early levels of circulating free neutrophil-derived DNA produced by NETs are associated with multiple organ failure, and death [166].

PMNs exhibit quantitative and qualitative differences related to developmental age [167, 168]. Rapid depletion of bone marrow PMN reserves during infection, particularly in neonates [169], can lead to neutropenia with consequent impaired antimicrobial defenses and significantly increased risk for death [170]. Neutropenia is particularly common in gram-negative sepsis in neonates [171]. PMN respiratory burst activity may also suppressed during sepsis and may contribute to poor microbicidal activity [172–174]. Release of immature PMN forms (bands), which have greater dysfunction than mature PMNs [175], may further predispose to adverse outcomes.

Antigen-Presenting Cells (APCs)

The role that APCs play in the host immune response and pathophysiology of sepsis is incompletely characterized. Monocytes, macrophages, and dendritic cells amplify cellular recruitment through production of inflammatory mediators and activation of endothelium, phagocytosis and killing of pathogens, and antigen presentation to T and B cells of the adaptive immune system. DCs are "professional APCs" and are depleted from the spleen and lymph nodes with sepsis in animal models and may be important for survival [176]. Monocytes and macrophages are closely related to PMNs (common myeloid progenitor) and can kill pathogens by similar means. Circulating monocytes differentiate into macrophages following exposure to maturing cytokines and exit the blood stream into tissues. Important substances produced by stimulated monocytes/macrophages that may contribute to sepsis and septic shock include complement components, cytokines (both pro and anti-inflammatory), coagulation factors, and extracellular matrix proteins [177].

Vascular Endothelium

Recent studies have shown the critical importance of vascular endothelial activation in the early recognition and containment of microbial invasion. Expression of TLRs allows endothelium to become activated in the presence of microbial components, leading to production of cytokines and chemokine gradients, as well as adhesion molecules (VCAM, ICAM, L, P, and E-selectins, etc.). These substances all act in concert to attract circulating leukocytes and facilitate adherence [178–182]. Vasoactive substances released from activated leukocytes, platelets, and endothelial cells include platelet-activating factor (PAF), thromboxane (TBX),

leukotrienes (LTE), nitric oxide (NO), histamine, bradykinin, and prostaglandins (PGE) [183, 184]. These substances are all necessary to attract immune cells (primarily PMNs) to the site of infection and to facilitate pathogen containment. Stimulated endothelium can be a double-edged sword, however, because excessive activation can lead to vascular dilation and leak which are a driving forces behind the severe consequences of septic shock [178, 185]. Systemic overproduction of cytokines and vasoactive substances including NO are associated with circulatory alterations and organ failure. The balance of NO and endothelin-1 (ET-1), which is a vasoconstrictor, may be disrupted with endothelial damage, favoring the constrictive effects of ET-1 leading to ischemia and injury [186]. This phenomenon may explain in part why NO inhibitors increased mortality in adults with septic shock [187]. Glucocorticoid receptor is the target for the endogenous, adrenally produced steroid corticosterone. Endothelial GR is a critical negative regulator of NO synthase expression and NF-κB activation [188], demonstrating its role of endothelium in protecting the host during sepsis. Recent studies revealed a potential role of plasma angiopoietin protein during pediatric septic shock [189]. Angiopoietin-1 (protects against vascular leak) was reduced while angiopoietin-2 (promotes vascular permeability) was elevated highlighting a novel potential therapeutic opportunity to reduce end organ injury with pediatric septic shock.

Activated or damaged endothelium establishes a prothrombotic environment that can result in local microvascular occlusion [154] or progress to DIC [190]. Endothelial cell apoptosis, detachment from the lamina, and alterations in vascular tone combine to promote capillary leak of proteins and fluid leading to hypovolemia and shock [191]. Using transgenic mice, it was recently shown that pulmonary endothelial cells sense bloodborne bacteria and their products [178] while alveolar macrophages patrol the airspaces for pathogens [192]. These data illustrate the role of endothelium help to explain in part the occurrence of ARDS and PPHN associated with severe sepsis in the absence of a primary pulmonary infectious focus.

Pathophysiology of Sepsis

Cardiovascular

The most common organ dysfunction associated with sepsis is cardiovascular. As discussed above, septic shock is really a composite of hypovolemic, cardiogenic, and distributive shock. Distributive shock is related to endothelial NO production that leads to excessive vasodilation. Cardiogenic shock may be related to mitochondrial death (induced by RNI and ROI) with subsequent myocardial dysfunction. In addition, some of the mediators released by the innate immune system are likely myocardial depressant factors [193]. Hypovolemia (absolute or relative) is very common. Peripheral vasoregulation abnormalities and myocardial dysfunction may play a larger role in hemodynamic derangements in pediatric patients, especially infants and neonates. Factors contributing to developmental differences in hemodynamic responses include altered structure and function of cardiomyocytes, limited ability to increase stroke volume and contractility, and contributions of the transition from fetal to neonatal circulation [65, 194–197]. In adults, septic shock is most commonly characterized by reduced systemic vascular resistance and elevated cardiac index [198]. In children, as discussed above, reduced cardiac output and increased systemic vascular resistance is more common [57–64]. The hemodynamic presentation in neonates is much more variable [199] and complicated by an unclear association between a normal blood pressure and adequate systemic blood flow [200, 201]. Myocardial dysfunction can lead to ventricular wall stretch that in turn elevates brain natriuretic peptide (BNP). BNP levels have utility as prognostic indicators of mortality [202] in older patients with sepsis and in post-operative children [203].

Immune System

Following severe sepsis or septic shock, there is an increased risk of subsequent infection and mortality [204]. This phenomena is termed "immunoparalysis" and is associated with reduced MHC class 2 expression and TNF-α production by mononuclear cells following endotoxin stimulation. In addition to altered monocytic responses, there is significant loss of lymphoid $CD4^+$ T and B cells via caspase-dependent apoptotic pathways [205, 206]. Whether by clonal selection, apoptosis, or elevated endogenous glucocorticoid levels [207–209], lymphocyte loss may lead to a state of immune compromise following the acute phase of sepsis [207, 209–214]. New data suggests that IL-7 may play an important role in promoting T-cell activation and the prevention of apoptosis [215]. The importance of immunoparalysis has been convincingly demonstrated in infected adults [216–219] and children [204]. However, immunoparalysis following sepsis may not impact the preterm neonate in whom adaptive immune function is less well developed [220, 221].

Mechanisms behind sepsis and post-sepsis immune alterations are beginning to emerge. The intensity of the inflammatory response may be modified by neural-based mechanisms. T cell-secreted acetylcholine acts on macrophages to reduce production of TNF, IL-1, IL-18, HMGB1, and other cytokines [222]. The role of vagal tone in the pediatric host response to sepsis is unclear. Discovery and characterization of the impact of epigenetic-mediated immune system functional alterations following sepsis is an area of

intense research. DNA methylation as well as post-translational modification of histone proteins (methylation, acetylation, phosphorylation, ubiquitination, sumoylation) may occur after sepsis [195, 223]. These DNA alterations may modify transcription factor access of gene-specific promoter regions ultimately leading to short and long-term changes in gene expression and immune function.

In adults, absence or dysfunction of the adaptive immune system has a profound impact on survival in preclinical models [205]. Genome-wide mRNA expression profiling (GWEP) during pediatric septic shock revealed widespread repression of gene pathways corresponding to the adaptive immune system [224]. In adult animals, B cells (and in particular B cell cytokine production) and not T cells were shown to be important in the early host response [225]. Interestingly, experimental data using neonatal mice lacking an adaptive immune system (RAG-1$^{-/-}$) showed no difference in early polymicrobial sepsis survival as compared to wild-type animals with a present adaptive immune system [226]. As these findings illustrate, the contribution of adaptive immunity for protection and response against sepsis, and in particular which components are protective, is unclear in the most immature and requires further investigation.

Pulmonary

Acute hypoxic respiratory failure, acute respiratory distress syndrome, and acute lung injury are common pulmonary complications associated with severe sepsis. Destruction of the alveolar capillary membrane leads to refractory hypoxemia. Following direct or indirect insults to the lung, alveolar macrophages produce chemokines that mitigate PMN influx to lung parenchyma. Activated PMNs release ROI/RNI that damage endothelial and epithelial barriers leading to leakage of protein-rich edema fluid into the air spaces. Other pulmonary complications with severe sepsis may include secondary surfactant deficiency [227], pulmonary edema, primary or secondary pneumonia [228], and reactive pulmonary hypertension [194, 229].

Renal

Infection is an important predictor of acute kidney injury in children [230]. Over 40 % of septic children or adults manifest AKI on the first day of hospitalization. The pathophysiology of AKI with sepsis is incompletely characterized but historically been attributed to ischemia-reperfusion injury following cardiogenic and hypovolemic shock. More recently, other factors including patient age, body-mass index, malignancy, intra-abdominal source of infection, microcirculatory dysfunction, kidney energy failure, immune-mediated injury and apoptosis, and nephrotoxin exposure also contribute to the development of AKI with sepsis.

Hepatic

Hepatic injury and dysfunction are frequent associations with severe sepsis. Mechanisms include reduced hepatic perfusion associated with septic shock and mitochondrial energy failure. Reductions in coagulation and complement factors, acute phase reactants as well as increases in transaminases and bilirubin are commonly seen especially with decreased perfusion states. Cytokines and nitric oxide reduce CYP 450 activity in vitro and in vivo. CYP 450-mediated drug metabolism is decreased in children with sepsis, related in part to the degree of inflammation and organ failure [231]. Hepatocyte destruction and lymphocyte infiltration are associated with increased soluble Fas (CD95, sFas) and sFas ligand levels [232]. Plasma sFas levels are increased with severe sepsis, persistent multiorgan failure (MOF), mortality, and correlates with serum IL-6, IL-10, nitrite + nitrate levels. Plasma sFasL is increased in liver failure-associated MOF, mortality, and was associated with viral infection but was not increased in severe sepsis and did not correlate with inflammation.

Multi-organ Dysfunction Syndrome (MODS)

Sepsis that leads to multi-organ dysfunction syndrome (MODS) carries a bleak prognosis. Inadequate cardiac output and microcirculatory failure, which may be combined with formation of microthrombi and DIC, can lead to poor perfusion to the kidney [233, 234], liver [235], gut [236], and CNS [237–241]. Recent studies suggest that the mechanism of organ failure in sepsis may relate to decreased oxygen utilization associated with mitochondrial dysfunction rather than or in addition to poor oxygen delivery to tissues [242, 243]. Mitochondrial dysfunction can initiate activation of cell death pathways including apoptosis, pyroptosis, necrosis, and NETosis (i.e., cell death mediated by neutrophil extracelluar traps). DAMPs (including nucleosomes and microparticles) created by activation of these cell death programs further amplify the host immune response.

BPI is a component of PMN granules that is bactericidal towards gram-negative bacteria and inhibits LPS-mediated inflammatory responses. Plasma BPI concentrations in critically ill children with sepsis syndrome or organ system failure both had higher median plasma BPI concentrations than critically ill controls without sepsis or organ failure. Plasma BPI concentrations were also positively associated with pediatric risk of mortality score [140]. Free radicals play an important role in the inflammatory process of sepsis [244].

In a piglet neonatal sepsis model edaravone, a novel free radical scavenger, increased MAP and cardiac output, lowered heart rate, hydroperoxide, nitrite, and nitrate levels, delayed the TNF-alpha surge, prevented HMGB1 elevation, and was associated with longer survival times [245]. Elevated plasma nitrite/nitrates and increased organ failure scores are present in children with sepsis with an exaggerated proinflammatory state and a robust anti-inflammatory response [246]. Increased plasma nitrite and nitrate concentrations are associated with the development of multiple organ failure in pediatric sepsis [247].

Several other mediators of MODS have been recently described and are currently under investigation. Elevated MMP8 mRNA expression and activity in septic shock correlates with decreased survival and increased organ failure in pediatric patients. MMP8 is a direct activator of NF-κB [248]. Inhibition (genetic or pharmacologic) of MMP8 leads to improved survival and a blunted inflammatory profile in a murine model of sepsis. GWEP revealed zinc homeostasis as an important feature of pediatric sepsis [249–251]. Prophylactic zinc supplementation reduced bacterial load and mortality in a murine model of peritoneal sepsis [252]. PBMC PPAR-α gene expression is decreased with severe sepsis. PPAR-α knockout mice exhibit a decreased inflammatory response and poor bacterial clearance in septic animals [253]. PPAR-γ exhibits altered expression and activity in PBMCs from children with septic shock [254]. Kruppel-like transcription factor 2 (KLF2) is a potent regulator of myeloid cell activation. Myeloid cell KLF2 expression is reduced with hypoxia and exposure to bacterial products, and a reduction of KLF2 is associated with increased NF-κB mediated HIF-1α transcription [255].

Management of Sepsis

Over two decades of clinical research looking searching for the so-called "magic bullet," or a mediator-specific therapeutic agent designed to abrogate a specific target in the host inflammatory response to sepsis, have been largely disappointing [256]. Several experts have speculated on why the vast majority of therapeutic trials in sepsis have failed [183, 257–259]. One commonly cited reason is the sheer complexity of the sepsis phenotype. As discussed above, there are several hundred genes that are differentially expressed in sepsis [249, 251, 260–262], many of which are involved in redundant and overlapping pathways. Aside from prevention (which is of significant importance) then [4, 263], the crux of pediatric sepsis management rests upon three important therapeutic principles or pillars – (i) early recognition of sepsis, (ii) early source control and antibiotic administration, and (iii) early reversal of the shock state [6]. These three pillars are based upon the American College of Critical Care Medicine's consensus guidelines for the management of critically ill neonates and children with septic shock (Fig. 30.4) [67].

Early Recognition

Early recognition and treatment is the cornerstone of sepsis therapy and represents the first pillar in management. Unfortunately, early recognition and diagnosis of sepsis, especially in children, remains a significant challenge, even in developed countries with advanced health care delivery systems [4, 256, 264]. Failure to recognize the signs and symptoms of sepsis and to institute timely and appropriate care leads to higher mortality rates in children and adults [54, 265–271]. There are no simple, straightforward blood tests that can reliably diagnose patients with sepsis. While early evidence suggests that the biomarker procalcitonin is more sensitive than C-reactive protein (CRP) in detecting serious bacterial illness in children with fever [272], additional studies are required. The currently available test for procalcitonin is relatively inexpensive and readily available. Interleukin (IL)-27 may also be a more accurate biomarker compared to CRP, especially when used in conjunction with procalcitonin – though again further studies are required [273, 274]. Until these biomarkers are studied more extensively, sepsis will remain primarily a clinical diagnosis based upon the recognition of a constellation of signs and symptoms (i.e., SIRS) that occur with infection.

As Machiavelli stated in the quote at the beginning of this chapter, in its early stages, when treatment is most effective, sepsis is virtually indistinguishable from other, more benign febrile illnesses. Early recognition of sepsis therefore requires a heightened awareness and increased index of suspicion on the part of the clinician, and traditionally a substantial amount of clinical experience [275–277]. Sustained tachycardia in absence of fever, tachypnea or respiratory distress in absence of pulmonary disease or out of proportion to other symptoms, subtle changes in skin perfusion, and altered mental status are all highly suggestive of possible sepsis.

Early Source Control and Antibiotic Administration

Early source control and antibiotic administration represents the second pillar in the successful management of pediatric sepsis. Autopsy studies in adults have shown that the failure to diagnose and appropriately treat infections with antibiotics or surgical drainage is the most common avoidable error in the treatment of sepsis [278, 279]. Multiple studies have demonstrated the importance of early source control (which may include surgical removal of the nidus of infection) and

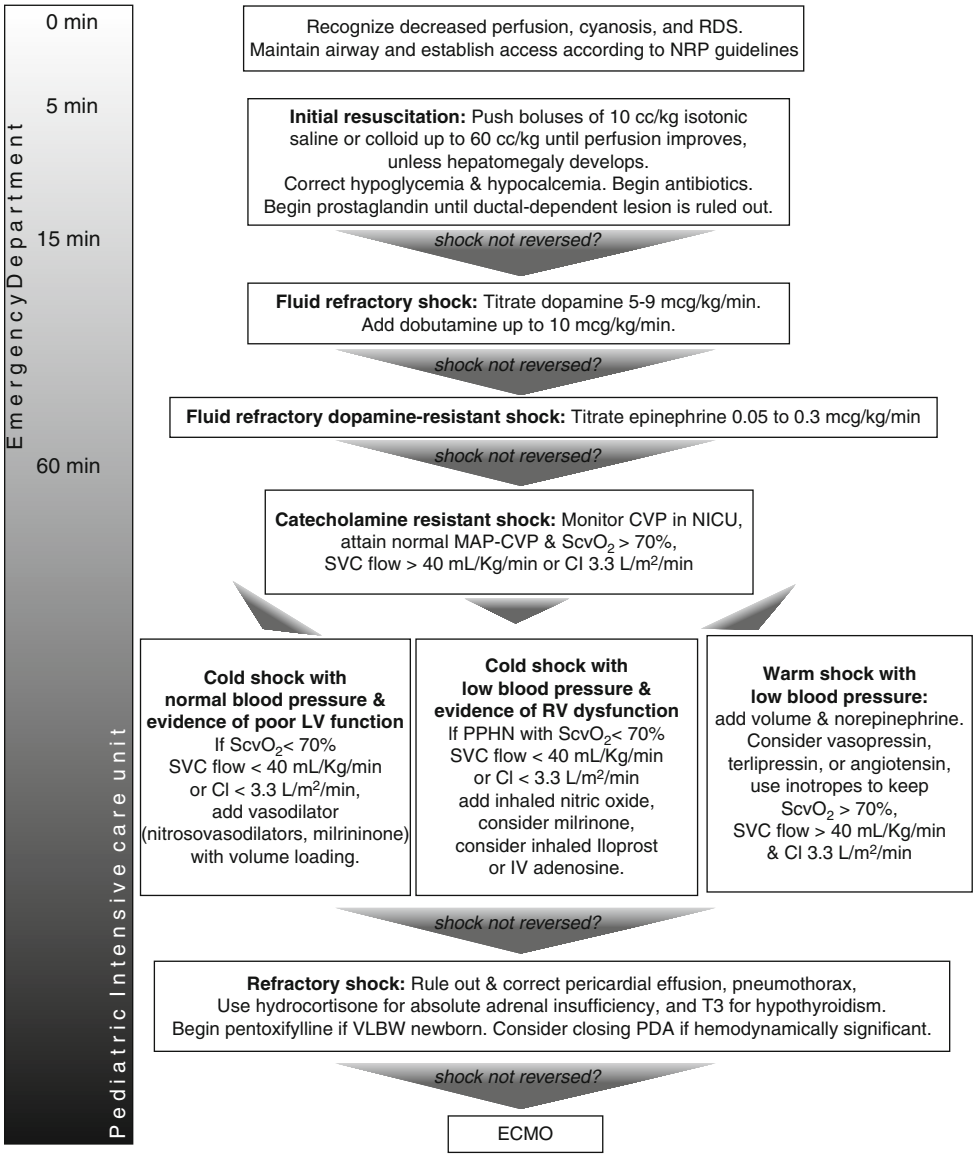

Fig. 30.4 American College of Medicine consensus guidelines for the management of critically ill children with septic shock (Reprinted from Brierley et al. [67]. With permission from Wolters Kluwer Health)

antibiotic administration. For example, Gaieski and colleagues showed that mortality significantly increased when antibiotics were delayed beyond 1 h in critically ill adults presenting to the ED with severe sepsis and septic shock [280]. A study by Kumar and colleagues showed that only 50 % of patients received antibiotics within 6 h of documented hypotension, which was associated with increased risk for mortality [267]. A protocolized approach to the management of sepsis has been shown to improve the time to administration of antibiotics in several studies involving both children [281–283] and adults presenting to the ED [284–289]. Indeed, this kind of approach has even been successful in resource-poor countries. For example, studies conducted in a rural population in India showed that home administration of oral and injectable antibiotics to neonates with perinatal-acquired sepsis resulted in significant reductions in sepsis-related neonatal mortality – sustained over a 10-year period [290, 291].

Early source control and antibiotic administration have also been emphasized in the highly successful Surviving Sepsis Campaign (SSC) [292], a joint collaboration between the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine. The resuscitation bundle for managing critically ill adults with sepsis calls for broad-spectrum antibiotics to be administered within 3 h of ED admission and/or 1 h of ICU admission [293–295]. Notably, the SSC (discussed further below) enrolled over 15,022 patients from 165 centers from January, 2005 through March, 2008. Compliance with the resuscitation and management bundles was associated with a significant reduction in hospital mortality [296].

Early Reversal of Shock

Early reversal of the shock state with aggressive resuscitation targeted at rational therapeutic endpoints represents the third pillar in the management of pediatric sepsis. While it has been known for several years that early reversal of shock improves outcomes in critically ill children [54, 269, 297], the concept known as *early goal-directed therapy* (EGDT) was initially popularized following the publication of the study by Rivers and colleagues, which showed that EGDT significantly improved outcomes [298]. All patients had arterial and central venous catheters placed in the ED, and therapy was protocolized to achieve a CVP 8–12 mmHg with fluid resuscitation, MAP >65 mmHg and <95 mmHg with vasoactive agents, and a superior vena caval oxygen saturation ($S_{svc}O_2$) greater than 70 % with inotropes and blood transfusion. Importantly, treatment in the conventional therapy group was targeted towards a CVP 8–12 mmHg, MAP >65 mmHg and <95 mmHg, and urine output >5 mL/kg/h. In-hospital mortality was significantly lower in the EGDT group compared to the conventional therapy group (30.5 % vs. 46.5 %, respectively, p = 0.009). Differences in outcomes were noted despite the fact that the groups received the same treatment after the initial 6 h of therapy.

The EGDT trial is one of only a few studies that have been published to date that have shown a reduction in mortality from sepsis and highlights the importance of early recognition and aggressive resuscitation of shock. A subsequent meta-analysis of 21 randomized, controlled trials of sepsis by Kern and Shoemaker [299] further highlights the importance of early, goal-directed therapy, demonstrating that when patients with acute critical illness are treated early to achieve optimal goals before the development of organ failure, significant reductions in mortality are achieved [294, 300]. In addition, there are currently three prospective, multicenter, randomized clinical trials going on in the United Kingdom, U.S., and Australia that are further testing the overall validity of this concept in critically ill adults with severe sepsis/septic shock. The Surviving Sepsis Campaign conducted a multicenter, international, prospective, collaborative involving over 15,000 patients worldwide. Increasing compliance with a 6-h resuscitation bundle (focused on early antibiotics and rapid reversal of shock) and maintenance bundle (focused more on lung-protective ventilation, stress ulcer prophylaxis, glucose control, corticosteroids for vasopressor-refractory shock, activated protein C) was associated with significant reductions in mortality at participating hospitals [296]. There has since been significant controversy regarding both the use of activated Protein C and "tight glucose control" in critically ill patients with severe sepsis and septic shock. A similar quasi-experimental study in Spain showed that compliance with the resuscitation bundle was more important than the maintenance bundle [301].

Table 30.5 Surviving Sepsis Campaign (*SSC*) bundles

To be completed within 3 h
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
To be complete within 6 h
1. Apply vasopressors (for fluid-refractory hypotension) to maintain a mean arterial blood pressure ≥65 mmHg (adult)
2. If the patient remains hypotensive despite fluid resuscitation or initial lactate ≥4 mmo/L
(a) Measure central venous pressure (*CVP*)
(b) Measure central venous oxygen saturation ($S_{CV}O_2$)
Remeasure lactate if initial lactate was elevated

Based on these results and the aforementioned controversies, the Surviving Sepsis Campaign has changed the bundles to de-emphasize care beyond 6 h (see the Surviving Sepsis Campaign website at http://www.survivingsepsis.org/Bundles/Pages/default.aspx) (Table 30.5).

Preliminary studies suggest that EGDT may be beneficial in select groups of critically ill children with sepsis [54, 282, 283, 302, 303]. Additionally, investigators at St. Mary's Hospital-London developed a protocol for managing critically ill children with meningococcal sepsis [297] and were able to demonstrate a dramatic reduction in mortality from 23 % in 1993 to 2 % in 1997 [266]. This protocol similarly emphasized early recognition and has been modified [269] and adapted into a National Institute for Health and Clinical Excellence (NICE) guideline in the United Kingdom [304].

Based upon the studies published above, it is imperative that resuscitation should begin as soon as the sepsis syndrome is recognized, usually in the ED, and should not be delayed until admission to the PICU [54, 57, 305, 306]. During the first 6 h the aim is to achieve the following goals:

1. Capillary refill <2 s
2. Urine output ≥1.0 mL/kg/h
3. Normal pulses, without difference between peripheral and central pulse
4. A central venous oxygen saturation ($S_{svc}O_2$) of >70 %
5. Declining lactate and base deficit
6. Improved level of consciousness

Fluid Resuscitation

Critically ill children with severe sepsis and/or septic shock almost universally have decreased effective intravascular volume for a variety of reasons. Many of these children have had poor oral intake of fluid for a period of time prior to developing sepsis. With the development of increased vascular permeability, intravascular volume has been lost due to third spacing. Finally, peripheral vasodilation related to excessive NO production (see above) results in an abnormally

increased vascular capacitance, decreasing the effective circulating volume. Aggressive fluid resuscitation with crystalloids or colloids is therefore essential to increase survival of septic shock in children. This goal can be reached by administering 20 mL/kg boluses over 5-10 min, repeated as necessary to achieve the hemodynamic goals stated in the preceding paragraph [305, 306]. Large fluid deficits are typically encountered, requiring 60 mL/kg volume resuscitation or occasionally much higher amounts [305]. Transfusion of packed red blood cells should be considered to maintain hemoglobin levels at levels consistent with adequate oxygen delivery, though the optimal hemoglobin for infants and children with septic shock is not currently known.

The available evidence suggests that the different types of intravenous fluid available for fluid resuscitation are similar in terms of efficacy, both in pediatric [307–310] and adult studies [311–313]. There is perhaps one caveat, in that there is some preliminary data suggesting a mortality benefit with colloid compared to crystalloid in critically ill children with severe sepsis secondary to malaria [314, 315]. In recent years, several studies have shown a correlation between fluid overload and increased mortality in critically ill children requiring renal replacement therapy [316–319]. Fluid overload has also been shown to correlate with impaired oxygenation, longer duration of mechanical ventilation, and increased PICU and hospital length of stay (LOS), even in critically ill children who do not require renal replacement therapy [320]. Preliminary data from our group suggests that fluid overload is associated with worse outcomes in critically ill children with a low initial probability of mortality, but not in children with an intermediate-risk or high-risk of mortality (*Wong, personal communication*).

The recently published FEAST trial has led to further questions on the utility of fluid resuscitation in critically ill children with severe sepsis and septic shock. In this prospective, randomized, controlled study, children presenting to the hospital (in Uganda, Kenya, or Tanzania) with a severe febrile illness received one of three treatments: 20–40 mL/kg 5 % albumin, 20–40 mL/kg 0.9 % saline, or no fluid bolus. There were no differences in mortality at 48 h between the saline (110/1,047 children, 10.5 %) and albumin (111/1,050 children, 10.6 %) groups, though mortality was lowest (76/1,044 children, 7.3 %) in the control group that did not receive a fluid bolus. These results were consistent across all sub-group analyses [321]. A follow-up analysis of these results showed that excess mortality occurred as a result of cardiovascular collapse and not fluid overload (pulmonary edema, neurologic deterioration, etc.) [322]. Given the accumulation of several decades of experience with intravenous fluid resuscitation, it would seem premature to abandon (or even temper) this therapy without additional data. In addition, it should be noted that the FEAST study and the majority of the aforementioned studies comparing crystalloid to colloid in children were performed in patient populations (e.g., dengue fever, severe malaria, severe malnutrition, etc.) that are quite different from the majority of critically ill children with shock in the developed world. Whether these findings can be generalized to different populations around the world remains an area of active study. In light of the remaining questions and available data, the usual practice in most PICUs is to initiate volume resuscitation with crystalloid fluids as a first line and follow with colloid if needed.

Collectively, these data further strengthen the concept of carefully titrating fluid resuscitation and other therapies to rational therapeutic endpoints in a protocolized fashion, consistent with the American College of Critical Care Medicine Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock [67]. Again, reliable implementation of these guidelines has resulted in improved outcomes in at least a few published reports [54, 302, 303].

Hemodynamic Support

While the principles of hemodynamic monitoring and support have been discussed elsewhere in this textbook, a brief discussion here is justified. In the case of fluid refractory shock, inotropic or vasoactive support should be started without delay. Again, the most common hemodynamic derangements observed in critically ill children with septic shock are low cardiac output and high systemic vascular resistance (i.e., so-called *cold shock*). Dopamine has traditionally been the initial agent of choice for infants and children with septic shock [306], though the choice of additional agents will be determined by the clinical condition of the child. For example, dobutamine or epinephrine may be preferable in children with low cardiac output and poor peripheral perfusion (*cold shock*), especially given the association of dopamine with increased morbidity and mortality in several studies [323]. In addition, there have been some observational studies in both critically ill children and adults suggesting that dopamine may be associated with an increased risk of morbidity and mortality [324–326]. Norepinephrine is the preferred agent for children with normal cardiac output and bounding peripheral pulses (*warm shock*). A type III phosphodiesterase inhibitor such as milrinone may also improve perfusion in children with *cold shock*, who are adequately volume resuscitated, though hypotension is always a risk with this agent. Regardless of the vasoactive regimen chosen, close monitoring of the oxygen delivery, as assessed by end-organ function, mixed venous oxygen saturation and a falling lactate levels, is necessary to tailor ongoing treatment. Finally, extracorporeal life support (ECLS) may be necessary and lifesaving in select patients [327–332].

Supportive Care

Children with sepsis may have poor nutrition prior to presentation and are often not fed in the first few days of illness. Because of increased metabolic rate and poor nutrition,

septic patients are frequently catabolic and at risk for the development of protein calorie malnutrition [333]. Intestinal ischemia in association with the loss of the mucosal barrier from malnutrition has been associated with translocation of bacteria and endotoxin from the intestine into the blood stream [334, 335]. Use of enteral feeding in critical illness has been shown to improve survival and decrease hospital stay [336]. The benefit of enteral feeding should be balanced with the risk of stressing the intestinal function in the face of poor splanchnic perfusion, especially in the presence of vasopressors such as epinephrine and norepinephrine [337, 338]. Regardless of the mode of feeding, adequate nutrition and nitrogen balance is important for maintaining adequate host immune function and achieving homeostasis. Malnutrition may adversely affect the immune function and the ability to have an appropriate immune response [339]. Finally, in the absence of enteral feedings, protection from stress-related gastrointestinal bleeding is advised.

Corticosteroids

High pharmacologic doses of corticosteroids were used in the past in an attempt to turn off the systemic inflammatory response associated with sepsis. However, most of the studies suggested that high-dose corticosteroids did not improve survival in septic patients and may even have worsened outcome by increasing the incidence of secondary infection [340]. However, more recent data suggests that patients, who are critically ill, in persistent shock, requiring vasopressors and mechanical ventilation, might benefit from physiological doses of corticosteroids [341]. This finding has not been confirmed in other studies [342]. Some investigators have postulated that some patients with sepsis may have a relative adrenal insufficiency despite normal serum cortisol levels, because of desensitization of corticosteroid responsiveness [343, 344]. This has been shown in critically ill children with meningococcal sepsis [345] and in other forms of sepsis [343]. Unfortunately, there have been no randomized, controlled studies of corticosteroid replacement in critically ill children with severe sepsis or septic shock. The most recent Surviving Sepsis Campaign guidelines [300] recommend corticosteroids only if the patient remains refractory to vasoactive medications. In addition, use of the ACTH stimulation test to discern between relative and absolute adrenal insufficiency is not necessary. The pediatric version of these guidelines suggests starting stress-dose hydrocortisone (50–100 mg/m^2/day hydrocortisone) in critically ill children with fluid-refractory and catecholamine-resistant septic shock and suspected or proven absolute adrenal insufficiency (i.e., after appropriate diagnostic workup with a random/basal serum cortisol level followed by an ACTH stimulation test). The diagnosis and treatment of adrenal insufficiency is discussed in great detail in other chapters of this textbook.

Conclusion

Sepsis remains a significant problem in pediatrics. The diagnosis remains a clinical one, and early recognition is absolutely critical. Additional treatment depends upon early source control and antibiotic administration, as well as early reversal of shock.

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Thrombocytopenia-Associated Multiple Organ Failure Syndrome

31

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Abstract

Thrombocytopenia-associated multiple organ failure (TAMOF) is a clinical syndrome often managed by critical care physicians. It is characterized by new onset thrombocytopenia in the setting of evolving multiple organ failure. TAMOF is an entity within the family of thrombotic microangiopathies, a spectrum of mixed coagulopathies and thrombotic disorders that include thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) on one end of the spectrum and disseminated intravascular coagulation (DIC) on the other. Autopsies performed in patients who have succumbed to DIC, TTP and HUS reveal disseminated microvascular thromboses with distinct findings that help to differentiate these three entities. Furthermore, our biologic and molecular understanding of the pathophysiologic processes governing DIC, TTP and HUS have significantly expanded and allow better laboratory delineation among these three entities. Tissue factor plays a pivotal role in the initiation and propagation of DIC. Von Willebrand factors and deficient ADAMTS-13 (a.k.a von Willebrand factor-cleaving proteinase) drive the pathology in TTP. Shiga toxins and the complement pathway drive the pathology in HUS. With better understanding of the biology of TAMOF syndrome, innovative therapies are currently being evaluated with the hope of reversing this destructive pathology.

Keywords

Thrombocytopenia-associated multiple organ failure • TAMOF • DIC • TTP • HUS • Thrombocytopenia • Platelets • Fibrin • VWF • ADAMTS-13 • Alternative complement pathway • Thrombotic microangiopathy • Disseminated microvascular thrombosis • Plasma exchange

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Introduction

Thrombocytopenia-associated multiple organ failure syndrome (TAMOF) is a clinical syndrome not infrequently encountered by critical care physicians in the intensive care unit. It is characterized by new onset thrombocytopenia (often with platelet counts dropping to less than 100,000/mm^3) in the setting of emerging or evolving multiple organ (systems) failure. The acute drop in platelet count in this syndrome suggests pathologic involvement of platelets as they form microvascular thromboses in the vascular beds of tissues and organs, leading to regional ischemia and injury and ultimately resulting in the observed multiple organ failure. Autopsies performed on patients who have died with TAMOF demonstrate widespread microvascular thromboses in all vital organs. Mortality from TAMOF syndrome remains high ranging from 5 to 80 % with current management strategy [1–10].

Pathophysiologically, TAMOF is an entity within the family of thrombotic microangiopathies (TMA's), a spectrum of mixed coagulopathies and thrombotic disorders that include disseminated intravascular coagulation (DIC) on one end of the spectrum and thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) on the other. Over the past decade, our biologic and molecular understanding of the pathophysiologic processes governing DIC, TTP and HUS have expanded considerably, allowing better laboratory delineation between these three distinct forms of TMA. This new knowledge has provided some analogous mechanistic insight into TAMOF pathophysiology that has motivated TAMOF investigators to explore innovative new therapeutic strategies with the hope of improving outcome in patients with TAMOF. However, more than 60 % of critically ill patients in the intensive care unit with TAMOF do not have overt clinical and biomarker evidence of DIC, TTP or HUS, underscoring our incomplete mechanistic understanding of TAMOF biology. In this chapter, we will review the TMA's, describing our current understanding of DIC, TTP, and HUS. We then discuss TAMOF and the different approaches to this syndrome.

Thrombotic Microangiopathy (TMA)

Thrombotic microangiopathies (TMA's) are a family of syndromes characterized by mixed coagulopathies and thrombotic abnormalities with a common clinical presentation of new onset thrombocytopenia. When severe, they are often associated with the development of multiple organ failure. The classification of TMA has been revised and updated as investigators learned more about the mechanisms of these syndromes. Classically, TMA has been categorized into primary or secondary, based on etiology or trigger [11,12]. TTP has been considered as primary TMA because its etiology is idiopathic. DIC has been considered as secondary TMA because an underlying trigger is usually identified such as sepsis, cancer, trauma, or other insults. Recently, the European Paediatric Research Group for HUS proposed a new classification for HUS, TTP and related disorders [13]. This group proposed to divide the classification into two parts. Part 1 includes etiologies that are reasonably advanced, which include infection-induced, disorders of complement regulation, ADAMTS-13 deficiency, defective cobalamine metabolism, and quinine-induced. Part 2 includes etiologies that are unknown but associated with certain clinical conditions such as human immunodeficiency virus infection, cancer, calcineurin inhibitors usage, pregnancy, systemic lupus erythematosus, glomerulopathy, and familial etiologies not included in Part 1. Part 2 also includes unclassified etiologies. Reclassification of TMA's will surely continue as investigators uncover new pathologic mechanisms.

Autopsies performed in patients who have succumbed to DIC, TTP and HUS reveal distinct findings that help to differentiate these three entities. Patients who die from DIC characteristically have fibrin-rich microthrombi throughout the body, whereas patients who die from TTP characteristically have von Willebrand factor (VWF)/platelet-rich microthrombi [14–16]. Patients who die from HUS have predominantly fibrin-rich microthrombi, but a subgroup also has VWF/platelet-rich microthrombi [16,17]. TTP has a significant involvement of myocardial arteries, whereas HUS has a striking involvement of the kidneys [15,17,18]. Thus, immunohistochemistry affirms that the molecular mechanisms within the spectrum of TMA can be rather distinct.

Disseminated Intravascular Coagulation (DIC)

DIC is usually triggered by an underlying pathology (Table 31.1). Autopsies performed in patients who have died from DIC reveal fibrin-rich microthrombi in small and mid-size vessels in all organs [14,15,19]. The cornerstone of treatment for DIC is treating the underlying inciting disease or problem. In 2001, the Scientific Subcommittee on DIC of the International Society of Thrombosis and Haemostasis (ISTH) proposed a consensus definition of DIC as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" [20]. To facilitate recognition of DIC, the ISTH recommended measuring platelet counts, fibrin-related marker (soluble fibrin monomers/fibrin degradation products), prothrombin time, and fibrinogen level [20]. The abnormalities of these global coagulation tests are tabulated to form the DIC score (Table 31.2). If the DIC score is ≥5,

Table 31.1 Clinical conditions associated with disseminated intravascular coagulation

1. Sepsis
2. Cancer
3. Trauma/burns
4. Obstetric complications
5. Toxins exposure
6. Vascular abnormalities

Table 31.2 Disseminated intravascular coagulation score by the International Society of Thrombosis and Haemostasis

1. Platelet count (>100 K/mm^3 = 0; <100 K/mm^3 = 1; <50 K/mm^3 = 2)
2. Elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products) (no increase = 0; moderate increase = 2; strong increase = 3)
3. Prolonged prothrombin time (<3 s = 0; >3 s but <6 s = 1; >6 s = 2)
4. Fibrinogen level (>1 g/L = 0; <1 g/L = 1)
5. Calculate scores. If score >5 = compatible with over DIC. If score <5 = suggestive of non-overt DIC; repeat next 1–2 days

then this is compatible of overt DIC. If the DIC score is <5, then this is suggestive for non-overt DIC.

In the intensive care unit, DIC can occur in 50 % of pediatric patients with severe sepsis and is associated with high morbidity and mortality [1,2,21,22]. Clinically, the patient presents with petechiae and purpura on the skin, and shock due to poor perfusion of the organs. When interventions are implemented to improve DIC, less fibrin deposition, improved organ failure, and increased survival have been observed [3,23].

Mechanism of DIC

In our current understanding of DIC pathogenesis, three major components are essential in the development of disseminated microvascular thromboses: (1) systemic inflammation; (2) thrombin generation, and (3) impairment of fibrinolysis. Tissue factor forms a pivotal role in the initiation and propagation of DIC. Tissue factor is expressed in numerous tissues in the body, but it is divided into two major sources – vessel wall or hematopoietic cells. Extravascular tissue factor is exposed when the vascular wall is injured. Leukocytes, primarily monocytes, express and release tissue factor after being stimulated by inflammatory cytokines or endotoxins in systemic inflammation such as infection. TNF-alpha and IL-6 induce tissue factor expression on monocytes and endothelium [24–27]. After its expression, tissue factor complexes with factor VIIa. This complex then activates factors IX and X, eventually leading to thrombin generation. This is the classic "extrinsic" pathway of coagulation. In animal models, investigators have shown that inhibition of the contact system (intrinsic pathway of coagulation) does not prevent the activation of coagulation leading to DIC [28]. However, inhibiting the tissue factor/factor VIIa pathway (extrinsic pathway) by monoclonal antibodies resulted in preventing the development of DIC and mortality in baboons that were injected with E. coli [29–31]. It is important to note that expression of tissue factor alone is not sufficient to initiate coagulation. Tissue factor must be "activated" and presented on a phospholipid surface to activate factor VII and initiate the extrinsic pathway. Platelets and serum factors are also necessary for large amount of thrombin generation and formation of fibrin thrombus [32,33]. As tissue factor initiates and propagates thrombin formation, the endogenous anticoagulants in the body such as antithrombin III, protein C, and tissue factor pathway inhibitor are all found to be impaired during DIC. Impaired synthesis, increase in consumption and degradation, and development of inhibitors have all been shown to be the cause of reduced anticoagulants activities [34]. Lastly, the body's natural fibrinolytic pathway, the breakdown of clots to maintain homeostasis during a prothrombotic state, is also impaired. Plasminogen-activator inhibitor type-1, a potent inhibitor of the fibrinolytic pathway, is significantly elevated in DIC and multiple organ failure [35–38].

Diagnosing and Managing DIC

More recently in 2013, the Scientific Subcommittee on DIC of the International Society of Thrombosis and Haemostasis published a "*Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines*" that stems from the British, Japanese, and Italian DIC treatment guidelines [39–42]. In summary, this subcommittee recommends that: (1) there is no gold standard for the diagnosis of DIC and no single test by itself that is capable of diagnosing DIC; (2) the cornerstone of DIC treatment is treating the underlying condition; (3) the transfusions of platelets, fresh frozen plasma (FFP), fibrinogen, and prothrombin complex concentrate is recommended in actively bleeding patients with low platelet counts, prolonged prothrombin time/activated partial thromboplastin time, hypofibrinogenaemia, or contraindicated FFP-transfusion, respectively; (4) therapeutic doses of low molecular weight heparin (LMWH) should be considered if thrombosis predominates; (5) prophylaxis for venous thromboembolism with prophylactic doses of unfractionated heparin or LMWH is recommended in non-bleeding patients; (6) the administration of antithrombin III, recombinant thrombomodulin, or activated protein C may be considered; (7) Generally, antifibrinolytic agents should not be used; and lastly (8) patients with severe bleeding, characterized by a marked hyperfibrinolytic state such as leukemia and trauma could be treated with antifibrinolytic agents.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP was first described by Dr. Moschcowitz in 1924 about a girl who abruptly died with petechiae, paralysis, and coma [43]. On autopsy, he found that her terminal arterioles and capillaries to be occluded with hyaline thrombi. Dr. Moschcowitz hypothesized that a "powerful poison which had both agglutinative and hemolytic properties" had existed in the blood of this girl. For decades, recognition of this entity remained entirely clinical, and building on Dr. Moshcowitz's observation, diagnosis of TTP was facilitated through the now classic clinical "pentad" of thrombocytopenia, hemolytic anemia, fever, central nervous system and renal abnormalities. It was not until 1982 that Dr. Moake suggested the "powerful poison which had both agglutinative and hemolytic properties" in the blood was ultra-large von Willebrand factor multimers (ULVWF) [44]. In 1997 Dr. Tsai further identified that the underlying pathophysiologic process of TTP results from a deficiency of ADAMTS-13 (a.k.a. VWF-cleaving proteinase). With ADAMTS-13 deficiency, ULVWF and large plasma VWF remain uncleaved and retain their hyper-adhesive properties in the blood. VWF multimers have binding sites to platelets and collagen. ULVWF and large plasma VWF then aggregate platelets to form VWF/platelet-rich microthrombi in all organs.

Autopsies in patients expired with TTP reveal the characteristic VWF/platelet-rich microthrombi. Furthermore, these autopsy studies reveal marked involvement of the heart in TTP cases compared to DIC and HUS cases [14,15,18,45]. TTP is divided into two categories: familial TTP and acquired idiopathic TTP. In familial TTP, mutations of *ADAMTS13* gene render this ADAMTS-13 enzyme (a.k.a. VWF-cleaving proteinase) inactive [46]. Currently, more than 80 mutations have been identified in patients with congenital TTP [47–51]. In acquired idiopathic TTP, ADAMTS-13 inhibitors such as IgG auto-antibodies to ADAMTS-13 have been shown to cause severe (<10 % activity) ADAMTS-13 deficiency [52,53].

Von Willebrand Factor Hyper-Adhesiveness in TTP

Von Willebrand factor (VWF) is the largest multimeric glycoprotein in human plasma with molecular masses ranging from 500 to 20,000 kDa [54]. It mediates the initial platelet adhesions to damaged vessel wall by bridging platelets through its receptor GP Ib-IX-V complex to exposed subendothelial collagen. It is synthesized by the endothelial cells and megakaryocytes as monomers that dimerize through C-terminal interchain disulfide bonds and them multimerize through the N-terminal interdimer disulfide bonds [55–57]. After synthesis, VWF is secreted by either the constitutive pathway of lower molecular mass (~500 kDa) dimers or the inducible pathway of larger and ultra-large VWF multimers [58,59]. The inducible pathway is primarily triggered by inflammatory stimulations [60–62]. ULVWF is not only extremely large but it is also exquisitely hyper-adhesive. It aggregates platelets spontaneously by forming high strength bonds with platelet receptor GP Ib-IX-V complex [63]. This prothrombotic ULVWF is rapidly, but partially cleaved by ADAMTS-13 enzyme before being released into plasma. As a result, plasma VWF binds and aggregates platelets only in the presence of modulators such as ristocetin or at high shear stress [64,65]. Deficiency of ULVWF proteolysis results in accumulation of ULVWF in plasma and on endothelial surface as demonstrated in patients with TTP.

ADAMTS-13 (a.k.a VWF-Cleaving Protease) Deficiency in TTP

ADAMTS-13 is a member of the ADAMTS (**A** **D**isintegrin **A**nd **M**etalloproteinase with **T**hrombo**S**pondin motifs) family, which is a subfamily of ADAMs. ADAMTSs are not membrane-bound and contain one or more of the thrombospondin-1-like motifs at the carboxy terminal of the protein, which are thought to interact with the extracellular matrix [46]. The *ADAMTS13* gene encodes a protein with 1,427 amino acids and its mRNA is detected in a variety of tissues, among which hepatic stellate cells, endothelial cells, and platelets [46,66–68]. ADAMTS-13 cleaves VWF at a single peptide bond of Tyr842-Met843 in the VWF A2 domain. The cleavage converts ULVWF, which spontaneously aggregate platelets, to smaller plasma forms that bind to platelets only with modulators, high fluid shear stress, or when they are immobilized onto a solid surface. The cleaved VWF is no longer prothrombotic, but maintains hemostatic functions.

Diagnosing and Managing TTP

The clinical "pentad" of TTP – thrombocytopenia, hemolytic anemia, fever, and CNS and Renal abnormalities – usually alerts the clinician of this syndrome. Elevation of lactate dehydrogenase (LDH) and the presence of schistocytes are helpful in complementing the evidence for a thrombotic microangiopathic process. ADAMTS-13 activity and VWF assays are still not available quick enough in many hospitals to make clinical decision. In TTP, ADAMTS-13 activity will be <10 % and VWF activity will be high with the presence of ULVWF [45]. The therapeutic strategies for TTP are to replenish ADAMTS-13 and to remove ADAMTS-13 inhibitors and ULVWF from the plasma. Fresh frozen

plasma, cryosupernatant (the cryoprecipitate-poor fraction of plasma), and solvent/detergent-treated plasma, all of which contain active ADAMTS-13, can be transfused to TTP patients. Steroids and/or rituximab (monoclonal antibody against CD 20 on B-lymphocytes) can also be given to reduce the production of IgG autoantibodies to ADAMTS-13 [69]. However, therapeutic plasma exchange is currently the treatment of choice for newly diagnosed TTP as it is recommended by the American Society for Apheresis with a category I indication – "*accepted as a first line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment*" [4]. Without treatment, TTP has a 100 % mortality but with therapeutic plasma exchange, the mortality is now less than 20 % [4–6]. The rationale for therapeutic plasma exchange is to remove the ULVWF and inhibitors to ADAMTS-13, and to replenish ADAMTS-13 [4,45].

Hemolytic Uremic Syndrome (HUS)

During the past decade, investigators have made significant progress in the understanding and management of HUS. The clinical "triad" of HUS is thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure. Fortunately, the majority of HUS cases have excellent outcome with supportive care and do not progress into multiple organ failure. However, HUS cases with central nervous system symptoms such as coma, seizures and stroke are more likely to develop TAMOF and associated with a higher mortality [8]. HUS is divided into two major clinical phenotypes: (1) infection-induced HUS, which includes infection with Shiga toxin-producing *Escherichia coli* (STEC) and neuraminidase-producing *Streptococcus pneumonia*, and (2) atypical HUS, which includes genetic and acquired disorders of complement regulation [10,70,71]. Autopsies performed on patients who have died of HUS reveal fibrin-rich microthrombi in the majority of the cases but rare VWF/platelet microthrombi are also seen [16,18]. Furthermore, autopsies in HUS cases reveal marked involvement of the kidneys with less frequent involvement of other organs, contrasting with TTP and DIC where all organs are involved [18].

Infection-induced HUS accounts for approximately 90 % of all HUS cases, and the majority (85–90 %) of the cases are caused by STEC [10,71,72]. In a typical STEC-HUS, diarrhea occurs 3 days after ingesting STEC contaminated food. HUS develops in approximately 6–15 % of the infected patients 2–10 days after bloody diarrhea [72,73]. STEC-HUS has commonly been affecting children until the recent outbreak in Germany in 2011 that affected mostly adults with 25 % of the infected patients developing HUS [7]. Mortality for diarrhea-associated HUS ranges from 5 to 9 % [7,8].

Atypical HUS accounts for approximately 10 % of all HUS cases [10]. Complement pathway genetic mutations account for 50–60 % and thrombomodulin mutations account for 5 % of atypical HUS cases. Mortality is approximately 25 % for all atypical HUS, but is 50–80 % for familial form of atypical HUS [9,10].

Mechanisms of HUS

Shiga toxins produced by enterohemorrhagic *E. coli* can initiate a pathologic cascade leading to HUS. Shiga toxins bind to glycosphingolipid surface receptor globotriaosyl ceramide expressed on the renal microvascular endothelium. The toxins are then internalized leading to inhibition of protein synthesis and cell death [74]. Shiga toxins also have been shown to (1) induce inflammation by activating monocytes to release inflammatory cytokines [75], and (2) induce a prothrombotic state by activating platelets [76], increasing tissue factor activity on glomerular endothelial cells [77], inhibiting ADAMTS-13 [78], and stimulating ULVWF release from glomerular endothelial cells [78]. Clinical association studies of STEC-HUS have shown that complement dysregulation occurs during the acute phase and normalized during convalescence [79–81]. Recently, investigators show evidences with in vitro and in vivo experiments that Shiga toxins can significantly promote complement activation leading to thrombosis [82]. In addition, in vitro experiments show that endothelial cells can synthesize alternative complement components that are assembled and activated on the endothelial cells-secreted ULVWF [83]. To summarize the linkage between Shiga toxins and complement pathway, Shiga toxins can induce the endothelium to release alternative complement pathway components and ULVWF, which are anchored onto the endothelium. The complement components are then assembled and activated on the ULVWF. The activated complement complex could then cause destruction of the local endothelium.

Uncontrolled alternative complement pathway activation can cause HUS. For the past 15 years, investigators have linked more than 120 complement mutations to atypical HUS [84]. In addition, autoantibody against Factor H, a regulatory complement protein, can interfere with Factor H function and cause HUS [85]. Complement system is a tightly controlled network of plasma proteins that is essential for immune surveillance and homeostasis. Complement activation results in pathogen removal and cell lysis [86]. The complement mutations associated with atypical HUS allow for the normally tightly regulated complement pathway to become unregulated and hyperactive after an inflammatory trigger. This leads to inflammation, and if severe will lead to uncontrolled systemic inflammation, disseminated microvascular thromboses, and multiple organ failure.

Diagnosing and Managing HUS

For the majority of STEC or diarrhea-associated HUS, supportive care is the current recommendation. However, for the diarrhea-associated HUS with central nervous system involvement and the non-diarrhea-associated HUS, thorough investigation of the pathophysiologic mechanism and therapeutic strategies should be extensively discussed. Complement pathway biomarkers should be evaluated for signs of hyperactivation along with a genetic evaluation. ADAMTS-13 activities and VWF profile should be evaluated for a TTP pathophysiologic process. DIC biomarkers should also be assessed.

Currently, therapeutic plasma exchange is recommended for **atypical HUS due to autoantibody to factor H** by the American Society for Apheresis with a **category I** indication – "accepted as a first line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment". Plasma exchange is also recommended for **atypical HUS due to complement factor gene mutation** with a **category II** indication – "accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment". Plasma exchange is not recommended (**category IV**) for STEC or diarrhea-associated HUS [4]. Direct complement inhibition with anti-C5 monoclonal antibody Eculizumab should be considered for atypical or non-diarrhea-associated HUS. Mounting evidences are accumulating for positive outcome in patients with atypical HUS treated with Eculizumab [87,88].

Cases that pose therapeutic strategy dilemma for the intensivists are (1) diarrhea-associated HUS with central nervous system involvement and (2) diarrhea illness with rapid progression into TAMOF. These cases encompass a mixture of probable pathologic mechanisms involving Shiga toxins, platelets, VWF, ADAMTS-13, complements, fibrin, and the endothelium. Until clinicians have the ability to tease out the exact pathologic mechanism, there is a biologic plausibility for the benefit of therapeutic plasma exchange with the goal of restoring homeostatic milieu by removing the accumulating harmful molecules and replenishing the depleted beneficial molecules. Indeed, case series have reported the benefit of plasma exchange in severe diarrhea-associated HUS [89–91]. In additions, case series have also suggested the benefit of using Eculizumab for the severe diarrhea associated HUS [92,93].

Thrombocytopenia-Associated Multiple Organ Failure (TAMOF)

In the intensive care unit, overt DIC has been observed in 40 % of patients with new onset thrombocytopenia [94–96]. TTP is rarely diagnosed in the ICU. HUS cases come in cluster and most cases do not required significant involvement from an intensivist. The mechanism of the other 60 % of patients with new onset thrombocytopenia in the intensive care unit is of great interest since new onset thrombocytopenia has been shown to be associated with higher mortality compared to non-thrombocytopenic critically ill patients [94,95,97–99]. Recently, investigators have observed that pediatric patients with TAMOF defined as platelet counts <100,000/mm^3 and at least two failing organs, have clinical, biomarkers and histological evidences of a thrombotic microangiopathic process [36,100]. Only 46 % of these TAMOF patients have evidence of an activated fibrin pathway with prolonged prothrombin time. None of these TAMOF patients have classic TTP, but 89 % of the patients have evidence of increase VWF-mediated thrombosis similar to TTP pathophysiology. Histopathologic findings in these TAMOF patients reveal VWF/platelet-rich and fibrin-rich microthrombi in the brain, lungs, and kidneys. In these TAMOF patients, mean ADAMTS-13 activity level is 39 %, which is lower than normal but not <10 % as in patients with classic TTP. ULVWF is present in 53 % of these TAMOF patients, which is abnormal because ULVWF is not seen in healthy children or adults [36,101]. Of note, all these pediatric TAMOF patients have concurrent sepsis. These investigators suggest that these critically ill children with TAMOF have an acquired ADAMTS-13 deficiency leading to a secondary TMA.

Other investigators have also shown that patients with acquired ADAMTS-13 deficiency associated with systemic inflammation have higher morbidity and mortality [102–105]. Currently, there is a growing list of proinflammatory molecules that can directly inhibit or proteolytically inactivate ADAMTS-13 (Table 31.3). In in vitro experiments, inflammatory cytokine IL-6 inhibits the cleavage of ULVWF by ADAMTS-13 under flowing condition [60]. Plasma free hemoglobin, which is released from red blood cell destruction in TMA, also inhibits ADAMTS-13 [106,107]. VWF antigen is elevated in sepsis and is associated with multiple organ failure and death [108,109]. VWF itself seems to have a negative feedback mechanism by inhibiting ADAMTS-13 [110]. For example, patients with type 3 von Willebrand disease, in whom there is a complete absence of VWF, have a significant decrease

Table 31.3 ADAMTS-13 inhibitors and proteolytic inactivators

ADAMTS-13 inhibitors
1. Interleukin-6
2. Shigatoxins
3. Plasma free hemoglobin
4. Plasma von Willibrand factor
5. IgG auto-antibody
ADAMTS-13 proteolytic inactivators
1. Granulocyte elastase
2. Plasmin
3. Thrombin
ADAMTS-13 = a disintegrin and metalloprotease with thrombospondin motifs-13

in ADAMTS-13 activity after infusion of VWF concentrates [111]. In septic milieu, activated neutrophils release reactive oxygen species that oxidize VWF and inhibit ADAMTS-13-mediated cleavage [112]. In addition, activated neutrophils also release elastase that proteolyzes ADAMTS-13 into inactive fragments [104]. Plasmin and thrombin, products of activated coagulation which are elevated in severe sepsis [113], are proteases that proteolyze and inactivate ADAMTS-13 [114]. Lastly, the first description of ADAMTS-13 inhibitors is neutralizing IgG autoantibodies found in patients with acquired TTP [52,53]. Patients with systemic inflammation and immune dysregulation could also develop neutralizing autoantibodies against ADAMTS-13. For example, patients with systemic lupus erythematosus, antiphospholipid syndrome, and other immune dysregulated states have been reported to have higher prevalence of ADAMTS-13 autoantibody [115,116]. Septic patients with unresolved infection and multiple organ failure have immune dysregulation with monocyte deactivation. Characteristically, these patients have cytokines production profile associated with T-helper-lymphocytes 2 subset (Th2) [117,118]. A gene knock-in mouse model demonstrates that proliferation of Th2 specific cells leads to polyclonal B cells activation resulting in elevation of autoantibodies and early onset systemic autoimmune disease [119]. Indeed, investigators have reported that severe sepsis patients have acquired ADAMTS-13 deficiency [36,100,102–104].

Large Animal Models of VWF-Mediated Thrombotic Microangiopathy and Acquired ADAMTS-13 Deficiency

Feys and colleagues have reported an elegant primate model that can produce a TTP phenotype by infusing monoclonal antibody to ADAMTS-13 [120]. Bockmeyer and colleagues have reported a porcine model of systemic inflammation and sepsis that can also produce an acquired ADAMTS-13 deficiency and histological evidence similar to TTP [121]. These two large animal models demonstrate that ADAMTS-13 or the regulation of VWF activity is vital in the development of a TTP phenotype. Thus, an acquired ADAMTS-13 deficiency secondary to the presence of its inhibitors and proteolytic inactivators, which are elevated during sustained systemic inflammation such as severe sepsis, could induce a TTP phenotype. These large animal models will serve as a much needed platform to try innovative therapies for TAMOF.

Current and Future Therapies for Thrombotic Microangiopathies

Currently, therapeutic plasma exchange (TPE) in conjunction with immune suppression is accepted as first-line therapy for TTP. This strategy has brought TTP mortality from 100 % down to less than 20 % [4–6]. Currently there is no monotherapy for overt DIC, even though various drugs have been tried such as heparin [122–124], antithrombin III [125], recombinant tissue factor pathway inhibitor [126], recombinant human activated protein C [1,127,128], protein C concentrate [129,130], and recombinant human soluble thrombomodulin [131]. DIC has a mortality of 22–50 % with supportive strategy [1–3]. Eculizumab, an anti-C5 monoclonal antibody, seems to be a promising drug for atypical HUS and possibly for diarrhea-associated HUS with multiple organ failure [87,88,92,93,132].

Replenishing ADAMTS-13 to treat TTP: In TTP, the obvious approach is to replenish the deficient ADAMTS-13. Investigators have reported that recombinant ADAMTS-13 could normalize VWF-cleaving activity in plasma of acquired TTP patients by overriding inhibitory antibodies [133]. In a murine model of congenital TTP, investigators showed that gene transfer therapy by recombinant adeno-associated virus-mediated expression of *ADAMTS13* variant could decrease mortality in a TTP phenotype [134].

Blocking VWF interaction with platelets to treat TTP: The main problem of TTP is the pathologic hyper-adhesive VWF. Investigators are now trying innovative drugs to decrease VWF adhesiveness by blocking VWF interaction with platelets. ARC1779, a nucleic acid macromolecule, and ALX-0681, an anti-VWF nanobody, are two drugs that block VWF interaction with platelets and are being tried in TTP primate models and human clinical trials [135–137].

Reducing the size of VWF multimers to treat TTP: N-acetylcysteine, a drug which is frequently used by intensivists to thin airway secretions, reduces the size and viscosity of mucus by reducing disulfide bonds connecting mucin monomers, which are the major glycoproteins in mucus. The overall structure of mucin and VWF are very similar [138]. Indeed, N-acetylcysteine can reduce the size and activity of VWF in human plasma and mice [139].

Blocking fibrinogen interaction with platelets to treat DIC: Various drugs have been tried to treat DIC without conclusive evidence of benefit. All of these drugs have targeted upstream from fibrin mesh formation. Recently, investigators have reported using a recombinant VWF A2 domain polypeptide, which has a newly described contact site for fibrin, to (1) in vitro inhibit platelets interaction with immobilized fibrinogen and to (2) in vivo decrease fibrin-rich microthrombi formation and improved survival in a lipopolysaccharide-induced DIC murine model [140].

Inhibit complement activation in severe diarrhea-associated HUS and TTP: Recently, investigators are suggesting that blocking the alternative complement pathway with Eculizumab in severe STEC-HUS and in refractory TTP might be an effective adjunct therapy [84,141,142]. Significant complement activation has been reported in

patients with acute episodes of TTP [143]. Thus, experts in this field are suggesting that pathologic complement hyperactivation might be the common pathway for atypical HUS, STEC-HUS, and TTP [84].

Therapeutic plasma exchange for TAMOF: Pathologic sustained systemic inflammation is the common pathway for the development of TAMOF. Proinflammatory molecules can (1) induce tissue factor synthesis and release, the key initiator for DIC; (2) stimulate the release of ULVWF, the pathologic molecule in TTP; (3) inhibit ADAMTS-13, the deficient protease in TTP; and (4) trigger the alternative complement pathway, the pathologic mechanism for HUS. Until clinicians have the tools to measure appropriate biomarkers to delineate out the pathologic mechanisms and have the appropriate drugs to treat these different phenotypes of TMA, resetting the plasma to its homeostatic milieu by therapeutic plasma exchange might be the only timely therapy that is available. Treating the underlying trigger for TAMOF is the key. However, removing the harmful molecules and replenishing beneficial molecules by plasma exchange would provide crucial time for treating the underlying trigger and alleviating the pathologic mechanisms of TMA. Currently, the American Society of Apheresis gives a category III recommendation- "*Optimum role of apheresis therapy is not established. Decision making should be individual*ized"- for therapeutic plasma exchange in *sepsis with multiple organ failure* [4]. A consortium of pediatric intensive care units in the U.S. had entered a registry for using therapeutic plasma exchange for TAMOF. The initial data show that there is a trend toward beneficial treatment effect of plasma exchange in pediatric TAMOF [144,145]. A multicenter randomized control trial for the use of therapeutic plasma exchange for TAMOF is warranted.

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Toxic Shock Syndrome in Children

32

Yu-Yu Chuang and Yhu-Chering Huang

Abstract

Toxic shock syndrome (TSS) is an acute, toxin-mediated illness characterized by fever, rash, rapid-onset hypotension, multi-organ failure, and desquamation. TSS represents the most fulminant form of the diseases caused by toxin-producing strains of Staphylococcus aureus and Streptococcus pyogenes (group A streptococcus) and is the best example of superantigen-mediated disease. Toxins produced by the staphylococci and streptococci act as superantigens that can activate the immune system by bypassing certain steps in the usual antigen-mediated immune response sequence, resulting in massive cytokine release. This massive cytokine release is responsible for the clinical manifestations of TSS. The host-pathogen interactions, the virulence factors, and absence or presence of immunity determines the epidemiology, clinical syndrome and outcome. Treatment of a child with TSS includes early recognition of disease, source control, and administration of antimicrobial agents, including drugs capable of suppressing toxin production. Supportive therapy, aggressive fluid resuscitation, and vasopressors remain the main elements. Adjuvant therapy with intravenous immunoglobulin containing neutralizing antibodies can block the superantigens.

Keywords

Toxic shock syndrome • Staphylococcus aureus • Group A Streptococcus

Introduction

Toxic shock syndrome (TSS) is an acute, toxin-mediated illness characterized by fever, rash, rapid-onset hypotension, multiple organ system dysfunction and failure, and desquamation. TSS represents the most severe form of the diseases caused by toxin-producing strains of Staphylococcus aureus and Streptococcus pyogenes (group A streptococcus). A similar clinical syndrome was also reported after colonization with other bacteria capable of producing disease through toxin production [1]. The initial description of the illness as a disease of children was in 1978 by Todd and colleagues. Case definition for staphylococcal toxic shock syndrome was established in the1980s, and many reports were published regarding association of TSS with tampon use. In the late 1980s, a resurgence of highly invasive streptococcal infections, including a toxic shock-like syndrome was noted worldwide, and a consensus case definition for streptococcal TSS was subsequently proposed in 1993. The incidence of streptococcal toxic shock has remained stationary through the years after its resurgence in the late 1980s. Toxic shock syndrome is the best example of a superantigen-mediated disease. Toxins produced by staphylococci and streptococci act as superantigens that can activate the immune system by bypassing certain steps in the usual antigen-mediated immune response sequence. The microbial superantigens serve as the central mediators of the systemic effects observed

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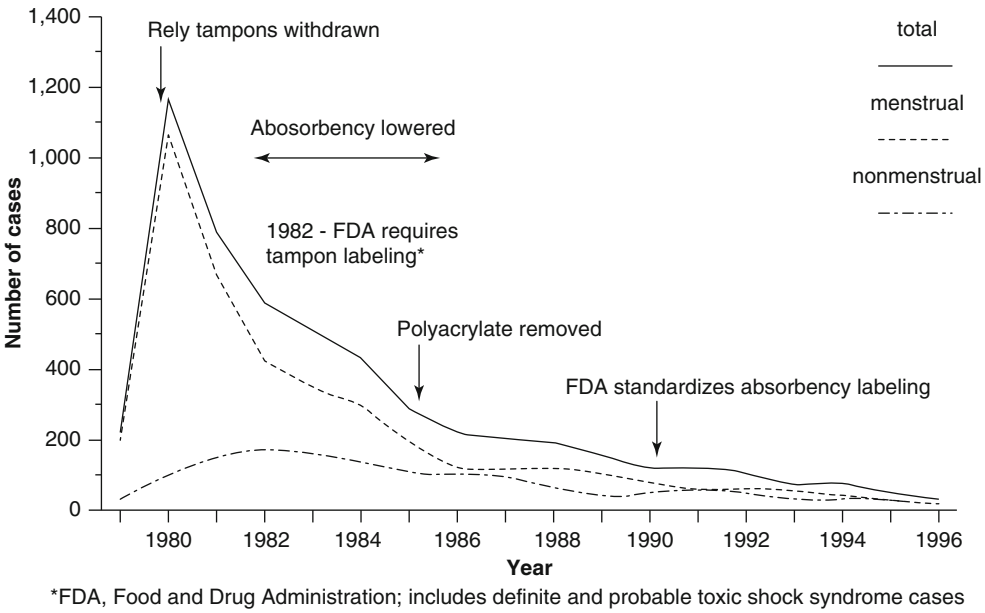

Fig. 32.1 Toxic shock syndrome cases, menstrual vs. nonmenstrual, United States, 1979–1996. * *FDA* Food and Drug Administration; includes definite and probable toxic shock syndrome cases

in TSS. The host-pathogen interactions, the virulence factors, and absence or presence of immunity determine the epidemiology, clinical syndrome, and outcome.

Epidemiology

Staphylococcal Toxic Shock Syndrome

TSS associated with S. aureus was first reported in healthy children in 1978 [2]. This syndrome was apparently described earlier as staphylococcal scarlet fever, a sporadic disease entity known since 1927 [3]. An epidemic soon followed in 1980 and most of the cases were associated with the use of highly absorbent tampons in white healthy young menstruating women [4, 5]. The incidence of menstrual TSS was reported to be 6–12 per 100,000 women, which declined to 1 per 100,000 women in 1986 [6, 7]. A local increases from 0.8 per 100,000 in 2000 to 3.4 per 100,000 in 2003 was reported in Minnesota [8]. These estimates included both menstrual and non-menstrual cases and may represent increased recognition rather than an overall increase in incidence. Menstrual TSS declined from 91 % from 1979 to 1980 to 71 % from 1981 to 1986 and 59 % during 1987–1996 [7] (Fig. 32.1). Case fatality rates also declined for menstrual TSS from 5.5 % in 1979–1980 to 2.8 in 1981–1986 and 1.8 % in 1987–1996 [9]. Factors contributing to the decline in menstrual TSS included changes in tampon composition, decrease in tampon absorbency, changes in usage pattern, standardized labeling, and greater awareness among women and physicians [6, 7]. However, use of tampon remains a significant risk factor for TSS [10].

With the decline in menstrual TSS, nonmenstrual TSS now accounts for approximately one-half of the reported TSS cases [6, 7]. Overall, 93 % of all TSS and 73 % of nonmenstrual TSS occurred in women and 87 % were whites [9]. Of the nonmenstrual cases of TSS, 18.3 % were reported after surgical procedures, 11.5 % were postpartum or post-abortion, and 23 % were nonsurgical cutaneous lesions [9]. Fifty cases of TSS in children ≤5 years of age were reported between 1979 and 1996 – more than half of these occurred in children ≤2 years of age, and 62 % were associated with nonsurgical cutaneous lesions. TSS associated with nonsurgical cutaneous lesions was higher among younger patients than other nonmenstrual cases. The overall case-fatality rate in children was 4.1 % [9]. The mortality rates were 3 % for menstrual and 5 % for nonmenstrual cases [9]. A French surveillance study of 55 TSS cases over a 30-month period has suggested that non-menstrual staphylococcal TSS is more prevalent than menstrual TSS, 62 % of the cases. There were no deaths in the menstrual TSS cases compared with a mortality of 22 % for non-menstrual cases [11].

The proportion of cases reported after surgical procedures increased from 14 % during 1979–1986 to 27 % during 1987–1996 [9]. No significant change in the case-fatality rate for nonmenstrual TSS has occurred, 8.5 % in 1979 and 1980, 5.3 % in 1981–1986 and 6 % in 1987–1996 [9, 10]. The incidence of postoperative cases of TSS following all types of surgery was estimated to be 3 per 100,000 population, but it was higher following ear, nose and throat surgery (16.5/100,000 population) [12]. It was estimated that 3–13 % of children admitted to the burn unit develop TSS [13, 14]. The number of TSS reported in children aged younger than 10 years of age is quite low despite a low antibody titer to TSST-1 and the increased prevalence of nasal colonization (10 %) with TSST-1 positive strains [15, 16].

Risk factors for nonmenstrual TSS include colonization of a toxin-producing strain of S. aureus, absence of protective antitoxin antibody, and an infected site. Staphylococcal TSS has been reported in association with any primary staphylococcal infection, after surgery with wound infection [17], following any disruption of the skin or mucous membrane, such as burns [13, 14], influenza [18], and placement of a foreign body. Sometimes cases have no obvious site of infection [19–21].

TSS caused by methicillin-resistant S. aureus (MRSA) strains has been found in Japan [22], the United States [23], and Europe [24, 25]. A toxic shock-like syndrome due to MRSA strains producing TSST-1, neonatal toxic-shock syndrome-like exanthematous disease (NTED) was described initially in Japan [22] and subsequently in France [25]. Infants developed systemic exanthema, thrombocytopenia, elevated acute-phase reactants and fever during the first week of life [22]. They are colonized with MRSA that produces TSST-1 and SEC [26]. In a series of 27 patients in France with MRSA producing TSST-1, five had TSS, two had NTED, one had staphylococcal scarlet fever, nine had toxic shock syndrome but did not fulfill all the criteria of TSST-1 mediated syndrome (fever and rash), and the rest had suppurative infections. Eight of the 27 patients with TSST-1 positive MRSA isolates were community acquired, and the rest were hospital-acquired or had an unknown site of acquisition. These MRSA clones were mainly isolated from children [27]. Another study compared the genetic relatedness and superantigen production in 32 community acquired MRSA, 32 hospital-acquired MRSA, and 21 nonmenstrual TSS S. aureus isolates. The 31 related CA-MRSA isolates produced either staphylococcal enterotoxin B (15 %) or C (81 %). None of these isolates produced TSST-1. None of the hospital acquired MRSA isolates produce enterotoxin B or C, or TSST-1. Six of 21 nonmenstrual toxic shock strains were indistinguishable or highly related to the CA-MRSA, 16 isolates made either SEB or SEC, none made TSST-1 [28]. This study suggests that community-acquired MRSA are more likely to cause TSS.

Streptococcal Toxic Shock Syndrome

In 1987 Cone et al. [29] reported two patients with symptoms similar to TSS and positive Group A streptococcus (GAS) cultures, later calling these cases Streptococcal toxic shock like syndrome (STSS). In the late 1980s, an emergence of toxic shock-like syndrome was reported [30, 31] and a consensus case definition was subsequently established in 1993 [32]. The annual incidence of invasive group A streptococcal disease in developed countries had been stable for the past decade and was 2.0–4.0 cases per 100,000 persons per year [33–36]. A recent surveillance study of ten sites in the United States showed that the annual incidence of invasive GAS was 3.5 cases per 100,000 persons [36]. The incidence varied by site, ranging from 2 to 5.9 cases per 100,000 persons. Seasonal variation was also observed, with most cases occurring in the winter and early spring [36]. Sites variation was also found previously in United States [35], Canada [37], and Europe [38]. Variations may be due to differences in the circulating emm (M protein gene) types and the population's susceptibility to a particular emm type, or prevalence in risk factors for invasive GAS infections such as chronic diseases, race, or crowding [39, 40]. The incidence and mortality rate of invasive GAS infections in the United States remained relatively stable from 1996 to 2004 [35, 36]. This rate is consistent with rates found in Canada (3.8 cases per 100,000 persons) [37], Europe (3.1–3.3 cases per 100,000 persons), and the United Kingdom (3.5–3.6 per 100,000 persons) [38]. This is in contrast with the epidemiology reports of increasing incidence and severity in the 1980s and 1990s [41, 42]. The incidence was highest among those ≥65 years old (9.4 cases per 100,000 persons), followed by children <1 year (5.3 per 100,000 persons) and black persons (4.7 cases per 100,000 persons) [36].

The incidence of streptococcal TSS among the invasive GAS infections was 5.7 %, and was lower in children aged <10 years (4.6 %) than in those aged >10 years (5.9 %) [36]. Case-fatality rates for streptococcal toxic shock syndrome was 43.2 % and was lower in children aged <10 years (7.1 %) than those aged >10 years (49.4 %) [36]. Children less than 10 years are less likely to develop streptococcal TSS and have a lower mortality rate than adults [35, 36, 43]. Overall mortality rates in published series range from 5 % to 10 % in children and 30–80 % in adults [44]. Factors associated with death include increasing age, streptococcal toxic shock, meningitis, necrotizing fasciitis, pneumonia or bacteremia and having emm types 1, 3, or 12 [36].

In a review of 39 cases neonatal invasive group A streptococcal disease, four (17 %) had a toxic shock -like syndrome among the 24 early onset disease and one (7 %) among the late onset disease [45]. Common characteristics of the early onset disease were respiratory distress, rapid deterioration and high mortality. About 25 % had an exanthema, lack of fever and leukopenia was frequent. The predominant serotype was M1.

Clusters of invasive group A streptococcal infection, including the streptococcal TSS, in households, nursing homes and hospitals have been described [46–48]. A family cluster of STSS involving three children caused by a single clone documented further person-to-person transmission and risk in household contacts [46]. Results of a population-based active surveillance in Canada suggest that the rate of secondary invasive GABHS infection is approximately 2.9 cases per 1,000 household contacts. The risk of colonization in the household is associated with younger age and four or

more hours of contact with infected person per day, but the risk of disease is greatest in the elderly despite low carriage rate [49]. Another population based surveillance in three counties in California and Portland, Oregon reported a rate of 66.1–132/100,000 household contacts (confirmed/probable case) [50]. Thus, the relative risk of invasive GAS among close contacts from the two studies varied from 19 to 200 times increased risk. The currently available evidence does not support routine administration of chemoprophylaxis to close contacts. The risk of invasive GAS infection in close contacts, while higher than the risk for sporadic disease, is still low and the benefit from antibiotic prophylaxis is not known [51]. Appropriate information should be given to all household contacts about the clinical manifestations of invasive GAS and to seek immediate medical attention if they develop symptoms [51]. Physicians should base the decisions regarding chemoprophylaxis on their assessment of the risk associated with each individual case.

Varicella is a well documented risk factor for invasive GAS infections including STSS in previously healthy children [44, 49, 52, 53]. About 15 % of children with invasive GAS diseases had a history of varicella during the month before their illnesses and usually associated with a soft-tissue infection. The attack rate for invasive GAS infection in children within 2 weeks after chickenpox was 5.2 per 100,000. Chickenpox was associated with a 58-fold increased risk of acquiring invasive GAS infection [52]. However, a retrospective study over a period of 9 years showed a dramatic reduction in the rate of varicella associated invasive GAS infection as the percentage of all invasive GAS infections after the introduction of universal varicella vaccination [54]. The rate of varicella associated-invasive GAS hospitalizations decreased from 27 % in the pre-vaccine era (1993–1995) to 16 % during vaccine implementation (1996–1998) and 2 % during widespread vaccine use (1999–2001) [54].

The association between non-steroidal anti-inflammatory drugs (NSAIDs) and the streptococcal TSS is uncertain. The use of NSAIDs may mask signs of disease progression by relieving pain, reducing swelling and suppressing fever, thus contributing to a delay in diagnosis, or predisposing to more severe streptococcal infection and shock [30]. NSAIDs can inhibit granulocyte function and enhance production of cytokines [55]. The use of NSAIDs was associated with an increase risk of invasive GAS infections in children with varicella infection [56, 57]. However, a multicenter case control study suggested that parents use ibuprofen to treat high fever and severe illness, which seems to identify children at high risk for invasive GAS infection [58].

The most prevalent emm types were emm 1, 3, 28, 12, and 89, accounting for 55 % of the invasive isolates in 2000–2004 in the United States [36]. The data from Europe during 2003–2004 showed very similar findings. STSS and necrotizing fasciitis were caused by a number of emm types but they are particularly associated with emm 1 and 3 [59]. However, country–specific emm distributions differed markedly, such as emm 87 which was confined to the United Kingdom. In Sweden, high rates of emm 81 and 89 were seen, whereas emm 28 was the most prevalent in Denmark and emm 89 accounted for only 7 %. In Finland, 45 % of the isolates were emm 28, while emm 3 isolates was negligible [59]. Streptococcal pyrogenic exotoxins (SPEs) A, B and C have been associated with severe invasive GAS infections and STSS [60]. In Taiwan, SPE A was present in only 13 % of streptococcal TSS-associated strains while SPE B was present in all the invasive isolates [61].

Pathophysiology

The clinical manifestation of shock, erythroderma, and multiorgan system involvement in TSS are mediated by bacterial toxins that act as superantigens. Superantigens are a group of proteins that can activate the immune system by bypassing certain steps in the usual antigen-mediated immune response sequence (Fig. 32.2). Superantigens are not processed within the antigen-presenting cell before being presented to T cells. Instead, they bind directly to molecules of the major histocompatibility complex (MHC) class II molecule, which requires recognition of only one element of the T-cell receptor Vβ, to trigger a massive T-cell activation, 20–30 % of the host T-cells, whereas, conventional antigens activate only about 0.01–0.1 % of the host T-cells [63]. The net effect is a massive release of cytokines.

Superantigens bind at sites distant to the conventional peptide-binding area, primarily to the variable Vβ region on the T-cell receptor, although some bind at α chain [62]. The interaction of superantigen with specific T-cell receptor Vβ regions induces clonal expression of T cells possessing those specific Vβ T-cell receptor patterns and allows identification of a characteristic Vβ signature for the superantigen concerned and may be diagnostically useful [64, 65].

Superantigens have also evolved diverse mechanisms for binding to the MHC class II molecule [62]. Most staphylococcal enterotoxins (SEs) bind HLA-DR preferentially, whereas many streptococcal pyrogenic exotoxins (SPEs) bind better to DQ. Differences between HLA-DR and DQ alleles might lead to differences between individuals in susceptibility to particular superantigens [66].

When the superantigen binds to T-cell receptor and MHC class II, there is rapid release of cytokines, interferon (IFN)-γ, interleukin (IL)-2, tumor necrosis factor (TNF)-β from the T-cells and IL-1 and TNF-α from macrophages. TNFα/β are major contributors to the capillary leak syndrome and IL-2 and IFN-γ are responsible for the rash [63]. IL-1 is an endogenous pyrogen that causes high fevers and mediates skeletal muscle proteolysis and is probably responsible for the

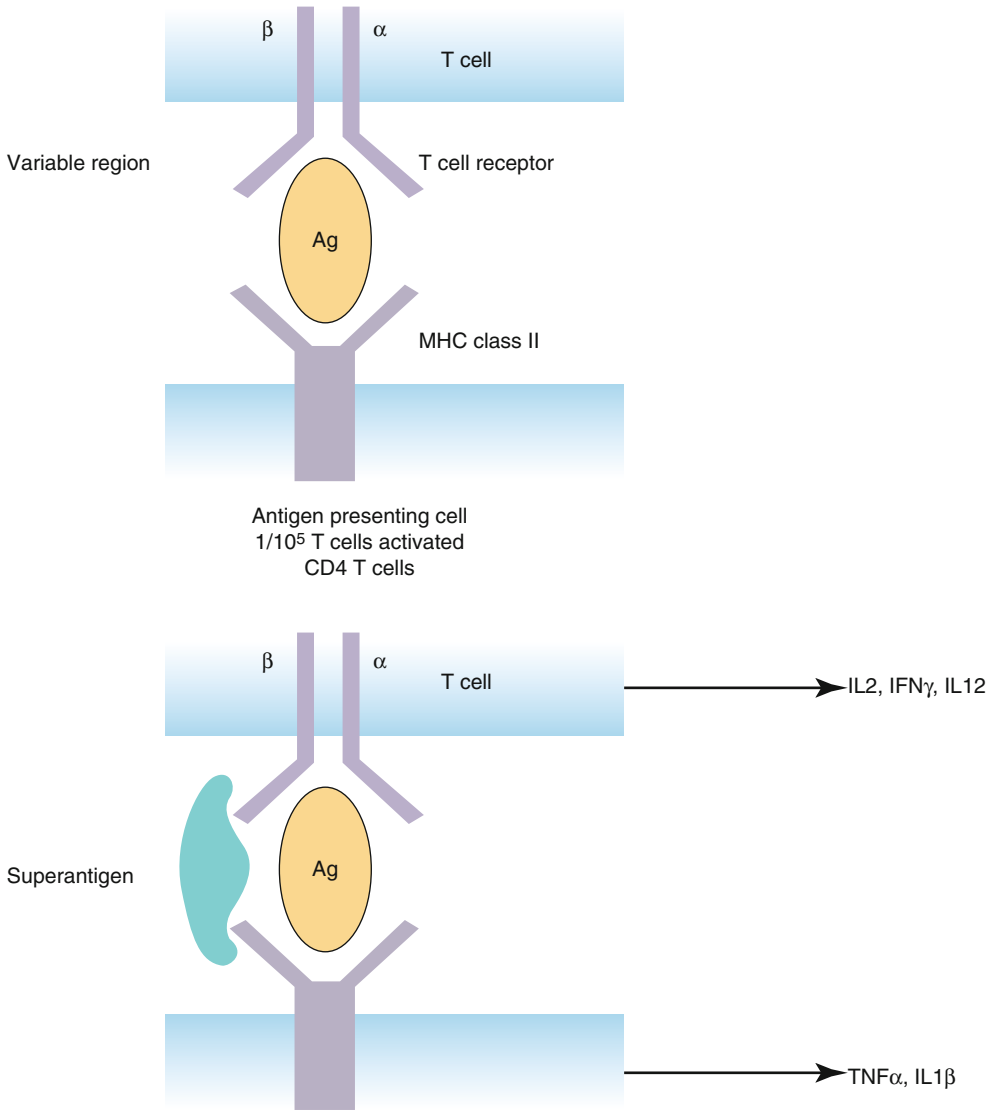

Fig. 32.2 Contrasting mechanisms of conventional antigen (*upper panel*) and superantigen presentation (*lower panel*). Superantigen is not processed by antigen-presenting cell before being presented to T cells. *IL-2* interleukin-2, *IL-12* interleukin-12, *IFNγ* interferon γ, *MHC II* major histocompatibility complex, class II, *TNF-α* tumor necrosis factor α (Adapted from Llewelyn and Cohen [62]. With permission from Elsevier)

myalgia and elevated creatine phosphokinase (CPK) commonly observed in patients with TSS [67]. Massive cytokine release is believed to be responsible for the most severe features of TSS, such as fever, hypotension, tissue injury and shock [62, 63]. TNF production inhibits random and chemotatic migratory polymorphonuclear leukocyte functions, thus TSST-1 producing S. aureus do not engender a purulent response [68]. In addition, TSST-1 and enterotoxin B repress the production of other S. aureus exotoxins, which account for the absence of purulence in S. aureus associated TSS [69].

Staphylococcal toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins (A, B, C, D, E, and H) are the family of superantigens that are the major toxins associated with staphylococcal TSS [70, 71]. TSST-1 is responsible for 75 % of the cases, enterotoxin B for 23 % and enterotoxin C for about 2 % of patients with TSS [70, 71]. TSST-1 is found in more than 90 % of menstrual TSS and about 50 % of nonmenstrual TSS. Various SEs are found in the other 50 % of nonmenstrual TSS [72]. The staphylococcal TSS often develops from a site of colonization rather than infection. The role of S. aureus in implicating TSS is well described. For example, vaginal isolation rate of S. aureus are as high as 98 % in the menstrual TSS compared to 8–10 % carriage rate in healthy control subjects [73]. Isolation of S. aureus from other sites is commonly observed in nonmenstrual TSS [72]. Finally, TSS recurs more frequently in the absence of antistaphylococcal antibodies [74].

Factors in vagina in the presence of hyperabsorbable tampons enhance the production of TSST-1 such as neutral pH, oxygen tension, carbon dioxide tension, and low magnesium concentration [75]. Menstrual blood flow is associated with elevated protein and the acidic vaginal environment reaches a pH of 7. The introduction of tampon into the normally anaerobic vaginal environment raised oxygen tension to

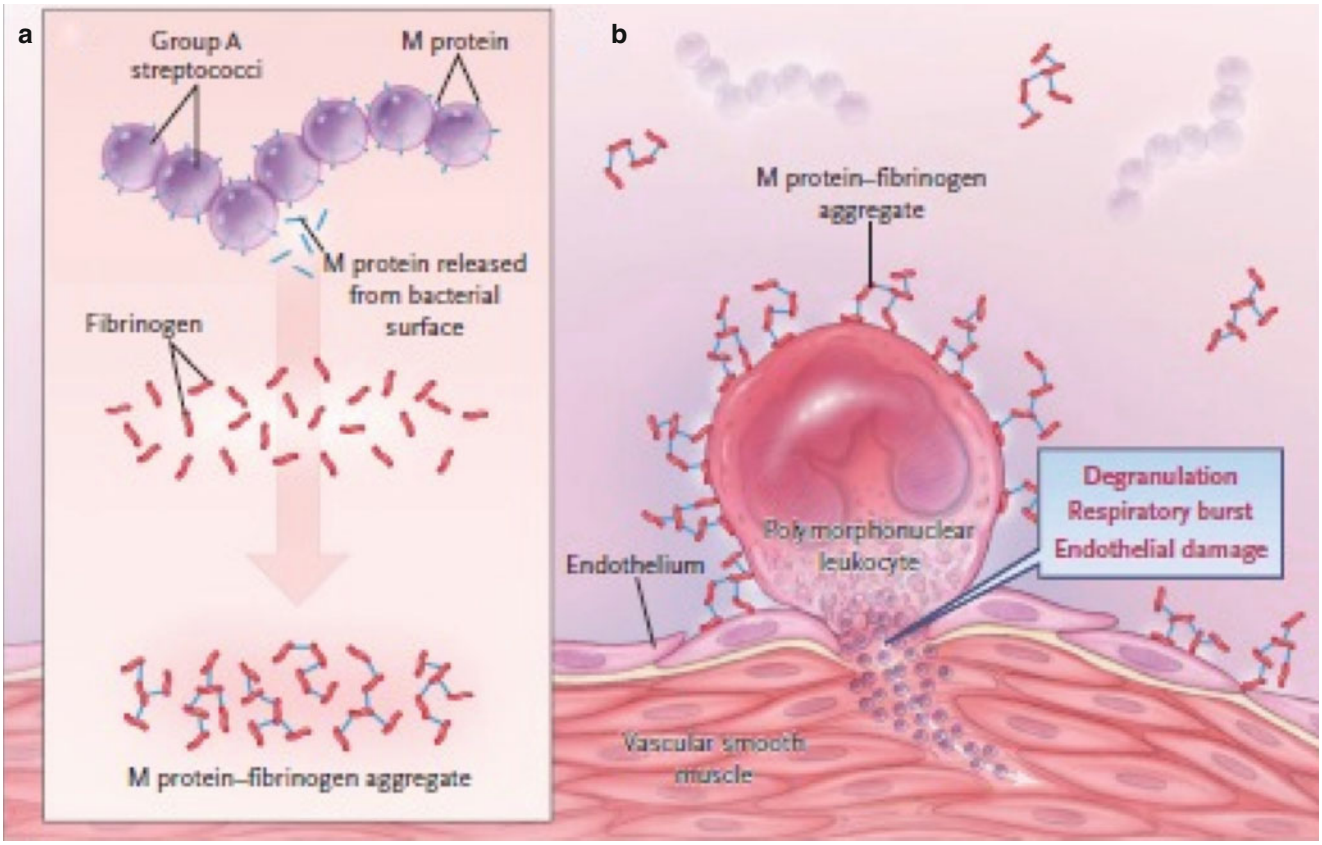

Fig. 32.3 Pathologic involvement of M protein in GAS-mediated TSS. M protein released from the fimbriae of GAS bind to fibrinogen forming large molecular weight complexes that aggregate by binding to integrins on circulating neutrophils. This aggregation results in binding of neutrophils to endothelial cells whereby their degranulation, respiratory burst with oxidant production and release of hydrolytic enzymes damages the endothelium resulting in hypercoagulability and vascular leak (Reprinted from Brown [79]. With permission from the New England Journal of Medicine)

atmospheric levels, and at the same time carbon dioxide levels recovered from low levels upon insertion to high levels associated with blood flow [76]. All patients with menstrual TSS had undetectable antibodies against TSST-1 at the onset of disease. Nonmenstrual TSS can occur in association with primary S. aureus infection, including postsurgical, postpartum or postabortion [12], burns [13], focal infections, such as pneumonia, or antecedent influenza infection [18].

Streptococcal pyrogenic exotoxins [SPE A, B, C, F (mitogenic factor), G, H, and J and streptococcal superantigen], the family of superantigens, are the major toxins associated with streptococcal TSS [77]. Some other virulence factors such as peptidoglycan, lipoteichoic acid, and killed streptococci are capable of inducing mononuclear cells to produce TNFα in vitro [77, 78]. The portals of entry for group A streptococci (GAS) include the vagina, pharynx, mucosa, and skin, accounting for 50 % of cases and frequently at sites of minimal or inapparent local trauma. The portal of entry is unknown in 50 % of invasive disease [77, 78]. Streptococcal pharyngitis that has developed into STSS is rarely reported [77]. Infections with viruses such as varicella and influenza [77] provide portals of entry in some patients. Adherence of the streptococci to the pharyngeal wall and then colonization are related to surface structures such as lipoteichoic acid and fibronectin-binding proteins. The M protein protects the streptococci from phagocytosis [78].

In addition to the exotoxins, GAS also possesses and expresses surface M proteins which are critical virulence factors associated with both colonization and resistance to phagocytosis. Numerous types of S. pyogenes M proteins have been identified on the basis of antigenic specificity which provides the major cause of antigenic drift. The M protein, located on the fimbriae has been shown to bind circulating fibrinogen and aggregate on neutrophils via integrin binding (Fig. 32.3). This interaction not only blocks subsequent binding of complement to the underlying peptidoglycan thereby allowing the GAS to avoid host clearance by inhibiting phagocytosis, but also activates circulating neutrophils to adhere to endothelium, and resulting damage to the underlying endothelium leads to a clinical feature

characteristic of the streptococcal TSS [79, 80]. It remains unknown as to whether this aggregation of M protein and fibrinogen can be therapeutically targeted.

Host Immunity

The host-pathogen interaction, the virulence factors and absence or presence of immunity determines the epidemiology, clinical syndrome and outcome. The absence of antibody to the superantigens appears to be a major risk factor for the development of both staphylococcal and streptococcal TSS and explains partly why not all patients exposed to virulent strains develop TSS. The prevalence of antibodies against TSST-1 is >90 % in adults but lower in the pediatric population [15]. In one study, antibody to TSST-1 was 47 % at age 1 year, 58 % at age 5 years and 70 % by age 10 years [81]. In a burn unit in UK, only 50 % of the children <4 years old had antibodies to TSST-1 on admission, which reflected the low prevalence of antibodies in children [13, 14]. Transplacentally acquired antibody was evident in 90 % of infants [81]. Mucosal colonization with TSST-1 producing S. aureus strains may result in antibody formation since 90 % of adults have antibody to TSST-1 without having TSS. An inability to generate anti-TSST-1 antibody after an episode of staphylococcal TSS predisposes patients to recurrent episodes and may be due to the ability of TSST-1 to suppress immunoglobulin-secreting cells [63] through two possible mechanisms. First, superantigen activation of CD4+ T cells results in T-helper type 1 cytokine release (IL-2, INF-γ, and TNF β), with minimal T-helper type 2 response. Since T-helper 2 subsets produce cytokines such as IL-4 and IL-5 that support B-cell proliferation and differentiation, lack of T-helper type 2 response may inhibit production of neutralizing antibody and inhibit extracellular bacterial clearance. Second, TSST-1 can induce T cell-dependent B-cell- apoptosis, but only when exposed to high levels of toxin. This may explain why infection did not resolve in some patients, and why in some patients TSS is recurrent [63].

The association between the lack of antibodies to SPEs in healthy individuals and the development of invasive streptococcal disease has been established [82]. Presence of antibody to SPEs has been shown to decrease the risk of severe infection. Antibody to the M-protein confers protection against invasive infection by enhancing phagocytosis [77, 78]. Low levels of protective anti-M1 and anti-superantigen neutralizing antibodies in plasma may contribute to host susceptibility to invasive streptococcal infection but do not modulate disease outcome. The absence of a high rate of invasive infection is the presence of significant herd immunity against the virulence factors responsible for streptococcal TSS (Fig. 32.4). This explains partly why epidemics have not occurred and how GAS can cause different clinical manifestations [77]. In addition, researchers have discovered that a person's MHC class II haplotype affects the regulation of cytokine release in response to superantigen, resulting in affecting the outcome of invasive GAS infection [83]. Patients with DRB1*1501/DQB1*0602 haplotype seem to have an attenuated inflammatory cytokine response to GAS superantigen and thus have protection against the development of severe systemic disease. Host factors have to be involved in the manifestations of GAS infection [83].

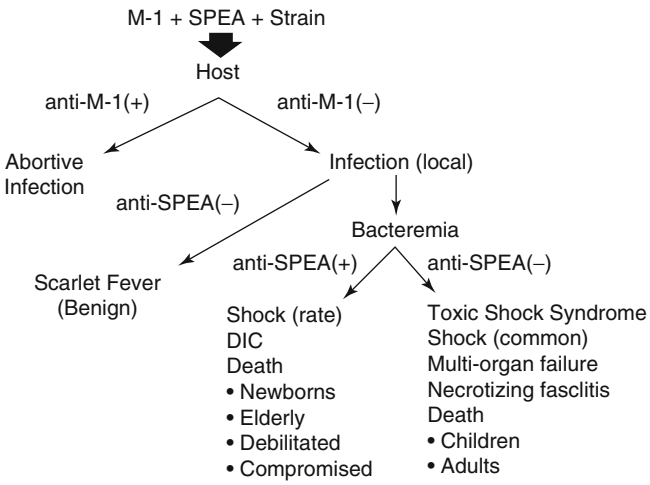

Fig. 32.4 Pathogenesis of scarlet fever, bacteremia, and toxic shock syndrome. *M-1⁺SPEA⁺* a GAS strain that contains M protein type 1 and streptococcal pyrogenic exotoxin A (SPEA), *anti-M-1*(+) the presence of antibody to M protein type 1, *anti-M-1*(-) the absence of antibody to M protein type 1, *anti-SPEA(+)* antibody to SPEA, and *DIC* disseminated intravascular coagulation (Adapted from Stevens [77])

Clinical Manifestations

TSS caused by either S. aureus or S. pyogenes is characterized by an acute, progressive illness associated with fever, hypotension, and multi-system failure. Multi-system involvement is usual at the time of presentation. Clinical case definitions have been proposed for both syndromes (Tables 32.1 and 32.2). However, these case definitions were used for epidemiologic surveillance rather than clinical practice, and should not be used to exclude a case that is highly suspicious for TSS, if all the criteria are not met. Staphylococcal TSS differs from streptococcal TSS in a number of aspects. Table 32.3 summarizes the differences [85]. The presence of profuse watery diarrhea, vomiting, generalized erythroderma, conjunctival injection, severe myalgias are more frequent in staphylococcal TSS. Local or deep seated soft tissue infections, such as cellulitis, abscess, myositis, or necrotizing fasciitis, associated with increasing pain are common with streptococcal TSS. The presence of a foreign body at the site of infection is common in staphylococcal TSS.

Table 32.1 Staphylococcal toxic shock syndrome: clinical case definition

Fever: temperature >≥38.9 °C (102.0 °F)
Rash: diffuse macular erythroderma
Desquamation: 1–2 week after onset, particularly palms and soles
Hypotension: systolic blood pressure <≤90 mmHg for adults; lower than fifth percentile by age for children younger than 16 years of age; orthostatic drop in diastolic blood pressure of >≥15 mmHg from lying to sitting; orthostatic syncope or orthostatic dizziness
Mutisystem involvement: three or more of the following:
A. Gastrointestinal: vomiting or diarrhea at onset of illness
B. Muscular: severe myalgia or creatinine phosphokinase level greater than twice the upper limit of normal
C. Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
D. Renal: serum urea nitrogen or serum creatinine level greater than twice the upper limit of normal or urinary sediment with ≥5 white blood cells per high-power field in the absence of a urinary tract infection
E. Hepatic: total bilirubin, aspartate aminotransferase, or alanine aminotransferase level greater than twice the upper limit of normal
F. Hematologic: platelet count, $<100\times10^9$/L ($<100\times10^3$/μL)
G. Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
Negative results on the following tests, if obtained:
A. Blood, throat, or cerebrospinal fluid cultures; blood culture may be positive for *Staphylococcus aureus*
B. Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles
Case Classification
Probable: a case with 5 of the 6 aforementioned clinical findings
Confirmed: a case with all 6 of the clinical findings, including desquamation. If the patient dies before desquamation could have occurred, the other 5 criteria constitute a definitive case

Based on data from Wharton et al. [84]

Table 32.2 Streptococcal toxic shock syndrome: clinical case definition

I. Isolation of group A β-hemolytic streptococci
A. From a normally sterile site (eg, blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy specimen)
B. From a nonsterile site (eg, throat, sputum, vagina)
II. Clinical signs of severity
A. Hypotension: systolic blood pressure <90 mmHg in adults or lower than the fifth percentile for age in children
and
B. Two or more of the following signs:
1. Renal impairment: creatinine level, >177 μmol/L (≥2 mg/dL) for adults or two times or more the upper limit of normal for age
2. Coagulopathy: platelet count, $<100\times10^9$/L ($\leq100\times10^3$/μL) or disseminated intravascular coagulation
3. Hepatic involvement: alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels two times or more the upper limit of normal for age
4. Adult respiratory distress syndrome
5. A generalized erythematous macular rash that may desquamate
6. Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene
An illness fulfilling criteria IA and IIA and IIB can be defined as a *definite* case. An illness fulfilling criteria IB and IIA and IIB can be defined as a *probable* case if no other cause for the illness is identified.

Adapted from The Working Group on Severe Streptococcal Infections [32]. With permission from American Medical Association

Both can occur without an identifiable focus of infection, or with any form of invasive infections such as pneumonia, osteomyelitis, pyogenic arthritis, or endocarditis. Recurrent episodes of TSS occur in both menstrual and nonmenstrual forms of staphylococcal TSS but not in streptococcal TSS. Toxic shock syndrome can be confused with meningococcemia, Rocky Mountain spotted fever, septic shock, Kawasaki disease, ehrlichiosis, scarlet fever, measles, systemic lupus erythematosus.

Staphylococcal Toxic Shock Syndrome

The onset of illness is abrupt, with fever, hypotension and skin manifestations. Chills, malaise, headache, sore throat, myalgias, muscle tenderness, fatigue, vomiting, diarrhea and dizziness or syncope are associated symptoms. Diffuse erythroderma develops within 24–48 h. Confusion, somnolence, irritability, and agitation may occur due to cerebral ischemia and edema. Other skin and mucous membranes manifestations

Table 32.3 Features of staphylococcal and Streptococcal Toxic Shock Syndromes (TSS) in children

	Staphylococcal TSS	Streptococcal TSS
Superantigen toxins	TSST-1 (menstrual TSS), SEA, B, C1-3, D, E (non-menstrual TSS), SEG-I (Kawasaki disease)	SPEA, SPEC, SSA, Mitogenic factor (MF), SPEG, H, J, SMEZ
Predisposing factors	Tampons, burns, wounds	Varicella, NSAID, wounds
Associated sites of infection	Superficial, such as impetigo, burns, diaper rash, genital tract, surgical-site infection	Deep, such as site of blunt trauma, necrotizing fasciitis, myositis, septic joint, surgical site infection
Soft tissue infection	Rare	Common
Abrupt severe pain	Rare	Common
Rash	Very common	Less common
Vomiting, diarrhea	Very common	Less common
Elevated creatine kinase	Rare	Common in fasciitis/myonecrosis
Bacteremia	<5 %	60 %
Desquamation	7–14 days	Less common
Mortality	About <3 %	30–70 %

Adapted from Stevens [85]. With permission from Elsevier

include conjunctival hyperemia or hemorrhages and beefy red edematous mucous membranes. Desquamation is a characteristic late feature occurring 10–21 days after the onset of illness [86]. The onset of illness in menstrual TSS is 2–3 days of menstruation [86] and the onset in post-surgical cases is 2–4 days but can be as short as 12 h [17].

The clinical features of menstrual and nonmenstrual are similar in most cases. In menstrual TSS, edema and erythema of inner thighs and perineum with a normal uterine and adnexal examination may be found. In nonmenstrual TSS, other foci of infection may be present. Previous antibiotic treatment and hospital exposure, predisposing to colonization with toxigenic strains of S. aureus are more common in nonmenstrual TSS [87]. In addition, patients are found to have a delayed onset of symptoms, more frequent central nervous system manifestations [11, 21] and renal complications [21], less frequent myalgia and arthralgia, and higher degree of anemia [87]. In postoperative TSS, the surgical wound site may have no signs of inflammation. The organism usually originates from the patient's own colonization disrupted by surgery or trauma. After onset of symptoms, the progression is rapid and multi-organ failure can be present in 8–12 h.

Laboratory abnormalities include increase in immature neutrophils, thrombocytopenia, and anemia. Disseminated intravascular coagulation (DIC) may be present. Elevated blood urea nitrogen and creatinine, abnormal liver function tests, hypocalcemia, hypoproteinemia, and elevated creatine phosphokinase may be present, which will return to normal within 7–10 days of disease onset [86]. Blood cultures are positive in less than 5 % of patients. Cultures from sites of infection are usually positive and should be obtained [21].

The diagnosis of staphylococcal TSS is based upon clinical presentation using the Centers for Disease Control and Prevention (CDC) case definition. However, some cases do not satisfy the diagnostic criteria and thus cannot be correctly diagnosed because of a complicated clinical presentation. TSS in neonates or neonatal TSS-like exanthematous disease, and TSS with puerperal infection caused by MRSA, have been shown with an expansion of T-cell-receptor Vβ 2-positive T cells by flow cytometric analysis [88]. Diagnostic systems incorporating laboratory techniques are essential for the rapid and definitive diagnosis of TSS.

Recurrent TSS has been well described and found to occur in as many as one-third of patients who have TSS. Persistent colonization with a toxin-producing strain of S. aureus and persistent absence of neutralizing antibody contribute to the development of recurrent TSS. This occurs among patients who fail to develop a humoral immune response to the staphylococcal toxin. Patients can be identified by means of antibody testing, and recurrences can be reduced by abstaining from tampon use and treatment with an antistaphylococcal antibiotic [19, 74, 89]. Recurrent menstrual TSS is generally milder than the initial disease. Recurrence can occur days to months after the initial episode [74].

Streptococcal Toxic Shock Syndrome

Persons of all ages can be affected and most children do not have any predisposing underlying disease. Pain is the most common initial symptom of streptococcal TSS and is abrupt in onset and severe, with preceding tenderness. Flu-like symptoms characterized as fever, chills, myalgia, nausea, vomiting and diarrhea are present in 20 % of patients. Fever is the most common early sign. Confusion, combativeness or coma is manifest in some patients. Eighty percent of adults have a localized soft tissue infection that may progress to necrotizing fasciitis or myositis and require surgical debridement, fasciotomy or amputation [77]. Abdominal pain and cholecystitis have been reported as rare clinical manifestations

in children with streptococcal TSS without skin and soft tissue infection [90]. Streptococcal TSS is a very rare complication of streptococcal pharyngitis in adults [91] but is more common in children [92].

Laboratory data may reveal hepatic or renal impairment. Hypoalbuminemia, hypocalcemia, elevated creatinine kinase, and increased immature neutrophils are present. Blood cultures are positive in 60 % of cases [77]. Cultures from sites of infection are usually positive and remain so for days even after appropriate antibiotics [77].

Children <10 years with invasive streptococcal disease are more likely to present with bacteremia without focus, osteomyelitis or a central nervous system infection and are less likely to present with necrotizing fasciitis or endocaridtis/pericarditis [35, 36]. Cellulitis and upper respiratory infection are also common. In contrast to those in adults, necrotizing fasciitis occurs only in 4 % of children [52].

The initial clinical presentation of patients with streptococcal TSS is often nonspecific and many patients have been treated as outpatients on one or more occasions before admission [77]. Physicians should have a high index of suspicion for this syndrome, especially in persons at increased risk, such as children with varicella or chronic underlying illness. Clues suggesting streptococcal TSS may include the absence of respiratory signs or a contact history, more localized or severe pain rather than generalized myalgia, and the presence of a skin lesion or history of blunt trauma at the site of pain [77].

Management

Currently, there is no definitive treatment against the toxins. Treatment for TSS includes supportive hemodynamic stabilization, surgical debridement if the site of infection is identified, removal of tampon or foreign body, and antibiotics for the underlying infection. Basic principles of septic shock management apply to the management of TSS. Rapid fluid resuscitation with large volumes of intravenous fluids are frequently required to maintain perfusion because of hypotension and diffuse capillary leak and vasodilation. Initial treatment with a bolus of 20 ml/kg of isotonic crystalloid solution (0.9 % normal saline or lactated Ringer's solution) should be administered as rapidly as possible upon presentation. Boluses may be repeated and patients may need up to 60 ml/kg of fluid or more during the first several hours. Vasopressors agents such as dopamine and/or norepinephrine may be needed if fluid resuscitation alone is insufficient to ensure adequate perfusion of vital organs. Intubation and mechanical ventilation may be required during the acute phase due to altered mental status or acute lung injury/acute respiratory distress syndrome (ALI/ARDS). Acute kidney injury may progress to renal failure requiring dialysis. Laboratory and electrolyte abnormalities such as hypocalcemia, hypophosphatemia, and hypoalbuminemia are common and should be treated [93].

Initial parenteral antibiotic coverage for both S. aureus (including MRSA) and S. pyogenes should be instituted promptly because of the similarity in the clinical appearances of streptococcal and staphylococcal TSS [94]. Inadequate initial antibiotic therapy increases mortality in patients with severe sepsis and septic shock [95, 96]. There are no randomized controlled studies comparing antibiotic regimens for treatment of TSS, and thus recommendations are based on in-vitro animal studies and clinical case reports. Combined antibiotic treatment is used in order to achieve two goals. First, a bactericidal antibiotic (mainly parenteral ß-lactam) is administered to kill bacteria by destroying the cell wall. Second, because toxin production is linked to bacterial protein synthesis, an antibiotic which inhibits protein synthesis (clindamycin) is administered in order to decrease ongoing toxin production [94]. Recently, an increase in the number of reports of methicillin-resistant S. aureus as a cause of TSS have emerged in Europe [24], Japan [23] and North America [23]. Thus, initial treatment with vancomycin may be warranted until bacterial susceptibility is known.

Staphylococcal TSS

In addition to hemodynamic stabilization, a thorough search for possible sites of staphylococcal infections is mandatory to eliminate any preformed toxin and to prevent synthesis of new toxins. Vaginal examination and removal of a tampon or other foreign body should be undertaken. Surgical wounds should be considered as possible reservoirs of infections, even if no superficial signs of local infection or purulent discharge are present. Infected wounds should be opened and debrided, and any packing should be removed. Abscesses need to be drained and irrigated. Culture specimens from all possible sites should be obtained.

It is not clear whether antibiotics alter the course of TSS due to S. aureus, but high-dose ß-lactamase-resistant, antistaphylococcal antibiotics are indicated to eradicate the organism and prevent recurrences [5, 74]. These antibiotics are usually co-administered with clindamycin, which has inhibitory actions on protein synthesis and therefore toxin synthesis and may be more efficacious than cell wall active agents such as penicillin. In vitro, subinhibitory concentrations of clindamycin, erythromycin, rifampin and fluoroquinolones suppressed TSST-1 by 90 %, whereas ß-lactamase inhibitors, including nafcillin and cephalosporins, increase TSST-1 in culture, probably by lysis or increased cell membrane permeability [97]. Thus, the use of clindamycin in combination with a ß-lactamase–resistant antistaphylococcal agent results in potential beneficial effect by decreasing the synthesis of TSST-1.

Linelozid has been used successfully to treat staphylococcal TSS and has been shown to reduce TSST-1 production. In vitro analysis of TSST-1 synthesis of the S. aureus isolate from the patient showed maximal TSST-1 production occurred in the untreated, nafcillin treated, and vancomycin-treated cultures. Linezolid and clindamycin completely suppressed toxin synthesis. This supports the superior efficacy of protein synthesis inhibitors (clindamycin and linezolid) to cell wall active agents (vancomycin and beta lactam antibiotics) in TSS [98].

We recommend that all patients with suspected TSS receive empiric therapy with clindamycin (25–40 mg/kg/day in 3–4 divided doses) plus vancomycin (40–60 mg/kg/day IV in four divided doses). If culture and sensitivity are available, patients with TSS due to methicillin-suspectible S. aureus receive clindamycin plus oxacillin (150–200 mg/kg/day IV in 4–6 divided doses) or nafcillin (100–150 mg/kg/day IV in four divided doses) and patients with TSS due to MRSA receive clindamycin plus vancomycin. Antimicrobial therapy should be continued for at least 10–14 days to eradicate the organism and prevent recurrences by eliminating the carrier state [88]. Antibiotics do not shorten the duration of acute illness but they can decrease the organism load and the rate of relapse [5, 74]. The total duration should be based on the usual duration established for the underlying focus of infection [89].

In a study on the effect of topical antimicrobials on TSST-1 production, silver sulphadiazine, used routinely for burns, caused a fourfold increase in toxin production in 45 % of strains. Mupirocin decreased toxin production in 47 % of strains and caused no increased toxin from any strains [99]. Thus, if eradication of the carrier state in patients with S. aureus TSS is desired, patients should be treated with mupirocin if the nares cultures are positive.

Streptococcal Toxic Shock Syndrome

In addition to hemodynamic stabilization, prompt surgical exploration and debridement of any suspected deep-seated infection such as necrotizing fasciitis or myositis is mandatory. GAS remains exquisitely sensitive to ß-lactam antibiotics. Intravenous penicillin G (200,000–400,000 U/kg per day) in four to six divided doses is the drug of choice for GAS.

Despite the susceptibility to penicillin, invasive GAS infection such as necrotizing fasciitis, empyema, sepsis, subcutaneous gangrene and myositis are associated with a high mortality and morbidity when penicillin is used alone [30, 77, 78]. In a mouse model of streptococcal myositis, penicillin was ineffective when treatment was delayed for 2 h after onset of infection, whereas mice receiving clindamycin had improved survival even if treatment was delayed [100]. Eagle suggested that the failure of penicillin to eradicate the organisms may be due to the slow replication rate of the organisms when a large inoculum is present, or the inoculum effect. The large inocula may reach stationary growth phase rapidly and diminish the expression of penicillin-binding proteins (PBPs), the target sites for penicillin activity [101]. Clindamycin is more effective because (1) the antimicrobial activity is not affected by the inoculum size, (2) it acts by inhibiting protein synthesis, is not dependent on penicillin-binding proteins, and thus also inhibits the synthesis of antiphagocytic M protein and bacterial toxins (SPEs), subsequently reducing the superantigenicity of SPEs [102], (3) it has a longer post-antibiotic effect than beta-lactams such as penicillin, (4) it causes suppression of tumor necrosis factor [103]. A retrospective study of 56 children with invasive GAS infections demonstrated a favorable outcome more likely in patients who received clindamycin compared to those who received only a beta-lactams (83 vs 14 %) [104]. Thus clindamycin (25–40 mg/kg per day in three or four divided doses) administered intravenously is recommended in addition to penicillin as therapy for severe, invasive group A streptococcal infections. Clindamycin should not be used alone as initial empiric therapy because 1–2 % of S. pyogenes are resistant to clindamycin [94].

Adjunctive Therapy

Intravenous immunoglobulin (1–2 g/kg given once) may be beneficial when administered in addition to appropriate antimicrobial therapy. In vitro, intravenous immunoglobulin (IVIG) can inhibit T-cell activation by blocking or inactivating staphylococcal and streptococcal superantigens, resulting in a decrease in the production of inflammatory cytokines [105]. In vivo, several case reports have been published in which IVIG administration in toxic shock syndrome correlated with clinical improvement [106, 107]. The Ontario Streptococcal Study Group conducted a comparative observational study of the effect of IVIG on 30-day survival in 21 patients with streptococcal TSS. IVIG-treated patients (median dose of 2 g) were more likely than controls to survive for both 7 days (90 % vs. 50 %) and 30 days (67 % vs. 34 %). This observational study posed some difficulties in the interpretation of results, as to the comparability of the treatment and control group. Multivariate analysis revealed that IVIG administration and a lower Acute Physiology and Chronic Health Evaluation II score were associated with survival; the odd ratio for survival associated with IVIG therapy was 8.1 (95 % CI, 1.6–45). IVIG therapy enhanced the ability of patient plasma to neutralize bacterial mitogenicity and reduced T cell production of interleukin-6 and tumor necrosis factor-α. These findings supported that IVIG could effectively neutralize bacterial toxins in vivo and non-specifically inhibited cytokine synthesis and immune activation [108].

A randomized, double-blind, placebo-controlled trial included 21 patients compared IVIG to placebo in adults with streptococcal TSS. IVIG dose was 1 g/kg day1, 0.5 g/kg days 2 and 3; all patients also received intravenous clindamycin and penicillin for at least 14 days. The mortality at 28 days was 4 of 11 in the placebo group compared to 1 in 10 in the IVIG treated group (36 % vs 10 %), but statistical significance was not reached. A significant decrease in the sepsis-related organ failure assessment score at days 2 and 3 was noted in the IVIG group. A significant increase in plasma neutralizing activity against superantigens was noted in the IVIG group after treatment [109]. This trial provides further support for IVIG as an efficacious adjunctive therapy in streptococcal TSS.

The mechanisms of IVIG in the treatment of GAS TSS includes neutralization of streptococcal toxins, inhibition of T-cell proliferation, and inhibition of other virulence factors such as TNF-alpha and IL-6 [105, 109]. The neutralizing activity against purified superantigens was studied for five IVIG preparations. It is of interest that there was great variation in neutralizing activity of different brands and batches of immunoglobulin preparation. Neutralization of SPEA activity was significantly lower than that of other streptococcal superantigens for all brands tested [110]. In another study, Vigam-S (obtained from plasma collected from donors in the United States) had consistently high inhibition against all superantigens, while European IVIG preparations had the lowest activity; an Australian preparation had intermediate activity [111]. Darenberg et al. [112] further demonstrated that staphylococcal superantigens are not inhibited as efficiently as streptococcal superantigens by IVIG, and hence, a higher dose of IVIG may be required for therapy of staphylococcal TSS in order to achieve protective titers and clinical efficacy. Despite of these, complete neutralizing activity may be achieved by optimizing the type and dose of IVIG used.

Pediatric data regarding the use of IVIG in streptococcal TSS are limited to case reports [113–115]. A multicenter retrospective cohort study including 192 children with streptococcal TSS assess the mortality, clinical outcome and hospital cost among the IVIG treated group and no IVIG group. Differences in mortality between IVIG recipients and non-recipients were not statistically significant (4.5 % vs 4.5 %). They concluded that IVIG use was associated with increased cost but was not associated with improved outcomes in children with streptococcal TSS [116]. The author's conclusion is based on the overall mortality rate in untreated patients rather than lack of efficacy of IVIG in reducing mortality and morbidity, although the overall incidence and mortality due to this disease is lower among children than adults [35, 36]. The role of IVIG for streptococcal TSS remains controversial. The American Academy of Pediatrics committee on infectious disease recommendation for IVIG in STSS management is based on adult literature cited. The committee recommends that IVIG be considered for streptococcal TSS that is refractory to several hours of aggressive therapy or in the presence of an undrainable focus or persistent oliguria with pulmonary edema [94].

Several therapies which aim modifying the host responses to sepsis have limited success. The use of recombinant activated protein C in the treatment of sepsis has been studied in adult patients. Activated protein C has direct anti-inflammatory properties, including blocking of the production of cytokines by monocytes and blocking cell adhesion. The use of recombinant activated protein C in pediatric sepsis was currently under way in a randomized trial. Until results from the pediatric trial become available, careful attention should be considered to potential benefits and risks in the use of recombinant activated protein C [117]. The use of high-dose corticosteroids in adult patients with sepsis does not improve survival and may worsen outcome by increasing the frequency of secondary infections. Low-dose hydrocortisone was effective in one study in adult patients with septic shock but finding has not been confirmed by others [118]. In another study in adults, treatment with low-dose hydrocortisone accelerates shock reversal in early hyperdynamic septic shock. This was accompanied by reduced production of proinflammatory cytokines, suggesting both hemodynamic and immunomodulatory effects of steroid treatment [119]. In pediatric patients, no supporting data are available, and a randomized controlled trial in septic children is needed [120].

Recent Developments

Recent studies have undertaken the development of toxoid vaccines that may protect against the immunobiological effects of pyrogenic toxins superantigens, through antibody neutralization [121, 122]. These toxoids are not biologically toxic in standard animal models of streptococcal TSS, and they are not superantigenic when tested against human mononuclear cells. The toxoids are highly effective in inducing toxin-specific neutralizing antibodies, capable of neutralizing superantigenicity and protecting animals from streptococcal TSS [121, 122].

Two regions of marked sequence homology in the tertiary structure of superantigens have been identified in the SE/SPE toxins [123]. Research with peptides constructed that mimicked these regions showed that both peptides and antibodies produced against the peptides had blocking activity against a range of bacterial superantigens [124]. The mechanism of action is probably by blocking the superantigen MHC class II binding interaction [123]. This approach has encouraging results in animal models of toxic shock syndrome, but needs further clinical trials.

Researchers have also produced a murine monoclonal antibody (MAb) against TSST-1 [122]. In animal models, this MAb neutralized various superantigens activities induced by TSST-1 and staphylococcal exotoxins (SEA and SEB) in human peripheral blood mononuclear cells and protected against TSST-1- and SEs-induced lethality [125–127]. Further studies should be conducted to elucidate the mechanisms as well as the application to clinical cases.

Strategies for prevention of invasive GAS disease include infection control measures and prevention of secondary cases among postpartum and postsurgical patients [128]. Two multivalent vaccines were tested in clinical trials. A hexavalent vaccine evaluated in a phase 1 clinical trial involving 28 healthy adults was well tolerated and stimulated bactericidal antibodies that were not cross-reactive with human tissues [129]. A 26-valent vaccine that included 80–90 % of the serotypes that cause pharyngitis and invasive diseases in the United States was tested in 30 healthy adults and was found to be immunogenic and safe [130, 131]. Other non-M protein vaccine candidates [132], including C5a peptidase [133, 134] and surface markers, such as fibronectin-binding protein [135], group A carbohydrate [136], and the conserved C-terminal region of the M-protein [137], have been associated with reduced colonization and evoked protective immune response when tested in animal models.

New anti-toxin therapeutic approaches such as Vβ peptides, hemoglobin subunit inhibitors and glycerol monolaurate are in development for staphylococcal TSS treatment. Vaccination targets were cell-surface targets, including iron-regulated surface determinant B (IsdB). Exotoxins (Panton-Valentine leukocidin and alpha-toxin) and superantigen (SEB) are being evaluated in clinical trials as vaccine targets [138].

Conclusion

Toxic shock syndrome is the best example of superantigen-mediated disease. Superantigens have also been implicated in the etiology of clinical syndromes, such as Kawasaki disease, atopic dermatitis, autoimmune diseases, and some skin diseases. As new superantigens by staphylococci and streptococci are identified, we do not know yet as to why and how these toxins arise. The spectrum of disease results from differences in the immune response of the host. Therapeutic strategies should include agents that can inhibit these superantigens.

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Hospital-Acquired Infections and the Pediatric Intensive Care Unit

33

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Abstract

Hospital-acquired infections are an increasingly recognized problem within the pediatric intensive care unit (PICU). Within the PICU, the patient population is exposed to an environment known for invasive procedures, monitoring and potential close proximity to others with infectious processes. Additionally, the PICU patients often have factors that affect their immune status including young age, chronic immunocompromised states, chronic stress, poor nutrition and prolonged immobility. Development of catheter-associated blood stream inections, ventilator-associated pneumonias, device-associated urinary tract infections and surgical site infections is an ongoing issue. Within the PICU environment, catheter-associated blood stream infections are the most common nosocomial infection, while ventilator-associated pneumonias have the highest mortality. As PICU staff realize the impact on patient morbidity and mortality caused by hospital-acquired infections, measures that focus on infection control are becoming an increasingly important component of pediatric critical care. The best current approach for preventing PICU-acquired infections centers on strict adherence to infection control policies, early discontinuation of invasive devices, prompt recogition of developing infections, and appropriate use of antibiotic therapy. Insight into the organisms responsible for and the pathogenesis of PICU-related infections are crucial components to eradicating these potentially preventable clinical problems.

Keywords

Nosocomial infection • Hospital-acquired infection • Catheter-associated bloodstream infection • Ventilator-associated pneumonia • Catheter-associated urinary tract infection Surgical site infection • Ventricular shunt infection • Infection control • Quality improvement

Introduction

Critically ill children are increasingly vulnerable to a host of hospital-acquired infections. Despite a recent emphasis on infection control, nosocomial infections remain a significant cause of morbidity and mortality within the pediatric intensive care unit (PICU). Nosocomial infections (NI) can be defined as the acquisition of pathogenic microbial agents while a patient is hospitalized. The PICU is one of the most important hospital locations for the development of nosocomial infections. Within the PICU, the patient population is exposed to an environment known for invasive procedures, monitoring and potential close proximity to others with

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infectious processes. Additionally, the PICU patients often demonstrate varying degrees of immunocompromise. These often include young age, chronic immunocompromised states such as chemotherapy, chronic stress, poor nutrition and prolonged immobility. Not surprisingly, central line infections in PICU patients are nearly double those that occur on pediatric inpatient wards [1].

Nosocomial infection rates not only vary with age but also by hospital location. Significant differences have been noted in nosocomial infection rates between adult and pediatric ICUs. For example, the rates of ventilator-associated pneumonia and urinary tract infections are less frequent in PICUs compared to an adult ICUs, but the rate of central line associated bloodstream infections is higher [1]. As PICU staff realize the differences in nosocomial infections between adult and pediatric populations, hospital infection control measures are becoming an increasingly important component of pediatric critical care.

History and Epidemiology of Nosocomial Infections

The history of monitoring hospital-acquired infections has evolved over the past half century. Prior to the 1970s, hospitals often tracked their individual infection rates, but frequently used varying aspects of measurement. One of the first group collaboratives occurred in 1970, when the Centers for Disease Control and Prevention (CDC) established the National Nosocomial Infections Surveillance (NNIS) system. This was designed to generate a national database on the incidence, organisms, and operative procedure risks associated with hospital-acquired infections. In 1986, nosocomial infection data from PICUs and neonatal ICUs was added to the database. In 2005, the CDC established the National Healthcare Safety Network (NHSN) to supercede the NNIS and integrate its data with other legacy surveillance systems (i.e. Dialysis Surveillance Network and the National Surveillance System for Healthcare Workers).

The NHSN has standardized definitions of and collects data on central line-associated bloodstream infections, ventilator-associated pneumonias, and urinary catheter-associated urinary tract infections [2]. Like the NNIS system, the NHSN collects data from pediatric wards, PICUs and neonatal ICUs in addition to adult data. The NHSN surveillance reports are published annually, with the most recent report summarizing data from January through December 2009 [1]. This report includes data from 1749 hospitals, including 46 freestanding children's hospitals. Currently, 178 pediatric intensive care units submit data for evaluation, composed of 142 pediatric mixed medical/surgical ICUs, 15 pediatric medical ICUs, and 21 pediatric cardiothoracic ICUs.

In 1997, the Pediatric Prevention Network (PPN) was established to evaluate patient-level data and infection point-prevalence within pediatric ICUs. This network represents a collaboration between the National Association of Children's Hospitals and Related Institutions (NACHRI) and the CDC. Thirty-one hospitals participate in the PPN network, with 35 PICUs providing nosocomial infection data [3].

A recent publication using data from both the NHSN and PPN estimates that there are an average cumulative incidence of 14 all-cause PICU-acquired infections per 100 patients [4]. Older publcations reported a mean all-cause infection rate in the PICU from 6 to 12 % [5, 6]. In surveillance studies performed in developing countries, PICU nosocomial infection rates are higher than those reported in the United States, with rates reported of 20–25 % [7, 8]. Both the NHSN and PPN systems report primary bloodstream infections as the most common nosocomial infection in the PICU, followed by ventilator-associated pneumonias and device-associated urinary tract infections [1, 3]. Device-associated blood stream infections are also the most common nosocomial infection in the PICUs of many developing countries [7]. Interestingly, in adult ICUs within the U.Ss, UTIs have historically been and continue to be the most frequently reported nosocomial infection [1, 9].

As the studies above suggest, patient age clearly has implications on the development of nosocomial infections. Even in the pediatric age group, younger patients in the PICU are at increased risk of all cause nosocomial infections [8]. According to historic NNIS data, children >2 months of age but less than 1 year had the highest incidence of infection (39 %), followed by children <2 months of age (18 %), and children age 15 years (17 %) [5]. Prematurity appears to be a factor associated with development of nosocomial infections. Comparisons of hospital-acquired infections within the same institute consistently show higher rates in neonatal ICUs compared to pediatric ICUs [8]. The NHSN reported a pooled mean of 2.2 bloodstream infections per 1,000 central line days from the PICU data, compared to 3.4 infections among NICU patients [1]. Extremely premature infants within the NICU have even higher infection rates. Patients in the NICU are also noted to more frequently develop ventilator-associated pneumonias (0.71.1 vs. 1.11.8 per 1,000 ventilator days), with the extremely premature infant consistently demonstrating the highest infection rates.

In addition to age, many additional factors predispose PICU patients to acquisition of nosocomial infections. The patient's underlying illness, higher PRISM scores, length of PICU stay, long term antibiotic use, need for parenteral nutrition, and need for invasive devices are known to be associated with development of nosocomial infections [6, 10]. Patients receiving parenteral nutrition with lipids were 22 times more likely to develop a nosocomial infection [11]. Patients receiving more than 10 days of antibiotics were five times more likely to develop a PICU-acquired infection [10]. In the NSHN database, pediatrc patients with hematology/oncology disease processes were nearly twice as likely to

develop central line-associated blood stream infections [1]. These risk factors have also been noted in studies performed outside the United States. In a recent study from South America, development of a hospital-acquired infection in the PICU was associated with younger age, days of ventilator duration, need for blood products, use of glucocorticoids, and use of H2 blockers [12].

Several investigators have noted that the stress of critical illness itself may affect an individual's immune state. Prolonged lymphopenia is commonly noted in children with extended admissions to the PICU [13]. Investigators have coined the term "critical illness stress-induced immune suppression" (CRISIS) to describe this observation. Recent evidence demonstrates an association in pediaric patients with prolonged lymphopenia and the development of nosocomial infections, sepsis, and death [14].

The organisms responsible for PICU-acquired infections have evolved over time in response to shifting antibiotic pressure and vaccination strategies. In the 1980s, *Haemophilus influenzae* was the single most commonly isolated organism, followed by *Staphylococcus aureus* and *E coli* [15]. By the early 1990s, coagulase-negative staphylococci (CONS) had become the most common isolate in the United States, followed by *Pseudomonas aeruginosa* and *Staph. aureus* [16]. Recent blood culture surveys from European PICUs show that CONS remains the most frequent isolate (33 %), but there is an increasing number of *Candida albicans* isolates (30 %) as well as Enterobacteria (17 %) [17].

By the early twenty first century, pediatric intensivists noted a significant increase in the incidence of *Enterobacter* spp. and *Enterococcus* spp isolates [5, 18]. In the past decade, many PICUs noted the emergence of antibiotic-resistant organisms, especially organisms resistant to multiple agents. Examples of these new multi-drug resistant organisms include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, and *Enterobacter cloacae*. These organisms likely all evolved in response to antibiotic selection pressure in the PICU. In recent years, community-acquired methicillin-resistant *Staphylococcal aureus* (MRSA) has become a common cause of infections in the PICU. This organism has a different phenotype than the hospital-acquired MRSA variant and is the dominat variant of Staphylococcus in many parts of the United States [19].

Catheter Associated Bloodstream Infections

Scope of the Problem

Vascular access is crucial in the critical care setting, and central venous catheters (CVCs), peripherally inserted central catheters (PICCs), and arterial catheters, are commonplace in pediatric critical care units. Knowledge of the pathogenesis, diagnosis, management and prevention of nosocomial bloodstream infections is essential to the practice of pediatric critical care medicine. Due to diligent multidisciplinary, multinational efforts, rates of catheter-associated and catheter-related bloodstream infections (BSIs) in adults and children have decreased in the last decade. In 2009, an estimated 25,000 fewer CA-BSIs occurred among patients in ICUs in the United States than in 2001 [20]. Much ground has been gained in eradicating nosocomial BSIs; however, infection rates in pediatric ICUs remain higher than in their adult counterparts. Catheter related BSIs continue to significantly impact morbidity, mortality, length of stay, and hospital costs in pediatric ICUs.

The spectrum of infections associated with intravascular devices ranges from asymptomatic catheter colonization and local exit site infections to systemic bloodstream infections and septic thrombophlebitis. Adherence to standardized definitions of catheter-related infections is critical to make informed comparisons between the many studies performed in this area. The CDC and the Joint Commission recommend that the rate of central CA-BSIs be expressed as the number of CA-BSIs per 1,000 central venous catheter (CVC) days. Central line associated BSI (CLABSI) is defined as a primary BSI in a patient who has had a central line within the 48-h period before the development of the BSI. It should not be related to an infection at another site. Surveillance definitions of CLABSI overestimate the true incidence of catheter-related bloodstream infections (CRBSIs), because not all BSIs occurring in a patient with a CVC originate from the catheter. Infections may actually be attributed to other medical devices, such as urinary catheters, or be related to underlying pathology rather than the vascular access device itself. CRBSI is an ideal marker to track the total rate of all catheter-related infections because it represents systemic infection. CRBSI is defined as bacteremia or fungemia in a patient who has an intravascular device, >1 positive blood culture from a peripheral vein, clinical evidence of infection, and confirming appropriate microbiological cultures, in the absence of any other source of infection.

The NHSN report a pooled mean PICU CLABSI rate, representing 228,206 central line-days, of 2.2 [21]. Interestingly, when device utilization rates are compared, the pooled mixed medical/surgical PICU central line utilization ratio is amongst the lowest of all types of ICUs at 0.5. The central line utilization ratio for pediatric cardiothoracic ICUs was significantly higher than for the medical/surgical PICUs at 0.7. The central line utilization ratio of an ICU is defined as the number of central line-days divided by the number of patient days. It is one measure of the unit's invasive practices that increase extrinsic risk factors for nosocomial infection. The central line utilization ratio may also serve as a marker of severity of illness of patients in the unit and allow more informed comparisons of BSI rate between units.

PICU cases with nosocomial BSI have both a significantly prolonged PICU and hospital length of stay, and

increased costs of hospitalization. The attributable operational cost per BSI infection is estimated to be approximately $39,000–46,000 and the annual cost of caring for patients with catheter-related infections ranges from $296 million to $2.3 billion [22–24]. The calculated attributable PICU mortality rate for nosocomial BSI is 13.1 %. Hospital mortality rate for nosocomial BSI is 23.7 % [23].

Risk Factors

Critically ill children have many potential predisposing factors that increase their risk of developing a CRBSI. These include host-related factors, catheter-related characteristics and the infection control-related practices of the intensive care unit. Patient-related risk factors include younger age, lower weight, histamine receptor-2 blockade, post-operative status, parenteral nutrition, higher PRISM score, prolonged antibiotic therapy, prolonged length of stay, and immune dysfunction [3]. Longer duration of catheter use may also affect CRBSI rates [25, 26]. In the pediatric cardiac ICU population, initial absolute neutrophil count <5,000 cells/μL, >3 units of blood product exposure, >7 central line days, and the use of hydrocortisone are all associated with higher rates of central line infection. In patients who underwent cardiac surgery, independent risk factors for central line-associated BSI are admission rate <5 kg, PRISM score >15, >3 units of blood product exposure, and prolonged mechanical ventilation >7 days [27]. In addition, the use of catheters for extracorporeal life support is also associated with an increased rate of CRBSI [28].

Catheter-related factors include the catheter material, the length of the catheter, and the site and timing of insertion. The highest infection risk seems to have occurred with polyvinyl chloride or polyethylene catheters. Catheters made of polyurethane and silicone elastomer (polytetrafluoroethylene, Teflon®), are smoother, more hydrophilic, less thrombogenic, and seem to have fewer infectious complications [29–31]. Antibiotic impregnated catheters are now widely available for children >3 kg, and a recent systematic review suggests they significantly reduce CRABSIs in adults and children [32].

The choice of insertion site seems to influence the subsequent risk of infection and may be related to the density of skin flora. Adult studies conclude that the risk of catheter colonization varies according to the insertion access site in the following ascendant order: subclavian = basilic < femoral < internal jugular [33]. The CDC's 2011 guidelines recommend using a subclavian site rather than a jugular or femoral site in adults when placing a non-tunneled CVC [24]. However, the CDC does not make a recommendation about catheter site in pediatric patients. Most studies in pediatric patients have demonstrated an equivalent risk of infectious complications with femoral and non-femoral catheters [34]. A large retrospective cohort study in pediatric patients found no difference in CVC infection rate among the three major sites of CVC insertion, and specifically between the femoral site compared with the subclavian and jugular cannulation [35].

The most common central venous catheter inserted in the PICU is the short- term, non-tunneled catheter, either with a single lumen or with multiple lumens. Non-tunneled CVCs account for the majority of CRBSIs. Tunneling a CVC appears to reduce the risk of catheter-related colonization and BSI, regardless of the location [36, 37]. Peripherally inserted CVCs are an increasingly popular alternative to subclavian or jugular vein catheterization. They can often be left in place for weeks to months as long as there is no malfunction, evidence of phlebitis, or infection. PICCs appear to have an acceptably lower incidence of infection vs. non-tunneled CVCs. Similar to non-tunneled catheters, prolonged catheter dwell time, pediatric ICU exposure, and administration of parenteral nutrition are reported to be important predictors of PICC-associated CLABSI in hospitalized children [38]. Of all central lines, surgically implanted ports have the lowest incidence of infection, although they carry the burden of surgical removal as well as insertion [24]. The addition of multiple lumens is thought to increase infection risk [39]. With respect to peripheral arterial catheters, pediatric studies have shown a low incidence of infection. However, the risk increases with the use of a system that permits backflow of blood into the pressure tubing and with increased duration of use [40, 41].

Pathogen-related risk factors are, in part, responsible for the unique spectrum of microorganisms commonly implicated in causing line infections and the difficulty with eradication. A battery of intrinsic virulence factors have been identified in some of the common nosocomial organisms like Staphylococcus, especially with respect to the interaction of the bacteria with the surface of the catheter. Some strains of CONS produce an anti-phagocytic exocalyx referred to as "slime". Several host factor-binding proteins (eg. Fibrinogen receptor ClfA and the fibronectin-binding proteins FbpA and FbpB) also appear to be important in the adherence of *Staph. aureus* to the catheter surface [42].

Diagnosis

The Infectious Disease Society of America's Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection, most recently updated in 2009, provides an evidence-based framework for the diagnosis of CRBSIs in adults and children [43]. Blood cultures are obviously the mainstay of the diagnosis of CRBSIs. Further, the ISDA guidelines recommend that a dedicated phlebotomy

team rather than bedside staff draw blood cultures. It is imperative that blood cultures are drawn prior to the initiation of antibiotic therapy. Peripheral and central cultures are mandatory, unless a blood sample cannot be drawn from a peripheral vein, in which case it is recommended that at least two blood samples should be drawn from the central line, through different lumens of the catheter if applicable. A definitive diagnosis of CRBSI requires that the same organism grow from at least one percutaneous blood culture and from a culture of the catheter tip, or that two blood samples (one from the catheter hub as well as peripheral vein) are positive. Quantitative blood cultures are recommended, and a colony count of microbes from the catheter that is at least threefold greater than the colony count from peripheral blood best defines CRBSI. For patients in whom peripheral culture is impossible, if two samples are obtained from different lumens of the central line, then the colony count for blood drawn from one of the lumens should be at least threefold greater than the colony count obtained from the second lumen. When catheter tips are cultured, growth of >15 colony-forming units (CFUs) from a 5 cm segment of a catheter tip by semiquantitative (roll-plate) culture or growth of 10^2 CFU from a catheter by quantitative (sonification) broth culture defines colonization. In addition, if antibiotic impregnated or coated catheters are used, specific inhibitors for those antibiotics should be used in the culture media.

Pathogenesis

Common commensal skin organisms are responsible for the majority of CRBSIs. Pooled NNIS data from 1992 to 1997 show that CONS (37.7 %), followed by Enterococci (11 %), *Staphylococcus aureus* (9 %) and Candida spp (9 %) are the most frequently isolated causes of PICU-acquired BSIs [4]. Antimicrobial resistance continues to be an increasing problem. This is exemplified by Staphylococcus isolates. Sixty percent are now methicillin-resistant. Also, a 50 % increase is noted in third generation cephalosporin non-susceptible *Klebsiella* isolates over recent years. Fungi, especially species of Candida, account for an increasing percentage of BSIs. Almost a third of isolates in a recent European survey grew *Candida albicans* [17]. Perhaps of more concern, nearly 50 % of Candida BSIs are caused by non-albicans species, including *C. krusei* and *C. glabrata*, which are often non-susceptible to fluconazole [44, 45].

The concept of catheter contamination is central to understanding the pathogenesis of CRBSI. The development of CRBSI is a time-dependent process. Overt systemic infection is preceded by catheter contamination and then colonization. The skin and the hub are the most common sources of colonization. For short-term, non-tunneled catheters (insertion <1 week), the most common route for catheter contamination is extraluminal (skin exit-site originated). It involves the direct migration of microorganisms to the catheter's external surface from the skin penetration site and extension along the subcutaneous tract. For long-term central lines, endoluminal contamination (hub originated) is well substantiated and is due to microorganisms extending along the luminal surface from the catheter hub. Rarely, hematogenous seeding from a distant source like the urinary tract might lead to catheter contamination. Fortunately, with implementation of infection control measures, contaminated infusates are now rarely responsible for bloodstream infections.

The actual colonization of the catheter is a complex process with a silent natural history. It involves the interplay of at least three factors: microorganism adhesion factors, the catheter material (roughness/texture, hydrophobicity), and the host response (biofilm and thrombin sheath formation). During biofilm formation, host proteins such as fibronectin, fibrinogen and von Willebrand factor, deposit along the catheter surface and serve as receptors that help trap the microorganisms [46]. Nearly all indwelling intravascular catheters develop a biofilm layer within 24 h after insertion. This biofilm anchors the embedded bacteria in a nutritionally advantageous environment. Thus, they become protected from host defense mechanisms as well as from antibiotics. The clinical correlate for such a mechanism comes from the widespread recognition that it is often impossible to eradicate the primary focus of infection in the implanted catheter, despite the use of antimicrobials with proven *in vitro* activity. In the final step of the continuum of CRBSI, the microorganisms may disaggregate from the macrocolony and disperse into the bloodstream resulting in remote metastatic and embolic complications.

Management and Prevention

Treatment of CRBSIs often involves consultation with pediatric infectious disease specialists as well as hospital infection control staff. The 2009 ISDA guidelines provide intensivists with evidence-based therapies [43]. In general, the guidelines recommend that empiric therapy include vancomycin in health care settings with an elevated prevalence of MRSA. If the MIC for vancomycin is ≥2 mcg/mL (according to local antibiograms) alternative agents such as daptomycin should be used. Empiric coverage for gram-negative organisms should be based on local antimicrobial sensitivities and severity of disease and would usually include a fourth-generation cephalosporin, carbopenem, or beta lactam/beta lactamase combination, with or without an aminoglycoside. The ISDA recommends that long-term catheters be removed with any of the following conditions exist: severe sepsis, suppurative thrombophlebitis, endocarditis, bloodstream infection

that persists despite >72 h of appropriate antibiotic therapy, or infections due to *Pseudomonas aeruginosa*, fungi, or mycobacteria. In addition, the ISDA recommends that short-term catheters be removed for all gram-negative bacilli infections. When catheter salvage is attempted, additional blood cultures should be obtained and the catheter removed if cultures remain positive 72 h after initiation of appropriate therapy. Length of treatment depends on the type of line (short term vs. long-term), whether or not the infection is uncomplicated or complicated, the clinical implications of the infection, and the type of organism involved.

In the circumstance of a suspected catheter-related infection, catheter removal may not be technically feasible for many critically ill infants and young children. The decision to remove the catheter must give weight to factors such as the child's underlying condition and need for intravascular access, catheter-type (whether short-term non-tunneled or long-term surgically implanted catheter), pathogen type, antimicrobial sensitivity, risk to the child of removal and replacement, and the likelihood of successful replacement at another site. Catheter-salvage has to be given consideration when the clinical picture consists of one of the following: limited vascular access sites, severe coagulopathy and tunneled catheters (including hemodialysis catheters), or infection with low virulence pathogens such as *Staph. epidermidis*. Several studies have reported management of catheter-related bacterial infections with a catheter-salvage approach [47, 48]. Antibiotic lock therapy can be tried for catheter salvage when infection with coagulase-negative staphylococci is documented and no systemic signs of sepsis, such as hypotension, are evident. Most of these patients are likely to need systemic therapy as well [24, 49]. The theory behind the antibiotic lock technique (filling the lumen of the catheter with a highly concentrated antibiotic solution and leaving the solution to dwell for several hours at a time) is to avoid the use of systemic antibiotics while delivering a high concentration of antibiotics to the catheter-associated pathogens. The usefulness of such prophylaxis has been shown effective, especially in neutropenic patients with long-term catheters [50–52]. Treatment of catheter-associated fungemia without catheter removal has a low success rate and may be associated with higher mortality [53].

Strategies to reduce CRBSIs hold the promise of improved patient outcomes and reduced health-care costs. The cornerstone to effective prevention is the adherence to basic infection control practices (risk factor modification) [54]. In addition, prominent experts in the field have commented that the failure to adhere to valid strategies of infection control may constitute an error of omission and may represent an error in patient safety [24]. The CDC guidelines for the prevention and management of catheter-related infections are evidence based and a must-read for all healthcare workers involved with insertion and maintenance of central vein catheters. The 2011 CDC guidelines recommend that institutions use hospital-specific or collaborative-based performance improvement initiatives to employ "bundled" strategies in order to decrease CRBSI rates [24]. Performance indictors aimed at decreasing CRBSI rates include hand hygiene, use of maximum barrier precautions, chlorhexidine site disinfection, and promptly removing unnecessary central venous catheters [55]. Surveillance practices and adherence to published guidelines vary widely [56]. Improving compliance with both insertion and maintenance bundles will be an important focus of many quality improvement projects.

The National Association of Children's Hospitals and Related Institutions (NACHRI) developed a quality-improvement collaborative to identify and test the impact of pediatric specific catheter-care practices in reducing pediatric CRBSI rates. The group developed two "bundles", one for insertion of CVCs and one for maintenance, based on the CDC guidelines as well as expert consensus opinion. Average CA-BSI rates were reduced by 43 %. Compliance with the "bundles" was high, and adherence to the maintenance bundle was found to a significant predictor of an infection-rate decrease [57]. Table 33.1 summarizes some of the recommendations with pertinence to the PICU population.

Antimicrobial-impregnated catheters may be a useful adjunct to infection control measures as they have proven efficacy in preventing intravascular device infections in appropriate patient populations. The two types of antimicrobial-impregnated central venous catheters that have been studied thoroughly chlorhexidine/silver sulfadiazine and the minocycline/rifampin. Head-to-head comparison in adults at high risk for catheter-related infection found a significant advantage to using the minocycline/rifampin–impregnated catheters [58]. Studies in pediatric populations are scarce. The 2011 CDC guidelines for prevention of intravascular catheter related bloodstream infections recommend the use a chlorhexidine/silver sulfadiazine or minocycline/rifampin-impregnated CVC in patients whose catheter is expected to remain in place >5 days [24].

Preventive strategies that are likely applicable in the PICU population include antimicrobial catheter flushes and prevention of thrombus formation. These promising strategies are supported by clinical data but need additional comparison studies. Heparin-bonded central venous lines have been shown to significantly reduce thrombotic and infective complications in critically ill children [59]. Of note, preventive strategies do not include routine replacement of CVL catheters [24].

As part of CVL best practice bundles, skin decontamination at the insertion site is critical. Although data regarding the use of the chlorhexidine-impregnated sponge in children are limited, several controlled studies show a significant decrease in colonization among those in the treatment group [60, 61].

Table 33.1 Preventive strategies for intravascular and urinary catheter-related infections

	What works	What might work	What does not work
Vascular catheters	Catheter removal when no longer essential	Antibiotic lock solutions	Cutdowns for arterial/central access
	Proper hand hygiene	Antiseptic or Antimicrobial impregnated catheters	Scheduled guidewire exchanges of CVCs
	Designated intravenous therapy team	Heparin-bonded catheters	Topical antibiotics at insertion site
	Healthcare worker education and training programs	Chlorhexidine gluconate impregnanted sponge dressings	Systemic antimicrobial prophylaxis
	Maximal aseptic barrier precautions for insertion		
	2 % chlorhexidine-based preparation for skin antisepsis		
	Appropriate nursing: patient staff ratio		
	Use midline catheter or PICC if need for i.v. access >6 days		
	Use a CVC with minimum number of ports/ lumens		
	Proper selection of pressure monitoring systems		
	Sterile gauze or semi-permeable transparent dressings		
	Judicious selection of catheter type and insertion site		
	Replace tubing used for blood or lipid emulsions within 24 h		
	Minimize access port/hub contamination		
Urinary catheters	Insertion using aseptic technique	Antiseptic or Antimicrobial-impregnated catheters	Therapy for asymptomatic bacteriuria
	Closed drainage system		
	Catheter removal when no longer essential		
	Ensure dependent drainage		
	Minimize manipulations of the system		
	Intermittent catherization (an alternative if longer duration of need)		

Abbreviations used: *CVC* central venous catheter, *PICC* peripherally inserted central catheter

The 2011 CDC guidelines for the prevention of intravascular catheter-related infections recommend the use of chlorhexidine-impregnated sponge dressings for temporary short-term catheters in patients older than 2 months of age [24]. Promising new strategies awaiting clinical trials include antiseptic or antimicrobial hubs, active antimicrobial iontophoresis, and novel suture-less catheter securement devices.

Ventilator-Associated Pneumonia

Scope of the Problem

Ventilator-associated pneumonia (VAP) is the second most common hospital-acquired infection in the PICU after bacteremia [4, 62]. It is defined as a pneumonia developing in intubated and mechanically ventilated patients. In the past, the diagnosis of VAP was only made if the pneumonia occurred more than 48 h after institution of mechanical ventilation. However, in the United States, the most recent NHSN guidelines state that there is no minimum time after initiation of mechanical ventilation necessary for a pneumonia to be considered ventilator-acquired [2].

The incidence of VAP has declined in the past decade but still remains an important source of morbidity and mortality in the PICU. Large pediatric studies are limited, but in 2002 a prospective study showed that approximately 5 % of mechanically ventilated children in the PICU developed VAP and 20 % of those died [63]. Due to awareness and implementation of prevention measures, VAP incidence density within the PICU has declined from 5.9/1,000-ventilator days in 1997 to a pooled mean of 0.7–1.1/1,000 ventilator days in 2009 [1, 5]. Cardiothoracic PICUs had overall slightly lower rates than medical or combined medical-surgical PICUs.

Diagnosis

The diagnosis of VAP is controversial in pediatric patients. Current NHNS criteria are based on a combination of clinical, radiologic, and laboratory findings [2]. No single test is

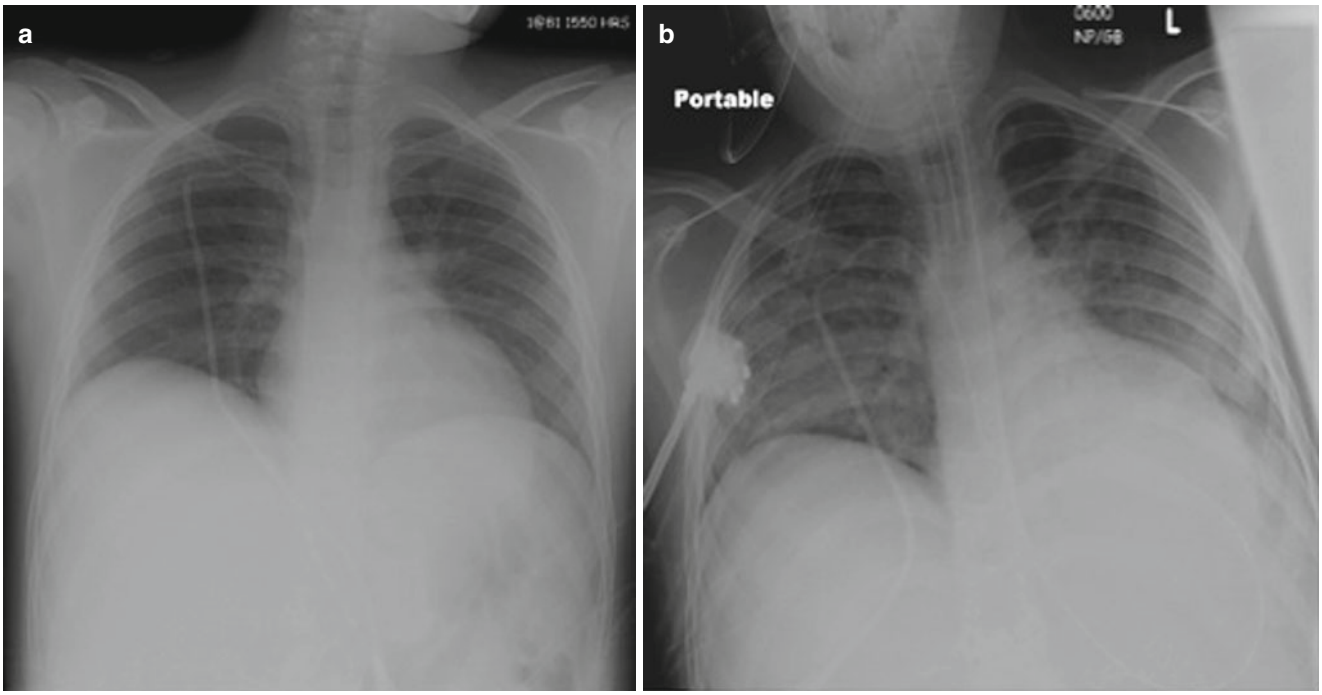

Fig. 33.1 Ventilator-associated pneumonia. (**a**) Baseline chest radiograph of a patient with acute lymphocytic leukemia who presents with a graft vs. host crisis. (**b**) Within 72 h of intubation, the patient develops a new left lower lobe infiltrate. Quantitative bronchoalveolar lavage cultures grew *C albicans*

diagnostic. Adding to the difficulty in diagnosis, children with tracheitis, pulmonary contusions, atelectasis, or with early community acquired pneumonias admitted without radiographs can be confused with VAP. For academic and surveillance purposes, the NHSN criteria have become the *de facto* standard for diagnosis of VAP in the United States and are increasingly adopted worldwide. There remains, however, a significant need for more rigorous adoption of uniform standards for diagnosis of VAP in the pediatric population [62].

The diagnosis of VAP should be suspected in a patient who is mechanically ventilated and has two serial radiographs that show a new, progressive, or persistent infiltrate, cavitation, or pneumatocele (Fig. 33.1). However, a single radiograph in a patient without underlying cardiac or pulmonary disease is sufficient [2]. In addition, there are concurrent clinical findings that must be present and are age-specific. In patients of any age, either fever without another specific cause, and leukopenia or leukocytosis must be present plus any *two* of the following clinical signs: (1) new purulent secretions or change in character or quantity of secretions, (2) apnea or tachypnea, (3) cough, (4) rales or bronchial breath sounds and, (5) worsening gas exchange. Recognizing that VAP may present differently in younger pediatric patients, alternate criteria for infants ≤1 year old with radiologic changes are worsening gas exchange and any *three* of the following: (1) temperature instability, (2) leukopenia or leukocytosis with left shift, (3) apnea, tachypnea, retractions, or grunting, (4) wheezing, rales, or cough, (5) new onset purulent sputum or change in character or quantity of sputum, and (6) either bradycardia or tachycardia. Children >1 or ≤12 must have radiologic changes and at least three of the following: (1) fever or hypothermia without other cause, (2) leukopenia or leukocytosis, (3) new onset purulent sputum or change in character or quantity of sputum, (4) new onset or worsening cough dyspnea, apnea or tachypnea, or (5) rales or bronchial breath sounds, worsening gas exchange.

Laboratory evidence of VAP may be substituted for one of the clinical criteria. These include: (1) positive blood culture not related to a known source, (2) positive pleural fluid culture, (3) a quantitative bronchoalveolar lavage (BAL) culture showing $\geq 10^4$ CFU/ml or protected brush specimen with $\geq 10^3$ CFU/ml, (4) presence of >5 % intracellular bacteria on Gram stained BAL specimen, or (5) positive histopathology. Many consider the presence of bacteria from a bronchoalveolar lavage or protected brush specimen in a ventilated patient sufficient to make the diagnosis of VAP. Unfortunately, the size of the endotracheal tube may impose technical limitations and no single approach toward lower airway sampling is possible. For simplicity, many clinicians obtain an endotracheal aspirate using a sterile suction catheter to sample endotracheal secretions when considering a diagnosis of VAP. However, use of qualitative endotracheal aspirate culture is controversial owing to high liklihood of

contamination or colonization of the endotracheal tube by upper airway organisms. For example, in one pediatric study the presence of positive endotracheal aspirates alone was only 41 % specific for VAP [64]. If clinical criteria and radiographic criteria are present, intracellular organisms are noted on gram stain, and a single agent is grown from the endotracheal specimen, the sensitivity increases to near 90 %. Quantitative endotracheal aspirate culture may be of use considering the ease of sampling compared with the expense and risk of complications inherent in bronchoscopic methods. A recent study showed that positive quantitative endotracheal aspirate cultures with a threshold of $\geq 10^5$ CFU/ml compared relatively favorably with bronchoscopic and non-bronchoscopic BAL, yielding a sensitivity of 84 % and a specificity of 77 % [65].

Alternatively, when diagnosing VAP, a blind protected BAL may be a useful tool. In one study, repeated blind, protected BAL specimens showed excellent reproducibility of microbiologic and cytologic results. Repeated samples had concordance of 86 % for bacterial identification and 79 % for quantitative analysis [66]. Another study in pediatric patients demonstrated that a threshold of at least 10^3 CFU/ml from a BAL specimen was needed to adequately make support the diagnosis of VAP [67]. A "bacterial index", which is the sum of the log of all species obtained by BAL, greater than five had the greatest validity as a supportive diagnostic test when compared to culture, gram stain and presence of intracellular bacteria [67].

Pathogenesis

The pathogenesis of VAP in the pediatric population has not been well studied. In adults, colonization of the oropharyngeal tract with pathogenic flora seems to be a central event. This is followed by aspiration of contaminated secretions into the lower airway, subsequently overwhelming local and systemic immune defenses. The presence of an endotracheal tube facilitates bacterial colonization of the tracheobronchial tree. Pooled airway secretions above the endotracheal tube cuff and/or within the oropharynx are also thought to be a source of pathogenic bacteria. In particular, this has led to the development of endotracheal tubes with proximal suction lumens to drain pooled oral secretions as a method of prevention of VAP. There are no efficacy studies in pediatrics.

Risk Factors

Multiple risk factors predispose do the development of VAP. The presence of an endotracheal tube is axiomatic. In general, as with other hospital-acquired infections, the elderly and the very young are at highest risk. Within the PICU, pediatric patients between 2 and 12 months are the most likely to develop VAP [63]. Duration of intubation is an important risk factor, but the risk of developing VAP is not constant over the duration of intubation [62, 68, 69]. In adults, it is more likely to develop in the first week of intubation (3 %/day) and by the third week the risk drops to 1 %/day [70]. Other associated risk factors include immunodeficiency, immunosuppressive therapy, histamine type 2 receptor blockade and prolonged neuromuscular blockade. Patients admitted for burns, major trauma, neurosurgery, genetic syndromes, or primary respiratory failure are at highest risk for VAP. Repeated tracheal intubation, multiple central venous catheters, transfusion of blood products, thoracentesis, transport out of the PICU and the presence of a primary blood stream infection also significantly incressed the risk of VAP [63, 71–73].

Pseudomonas aeruginosa, *Staphylococcus aureus*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* are commonly associated with VAPs in children. In pediatric aged populations, *Pseudomonas aeruginosa* is the most frequently reported isolate, followed by *Staphylococcus aureus* [65, 69, 74]. Among adult patients, *Staphylococcus aureus* was most commonly isolated (28 %) with 44 % of the cultures showing methicillin resistance. While relatively rare in previous surveys, MRSA and Acinetobacter are now emerging as frequent pathogens in the PICU [65, 75].

The microbiology of ventilator-associated pneumonias changes over the duration of intubation. Early onset VAP (within 4 days of intubation) shows a higher proportion of gram-positive isolates such as *Staphylococcus aureus*. Late onset VAP (after >5 days of intubation) shows significantly more gram-negative isolates such as *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *E. coli*, with the later isolates trending toward more drug-resistant strains [74, 76]. Thus, effective antimicrobial therapy has become much more difficult to empirically predict. Viral ventilator-associated pneumonias are far less commonly reported than bacterial pneumonias but may be underestimated. It is thought that viruses cause up to 2.5 % of hospital-acquired pneumonias [77].

Management and Prevention

Appropriate treatment of VAP is critical. Treatment should be focused on the appropriate antibiotic choice, shortest possible duration of antibiotic therapy, earliest possible tracheal extubation, and modification of antibiotic therapy based on culture data. Sadly, clinicians often choose an antibiotic regimen that has little activity against the actual pathogen. Patients who receive ineffective initial antibiotic therapy have a threefold higher attributable mortality compared to those who are treated with appropriate antibiotics [78].

Clinicians have tools to optimize the initial choice of antibiotic therapy. Pediatric intensivists need to know which pathogens are prevalent within their unit, as well as their susceptibility profiles. Antibiotic pressure may select for antibiotic resistant pathogens. Antibiotic duration should be as short as possible with empiric antibiotic coverage discontinued if clinical or laboratory evidence subsequently shows VAP is not present [62, 70]. Typically, a 7-day course is adequate with demonstrated infection. Discontinuation of antibiotics once infection is ruled-out is important. If treatment is appropriate, the patient should show a decrease in colony-forming units/ml on BAL, WBC count, temperature and improved oxygenation within 3 days.

Emphasis on VAP education for PICU staff should not focus on antibiotic treatment alone. Prevention has not only been shown in pediatric age groups to improve mortality, but also decreases morbidity and hospital costs. The optimal prevention strategies in children are not extensively individually tested, but consensus is emerging that they should include a multidisciplinary approach that relies on physician, nursing, and respiratory therapy ownership. In recent years the CDC and and other professional groups have issued guidelines for prevention of VAP in adult patients [79–82]. Pediatric preventative measures have adopted most of these recommendations where practical. When applied together as a "bundle" (Table 33.2) many pediatric investigators have noted significant decreases in VAP with resultant decreased cost and length of stay [83, 84]. As an example, in one PICU study use of a VAP prevention bundle decreased the VAP rate from 5.3 to 0.3/1,000 ventilator days [69].

Prevention of VAP not only improves the patient's quality of care, it is also cost effective. Development of VAP is associated with a greater PICU and hospital length of stay. In one study, the mean stay in the PICU increased to 34 days for patients with VAP, compared to 15 days for ventilated patients without VAP [83]. More recently, it was shown that the mean length of stay (LOS) for patients with VAP was 26.5 ± 13.1 days compared to 17.8 ± 4.7 days in those without VAP, with an attributable additional cost per VAP episode of $51,157 [84].

Table 33.2 Recommendations for the prevention of pediatric ventilator-associated pneumonia

Ventilator Circuit Guidelines
Meticulous hand washing before and after ventilator contact or patient suctioning
Do not change ventilator circuits or in-line suction catheters unless visibly soiled
Do not use heat-moisture exchangers for patients with excessive secretions
Drain condensation away from patient, using appropriate technique to avoid contamination of water reservoir
Use sterile water in ventilator humidifiers
Intubation Tube Guidelines
Consider non-invasive positive-pressure ventilatory (NIPPV) support when applicable
Avoid nasal intubation to decrease the risk of hospital-acquired sinusitis
Secure endotracheal tube to avoid unnecessary extubation and re-intubation
Maintain adequate ventilation pressure and in older patients, consider cuffed endotracheal tubes
In older patients (ETT size 6.0 or greater), consider placement of endotracheal tube with a dorsal lumen proximal to the cuff to facilitate drainage of subglottic secretions
Suctioning
Suction only when necessary to avoid introducing organisms into the bronchoalveolar tree
Consider in-line suction catheters
Use clean gloves for in-line suctioning and sterile gloves for single use suction catheters
Do not store catheters where they can contaminate ventilator circuit or clean supplies
General
Avoid use of unnecessary antibiotics
If possible, limit use of H_2-blockers
Education of ICU health care workers about risks associated with the development of ventilator-associated pneumonia
Maintain cohorting and use of gowns and gloves in patients infected with pathogens known to spread through aerosolized droplets (i.e. RSV) or in patients colonized with multi-antibiotic resistant organisms
Regularly rotate patient and utilize semi-recumbent or prone rather than supine positions
Avoid unnecessary chest physiotherapy
Nutritional support, although no clear advantage as to route of enteral feeds
Consider ventilator-weaning protocols
Consider non-invasive ventilation

Hospital-Acquired Infections of the Urinary Tract

Scope of the Problem

Hospital-acquired urinary tract infections (UTI) are a significant cause of morbidity and potential mortality in the ICU population. The majority are associated with urinary tract instrumentation, and most frequently with in-dwelling urinary catheters. These are designated catheter-associated urinary tract infections (CAUTI). In adult ICUs in the U.S., urinary tract infection constitutes the number one hospital-acquired infection (HAI), and is the third most common HAI in the pediatric population. Among adults hospitalized in the United States, hospital-acquired UTIs result in approximately one extra day of hospitalization per patient, and up to $131 million additional costs per year [85, 86]. Although the costs of CAUTI are not as high as CLABSI or VAP, hospital-acquired UTIs are a cause for concern as they are a major

reservoir of resistant pathogens. The most important of these include multidrug-resistant *Enterobacteriacae*, (*Escherichia coli*, Klebsiella, Enterobacter, Proteus, and Citrobacter), as well as *Pseudomonas aeruginosa*, Enterococci, Staphylococci and *Candida spp* [87, 88].

The 2009 pooled NHSN data showed that the mean CAUTI infection rate (number of CAUTI/urinary catheter days × 1000) in combined medical/surgical PICUs is 2.8, with cardiothoracic PICUs and medical-only PICUs at 2.7 and 0.8 respectively [1]. This is in comparison to an overall rate was 4.0 for pooled PICUs in 2004 and 5.2 from older NNIS data (1990–99) [9]. The apparent decline in density-incidence may be due to an increasing emphasis on CAUTI prevention, but a direct comparison over time is difficult due to changing CDC surveillance definitions that remove asymptomatic bacteriuria as a sole diagnostic criterion [89, 90]. Utilization ratios for urinary catheters (number of catheter days/total patient care days) in PICUs has declined slightly during this time to 0.28 in combined medical/surgical PICUs, 0.25 in cardiothoracic PICUs and 0.15 in medical-only PICUs [1].

Risk Factors

Published studies show that the major extrinsic risk factor for hospital-acquired UTI is the use of an indwelling urinary catheter [5]. NNIS data showed that 95 % of hospital-aquired UTIs in medical ICUs and 77 % in pediatric ICUs were catheter-associated [5]. Several studies have prospectively evaluated risk factors for urinary catheter–associated UTI. In adult studies, multivariate analyses have identified increased duration of catheterization (especially ≥7 days), female sex, lack of receipt of systemic antibiotic drug therapy, diabetes mellitus, azotemia (serum creatinine >2.0), and disconnection of the catheter-collecting tube junction and drainage tube above the level of bladder or below the level of collection bag as risk factors for nosocomial UTI [91–93]. Pediatric studies have demonstrated the following risk factors: younger age (newborns and infants), previous surgery for congenital heart disease, duration of catheterization ≥ 3 days and duration of ICU stay [94–96]. Gender has not been a consistently identified risk factor, unlike the clear female predominance in community-acquired UTI and in adult hospital-acquired UTI [94–96]. Interestingly, secondary bacteremia from CAUTI is thought to be lower in children than in adults and the overall attributable mortality of CAUTI in children is thought to be minimal [94, 96, 97].

The microbiology of CAUTI is different from that of community acquired UTI. Gram-negative enteric organisms remain the most common cause of pediatric hospital-acquired UTI, but fungi have become an increasingly prevalent cause. Published NNIS data from 2008 from multiple adult and pediatric hospitals showed that *Escherichia coli* was the most commonly reported isolate (21.4 %), followed closely by Candida species (21 % with 14.5 % *Candida albicans*). Other common pathogens identified in order of frequency were Enterococcus (14.9 %), Pseudomonas (10 %), Klebsiella (7.7 %) Enterobacter (4.1 %), and coagulase-negative Staphylococcus (2.5 %) [88]. Data from a study conducted in a large multidisciplinary tertiary care PICU also show the increasing importance of yeasts as a urinary tract pathogen. In that population, gram-negative organisms and yeasts together accounted for 82 % of all pathogens. Additionally most infections were unimicrobial and 20 % of organisms were antimicrobial resistant [95].

Diagnosis

For epidemiological purposes, revised published CDC guidelines should be used to diagnose CAUTIs [2]. CAUTI is confirmed in a patient who has or has had a urinary catheter within the last 48 h and who has clinical symptoms and a urine culture of $>10^5$ of no more than two organisms, or between 10^3 and 10^5 organisms if symptoms are present and there is an abnormal urinalysis [2]. Compared to previous guidelines, a major change has been removal of asymptomatic bacteriuria (ASB). ASB can be considered evidence of a true UTI if identical uropathogens are grown from blood cultures in addition to the positive urine culture.

Pathogenesis

The pathogenesis of urinary catheter-related UTI is similar in some ways to the process described with indwelling vascular catheters. Most microorganisms causing CAUTI derive from the patient's own perineal flora or from the hands of healthcare personnel. The entry of a urinary catheter bypasses the normal host defenses at the urinary meatus. This allows the entry of pathogens into the bladder and also allows for the formation of a biofilm, similar to the process in vascular catheters [93]. Organisms gain access to the bladder by one of two main routes. The principle route of acquisition is the extraluminal route. Colonization occurs either early, at the time of catheter insertion, or late due to colonization of the meatus and the ascent of microorganisms from the perineum along the surface of the catheter. The second pathway for microorganisms to enter the bladder is the intraluminal route. This occurs by reflux of organisms from a contaminated drainage bag (e.g. handling by healthcare workers) or by a break in the closed drainage system (e.g. irrigation of the bladder without proper asepsis). The contaminated urine can ascend from the bag into the catheter by capillary action or when the bag is raised above the level of the bladder (e.g. during transport) [54, 93].

Management and Prevention

Careful fluid input and output monitoring requires the use of indwelling urinary catheters; they are an integral part of the management of many critically ill infants and children. This is especially true for ICU patients with organ failure, complex congenital heart repairs, and severe sepsis. The need for continued catheterization must be balanced against the increased risk of catheter-related urinary tract infection. At the top of the list of effective strategies for prevention of CAUTI is the least "novel" of technologies: risk factor modification. Minimizing the duration of catheterization may be the single most important modifiable variable. Application of basic principles of infection control and using a closed drainage system will prevent many infections. Table 33.1 lists items that are useful in device-associated urinary tract infection control strategies.

Numerous trials in adult patients evaluating oral antibiotics, urinary acidifying agents, antimicrobial bladder washes, antimicrobial drainage bag solutions, and topical disinfectants all point to the same conclusion: bacteriuria and UTI can be suppressed temporarily, but resistant flora eventually appear [54, 90]. Antibiotic- and silver alloy-impregnated urinary catheters are a novel therapy and the current focus of many clinical trials. They appear to decrease the incidence of ASB in adults catheterized for short periods of hospitalization, but there was no clear indication if this reduced the risk of CAUTI compared to standard catheters in a large meta-analysis of adult patients [98]. Thus, a firm recommendation cannot yet be made for their use. Another possible new therapy is the technique of bacterial interference, or the use of benign non-pathogenic bacteria to prevent colonization and symptomatic infection with pathogenic organisms. Clinical trials in the pediatric population have not yet been published.

Surgical Site Infections

Scope of the Problem

Post-operative patients make up an important subset of all pediatric intensive care unit patients. Surgical site infections (SSIs) are those infections that occur in the surgical patient within 30 days of an operation or within 1 year of the operation if an implant was placed and meets specific criteria as defined by the NNIS system. SSIs are classified as: (1) superficial incisional (superficial to fascia/muscle), (2) Deep incisional (within fascia/muscle), or (3) organ/space (deep to fascia/muscle). Infections are further classified by risk index category as determined by the American Society of Anesthesiologists (ASA) preoperative assessment score, the degree, if any, of surgical field contamination, and the duration of the surgical procedure. The degree of contamination is categorized as follows: Class I (clean), class II (clean-contaminated), class III (contaminated), and class IV (dirty-infected) [99]. The NHSN system now monitors SSIs and reports rates of SSI for specific surgical procedures and risk categories.

SSIs are an increasingly common clinical issue, accounting for 14–16 % of all nosocomial infections among hospitalized patients [99]. It is estimated that SSIs occur in at least 2 % of all hospitalized patients who undergo surgical procedures [100]. However, the largest to date prospective multicenter study of pediatric SSIs in the United States in 1998 revealed a 4.4 % incidence of SSI in 846 general pediatric surgery patients at three large children's hospitals [101]. Of note, that study did not include cardiothoracic, orthopedic, or neurosurgical procedures. Analysis of data from hospitals participating in the NNIS system indicates that, among the 98,987 deaths (adults and children included) caused by or associated with HAIs in 2002, 8,000 were surgical site infections (SSIs) [100]. In the pediatric ICU specifically, during the years 1992–1997, between 6 and 10 % of NIs were SSIs [5]. The most common infections were skin infections, followed in most age groups by intra-abdominal abscesses and soft tissue infections. Mediastinitis was an important SSI in children and infants less than 5 years of age, due to early surgery for congenital heart defects. The most frequent types of preceding surgical procedures were chest surgery, including cardiovascular surgery (41 %); gastrointestinal surgery (24 %); neurosurgery (13 %); transplant surgery (8 %); orthopedic surgery (5 %); vascular surgery (3 %); and head and neck surgery (3 %) [5].

Risk Factors

Several pediatric-specific studies have examined risk factors for SSI. Both host factors and procedural risk factors appear to play roles in the development of SSIs in infants and children. The youngest patients, particularly neonates, are at greater risk for SSI. A large Spanish prospective study of 3,700 postoperative children identified eight risk factors associated with SSI: (1) use of a peripheral venous catheter, (2) higher degree of wound contamination, (3) use of a central venous catheter, and (4) urologic surgery (vs. general surgery), (5) having >1 diagnoses, (6) use of a urinary catheter, (7) duration of surgery, and (8) postoperative length of stay [102]. Other independent risk factors that have been shown to be associated with SSI are African-American race, implantable device placement, and postoperative admission to the intensive care unit [103].

The microbiology of SSIs often varies according to the type of surgical procedure. Most organisms originate from the patient's own flora, although some pathology may arise from other sources, including surgical equipment, operating room personnel, and implanted devices [99]. A recent study

which examined over 8,000 patients who were re-admitted with a culture-confirmed SSI between the years 2003 and 2007 found that methicillin-sensitive *Staph. aureus* was the most commonly cultured organism, followed by MRSA and CONS. Together, Staphylococci species accounted for approximately 50 % of infections. The authors found that MRSA became increasingly common during the course of their study and was often a component of polymicrobial infections. The most commonly encountered gram-negative species was *Pseudomonas aeruginosa*, found in 2.1 % of cultures. Polymicrobial infections were common, accounting for approximately 33 % of infections [104]. Among pediatric patients, MSSA was also the most commonly cultured single organism, followed by MRSA. Polymicrobial infections accounted for 21 % of infections, and monomicrobial gram-negative cultures accounted for 6 % of infections [103]. In the largest PICU-specific study of nosocomial surgical infections, staphylococcus species were the most commonly isolated organisms, although *Pseudomonas aeruginosa* was the most commonly isolated pathogen in gastrointestinal surgery [5].

In addition to contributing to morbidity and mortality, SSIs increase hospital length of stay and hospital costs. Older adult studies have estimated costs between $3,000 and $29,000 per SSI [105]. However, a recent matched cohort study of pediatric patients with SSIs revealed that on average, length of hospital stay was increased by 10.6 days and costs were increased by greater than $27,000 for each patient with a SSI [106].

Management and Prevention

The 1999 Guidelines for Prevention of SSI published by the Hospital Infection Control Practices Advisory Committee serves as the basis of SSI prevention efforts and detail evidence-based interventions targeted toward the perioperative and operative milieu [99]. In addition, the recommendations for the Institute for Healthcare Improvement (IHI) 100,000 Lives campaign have been extended to pediatric patients. In general, antimicrobial prophylaxis should be administered intravenously within 0–60 min prior to surgical incision and redosed during the procedure, depending on the length of the operation. A large multicenter study in adult surgical patients showed a strong relationship between the timing of antibiotic administration and SSI risk, with a trend toward lower risk occurring when prophylaxis with cephalosporins and other antibiotics with short infusion times were administered within 30 min prior to incision. Antibiotics with longer infusion times such as vancomycin should be administered within 60 min and no longer than 2 h prior to incision [107]. Antibiotics should be selected based on the surgical site and common pathogens related to specific operations. Antibiotic use as "prophylaxis" after 24 postoperative hours is not efficacious, seldom warranted, and should be discouraged.

Specific SSIs Commonly Encountered in the PICU

Cardiothoracic Surgery

The post-operative cardiothoracic surgery patient in the ICU is at risk for SSI, including wound infection, sternal osteomyelitis, and mediastinitis. In pediatric cardiac surgical patients, the rates of reported SSI range from 1.7 to 8 per 100 cases [108–114]. Multiple studies have examined risk factors for SSI in pediatric cardiac surgery patients and have identified age younger than 1 month, the diagnosis of a genetic syndrome, preoperative hospitalization for greater than 48 h, higher ASA score, intraoperative hypothermia, need for multiple procedures during the same operation, duration of surgery, hypoplastic left heart syndrome, femoral catheter presence, postoperative receipt of total parenteral nutrition, and presence of temporary pacing wires for >3 days as risk factors for SSI [108, 112–115]. A 2009 study of patients with cardiac SSI found that independent risk factors for any type of SSI were age younger than 1 year and duration of cardiopulmonary bypass greater than 105 min [116].

Although relatively infrequent, mediastinitis is the most serious of SSIs associated with pediatric cardiac surgery and carries a high risk of morbidity and mortality. Mediastinitis is infection involving the mediastinum or sternum and meets the CDC criteria for organ/space SSI. To meet criteria for mediastinitis, the patient has to meet at least one of the following criteria: (1) have organisms cultured from mediastinal tissue or fluid, (2) evidence of mediastinitis seen during a surgical operation or histopathologic examination, (3) have fever, chest pain, or sternal instability *and* at least one of the following: purulent discharge from the mediastinum, bacteremia or organisms cultured from mediastinal wound discharge, or mediastinal widening on chest radiograph. Various studies have found incidence rates for mediastinitis in pediatric cardiac surgery patients of 0.2–3.9 % [117–121]. The largest study of mediastinitis in congenital heart surgery patients found that gram-positive organisms were present in 67 % of cases and gram negative organisms were present in 30 % of cases. Concurrent bacteremia was very common and found in over 50 % of cases. Delayed sternal closure has been found to be an independent risk factor for the development of gram negative mediastinitis [120].

Craniofacial Surgery

Surgical site infections following craniofacial surgery can be difficult to treat and can change both medical and cosmetic outcomes. While mortality associated with pediatric craniofacial surgery performed at experienced centers is low, factors such as implanted materials used in procedures as well as the

common need for multiple procedures to address complex malformations increase infection risk in these patients [122]. Two relatively recent studies with large numbers of patients reveal an SSI rate of 2.5–3.2 % [122, 123]. *Pseudomonas aeruginosa* and *Candida albicans* are the most frequent pathogens in craniofacial SSIs, although polymicrobial infections are common [122, 123]. Risk factors for SSIs in craniofacial surgery include: (1) complicated preoperative diagnoses such as genetic syndromes, (2) long duration of surgery (3) closure of skin under tension, (4) more than four surgeons present during surgery, (5) PICU stay longer than 2 days, and (6) use of a ventilator after surgery [122]. Tracheostomies and ventriculoperitoneal shunts have not been identified as a risk factor for infection [122, 123]. Antibiotic prophylaxis with first-generation cephalosporins is used most commonly, with some centers dosing for 24 h for cranial vault remodeling and others continuing antibiotics until drain removal. Significant infections often require aggressive surgical management for drainage and debridement.

Neurosurgery

Nosocomial central nervous system infections usually involve a surgical site or presence of a foreign body such as a ventriculoperitoneal shunt, intracranial pressure monitor, or externalized ventricular drain (EVD). For combined adult and pediatric patients from 2006 to 2008, the pooled mean rates for craniotomy-associated SSIs are 2.15 for low risk patients and 4.66 per 100 operations for higher risk patients. For ventricular shunts, the pooled mean rates for SSIs are 4.0–5.9 per 100 operations [124]. When all shunt infections are considered, rates are between 5 and 15 %. This increase reflects the fact that many of these shunts become infected over a year after insertion [125]. Ventricular shunt infections contribute to a significant number of PICU hospitalizations yearly because of these patients' needs for close monitoring of their mental status as well as the complexities of care involved. Shunt infections accounted for the most hospital charges outside of the neonatal period and increased length of stay significantly [126]. Shunt infections have been associated with complications such as seizures and electrolyte disturbances [127]. An older, but to this date unreplicated, retrospective 20 year study of shunt infections found associations between shunt infections and decreased intellectual performance and overall increased mortality [128].

Independent risk factors for ventriculoperitoneal shunt infection include premature birth, previous shunt infections, intraoperative use of the neuroendoscope, postoperative CSF shunt leak, and intraoperatively breached gloves [125, 129]. Most commonly, organisms found as skin flora, including CONS, *Staphylococcus aureus*, and proprionibacterium are cultured from infected shunts [130, 131]. Management strategies for infected ventricular shunts vary. A 2001 survey of pediatric neurosurgeons found that most surgeons remove the infected shunt and place an external ventricular drain, while others externalize the shunt itself. Duration of antibiotic therapy was also found to vary, with treatment lengths ranging from 5 to 24 days [132]. A multicenter study of a standardized protocol for ventricular shunt procedures showed an absolute risk reduction of 3.15 % and a relative risk reduction of 36 % with utilization of the protocol. Significant components of the protocol included routine administration of pre-operative and peri-operative antibiotics, double-gloving to prevent contamination of shunt with skin flora, and injecting the shunt reservoir with vancomycin and gentamycin prior to closure [133]. The use of antibiotic impregnated ventricular shunts and external ventricular drains remains controversial, but may decrease incidence of shunt infection [134].

Infection of intracranial pressure monitors and external ventricular drains is a complication in the treatment of both traumatic brain injury and hydrocephalus. The use of prophylactic antibiotics, while common, is controversial and may increase the incidence of resistant gram-negative pathogens [135–137]. Further data is needed to determine the best practice regarding antibiotic prophylaxis for intracranial pressure monitors and external ventricular drains.

Orthopaedic Surgery

Spinal fusions for idiopathic or neuromuscular kyphoscoliosis are common admissions to the PICU. While many of these procedures fall into the low risk index categories, some procedures are performed on patients with complex medical histories resulting in higher risk. The pooled infection rate means for spinal fusions (adults and children) vary from 0.7 to 4.15, depending on risk category. Wound infections develop more commonly in patients with neuromuscular scoliosis compared to idiopathic scoliosis [138]. Wound infections following spinal surgery result in pseudoarthrosis as well as prolonged hospital stay and recovery [139]. Deep infections often require surgical debridement, drainage, and possibly removal of hardware [140]. Significant risk factors for deep SSI after spine surgery include: previous spinal surgery, presence of complex underlying medical condition, younger age, greater than ten vertebrae fused, higher intraoperative blood loss, and the presence of a ventriculoperitoneal shunt [141]. In addition, as with many other SSIs, inappropriate timing of preoperative antibiotic prophylaxis has been found to be a significant independent risk factor for deep SSI in spinal fusion [141].

Transplant Surgery

Solid organ transplants have some of the highest SSI rates among all surgical procedures. Immunosuppression as well as debilitated pre-operative states contribute to increased risks of SSIs. Pooled mean infection rates for solid organ transplants are 3.28 per 100 heart transplants, regardless of

risk category, with lower infection rates following kidney transplants, and significantly higher rates following liver transplants [124]. In addition to standard pre- and perioperative infection control measures, increased compliance with strict hand washing and the use of gown and glove isolation in the PICU have been found to be associated with a significant reduction in nosocomial infections in children undergoing solid organ transplantation [142]. Active surveillance to detect SSI is also important in preventing poor outcomes in solid organ transplant patients.

Infection Control in the PICU

Infection control measures within the PICU are increasingly important. The U.S. Department of Health and Human Services estimates that health-care-associated infections affect 5 % of patients hospitalized each year in the United States [143]. Knowledge of risk factors, prevalence and infection control bundles is vital to the developent of pediatric intensivists. Nosocomial infection rates are now routinely monitored both as benchmarks for assessing the quality of patient care and for reimbursement. Morbidity and mortality from hospital-acquired infections is known to be both preventable as well as a significant contributing factor to spiraling health care costs in the United States.

Multiple sources within the PICU for nosocomal infections are well-established. Within the PICU, utilization of medical devices such as central vascular catheters, mechanical ventilation, and urinary catheters is a well-recognized factor that influences the development of hospital-acquired infections. Other factors also play a role, including the environment (humidity, air quality, distance between patients), adherence to hand hygiene by health care workers, immune and nutritional status of the host, use of antimicrobial therapy, and length of stay [144]. Since most hospital-acquired infections in the PICU are associated with the use of intravascular catheters, mechanical ventilation, or urinary catheters, most infection control measures are focused on use of proper sterile barrier techniques, use of sterile water in ventilator humidifiers, proper timing for ventilator circuit changes, prompt removal of devices, and proper preparation and handling of intravenous fluids.

Multiple disease outbreaks have been implicated with environmental factors [144, 145]. Unit design is especially important. While large open areas ("open wards") provide access to patients, they pose great problems for infection control. Distance between patients greatly influences some hospital-acquired infection rates. Transmission between patients could be possible because of close proximity or as a consequence of absence of barriers between patients. As an example, patients with respiratory infections caused by influenza or respiratory syncytial viruses can transmit virus to individuals within the recognized "drop zone" of large droplets (~3 ft). Units with separate rooms for patients are optimal, allowing isolation when necessary. During the annual respiratory season observed in the northern United States, cohorting patients with bronchiolitis symptoms can be considered as an added infection control measure. Whenever possible, PICU nursing staff caring for patients with respiratory viral illnesses should not care for patients who are either high-risk or immunocompromised.

High-risk immunocompromised patients are frequently admitted in the PICU. These patients are at risk of opportunistic infections by organisms such as *Aspergillus*. Ideally, immunocompromised patients are placed in private rooms with positive-pressure or positive-air flow. Many transplant or cancer units have high-efficiency particulate air (HEPA) handling with high number of air changes per hour (ACH) in their "protective environment" rooms. Most PICUs do not require this type of air handling. However, if available, rooms in the PICU should have at least six ACH.

Every PICU needs to be capable of caring for patients with airborne-transmitted pathogens such as tuberculosis, measles, and varicella. Units must have an adequate number of "airborne infection isolation" rooms. These rooms must have negative-pressure or negative-air flow air handling (air flows into the room from the adjacent space or corridor when the door is opened). These rooms should have a minimum of six ACH if construction of room was done before the year 2001 or 12 ACH if built after 2001. The air from these rooms must be vented out of the hospital and not re-circulated unless filtered [146].

Patients colonized with resistant organisms such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant Enterococci pose special problems for isolation. Many hospitals have reported outbreaks within itensive care units with these organsms. Conventional wisdom holds that nosocomial infections manifesting in the ICU represent microorganisms acquired from within this high-risk environment. This is not necessarily true. The contribution of the patient's own flora was highlighted in an elegant study from the United Kingdom. The investigators demonstrated that the majority of infections (59.8 %) diagnosed during prolonged PICU stays (≥4 ICU days) were actually due to microorganisms imported into the ICU from the patient's own flora and predominantly occurred in the first week of PICU stay. Microorganisms associated with the microbial ecology of the ICU caused the other 38.9 % of infections [147].

Numerous clinical studies and reviews have consistently demonstrated that appropriate hand disinfection or washing remains the single most effective measure to decrease the spread of nosocomial infections [142, 144–146, 148]. The importance of proper hand hygiene cannot be overemphasized. Hand hygiene can be greatly improved if access to hand washing facilities and antiseptic hand sanitizer

dispensers can be facilitated and encouraged. At least one hand washing station should be provided for every three patient beds in an open area floor plan. These should be equipped with hands-free operable controls [148]. In units with separate rooms, each room should have a sink and soap and hand sanitizer dispensers. Since not all health care workers prefer to use hand sanitizers, sinks provide an appropriate alternative. The CDC has published guidelines for hand hygiene. In a nationwide survey concerning routine hand washing, significantly more positive attitudes toward the practice guidelines were found among staff in pediatric as compared with adult ICUs [149]. Further, nursing staff had more positive attitudes toward hand hygiene guidelines when compared with physicians. Inadequate hand washing (and use of artificial fingernails) has been associated with multiple outbreaks within ICUs [150]. Hand hygiene is clearly an area in many PICUs where simple education and vigilance will pay enormous dividends.

Strict gown and glove use has been shown to decrease nosocomial infections in the PICU [151]. However, it appears to be no more effective than strict hand washing and it is difficult to maintain increased compliance. When utilized together, gown and glove use and hand washing have an additive protective effect in decreasing nosocomial infections in immunocompromised patients within the PICU. Maintaining routine use of barrier precautions among ICU staff is difficult. While use of barrier methods such as gloves, gowns and masks clearly minimize transmission, adherence to their proper use often deteriorates over time [142].

Proper disinfection of PICU rooms is critical, especially when a patient is colonized or infected with resistant organisms. Organisms such as RSV may survive on hard surfaces and fomites for hours, allowing for the transmission between patients. Bacteria such as vancomycin-resistant enterococci (VRE) and MRSA can survive even longer. Inappropriately cleaned rooms have been implicated in the transmission of resistant organisms [146, 152, 153]. Since patient's colonization status with resistant organisms is often unknown, proper room cleaning is imperative after discharge of all PICU patients.

The frequency of isolation of resistant organisms such as VRE, MRSA and extended-spectrum-lactamase (ESBL)-producing gram-negative rods varies between institutions [154]. Unfortunately, they are being isolated in greater frequency. Each PICU should have information about their hospital and unit's prevalence. Knowledge of unit-specific susceptibility antibiograms can assist clinicians greatly in selecting the most appropriate empiric antimicrobial therapy for patients with suspected hospital-acquired infections [155, 156]. Antimicrobial resistance can be reduced only if the PICU physician uses antimicrobial therapies more appropriately. Access to molecular assays such as pulsed-gel field electrophoresis is critical in determining the extent of outbreaks and the need for special infection control measures [157].

Appropriate nursing-to-patient ratio has been found to be important in the prevention of hospital-acquired infections, especially ventilator-associated pneumonias [158]. Low nurse to patient staffing levels as well as the presence of non-permanent or "float" nurses have been shown to increase the risk of CLABSI [159, 160]. Patient-nurse ratios are often detemined by patient acuity, but in general should not exceed 1:2. When nursing staffs are forced to "ration" care due to heavy workload assignments or when PICU nursing personnel are reduced, the risk of PICU nosocomial infections increases [158, 161]. PICU staffing is a growing problem, with both nationwide nursing shortages in the United States, as well as increasing hospital bugetary constraints.

The prevention of PICU-acquired infections is a complex endeavor that requires a thorough adherence to well designed practices and engineering controls. In most hospitals, colaboration is crucial. Hospital infection control programs have active surveillance measures in place to detect infections in a timely manner. They will typically contact the clinician and are helpful in instituting necessary preventive measures. The sharing of information between infection control practitioners, unit nursing staff, and medical directors generally results in the identification of problems and their resolution.

Lapses in compliance may result in preventable hospital-acquired infections, which may have devastating consequences. Adoption of healthcare ordersets or "bundles" for VAP and CLABSI have become the focus of quality improvement efforts in many pediatric facilities. Specific measures within the PICU such as antibiotic rotation, selective decontamination of the gastrointestinal tract, or antibiotic-impregnated catheters are also currently being investigated, but are not recommended yet for nationwide implementation [151, 162, 163].

Conclusion

Nosocomial infections in the PICU remain a significant but potentially preventable source of morbidity and mortality. The risk of infection in PICU patients remains high because invasive devices allow organisms to bypass normal host defenses. Additionally, PICU patients often have coexisting organ system dysfunctions or degrees of immunocompromise. While blood stream infections are the most common nosocomial problem in the PICU, ventilator-associated pneumonias have the highest mortality. The overall attributable mortality due to nosocomial infections within the PICU is estimated at 11 % [6]. The mortality associated with nosocomial infections is multifactorial. Clearly the patient population, underlying disease, number of organ systems affected, need for invasive therapies, and the microorganisms responsible all contribute to the risk of developing a hospital-acquired infection.

Nosocomial infections have a significant economic impact on the United States healthcare system. The patient population within the PICU is unique. They tend to not have the chronic diseases noted in the adult ICU population and are more likely to have a sequelae-free recovery. Thus, PICU nosocomial infections have a potentially enormous effect on productive years of life lost. Nosocomial infections add an additional four billion dollars annually to US health care expense both in direct costs and future wages lost [164]. Additionally, a majority of prospective payment systems refuse to pay the additional reimbursement caused as a consequence of treating a nosocomial infection [165, 166].

Even the most conservative estimates suggest that one third of all nosocomial infections in the US could be prevented by following established infection control programs. In a recent study in adults, strict compliance with hand washing, sterile procedures, hospital and national infection control policies, and empowering the ICU nursing staff to stop the procedure essentially stopped the occurrence of BSIs [167]. Use of infection control bundles directed at improving compliance with infection control policies is having a dramatic effect on ICU-acquired nosocomial infections. In 2001, the Centers for Disease Control and Prevention reported an estimated 43,000 CLABSIs cases in adult and pediatric ICUs in the United States. By 2009, this number had decreased to 18,000 [20].

The best current approach for preventing PICU-acquired infections centers on strict adherence to infection control policies, early discontinuation of invasive devices, and appropriate isolation strategies. Insight into the organisms and sensitivites of PICU-related infections is a crucial component in the success of any hospital infection control guidelines. Research into best preventive strategies is ongoing and likely to significantly alter our practice of intensive care medicine in the near future.

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Anaphylaxis

34

Shilpa K. Shah and Erika L. Stalets

Abstract

Anaphylaxis is a life-threatening systemic hypersensitivity reaction caused by the release of mediators, most notably histamine, from mast cells and basophils. The underlying mechanism may be immunologically mediated, non-immunologic, or idiopathic. These mediators lead to deleterious effects on multiple organ systems and symptoms occur within seconds to minutes after exposure to a trigger. The epidemiology and pathophysiology of anaphylaxis will be reviewed in this chapter, as will the clinical presentation and management. Given the rising incidence of pediatric anaphylaxis, it is becoming increasingly important for child healthcare providers to recognize and rapidly treat this disease process. Symptoms may be relatively benign or severe and fatal. They can include classic allergic symptoms such as sneezing, hives, and angioedema, but also dizziness, blurred vision, chest pain, abdominal pain, or acute respiratory arrest. Immediate treatment with epinephrine and isotonic volume resuscitation can be life-saving for patients with anaphylaxis. Additional interventions and therapies are discussed in the chapter, including the management of cardiopulmonary arrest due to anaphylaxis. A key component of anaphylaxis treatment is prevention, which requires identification of the causative agent and avoidance whenever possible. Additionally, given the rapid onset of symptoms and the risk for severe morbidity and mortality, patient and family education, prescription of an epinephrine auto-injector device, and referral to an allergist are equally important in preventing anaphylaxis.

Keywords

Anaphylaxis • Anaphylactic shock • Food allergy • Histamine

Introduction

The term anaphylaxis is derived from the Modern Latin terms *ana*, meaning against, and *phylaxis,* meaning guarding or protection [1]. The World Allergy Organization defines anaphylaxis as a "severe, life-threatening generalized or systemic hypersensitivity reaction" [2]. Knowledge of the presentation, causes, mechanisms and treatment of anaphylaxis is imperative for the pediatric intensivist.

Epidemiology

Accurate incidence of anaphylaxis is difficult to ascertain secondary to inconsistent definitions and inadequate data. A recent review of the literature found reported lifetime prevalence of anaphylaxis to range from 0.05 to 2 % [3]. However, correlating with an increase in the incidence of allergy, the incidence of anaphylaxis, especially for children, is rising worldwide. Incidence is particularly increasing for food-induced anaphylaxis [4–6]. Risk factors for anaphylaxis include asthma,

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history of atopy, previous history of anaphylaxis, and mastocytosis [3, 7, 8]. One study found that the use of angiotensin converting enzyme (ACE) inhibitors was associated with an increased risk of severe reactions to insect sting in adults [9]. Interestingly, some investigators have found a correlation between higher latitude and increased incidence of anaphylaxis, especially in children. This has led some to postulate that vitamin D deficiency may be a risk factor for anaphylaxis [5]. A person's gender also plays a role. In children, males appear to have a greater incidence of anaphylaxis, but this ratio changes in adulthood, with females having a higher incidence later in life [4, 7, 10–12].

Despite the increase in anaphylaxis incidence, anaphylaxis death rates remain stable. A notable exception is the significant increase in deaths from drug-induced anaphylaxis beyond the increased incidence of drug-induced anaphylaxis. In studies of fatalities, drugs are implicated in up to 50–60 % of cases, insect stings in about 20 %, and food in 10–20 %. Risk factors for death from anaphylaxis include active asthma, peanut or tree nut allergy, delayed or lack of use of epinephrine, and previous history of severe reactions [4, 13–17].

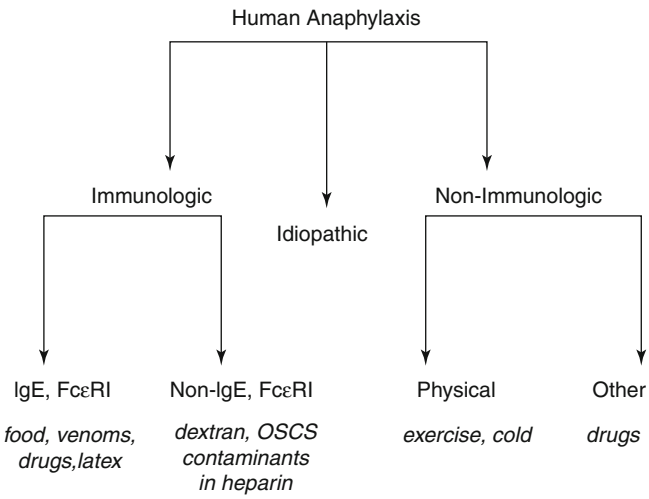

Fig. 34.1 Mechanisms underlying human anaphylaxis. Anaphylaxis is commonly mediated through an immune IgE-dependent mechanism. Rarely, it occurs through another immune mechanism. Uncommonly, it occurs through direct (non-immune) activation of mast cells. Idiopathic anaphylaxis, currently a diagnosis of exclusion, presents opportunities for identification of previously unrecognized triggers, elucidation of pathophysiologic mechanisms, and identification of patients with mastocytosis or clonal mast cell disorders. *FcεRI* high affinity IgE receptor, *OSCS* oversulfated chondroitin sulfate (Reprinted from Simons [18]. With permission from Elsevier)

Pathophysiology

Anaphylaxis is classified by underlying mechanism: immunologic, non-immunologic, or idiopathic. Terms such as anaphylactoid and pseudoanaphylaxis are no longer recommended; all fall under the umbrella of anaphylaxis (Fig. 34.1) [3, 18–20].

The most common immunologic mechanism of anaphylaxis is an IgE mediated reaction to an allergen. The allergen elicits IgE antibody production. IgE then binds to the high affinity IgE receptors (Fcε(epsilon)RI) on mast cells and basophils. Upon re-exposure to this allergen, crosslinking and subsequent aggregation of these bound antibodies triggers mast cell and basophil degranulation causing release of mediators. This mechanism is responsible for the majority of anaphylaxis cases. Triggers are myriad and include food, drugs, insect stings (i.e. from hymenoptera venom), latex, seminal fluid, animal dander, plant pollen, and in some cases, radiocontrast media [3, 19–21].

Immunologic mechanisms independent of IgE have been described but are incompletely understood. Although rare, both IgG and complement-mediated mechanisms, including activation via immune complexes, have been implicated. The end result is still mast cell and basophil degranulation with release of mediators. Dextran, monoclonal antibodies such as infliximab, and radiocontrast media have all been reported to trigger non-IgE mediated anaphylaxis [3, 19, 20].

Non-immunologic mechanisms underlie anaphylaxis triggered by agents and physical stimuli that cause direct mediator release. Examples include opiates, ethanol, cold, sunlight and exercise. Additionally, activation of the contact system can occur when blood is exposed to dialysis membranes or when radiocontrast media is administered. Aspirin and other NSAIDs may contribute to anaphylaxis via abnormalities in arachidonic acid metabolism. Some cases of anaphylaxis may be idiopathic which should lead one to consider exposure to an unknown or unrecognized allergen or possibly a mast cell disorder [3, 19, 20]. The non-IgE mediated mechanisms of anaphylaxis were previously encompassed in the category of "anaphylactoid" reactions, but this term is no longer used [3, 19, 20] It should also be noted that some agents can cause anaphylaxis via more than one mechanism, e.g. radiocontrast media [3].

Triggers

Many triggers are listed above according to the mechanism by which they induce anaphylaxis. Depending on the population studied, the most commonly reported anaphylaxis trigger is food, accounting for 20–60 % of cases. Drugs account for 5–50 % of cases, insect stings in 11–30 %, and exercise in 3–9 %, with other causes being less frequent [3, 12, 22–26]. Interestingly, food-dependent exercised-induced asthma, which is exercised-induced anaphylaxis that occurs in proximity to consumption of certain foods, is more commonly reported in Asian countries, with a frequency as high as 14 % [4].

As the most frequent triggers of anaphylaxis, special attention should be given to food and drug allergies. The incidence of food allergy is increasing. As noted above, almost any food can cause anaphylaxis. Common foods causing anaphylaxis include peanuts, tree nuts, eggs, dairy products, seafood and fruits. Peanuts and shellfish are increasingly implicated, with a slower increase in cow's milk and egg-triggered anaphylaxis [13]. A new legume, lupin, is becoming more widely used in Europe and has been implicated in both allergy and anaphylaxis [4]. Cross-sensitization among foods can occur, as well as cross-sensitization between latex and certain foods, including banana, kiwi, papaya, avocado, potato and tomato [3].

The incidence of drug anaphylaxis appears to be increasing as is the number of deaths attributed to drug anaphylaxis. Of particular concern is the rise in perioperative anaphylaxis. While almost all drugs are capable of inducing an anaphylactic reaction, two classes of drugs are most commonly implicated: beta-lactam antibiotics and anesthetic agents [27]. Non-steroidal anti-inflammatory drugs and radiocontrast agents are the most commonly implicated triggers for non-immunologic anaphylaxis [4]. Monoclonal antibodies and immunotherapy allergens are increasingly utilized and have a higher incidence of anaphylaxis [3].

Mechanism of Symptoms

Whatever the mechanism leading to anaphylaxis, the symptoms are caused by release of mediators from activated mast cells and basophils. The signaling mechanisms and subsequent release of mediators from these cells is complex and still not fully understood. Mediators such as histamine, tryptase, carboxypeptidase A and proteoglycans are released from mast cells and basophils, triggering phospholipase A2 activation. Phospholipase A2 activity results in production of arachidonic acid, which is modified by cyclooxygenases and lipoxygenases. This results in the production of cytokines and inflammatory mediators, including prostaglandins, leukotrienes, platelet activating factor, and TNF-α, among others. These mediators induce vasodilation, increased vascular permeability, increased heart rate, glandular secretion, bronchoconstriction, pulmonary and coronary vasoconstriction and recruitment of other inflammatory cells including neutrophils. This complex process leads to the signs and symptoms observed in anaphylaxis [3, 19, 20].

Clinical Presentation

Part of the difficulty in the diagnosis of anaphylaxis can be attributed to the difference in diversity and severity of symptoms manifested by those affected. No single symptom is diagnostic and various organ systems may be affected. Skin and/or mucous membrane manifestations are the most common and are present in 70–90 % of cases. Cutaneous symptoms include urticaria or hives, pruritus, flushing, and swelling (angioedema) [3, 10–12, 22, 25, 26, 28]. Other affected organ systems may include the respiratory, cardiovascular, gastrointestinal and neurologic systems. Respiratory symptoms are present in up to 70–80 % of cases, and include shortness of breath, stridor or bronchospasm depending on the location of inflammation in the airway, hypoxemia/cyanosis, and even respiratory arrest. Other respiratory system symptoms may include rhinitis, sneezing, hoarse voice, or cough. Cardiovascular symptoms can range from hypotension to cardiovascular collapse and occur in 25–80 % of reported cases, with reviews from Asia reporting a higher incidence of cardiovascular symptoms. Gastrointestinal symptoms include cramping, vomiting and diarrhea, and are reported in up to 20–45 % of cases [3, 10–12, 22, 25, 26, 28]. Neurologic symptoms can include headache, dizziness, anxiety, or a feeling of impending doom [3, 10, 28, 29]. Infants and small children cannot describe symptoms, and signs may be nonspecific or difficult to interpret in this age group. In addition to those signs listed above, others may include drooling, spitting up, somnolence, irritability, crying, or abrupt changes in behavior, e.g. sudden cessation of play [30].

Biphasic or late phase reactions, in which anaphylaxis symptoms recur, have been reported in up to 20 % of adult cases and 6–11 % of pediatric cases. They may occur as late as 72 h after the initial symptoms have resolved, although the majority happen within 8 h. Clinical predictors for biphasic reactions in children include delayed epinephrine administration or needing more than one epinephrine dose or fluid bolus during the first episode of anaphylaxis. The second reaction may be the same, less severe, or more severe than the initial reaction and can be fatal. Given the incidence of biphasic reactions and the potential for significant morbidity and mortality, a 24 h observation period has been recommended following an anaphylaxis episode. The pathogenesis of this biphasic response is unclear and may involve delayed synthesis or release of mediators, or delayed recruitment of inflammatory cells [12, 31–33].

Differential Diagnosis

The differential diagnosis of anaphylaxis includes entities that mimic the cardiovascular, respiratory, gastrointestinal, neurologic and cutaneous symptoms of anaphylaxis, especially those that involve sudden onset of symptoms and/or a proximate response to a stimulus such as drug or food. These disorders can be classified by either symptoms or etiology; both paradigms are useful.

Table 34.1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely if any one of the following three criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
And At Least One Of The Following
(a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
(b) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours)
(a) Involvement of the skin-mucosal tissues (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
(b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
(c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
(d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours)
(a) Infants and children: low systolic BP (age specific) or greater than 30 % decrease in systolic BP[a]
(b) Adults: systolic BP of less than 90 mmHg or greater than 30 % decrease from that person's baseline

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PEF Peak expiratory flow, *BP* blood pressure
[a]Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years

Perhaps the best mimickers are those disorders caused by an excess of histamine, either endogenous, via mast cell degranulation, or from exogenous sources. Examples include mastocytosis and other disorders of mast cells or basophils, red-man syndrome, and scombroidosis, the histamine poisoning one may get from eating spoiled fish. Similar to those of anaphylaxis, skin and mucous membrane symptoms can be seen in acute urticaria, oral allergy syndrome, and non-allergic angioedema, e.g. hereditary angioedema. Alcohol, carcinoid syndrome, or other agents and disorders that cause flushing of the skin are also in the differential of anaphylaxis. Monosodium glutamate ingestion, also known as "Chinese restaurant syndrome", is related temporally to food ingestion and can cause nausea, vomiting, flushing, and chest pain, similar to anaphylaxis [34]. Differential diagnoses that show predominantly respiratory symptoms include acute asthma, vocal cord dysfunction, and foreign body aspiration. Cardiovascular mimickers include syncope and sudden catastrophic cardiovascular events such as a saddle pulmonary embolus, distributive shock or septic shock. Panic attacks, seizures, strokes, and disorders of autonomic regulation may manifest similarly to the neurologic symptoms of anaphylaxis [3, 19].

Diagnosis

Prompt recognition of anaphylaxis is critical given the potential for rapid deterioration and death. Unfortunately anaphylaxis lacks a universal hallmark for diagnosis. Clinical criteria for the likely diagnosis of anaphylaxis have been proposed by expert consensus but need to undergo testing and validation. These criteria are designed to facilitate the rapid recognition of anaphylaxis based on systemic organ system involvement, onset of symptoms, and exposure to allergen, be it known, likely or unknown. Table 34.1 outlines the diagnostic criteria [29]. Particularly important elements of the history include thorough review of known and/or likely exposure(s), and the timing and evolution of symptoms.

Although no single laboratory test can make the diagnosis of anaphylaxis, elevated plasma histamine level or serum tryptase level can help confirm the diagnosis. Neither test is specific for anaphylaxis so results must be interpreted in the clinical context. The plasma histamine level rises early (5–15 min) and normalizes quickly. Thus, histamine is ideally measured within 1 h after the onset of symptoms. Additionally, the half-life of histamine is only 2 min and it is falsely elevated with cell injury (e.g. hemolysis). Thus, the sampling method is crucial for an accurate result, i.e. the sample should be drawn with a wide-bore needle, kept cold, and processed promptly. Measurement of histamine or histamine metabolites may also be performed on a 24-h urine sample [3, 35].

Tryptase is another protein secreted by mast cells, and to a lesser extent, by basophils. Total tryptase concentration does not always increase in anaphylaxis, but is more likely to be elevated in severe allergic reactions compared with mild reactions. Tryptase is also less likely to be elevated in food-induced anaphylaxis. This is thought to be secondary to a combination of findings: a slower onset and more sustained duration of symptoms in food induced-anaphylaxis, more localized, versus systemic, mast cell degranulation and activation of basophils, and less tryptase in mucosal mast cells. Various tryptases have been described, including inactive pro-β tryptase and active mature forms of α tryptase and β tryptase. Mature serum β tryptase may be more specific for anaphylaxis and hence more useful in a situation like

mastocytosis in which baseline levels of pro-β tryptase are elevated. Tryptase should be measured within 3 h of symptom onset, and compared to a baseline level that is obtained 24 h after resolution of symptoms or from stored serum obtained prior to the anaphylaxis episode [3, 36, 37]. Research regarding more sensitive and specific tests to confirm the diagnosis of anaphylaxis is underway [38].

Additional testing can be more helpful to identify and confirm triggers for the patient with an episode of anaphylaxis. This testing can be done in several ways with variable accuracy, including skin tests, allergen-specific IgE measurements, and trigger-challenge tests. The details of these tests are beyond the scope of this chapter, but are an important part in the identification of triggers, risk assessment, and most importantly, the prevention of future anaphylaxis episodes by avoidance of known triggers.

Treatment

Effective treatment of anaphylaxis requires a high index of suspicion with early recognition and immediate institution of therapy. As with any critical illness, standard measures of attention to airway, breathing and circulation is essential, however prompt institution of specific pharmacologic measures can be lifesaving. One consensus statement suggests the following guide for order of therapies and interventions: Epinephrine, patient positioning, oxygen, fluids, inhalational therapy, vasopressors, antihistamines, corticosteroids, and then other agents [39].

Epinephrine

Epinephrine is the mainstay of lifesaving therapy for anaphylaxis and thus should be prioritized above all other therapies or interventions [39–41]. The evidence for the use of epinephrine consists of uncontrolled studies, fatality studies, cohort studies, clinical observations and expert opinion; however, given the likelihood of death from anaphylaxis in the absence of treatment, it would be unethical to perform a placebo controlled randomized controlled trial [42, 43]. Minimal delay for the administration of epinephrine in the setting of anaphylaxis is crucial in preventing mortality. One review of fatal anaphylaxis cases found the median time from contact with allergen to respiratory or cardiovascular arrest to be 5–30 min, depending on trigger (iatrogenic, venom or food), with a range of 1–360 min. Most did not receive epinephrine before arrest [44].

Mechanism of Action

Epinephrine is an endogenous catecholamine that exerts its effects via binding of α and β adrenergic receptors found in nearly all tissues. Exogenous epinephrine has an identical mechanism of action. Epinephrine's most important actions relevant to the treatment of anaphylaxis include its effects on the cardiovascular and respiratory systems. Stimulation of α-1 and β-1 receptors causes systemic vasoconstriction and increases inotropy and chronotropy, respectively, with the net result being increased blood pressure and coronary blood flow. Vasoconstriction may also decrease mucosal edema. The β-2 receptor mediates bronchodilation and inhibition of mast cell release of histamine and other inflammatory mediators. Vasodilation via β-2 receptors is more pronounced in skeletal muscle than in other tissues, including the skin and subcutaneous tissues where the α-1 effect of vasoconstriction is more prominent. This is particularly relevant for route of administration. Adverse effects originate from actions on the same receptors and include increased myocardial oxygen demand, increased myocardial excitability and therefore arrhythmia, and CNS symptoms including headache, palpitations, tremor, and anxiety [45]. Rarely, the cardiovascular effects of epinephrine can lead to death, e.g. acute myocardial infarction or fatal arrhythmia. Usually, however, this has been reported in the setting of overdose or inappropriate administration. No absolute contraindication to the administration of epinephrine exists in the context of true anaphylaxis [44].

Modes of Administration

For the treatment of anaphylaxis, epinephrine has traditionally been administered by the subcutaneous, intramuscular (IM), or intravenous (IV) routes. Enteral epinephrine is rapidly metabolized in the gastrointestinal tract and liver, so is ineffective and not recommenced as a viable therapy [45]. Sublingual epinephrine is currently being studied as a potentially effective route of administration, but is not standard practice [46, 47]. Inhaled racemic epinephrine can be used for localized mucosal swelling of the upper airway, but for treatment of anaphylaxis, it is unreliable. Intramuscular injection is the most recommended and preferred route given the more rapid onset of action and peak effects compared with subcutaneous administration. These differences in time to peak concentration may be due in part to epinephrine-mediated vasodilation in skeletal muscle allowing faster absorption of the drug versus the vasoconstriction it causes in subcutaneous tissues which can impede absorption [45, 48–50]. Multiple doses may be needed therefore close clinical monitoring is essential. Though reports are lacking, anywhere from 6 to 36 % of cases of anaphylaxis reported in the literature required two or more doses of epinephrine. [51–56]. The appropriate time interval between repeated doses of epinephrine has not been studied. One guideline suggests re-dosing every 5 min with the recommendation that it may be repeated more frequently based on clinician judgment [39]. The IV route is preferred in a patient in arrest or with profound shock given the lack of circulation in muscle and peripheral

tissues. It can also be given via continuous infusion. In a canine model of anaphylactic shock, continuous IV infusion was the most effective mode of administration in regards to recovery and maintenance of adequate hemodynamics when compared to bolus IV or IM dosing [57]. Additionally, a prospective trial of 19 adult patients experiencing anaphylaxis in response to a diagnostic sting challenge demonstrated consistent and rapid clinical improvement when epinephrine was titrated for symptoms via continuous infusion [58]. The IV route has the greatest potential for adverse effects due to improper administration, so care should be taken when prescribing this route [59]. Patients who are at known risk for anaphylaxis or serious allergic reaction should be prescribed an auto-injector of epinephrine for administration in the community setting. See Table 34.2 for medications used in the treatment of anaphylaxis and their recommended doses.

Patient Positioning

Patients with anaphylaxis, especially those with hemodynamic compromise, should be placed in the supine position with elevation of the lower extremities. This will assist with venous return in a system with abnormally high peripheral capacitance and increased vascular permeability from vasodilation. Care should be taken to keep the patient in a supine position until hemodynamics have been stabilized and symptoms have resolved. Cardiovascular compromise and even death have been reported with a change to an upright position in a symptomatic patient [39, 83].

Oxygen Administration and Fluid Resuscitation

High flow oxygen is considered standard therapy for any patient with symptoms of anaphylaxis, especially when the reaction is prolonged or when hypoxemia is present. Fluid resuscitation with isotonic crystalloid or colloid solution should be infused rapidly for signs of hemodynamic compromise, such as tachycardia or hypotension. This will expand the intravascular volume in a system with both a higher than normal capacitance secondary to vasodilation as well as relative hypovolemia secondary to increased vascular permeability and capillary leak [39, 65, 84].

Inhaled β-agonists

In the setting of anaphylaxis with bronchospasm, inhaled β-2 agonists such as albuterol or levalbuterol can be useful in relieving bronchospasm. β-2 selective agonists exert effects on both β-1 and β-2 receptors, but act predominantly at the β-2 receptor. When administered via the inhalational route, they cause bronchodilation through smooth muscle relaxation [45]. They may also inhibit the release of inflammatory mediators from mast cells (e.g. histamine). Beta agonists should be given in conjunction with epinephrine, not as primary therapy [39, 65, 84]. They have been reported to be useful in the setting of bronchospasm with anaphylaxis unresponsive to epinephrine in patients taking β blockers [85]. Similarly, for airway edema, inhaled epinephrine can be utilized [39, 65].

Histamine Blockers

Established guidelines for the treatment of anaphylaxis advise the use of H_1 receptor blockers, and most also advocate the use of H_2 receptor blockers in conjunction [39, 65, 84]. Histamine, in addition to other inflammatory mediators, is released from mast cells and basophils as part of the immediate sensitivity response to a trigger and is the principle cause of anaphylaxis symptoms. Histamine effects are mediated by H_1, H_2, H_3, and H_4 receptors. The majority of anaphylaxis symptoms arise from stimulation of the H_1 and H_2 receptors, which will be the focus of discussion herein. H_1 and H_2 receptors are widely expressed on several cell types. Among others, H_1 receptors are found on smooth muscles cells, endothelial cells, and neurons in the central nervous system, and promote vasodilation, bronchoconstriction and GI motility. They are also responsible for the cutaneous itch associated with histamine release. H_2 receptors are found in gastric parietal cells, smooth muscle and cardiac muscle cells, mast cells and in the central nervous system. H_2 activation leads to gastric acid secretion, vasodilation, and bronchial mucus production. Of note, H_2 receptors on bronchial smooth muscle cells can mediate a degree of bronchodilation. Both H_1 and H_2 receptors cause increased vascular permeability and vasodilation, but H_1 receptors cause immediate and rapid vasodilation, and promote increased fluid transudation causing edema. H_2 receptors mediate a slower, longer lasting vasodilator effect. Both receptors are responsible for direct cardiac effects, including increased heart rate, shorter diastolic depolarization and slowed AV conduction [86, 87].

The recommendation for antihistamine use in anaphylaxis is largely from clinical use, basic science and animal research, and biologic plausibility. There is a paucity of quality, clinical evidence for the use of antihistamines in anaphylaxis [88]. However, more evidence exists regarding the effectiveness of antihistamines in less severe allergic disorders such as acute urticaria and allergic rhinitis. It is in these less severe allergic disorders that the combination of H_1 and H_2 blockers is variably more effective in controlling and resolving symptoms than H_1 receptor blockers alone [89]. It is unclear how much benefit patients obtain, if any, from use

Table 34.2 Drugs used in the treatment of anaphylaxis

Drug	Pediatric dose	Adult dose	Notes
Epinephrine [60, 61]			
Intramuscular (IM) 1:1,000 solution	0.01 mg/kg IM	0.2–0.5 mg IM	The IM route is recommended over the subcutaneous route. Fastest onset when given via IM route in the antero-lateral thigh [48, 49] Can be repeated every 5–15 min
Auto-injectors [62–64]	Manufacturers' recommendation: <30 kg, 0.15 mg IM Expert recommendation: <25 kg, 0.15 mg IM	Manufacturers' recommendation: >30 kg, 0.3 mg IM Expert recommendation: >25 kg, 0.3 mg IM	Auto-injectors are dosed as either 0.15 mg or 0.3 mg dose vials only
Intravenous (IV) 1:10,000 solution	0.01 mg/kg IV, up to 0.5 mg, over 20 min Continuous infusion: 0.1–1 mcg/kg/min IV. Up-titrate to shock doses to reach desired effect	0.1 mg IV, over 5 min Continuous infusion: 1–4 mcg/min IV. Up-titrate to shock doses to reach desired effect	Continuous infusions may be preferable to frequent bolus doses in severe or refractory reactions [58]
Corticosteroids [29, 39, 65–67]	0.5–2 mg/kg/dose IV methylprednisolone equivalent Prednisone 1 mg/kg PO, up to 50 mg	Methylprednisolone 50–120 mg IV Hydrocortisone 100–500 mg IM/IV Dexamethasone 4–20 mg IM/IV Prednisone 50 mg PO	Corticosteroids are not useful in the acute management of anaphylaxis; no evidence to support the theory that corticosteroids prevent protracted or biphasic reactions [29, 31, 33, 39]
Antihistamines [29, 61, 66]			
H_1 blockers – 1st generation	Diphenhydramine 1–2 mg/kg IV/IM/PO, up to 50 mg Hydroxyzine 0.5–1 mg/kg IM every 4–6 h as needed; or 2 mg/kg/day PO divided every 6–8 h	Diphenhydramine 25–50 mg IV/IM/PO Hydroxyzine 25–50 mg IM/PO every 6–8 h as needed	Common examples in each category, not an exhaustive list
H_1 blockers – 2nd generation	Cetirizine 6 month–2 year: 2.5 mg; 2–5 year 2.5–5 mg; 6+ yrs: 5–10 mg PO Fexofenadine 6 month-2 year: 15 mg; 2–11 year, 30 mg; 12 + yrs: 60 mg PO Loratidine 2–5 year: 5 mg, 6+ yrs: 10 mg PO	Cetirizine 5–10 mg PO Fexofenadine 60 mg PO Loratidine 10 mg PO	Second generation H_1 blockers are not available in IV formulation
H_2 blocker	Ranitidine 1.25 mg/kg IV; 2 mg/kg PO	Ranitidine 125 mg PO; 50 mg IV	Used alone, H_2 blockers have the theoretical risk of potentiation of bronchoconstriction via unopposed H_1 effect [68]
Vasopressin [61]	Continuous infusion for shock states, titrate to effect 0.01–0.48 units/kg/h IV	Continuous infusion for shock states, titrate to effect 0.6–2.4 units/h IV	Bolus dose treatment of anaphylaxis resistant to epinephrine described in **adults**: 2–5 units [60, 69, 70]
Norepinephrine [61]	0.05–1 mcg/kg/min IV, up-titrate to effect	0.05–1 mcg/kg/min IV, up-titrate to effect	
Glucagon [29, 71, 72]	20–30 mcg/kg IV (max 1 mg)	1–5 mg IV over 5 min followed by continuous infusion, 5–15 mcg/min, titrated to response	May be useful to reverse bronchospasm and hypotension refractory to standard therapy in patients taking beta blockers. May cause emesis
Isoproterenol [61]	Usual dose for brady-arrhythmias and AV nodal block:0.05–2 mcg/kg/min IV, titrated to response	Usual dose for brady-arrhythmias and AV nodal block: 2–20 mcg/min IV, titrated to response	Use described in one pediatric patient on beta blockers for epinephrine-refractory anaphylaxis to aprotinin during cardiac surgery. Dose used, 1.7 mcg/kg [73]
Methylene blue [74–81]	0.5–2 mg/kg (most commonly 1.5 mg/kg) bolus dose over 5–20 min, sometimes followed by continuous infusion of 0.5–1.5 mg/kg over 1 h	0.5–2 mg/kg (most commonly 1.5 mg/kg) bolus dose over 5–20 min, sometimes followed by continuous infusion of 0.5–1.5 mg/kg over 1 h	Used in epinephrine refractory anaphylaxis. Use caution in patients with G6PD deficiency due to risk of methemoglobinemia Cardiac angina and anaphylaxis has been reported after methylene blue use [82]

of both in anaphylaxis [43, 90]. Additionally, publications from the 1980s report resolution of refractory anaphylaxis with the H_2 blocker, cimetidine. However, it is not clear that this was a cause/effect relationship, and in fact, an H_2 blocker alone has the theoretical risk of potentiation of bronchoconstriction via unopposed H_1 effect [68, 91–93]. A variety of different antihistamine agents are available for use. First generation H_1 blockers tend to have more adverse effects, especially sedation, but the non-sedating H_1 blockers are not available in intravenous form. H_2 blockers are available in both enteral and intravenous preparations.

Corticosteroids

While ineffective in the acute treatment of anaphylaxis, corticosteroids are another adjunctive treatment and may, in theory, help alleviate protracted symptoms. There is, however, no evidence supporting the concept that their use will prevent a biphasic reaction [31, 33, 39]. The exact mechanisms of the anti-inflammatory effects of corticosteroids are not completely elucidated. They directly affect transcription, thereby inhibiting enzymes that facilitate the production of inflammatory mediators, including prostaglandins, leukotrienes and other cytokines [94].

As with other drugs used for anaphylaxis, quality, clinical evidence supporting corticosteroid use for the alleviation of anaphylactic symptoms is lacking [43, 95]. However, short term use is associated with fewer side effects, and the current guidelines recommend consideration of their use. Given the protracted onset of effect, more immediate and potentially lifesaving treatment, namely epinephrine and fluid resuscitation, should never be delayed by administration of corticosteroids [39, 65, 84].

Other Vasopressors

In a number of reported cases of anesthetic related, epinephrine resistant anaphylactic shock, vasopressin, terlipressin, norepinephrine, or the pure α1 agonists metaraminol and methoxamine have been used successfully when epinephrine failed [39, 60, 69, 96–100]. Vasopressin has been reported as successful treatment in cases of anaphylaxis secondary to insect sting [101]. Administration of these agents may be indicated in the setting of circulatory compromise/vasodilation unresponsive to multiple doses of epinephrine.

Other Agents

Patients receiving β blocker therapy have a greater risk of more severe and prolonged symptoms, especially hypotension and bradycardia [102]. In these patients, epinephrine, the mainstay of anaphylaxis therapy, will primarily result in α-adrenergic effects with little inotropy or chronotropy due to lack of β-adrenergic activation. This phenomenon has been reported in patients receiving therapy with non-selective β blockers as well as those taking cardio-selective β-1 blocker agents. Isoproterenol and glucagon have both been used successfully to increase cardiac output, heart rate, and blood pressure in patients under β blockade. Isoproterenol, a non-selective β agonist, competitively activates β-adrenergic receptors, even in the presence of β blockers. Glucagon bypasses the adrenergic receptors altogether and increases cardiac contractility and heart rate via activation of adenylate cyclase [73, 103–105].

Methylene blue has been reported as effective for treating refractory hypotension, especially in the context of anesthesia induced anaphylaxis as well as cases of idiopathic and contrast induced anaphylaxis [74–78]. Additionally, it has been used successfully for children with persistent vasodilation, or vasoplegic syndrome, following cardiopulmonary bypass. The vasoactive effect of methylene blue is thought to be identical in both entities) [106]. The mechanism by which it treats catecholamine refractory vasodilation is thought to be via inhibition of guanylyl cyclase and nitric oxide synthase [107]. Doses that have been used in published cases are shown in Table 34.2.

Treatment of Cardiorespiratory Arrest in the Management of Anaphylaxis

A patient who has progressed to cardiorespiratory arrest from anaphylaxis should receive resuscitation consistent with the standard basic and advanced pediatric life support guidelines, with a focus on simultaneously managing and reversing the effects of anaphylaxis [108]. At any sign of airway edema, including hoarseness, stridor, visible swelling of the tongue or oropharynx, the clinician should prepare for the potential need for advanced airway management. This includes, but is not limited to, controlling the airway early or electively, anticipating a smaller airway and gathering appropriate equipment, summoning the help of anesthesia colleagues, and being prepared to rapidly obtain a surgical airway if indicated. The administration of epinephrine should not be delayed; if an epinephrine auto injector is available, the dose should be used immediately. As noted above, however, in a state of shock or cardiac arrest, absorption may be delayed. Thus intravenous or intraosseous doses should be given as soon as access is obtained with consideration to a continuous infusion. Other vasopressors can be considered as discussed above. Given the degree of vasodilation and vascular permeability associated with anaphylactic shock, fluid resuscitation should be rapid and large in volume as capillary leak leading to relative hypovolemia and decreased preload may have contributed to the state of cardiovascular collapse. Early consideration of

extracorporeal membrane oxygenation (ECMO), especially in the case of in-hospital arrest should be considered, given the reversible nature of anaphylaxis [108].

Prevention

Prevention of anaphylaxis is the best treatment and involves two strategies: diagnosis and avoidance of known triggers and/or immunomodulation to desensitize the individual to the offending agent. In individuals with recurrent idiopathic anaphylaxis, prophylaxis with steroids, histamine blockers and/or anti-IgE antibody preparations may be indicated.

Equally important, however, are strategies to reduce the risk of death from anaphylaxis. This includes instruction to avoid the trigger or probable trigger, referral to an allergist for further work-up, and appropriate prescribing of epinephrine auto-injectors to those at known risk. Education about the epinephrine auto-injector for caregivers and patients is necessary and should include instructing them about the proper use of the device and to always carry it in a readily available way. It is important to be aware of the clinically relevant limitations of such "epi pens." They are available in either 0.15 or 0.3 mg doses. This presents an imperfect dosing strategy for pediatric patients with widely varying weights, and also poses great potential for over- or under-dosing. Given the length of the auto-injector needles, they may be too short for adequate intramuscular administration in obese patients. Additionally, the auto-injectors cannot be stored in extremes of temperature and have a short shelf life, thus replacement of them every 12–24 months, or more frequently, is necessary [62]. Parents and patients should also seek medical care anytime they utilize their auto-injector.

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Rheumatologic Disorders in the PICU

35

Steven W. Martin and Michael R. Anderson

Abstract

Rheumatologic diseases in children compromise a small but sometimes perplexing portion of patients admitted to the Pediatric Intensive Care Unit. Systemic Lupus Erythematosus (SLE) is the most variable and indiscriminate vasculitis affecting children. SLE may cause devastating injury to virtually any organ system and therefore must often be included in the differential diagnosis of critically ill children. Juvenile Idiopathic Arthritis (JIA) does not commonly require admission to the ICU in itself, but is associated with macrophage activation syndrome (MAS). MAS is a spectrum of hemophagocytic lymphohistiocytosis (HLH) which often calls for intensive care and aggressive therapies. Henoch-Schoenlein Purpura is a small vessel vasculitis affecting children commonly associated with intussusception, but may also give rise to significant cardioplulmonary complications. Kawasaki Disease is the most common vasculitis in children and the recently described Kawasaki Disease Shock Syndrome may require invasive monitoring and therapies. Antiphospholipid Antibody Syndrome, Goodpasture Disease, and Wegener's Granulomatosis while not common, give rise to complications which also may necessitate critical care. The following chapter discusses these disease entities and other rheumatologic illness affecting children and common complications arising from them which may indicate critical care. Included in the discussion are the most widely accepted diagnostic approaches and therapies, and supporting evidence is described.

Keywords

Systemic Lupus Erythematosus • Juvenile Idiopathic Arthritis • Macrophage Activation Syndrome • Kawasaki Disease • Kawasaki Disease Shock Syndrome • Antiphospholipid Antibody Syndrome • Infliximab • Henoch-Schoenlein Purpura • Goodpasture Disease Churg-Strauss Syndrome • Juvenile Dermatomyositis • Systemic Sclerosis

Introduction

In the general pediatric population, rheumatologic diseases vary greatly in their features and presentation. Thus, despite their infrequency, these disorders often must be included in the differential diagnosis when evaluating a critically ill child. It has been estimated that between 5 and 10,000 children within the United States carry the diagnosis of systemic lupus erythematosus [1], the most common connective tissue disease. In addition, 30,000–50,000 children suffer

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Table 35.1 Systemic lupus erythematosus

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	High affinity pathogenic IgG autoantibodies (anti-dsDNA, anti-Sm, etc.) bind to autoantigens and cause direct damage via complement activation [6]	Positive anti-dsDNA antibody
Ischemic stroke	Circulating immune complexes overwhelm clearance mechanisms and deposit in tissues due to their net anionic charge and/or binding to autoantigens by the antibodies in the complex. These complexes lead to complement activation and subsequent tissue damage [6]	Positive anti-Sm antibody
Hemorrhagic stroke		Positive antiphospholipid antibodies
Cerebral vein thrombosis		Positive ANA
Seizure		Low C3
Psychosis		Low C4
Delirium		Low CH_{50}
Depression		Positive anti-centromere antibody
Cardiac		Positive anti-SSa antibody
Myocarditis		Positive anti-SSb antibody
Cardiomyopathy		Proteinuria
Pericarditis		Urinary casts (red cell, hemoglobin, granular, tubular, or mixed) [7]
Endocarditis		
Pulmonary		
Pneumonitis		
Pulmonary hemorrhage		
Renal		
Glomerulonephritis		
Hematological		
Hemolytic anemia		
Leukopenia		
Lymphopenia		
Thrombocytopenia		
Thromboembolism		

from juvenile idiopathic arthritis (JIA) [2], the most common rheumatologic disease. The most common vasculitis in childhood, Henoch-Schonlein Purpura (HSP), has an estimated incidence of nine per 100,000 children [3, 4]. More rare rheumatologic diseases affecting children include antiphospholipid antibody syndrome (APS), juvenile dermatomyositis (JDM), Goodpasture disease, Wegener granulomatosis, Churg-Strauss syndrome, and scleroderma. The pediatric intensivist cares for rheumatology patients for varying reasons, related to the primary disease process, adverse effects of treatment for the underlying disease, and/or illnesses that are complicated by the underlying disease [5]. In the following sections, we will examine selected rheumatologic diseases affecting children, and will review their presentation, pathophysiology, complications, and management.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) (Table 35.1) is the prototypic, and most variable rheumatologic disease described to date, affecting all organ systems. SLE affects patients of all ethnicities and ages, but 15–20 % of patients are diagnosed in the first two decades of life [8]. SLE is extremely variable in presentation, organ system involvement, and disease progression [9, 10]. Patients with SLE are hospitalized in the intensive care setting for a wide array of diagnoses. One retrospective study of adult SLE patients requiring intensive care unit admission found that the primary diagnosis was infection in 41 % of admissions (the majority of which were diagnosed with septicemia), renal disease in 21 %, cardiovascular disease in 16 %, and coagulopathy (both thrombotic and hemorrhagic) in 14 % [11].

The pathogenesis of SLE differs depending on which tissues are examined and is best described in renal disease, which shows inflammation, cellular proliferation, and immune complex deposition affecting the glomerular basement membrane (GBM). Deposition of circulating immune complexes or *de novo* synthesis of immune complexes on the GBM activates the complement cascade, leading to cellular damage, cellular proliferation, and matrix deposition [12]. Tissue classification of lupus nephritis is complex secondary to the variability of disease expression among patients and among various glomeruli within one tissue biopsy [12]. The World Health Organization (WHO) has established a classification scheme based on light microscopy, immunofluorescence, and electron microscopy, which divides lupus nephritis into six classes. Findings range from class I with normal glomeruli by light microscopy,

immunofluorescence, and electron microscopy, to class VI where >90 % of observed glomeruli are sclerotic [12].

The cardiovascular system, including both the heart and blood vessels, shows pathologic changes due to the ongoing autoimmune process as well. Inflammation is seen in the pericardium, myocardium, and endocardium. Immunofluorescence studies have shown complement and immune complex deposition within the myocardial vessels as well as the myocardium itself [13].

CNS Complications of SLE

Approximately 20–30 % of children will develop CNS involvement, or neuropsychiatric lupus (NPS), during the course of their SLE, with 75–85 % of these developing during the first year [14, 15]. The term neuropsychiatric lupus describes 19 clinical situations seen in SLE patients, which may be the consequence of ongoing CNS vasculitis, peripheral nervous system involvement, or stroke due to associated antiphospholipid antibodies [16, 17]. Symptoms range from headache or memory impairment to psychosis, paralysis, seizures, and coma. When considering serious or life-threatening CNS lupus only (including seizures, stroke, major cognitive disorder, chorea, psychosis, major depression, and acute confusional state) Sibbit and colleagues found that 76 % of the patients in their series were affected during the 6-year study period [18]. A similar case series from Spinosa and colleagues reports nearly 62 % of patients with SLE diagnosed before age 16 years had NPS syndromes as defined by the American College of Rheumatology during their 14 year study period [19]. CNS disease has been reported as the initial presentation of SLE in 16–28 % of pediatric patients [15, 20, 21]. However, before CNS symptoms are attributed to the SLE, other entities such as infection, mass, or hemorrhage must be evaluated thoroughly.

Seizures

Seizure has been reported as the most common serious CNS complication of pediatric SLE, occurring in up to 51–61 % of patients [15, 18, 20, 22]. Seizures may be the initial presentation of disease [15, 18, 20, 22] and may portend a more severe disease course when present at diagnosis of SLE [23]. Seizures associated with SLE are usually easily controlled with standard antiepileptic therapy and remit with control of SLE, although status epilepticus has been reported [24]. Mecarelli and colleagues reported a case of SLE induced status epilepticus requiring barbiturate coma [25].

Cerebral Vein Thrombosis

Cerebral vein thrombosis (CVT), usually seen in association with antiphospholipid antibodies, has been associated with pediatric SLE more commonly than in adults [8]. The presence of a CVT in pediatric patients should be considered when there is a severe unremitting headache, especially when the patient has known antiphospholipid antibodies [26]. Head CT images are often normal in the presence of a CVT, but abnormalities are sometimes identified. The most common CT finding is the *delta sign* which appears as a central dark area in the torcula, corresponding to thrombus, surrounded by enhancing contrast representing flowing blood [27]. With early consideration of the diagnosis, imaging, and treatment, reported outcomes have been favorable [26]. Delays in diagnosis and/or therapy have been associated with progressive neurological deficits, and death [26].

Supportive medical and neurologic care, including hydration and seizure control, are the cornerstones of therapy for CVT in children [27]. Anticoagulation is considered by some to be appropriate therapy, but remains controversial, and the most appropriate agent remains unclear. Many studies have shown the safe use of anticoagulation in adult and pediatric patients with sinovenous thrombosis, but none has clearly shown significant benefit [28, 29]. In the acute phase, intravenous infusions of heparin have been most widely used [28, 30], but safe and effective use of low-molecular weight heparin has also been reported in pediatric patients without evidence of preceding intracranial hemorrhage [31–33]. Continued or intensified therapy for the underlying vasculitis is also appropriate [14]. Data regarding the use of thrombolytics in children with CVT are sparse. Studies regarding the use of thrombolytics for other forms of thromboses in children have shown effectiveness but with a low therapeutic index [34].

Stroke

Stroke has been reported in 3.4–12 % of pediatric patients with SLE [15, 20, 22] and in 20–40 % of patients with neuropsychiatric lupus [20, 22]. Strokes seen in pediatric SLE may be arterial ischemic strokes or sequelae of cerebral vein thrombosis. Most reports of stroke with pediatric SLE identify the concurrent presence of antiphospholipid antibodies (anti-cardiolipin antibody or lupus anticoagulant) [30]. Treatment of stroke in SLE patients is largely supportive, aiming at maintaining normothermia, hydration, and normal hemodynamics [30]. Anticoagulation is becoming accepted practice although the ideal agent remains controversial, but should be considered in these patients. Patients with antiphospholipid antibodies, particularly lupus anticoagulant, have a high risk of recurrent cerebrovascular disease [30, 35, 36] and therefore may be more likely to benefit from anticoagulation. Therapy should also include ongoing or intensified immunosuppressive therapy provided the absence of a contraindication [14].

Psychosis, Delirium, and Depression

Although children who present with depression, psychosis, delirium, or movement disorders secondary to SLE often have normal CSF findings and non-focal CT and MRI

studies, discrete lesions can sometimes be seen on CT and MRI [37]. If abnormalities are seen on MRI, they are usually diffuse gray and white matter lesions that dramatically improve or resolve with aggressive SLE treatment [38]. There are also reports of single photon emission computed tomography (SPECT) scan abnormalities in the parietal and frontal lobes [39], as well as diffuse small areas of decreased uptake [40]. Other than possibly supporting the diagnosis of neuropsychiatric lupus, the clinical utility of SPECT scan abnormalities remains unclear as they usually persist despite clinical improvement [8, 39–41] and may be present in pediatric SLE patients without clinical CNS disease [40]. Favorable outcome of neuropsychiatric SLE in both pediatric and adult patients has been reported after treatment with intravenous methylprednisolone and cyclophosphamide [16, 38, 42, 43].

Pulmonary Complications of SLE

Pulmonary involvement in adults with SLE is common, with infection being the most frequent complication [44]. The incidence of pulmonary involvement in children with SLE is difficult to estimate as the literature is limited primarily to case reports and small series; however published figures place the incidence anywhere between 5 and 67 % during the course of the disease, and acute lupus pneumonitis may be the first manifestation of disease [45]. Pulmonary hypertension, diffuse interstitial disease, pulmonary hemorrhage, pneumothorax, acute lupus pneumonitis, and *shrinking lungs* have all complicated SLE in pediatric patients [45].

SLE Pneumonitis

Acute lupus pneumonitis is difficult to clinically differentiate from an infectious process, and must be a diagnosis of exclusion [44, 45]. Mortality in adult patients with acute lupus pneumonitis is approximately 50 % [44]. Presenting symptoms include fever, dyspnea, tachypnea, hypoxia, cough, and occasionally hemoptysis [45]. On blood gas analysis, hypoxemia and a respiratory alkalosis are often seen [44]. Initial therapy should consist of corticosteroids; cyclophosphamide, plasmapheresis, or intravenous immunoglobulin may be added if there is no clinical response [44, 46]. One must be cognizant of the fact that treatment with cyclophosphamide has been linked with an increased risk for opportunistic infections and mortality [11, 47].

Pulmonary Hemorrhage

Pulmonary hemorrhage in SLE is an uncommon, but often deadly occurrence, with mortality approaching 80 % [45]. Symptoms associated with pulmonary hemorrhage are similar to those seen in pneumonitis, with cough, dyspnea, tachypnea, and hypoxia seen most commonly, in association with a sudden drop in hematocrit. Hemoptysis is an unreliable indicator of the presence or absence of pulmonary hemorrhage [44, 45]. Chest radiography will usually reveal patchy alveolar infiltrates, particularly in the lower lobes; however, infiltrates are not universally present [44]. Reported therapies consist of pulse methylprednisolone with or without cytotoxic agents [45, 48]. Respiratory failure associated with SLE and pulmonary hemorrhage requires aggressive ventilatory and hemodynamic support, and extracorporeal life support has been used successfully in conjunction with ongoing immunosuppressive therapy [49].

Cardiac Complications of SLE

SLE Pericarditis

Pericarditis is the most common cardiac complication of pediatric SLE; throughout the disease process, pericarditis is seen in up to 25 % of SLE patients, and can rarely be the first manifestation of disease [50, 51]. In adult patients, pericarditis is present in 6–45 % of SLE patients, and in autopsy series, as many as 60–80 % of patients have pericardial lesions [52]. Pericardial tamponade is a rare, life-threatening, but usually early complication of SLE [52], occurring in less than 4 % of pediatric patients [50, 53].

Pericardial fluid in SLE serositis is an inflammatory exudate consisting of fibrinous debris and inflammatory cells, which can mimic bacterial pericarditis [54]. An ANA titer of >1:160 in the pericardial fluid has been shown to be a sensitive, but not specific, indicator of underlying SLE [55]. While the presence of lupus erythematosus cells (phagocytic cells which have ingested the nucleus of another cell) in a pericardial aspirate has been shown to have high sensitivity and specificity [54, 55].

Therapy for SLE pericarditis is guided by severity. In pediatric SLE, pericarditis is usually mild, and effusions small [50]. In this setting, treatment is aimed at the underlying disease and consists of monitoring, steroids, antimalarials, and other immune modulators [50, 56]. The presence of a large pericardial effusion is an indication for ICU monitoring, and may warrant aspiration, particularly when present with diminished cardiac function or cardiovascular instability.

SLE Endocarditis

Verrucous endocarditis (Libman-Sacks endocarditis) describes the valvar vegetations seen in association with SLE. Most commonly these involve the mitral valve, but also involve the aortic, pulmonic, and tricuspid valves in order of decreasing incidence [50]. The lesions consist of deposits of immune complexes, cellular debris, and fibrin [57, 58]. In autopsy series, these nodular lesions have been found uniformly in SLE patients [59]. However, lesions detectable by echocardiography occur

generally in older adolescents and adults [50]. Rarely, heart failure from mitral insufficiency can be the clinical presentation in SLE, and require mitral valve replacement in childhood [60].

SLE Myocarditis and Cardiomyopathy

Although cardiac processes in association with SLE are widely recognized, clinically apparent acute myocarditis is a rare complication of SLE, particularly in infants and children [61, 62]. Even so, acute myocarditis has been reported as the initial presentation of SLE [63]. The literature regarding lupus-associated myocarditis is limited owing to the rarity of this clinical entity. Therefore, there is no consensus on the best management of SLE myocarditis [62]. The literature contains reports of poor responses of SLE myocarditis to steroid therapy [62, 64]; however, James et al. [62] state that further immunosuppression seems a reasonable approach in light of the underlying autoimmune process. In the adult literature, high dose intravenous corticosteroids are the norm, with anecdotal reports of other immunosuppressive agents (azathioprine and cyclophosphamide) and intravenous immune globulin providing some benefit [13, 65]. Data from Johns Hopkins suggest that the mortality of myocarditis associated with SLE is greater than that of primary myocarditis [66].

Infectious Complications of SLE

The most frequent complication, reason for admission to the ICU, and cause of death among SLE patients is infection [11, 67–72]. The rate of infectious complications in these patients is increased by therapy for the underlying disease [71, 73, 74], although SLE intrinsically increases the risk of serious infection [70, 73]. Localized infections are usually related to the underlying disease, while systemic infections are generally caused by immunosuppression from therapy, in particular corticosteroids [70].

Glucocorticoid therapy has multiple effects on immunity, including suppressing phagocytic function, cell-mediated immunity, and humoral immunity [70, 74]. As a result, the offending agents in infections related to glucocorticoid therapy are diverse. Defective phagocytic function places the patient at risk for gram-positive, gram-negative, and fungal infections [71, 74]. Ineffective cell-mediated immunity places the patient at risk for organisms such as Mycobacterium, Listeria monocytogenes, Salmonella, and Nocardia, as well as Histoplasma, Coccidiodes, and Cryptococcus [74]. Protozoal (Pneumocystis, Toxoplasma, and Strongyloides) and viral (cytomegalovirus, Epstein-Barr virus, and Varicella-zoster virus) infections are also related to defective cell-mediated immunity [74]. Multiple studies have reported that patients maintained on high dose corticosteroids, particularly more than 20 mg per day, are at increased risk for serious infections [75, 76]. In fact, one series reported that 90 % of infected patients on more than 40 mg per day of prednisone were bacteremic [76]. Although even lower doses have been shown to increase the risk [75].

Bacterial pathogens account for more than 90 % of infections in SLE patients [70], and the most frequently isolated organisms are S. aureus and enteric gram-negative bacteria [70, 71, 74]. Gram-negative sepsis or bacteremia was the cause of death in 32 % of SLE-related deaths in one series of 544 patients [71]. Patients with SLE have been found to be at increased risk for pneumococcal infections secondary to functional hyposplenism, hypocomplementemia, impaired chemotaxis, and defects in opsonization, all secondary to SLE itself [75].

Renal Complications of SLE

Two-thirds of children and adolescents with SLE will develop nephritis during the course of their illness, and in 90 % of these, the renal disease is present within 1 year of diagnosis [8], with diffuse proliferative glomerulonephritis being the most common form. Unfortunately this form of nephritis is the form most likely to progress to end-stage renal disease and/or death [8]. In patients with SLE admitted to the intensive care unit, renal failure has been associated with increased mortality [67].

Juvenile Idiopathic Arthritis (JIA)

Juvenile idiopathic arthritis (JIA) (Table 35.2), formerly known as juvenile rheumatoid arthritis (JRA), is a common rheumatic disease of childhood, responsible for significant morbidity. The underlying cause of JIA remains unclear, but an underlying immunogenetic susceptibility is likely required to react to an external stimulus thereby inducing disease [77]. Approximately 113/100,000 children currently carry the diagnosis of JIA, with an annual incidence of approximately 13.9/100,000 children 15 years old or younger [77].

Three types, or onset forms of JIA are currently described:, oligoarthritis (pauciarticular), polyarthritis, and systemic onset disease [77]. While oligoarthritis generally affects the large joints of the lower extremities, polyarthritis affects both large and small joints, often with 20–40 individual joints involved [77]. Systemic onset disease is characterized by a cyclical fever which may exceed 39 °C, in conjunction with a faint *salmon-colored* evanescent macular rash [77]. Hepatomegaly, splenomegaly, and lymphadenopathy are present with arthritis. Serositis in the form of pericardial effusion may be present as well [77].

Table 35.2 Juvenile idiopathic arthritis

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	Unknown etiology, but likely represents an exaggerated immune response to an infectious trigger in predisposed children [77]	Leukocytosis (WBC 30,000–50,000/mm^3)
Cerebral vasculitis		Thrombocytosis
Uveitis		Elevated ESR
Cardiac		Elevated CRP
Pericarditis		Elevated complement components
Endocarditis		Occasionally RF positive
Myocarditis/ cardiomyopathy		ANA sometimes positive (usually homogenous or speckled pattern) [78]
Pulmonary		
Diffuse interstitial fibrosis		
Gastrointestinal		
Hemorrhage		
Hepatomegaly		
Hepatitis		
Hematological		
Hemolytic anemia		
Anemia of chronic disease		
Macrophage activation syndrome		
Splenomegaly		

Although the overall mortality of JIA is low, when comparing affected individuals to non-affected individuals, the diagnosis of JIA does impart an increase in age-adjusted mortality [2]. Approximately two-thirds of deaths attributable to JIA are in patients with systemic onset JIA, which compromises only 10–20 % of all patients with JIA [2]. Deaths due to JIA are most likely secondary to infections, cardiac complications, and macrophage activation syndrome [2].

Infectious Complications of JIA

Similar to SLE, infections in patients with JIA are usually a complication of therapy for the underlying disease. The disease modifying drugs used most commonly in JRA include steroids and methotrexate. Other medications, including azathioprine, cyclosporine, and etanercept, have also been used. Although these medications have the potential for significant improvement in the daily function of patients with JIA, several of these medications carry risks of serious infectious complications. As discussed previously, steroid therapy has multiple effects on immunity, and sustained therapy, particularly at high doses, is associated with increased infection rates. With other disease modifying drugs available, steroids are generally reserved for severe systemic onset disease or life threatening complications of JIA [2].

Anti-TNF therapy is the newest class of medications currently being used for the treatment of JIA. Etanercept (Enbrel; Amgen Inc.) and infliximab (Remicade; Centocor Inc.) are two such medications. Etanercept is a human fusion protein of Fc IgG_1 and the p75 TNF receptor which has been FDA approved for use in rheumatoid arthritis and psoriatic arthritis. Its use has proven to provide improvement in patient functionality and pain, as well as slowed disease progression [79]. In children, etanercept has been shown to be well tolerated and effective in the treatment of JIA, particularly those with pauciarticular or polyarticular JIA [80]. Placebo controlled trials found no increase in the rate of serious infections between treatment and control groups [81, 82]. However, post-marketing reports of serious bacterial infections have been published. Patients who are prescribed etanercept with concurrent steroid therapy are at particular risk [83] and in patients with active sepsis etanercept has been shown to increase mortality [84].

Infliximab (Remicade; Centocor Inc.) is a monoclonal anti-TNF-α antibody which has also shown beneficial in the management of inflammatory arthritis [79], but is not currently labeled for use in JIA. In placebo controlled studies evaluating anti-TNF therapy, several studies have shown a similar incidence of serious bacterial infections (life-threatening or requiring hospitalization) to that of placebo [81, 82]. In post-marketing reports, anti-TNF therapy, infliximab in particular, has been associated with development of active tuberculosis. This most likely represents activation of a latent infection and patients should be screened prior to initiation of infliximab therapy [85].

Cardiac Complications of JIA

Pericarditis is a common complication of JIA, and may be present at diagnosis, or precede the development of arthritis [86], although usually not clinically significant [78]. Pericarditis occurs in as many as 30 % of patients, and in autopsy series, as many as 45 % [87]. Pericardial effusions seen with JIA are usually small and clinically insignificant, but cardiac tamponade requiring pericardiocentesis or pericadiectomy has been reported [88, 89]. Non-steroidal anti-inflammatory medications and intensification of anti-inflammatory therapy are usually effective [88, 90].

Valvar disease is a well known, but uncommon complication of JRA [91, 92]. The aortic valve is the most commonly involved; however, the mitral valve may also be diseased [93]. In a recent study of patients with HLA-B27-associated juvenile arthritis, 10 % were found to have aortic regurgitation of varying degrees after a mean of 3 years of illness, compared with none of the healthy control patients [93].

Table 35.3 Common features of macrophage activation syndrome

Clinical
Hepatomegaly
Lymphadenopathy
Splenomegaly
Hemorrhage
Persistent continuous fever[a]
Central nervous system dysfunction
Laboratory
Falling platelet count[a]
Hyperferritinemia[a]
Hemophagocytosis on bone marrow examination[a]
Elevated liver enzymes[a]
Falling leukocyte count[a]
Falling ESR[a]
Hypofibrinogenemia[a]
Hypertrigyceridemia[a]
Prolonged clotting times
Increased D-dimer

Based on data from Davi et al. [97]
[a]Denotes proposed diagnostic criteria

Generally, the severity of valvar disease correlates with articular disease and the degree of aortic regurgitation may be such that valve replacement is warranted [92]. Recently, the presence of rheumatoid nodules in the diseased valve has been described in a patient without other rheumatoid nodules [92]. Myocarditis is a commonly cited but rarely seen complication of JIA. It occurs with much less frequency than pericarditis, but carries higher mortality and severe sequelae. Patients who recover may be left with residual dilated cardiomyopathy [94].

Macrophage Activation Syndrome

Macrophage activation syndrome (MAS), also known as hemophagocytic syndrome, is an uncommon life-threatening complication of JIA (usually systemic JIA), brought about by an infection, medications (gold salts, NSAID's, or methotrexate), or autologous stem cell transplant [2, 95, 96]. MAS is a form of hemophagocytic lymphohistiocytosis (HLH) characterized by sudden onset of sustained fever, generalized lymphadenopathy, hepatosplenomegaly, and coagulopathy [2] (Table 35.3). Encephalopathy, respiratory distress or failure, and/or renal failure may develop [95, 98] with a mortality rate between 11 and 60 % [99, 100].

Laboratory studies which may suggest or support the diagnosis of MAS are a falling ESR, pancytopenia, elevated transaminases, increased triglyceride levels, elevated serum ferritin, and studies suggestive of a consumptive coagulopathy (elevated D-Dimers, PT, and PTT, decreased fibrinogen, and fibrin split products) [2, 98]. Bone marrow aspirates in MAS provide pathognomonic findings consisting of well differentiated macrophage proliferation with active phagocytosis of hematopoetic elements of the marrow [98]. Similar infiltration may also be seen in organs such as the liver and spleen [98, 100].

Differentiation of MAS from systemic JIA is important as therapy should be initiated early to prevent sequelae and death. The fever pattern seen with systemic JIA is usually cyclical with daily or twice daily spikes, whereas with MAS, the fever is high and unremitting [95, 98]. In MAS, the ESR falls precipitously, as opposed to systemic JIA, where it will be elevated. Also with MAS, there is a sudden drop in all hematologic cell lines, in contrast to systemic JIA, which is commonly accompanied by leukocytosis and thrombocytosis [95, 98]. Hypertriglyceridemia is another feature present in MAS which is not generally associated with systemic JIA [95].

First line therapy of MAS includes withdrawal of NSAID's, disease-modifying antirheumatic drugs and/or immunosuppressives, and early initiation of high dose steroid therapy (methylprednisolone). Despite initiating therapy, the disease may still progress [99]. Because cyclosporine has been useful in a familial form of HLH, it has been investigated in MAS as well. Mouy and colleagues [95] reported the use of cyclosporine in five children with systemic JIA and MAS with good outcome, and recommended its use with high dose parenteral steroids. Other authors recommend cyclosporine for MAS as well, particularly in patients unresponsive to steroids alone [99].

The prevailing current treatment protocols contain steroids and cyclosporine, but other disease modifying agents are gaining evidence for effective use in JIA and MAS. Etanercept (Enbrel; Immunex), a TNF-α blocker, has been used in JIA with good disease control, and its use for MAS has been reported with good outcome [101]. Others, however, have reported a possible link between etanercept therapy and the development of MAS [102]. Anakinra (Kineret; Amgen), an IL-1 receptor antagonist, is becoming widely used for maintenance therapy and has been reported as a treatment of MAS, capable of inducing rapid disease [103, 104]. Tocilizumab (Actemra; Roche), and IL-6 receptor antibody has been shown safe, effective, and well-tolerated in a phase III randomized, placebo-controlled trial in children with JIA and may prove to be an effective therapy in MAS complicating JIA [105, 106]. Tocilizumab is currently pending FDA approval is only available for compassionate use in the United States.

Henoch-Schoenlein Purpura (HSP)

Henoch-Schoenlein Purpura (HSP) (Table 35.4), the most common cause of purpura in children with normal platelet counts, is an idiopathic vasculitis syndrome involving the small vessels of the skin, gut, and glomeruli most commonly

Table 35.4 Henoch-Schoenlein purpura

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	Unknown etiology, IgA complex mediated small vessel vasculitis usually seen following a viral infection [3]	Thrombocytosis
Cerebral vasculitis		Leukocytosis
Seizure		Elevated ESR
Coma		Elevated CRP
Intracerebral hemorrhage		Antiphospholipid antibodies occasionally
Subarachnoid hemorrhage		Cryoglobulins occasionally
Chorea		Microscopic hematuria
Cardiac		Urinary casts
Myocarditis		Albuminuria
Myocardial necrosis		Sterile pyuria [3, 12]
Pericarditis		
Pulmonary		
Pulmonary hemorrhage		
Interstitial pneumonia		
Gastrointestinal		
Hemorrhage		
Intussusception		
Bowel perforation		
Esophagitis		
Obstruction		
Pancreatitis		
Renal		
Glomerulonephritis		
Nephrotic syndrome		

seen following a viral or streptococcal infection [3, 107, 108]. One study has shown a stronger correlation between an elevated serum Bartonella henselae antibody titer and HSP than with elevated ASO or anti-DNase B [109] titers, but this correlation is as yet unsubstantiated. HSP nephritis may represent a variant of IgA nephropathy [108].

Serious complications of HSP are uncommon, but include neurologic (seizure, intracranial hemorrhage, coma) [110–113], gastrointestinal (intussusception, obstruction, perforation, hemorrhage) [114], and renal (nephritis) [108]. There are two reported cases of myocardial necrosis associated with HSP, although there is some question as to whether another underlying diagnosis may have been present in at least one of the two cases [115, 116].

CNS Complications of HSP

Most believe that the incidence of neurologic involvement, from headaches to intracranial hemorrhages, with HSP lies somewhere between 2 and 10 %, but estimates have been as high as 20 % [110, 117]. More than 50 % of patients reported to have had neurologic complications had seizures, and most of these were generalized [110]. The etiology of the neurologic complications is unclear. Multiple possible causes, such as hypertensive encephalopathy, uremic encephalopathy, steroids, cytotoxic drugs, cerebral vasculitis and electrolyte imbalances are often simultaneously present in HSP [110]. Magnetic resonance imaging of patients with HSP who manifest seizures and/or encephalopathy has shown lesions consistent with demyelination in the posterior parieto-temporal region that resolve with clinical improvement [118–120].

Intracranial hemorrhage has been reported in less than ten patients [121, 122]. Most of the reported cases are intraparenchymal and parieto-temporal in location [121]. It is thought that in most cases, the vasculitis itself leads to a friability of vessels, allowing the hemorrhage. However, studies have linked HSP to a decrease of factor XIII, possibly contributing to hemorrhage. One recent report documented a low factor XIII level in a patient with HSP complicated by intracerebral hemorrhage [123].

Pulmonary Complications of HSP

A rare, but striking and potentially fatal complication of HSP is pulmonary hemorrhage. A recent retrospective analysis reported two of 136 patients with HSP experienced pulmonary hemorrhage [124]. Without rapid diagnosis and institution of treatment, pulmonary hemorrhage can progress to death [113, 125]. A review of the literature demonstrates that mortality in patients with HSP complicated by pulmonary hemorrhage approaches 50 % [113], but other authors suggest that mortality may depend on age, with lower mortality seen in younger children [126]. The treatment regimen reported by many authors for pulmonary hemorrhage in HSP includes aggressive ventilatory support, glucocorticoids, and occasionally cyclophosphamide, although no controlled trial has shown clear benefit of immunosuppressives [113, 127].

Gastrointestinal Complications of HSP

Intussusception is the most common, and best described, abdominal complication of HSP. The lead point is edematous bowel wall secondary to intramural vasculitis and hemorrhage [128]. Unlike spontaneous intussusception, which is usually ileocolic, intussusception in HSP usually involves entirely small bowel. This distinction is important as contrast enema is not useful when the pathology is proximal to the ileocecal valve. Bowel perforation is rare, and has decreased dramatically with earlier diagnosis [128]. Gastrointestinal

hemorrhage has been reported as a common abdominal complication of HSP, occurring in approximately 50 % of patients. The bleeding is usually minimal and self-limited, but may occasionally be massive and lead to hypovolemic shock [128–131].

Nephritis in HSP

Nepritis is the most common serious, long-term complication of HSP, affecting 85–90 % of children within 1 month of diagnosis and nearly all children within 6 months to varying degrees [132]. Rarely does nephritis warrant PICU admission, however patients with nephrotic range proteinuria may require admission for correction of fluid and electrolyte abnormalities. Standard therapy consists of glucocorticoids, but those resistant to steroids and more severely ill have been treated with ACE inhibitors, urokinase, plasmapheresis, cyclosporine A, cyclophosphamide, azathioprine, and mycophenolate in various regimens [133, 134]. The outcome of HSP nephritis is generally good with 1–2 % of all patients with HSP nephritis developing chronic renal disease [132] however, those with more severe disease may be at increased risk for the development of chronic renal disease and even end stage renal disease.

Kawasaki Disease

First described in Japan in 1967, Kawasaki disease (Table 35.5) is an acute, self-limited vasculitis affecting infants and children of all races. It is characterized by high fever, conjunctival injection, erythema of the oral mucosal, *strawberry* tongue, peripheral edema, cervical lymphadenopathy, and variable rash [135, 136]. Kawasaki disease (KD) affects approximately 3,000–4,000 children annually in the United States [135, 136]. The incidence of KD is approximately 112/100,000 in Japanese children <5 years old. In contrast, children <5 years old of Asian or Pacific island descent have the highest annual incidence in the United States at approximately 32.5/100,000 children [135]. Many features of KD (such as the presence of epidemics and seasonality, the age group affected, fever, self-limited course, and rash) suggest an infectious etiology, although none has been proven [135, 136].

The vascular inflammation seen with KD affects all vessels, but is more pronounced in the medium arteries, particularly the coronary arteries [136]. Inflammation and infiltration affects all layers of the arterial wall and results in destruction of the elastic lamina. Aneurysmal dilatation is a result of this destruction, and is not limited to the coronary arteries, having been reported in many muscular arteries throughout the body, including the axillary, celiac, femoral, iliac, mesenteric, and renal arteries [135]. Ultimately local scarring leads to stenosis of the affected vessel [136]. KD will lead to coronary abnormalities in 15–25 % of children if left untreated [135]. Nearly all deaths attributable to KD are a direct result of cardiac involvement [135].

Myocarditis, pericardial effusions, coronary rupture, cardiac tamponade, and myocardial infarction secondary to coronary thrombosis or stenosis may complicate KD [58, 135–138]. Myocarditis is common and likely universal. Diminished ventricular contractility is often seen on the initial echocardiogram [135]. The dysfunction is usually mild and improves after intravenous immune globulin, but may be severe [58, 135]. Pericardial effusions are common, seen on the initial echocardiogram in up to 30 % of patients with KD, but are generally small and clinically insignificant [58].

Giant coronary artery aneurysms (greater than 8 mm), seen in only 1 % of appropriately treated children, carry a mortality rate of approximately 4 % usually secondary to obstructive disease [58, 139]. Rupture of an aneurysm can occur and is rapidly fatal secondary to cardiac tamponade. There are reports of three children who have survived cardiac arrest after coronary rupture. All three had surgical intervention at the bedside and were taken to the operating

Table 35.5 Kawasaki disease

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	Unknown etiology, but may represent an exaggerated immune response to an infectious trigger in predisposed children [135]	Anemia
Irritability/mental status changes	Subendothelial and medial edema in affected vessels precedes neutrophil and then mononuclear, plasma cell, and lymphocytic infiltration. Cellular infiltration results in the destruction of the internal elastic lamina which causes fibroblast proliferation and eventual fibrosis [135]	Leukocytosis
Sensorineural hearing loss		Elevated ESR
Uveitis		Elevated CRP
Cardiac		Abnormal plasma lipids
Myocarditis		Hypoalbuminemia
Pericarditis		Hyponatremia
Mitral insufficiency		Thrombocytosis
Coronary aneurysms		Sterile pyuria
Coronary rupture		Elevated serum transaminases
Myocardial infarction		Elevated serum gamma glutamyl transpeptidase
Hematologic		CSF pleocytosis, [135]
Macrophage activation syndrome		
Gastrointestinal		
Hydrops of gall bladder		

room emergently for definitive coronary bypass grafting. One patient subsequently required heart transplantation [139, 140]. Macrophage activation syndrome (discussed previously) has also been reported in the context of Kawasaki disease [141].

Kawasaki Disease Shock Syndrome

Shock as a presentation of KD has become more widely recognized in recent years and has been described as Kawasaki Disease Shock Syndrome [142]. Clinically KDSS may be difficult to distinguish from toxic shock syndrome (TSS). Both are characterized by fever, desquamating rash, and mucous membrane erythema. In contrast, shock is a hallmark of TSS, but historically not considered a feature of KD, and coronary artery abnormalities often associated with KD are not seen in TSS. Several recent case reports and series have described KDSS and report that KDSS is more resistant to IVIG, more likely to require steroid or infliximab therapy, more likely to have a delayed diagnosis, and more likely to have coronary artery dilatation than KD without shock. KDSS has also been more commonly seen with female gender, lower platelet counts, higher band counts, and higher C-reactive protein measurements than KD without shock [142–144]. KDSS requires a vigilance to the diagnosis, particularly in the absence of early coronary artery abnormalities. IVIG should be considered early even if the diagnosis of TSS remains a question, as delay in treatment is associated with increased risk of coronary artery aneurysms.

Kawasaki Disease Management

Management of Kawasaki disease consists initially of supportive care, IVIG (2 g/kg), and high dose aspirin (80–100 mg/kg/day divided q 6 h). The aspirin dose is usually decreased to 3–5 mg/kg/day after the 14th day of illness [136]. Most experts agree that patients who fail to respond to the initial dose of IVIG should receive a second infusion of 2 g/kg, and steroid therapy should be reserved for failures after two doses of IVIG [135]. Although the exact mechanism of action is unknown, IVIG has consistently shown benefit if given within the first 10 days of illness [135]. With IVIG and aspirin, approximately 5 % of children with Kawasaki disease will develop transient coronary dilatation and only 1 % develop giant aneurysms [135]. A trial of dexamethasone with IVIG found no difference in the number of patients who developed aneurysms of the coronary arteries, but reported more rapid clinical improvement (defervescence) and decrease in C-reactive protein (CRP) [145].

Monoclonal antibodies have recently been used as a part of the therapy for Kawasaki disease. Abciximab (Reopro®, Eli Lilly and Company), a chimeric human/mouse monoclonal antibody directed against the platelet glycoprotein IIa/IIIb receptor, has been used to inhibit platelet aggregation in patients with giant aneurysms secondary to Kawasaki disease. Short-term outcome was reported as favorable in a case report with coronary thrombi [146]. In 15 patients with 50 coronary aneurysms, a trial of standard therapy (IVIG 2 g/kg once with aspirin 80–100 mg/kg/day) versus standard therapy with abciximab administered 24–48 h after IVIG found greater aneurysmal regression in the abciximab group [147]. However, current evidence lacks sufficient strength to recommend the addition of abciximab to first-line therapy.

Infliximab (Remicade®, Centocor) has been used in children at various centers for refractory Kawasaki disease. Reports of infliximab's efficacy are mixed, with some centers reporting benefit while others reporting no effect [148]. A recent retrospective analysis of 17 patients with refractory Kawasaki disease treated with infliximab reported rapid defervescence, often after a single dose [149]. A recent randomized prospective trial of infliximab therapy (5 mg/kg) versus a second infusion of IVIG in refractory KD found similar efficacy and safety between the two groups [150], but as the authors identified, several patients in the second dose IVIG group also received infliximab which may reduce any differences between treatment groups. With the growing body of supporting evidence infliximab is being used more commonly as a second teir therapy for KD [151]. As with abciximab, current evidence lacks the strength to recommend infliximab as initial therapy over IVIG.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (Table 35.6) or antiphospholipid syndrome (APS) is characterized by thromboembolic disease or immune thrombocytopenia caused by antibody-mediated platelet activation in the presence of antiphospholipid antibodies (aPL) [153]. Several aPL have been identified to date [154], with lupus anticoagulant (LA) and anticardiolipin (aCL) antibodies felt to be the most clinically relevant [153, 154]. In adults, the thromboembolic disease may be worsened by atherosclerotic disease and is accompanied by recurrent abortions [155]. APS remains a rare entity in pediatric patients that is often diagnosed after a clinical event prompts further investigation [153].

Primary APS refers to the above clinical situation with the presence of aPL antibodies on two occasions at least 6 weeks apart and the absence of a comorbid condition associated with aPL antibodies (such as SLE). Secondary APS describes a scenario with the presence of aPL antibodies, in the setting of vasculitis (SLE, JRA, HSP, among others), certain chronic infections (Lyme disease), or certain drug exposures (quinide, penicillin) [153].

Table 35.6 Antiphospholipid syndrome

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	Not completely understood;	Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, or anti-β2- glycoprotein I)
Stroke	(1) Antiphospholipid antibodies may interfere with function of proteins involved in coagulation regulation [152]	Prolonged activated partial thromboplastin time
Transient ischemic attack Amaurosis fugax	(2) Antiphospholipid antibodies may activate endothelial cells in turn promoting coagulation [152]	Prolonged kaolin clotting time Prolonged dilute Russell's viper venom time
Seizure	(3) Antiphospholipid antibodies may oxidize low-density lipoproteins which activates macrophages, ultimately causing endothelial damage [152]	Prolonged Texarin time
Chorea Transverse myelopathy Guillain-Barre syndrome Psychosis	(4) Antiphospholipid antibodies may directly activate platelets [152]	Thrombocytopenia Coombs' test positive [152]
Cardiovascular		
Myocardial infarction		
Libman-Sacks endocarditis		
Valvar regurgitation		
Valvar stenosis		
Pulmonary		
Pulmonary embolism		
Gastrointestinal		
Mesenteric artery thrombosis		
Renal		
Renal artery thrombosis		
Thrombotic microangiopathy		
Hematologic		
Widespread thrombosis		
Hemolytic anemia		
Evans' syndrome		
Disseminated intravascular coagulation		
Endocrine		
Addison's disease		
Obstetric		
Recurrent fetal loss		
Preterm delivery		
Preeclampsia		
Eclampsia		
Placental insufficiency		

Several authors have reported the presence of aPL antibodies in asymptomatic individuals. A study of over 700 presumably healthy adult volunteer blood donors in Indiana found that 8.1 % were positive for aPL antibodies [154]. In healthy children, less data is available, and reported frequencies range from 2 to 82 %, depending on testing methods, cutoff values used, and populations studied [156]. Experts estimate that the actual frequency most likely lies in the 5–10 % range [156].

In pediatric patients, a strong association between antiphospholipid antibodies and SLE has been found, and APS occurs most frequently as secondary APS with SLE in children [156]. Also of note is that children who present with what appears initially to be primary APS, may later develop SLE [156]. Similarly, some authors have reported a high prevalence of aCL antibodies in patients with JRA, unlike with adult rheumatoid arthritis [157]. Interestingly, aCL antibodies have been found to be the cause of false positive VDRL tests in some patients with SLE [158]. In a study of 57 Brazilian children and adolescents with SLE, investigators found that 63 % of the patients tested positive for aPL antibodies on at least one occasion during the 22 month

study period [155]. The investigators found that SLE remission was achieved less often in patients testing positive for aPL antibodies as well [155]. Other investigators have found a correlation between neuropsychiatric manifestations in pediatric SLE and positive testing for aPL antibodies [159].

Most complications of APS are thrombotic, and no major differences have been found between primary and secondary APS [154]. APS, much like heparin-induced thrombocytopenia, predisposes to both venous and arterial thromboses, but deep venous thrombosis remains the most common in both adult [154] and pediatric series [156], affecting 29–55 % of patients. Subsequent pulmonary embolus may occur in up to half of these patients [154]. Antiphospholipid antibodies have been associated with the first arterial ischemic stroke in children as well as adults [160, 161]. Whether aPL increase the risk of recurrent acute arterial stroke or TIA, however, remains unclear [162]. Sinovenous thrombosis has also been associated with aPL antibodies [32]. A recent study from the Canadian Pediatric Ischemic Stroke Registry found that the most common prothrombotic disorder identified in infants and children with sinovenous thrombosis was the presence of aCL antibodies (10 of 123 patients) [32].

Catastrophic antiphospholipid syndrome has been used to describe the minority of patients who present with acute and widespread vascular occlusions throughout the body [154]. This may be the initial presentation of APS in as many as 46 % of patients [163]. Diagnostic criteria include evidence of three or more organ system involvement, development of manifestations simultaneously or within less than 1 week, histopathologic evidence of small vessel occlusion, and laboratory confirmation of aPL antibodies [164]. The presence of all four of the above criteria indicates definite catastrophic APS, with the presence of only three or only two organ system involvement indicating "probable" catastrophic APS [164]. These patients often rapidly deteriorate and mortality has been reported to be near 50 % secondary to multiorgan failure [154, 163].

Optimal management of catastrophic APS is not known. Therapy should be aimed at supporting the involved organ systems, and suppressing progression of the microvascular disease [165]. The majority of patients receive a combination of several treatments that varies by institution [164]. A consensus statement from the Catastrophic Antiphospholipid Syndrome Registry Project Group published in 2003 states that patients with clinically suspected catastrophic APS should be managed with anticoagulation and "high doses" of steroids with plasma exchange and/or IVIG [164]. A recent report from the Catastophic Antiphospholipid Syndrome Registry found a higher recovery rate in patients treated with anticoagulants, plus steroids, plus plasma exchange, and some with IVIG [163]. Other authors have recommended reservation of plasma exchange for patients who do not respond to anticoagulation and steroids [165]. If such treatment fails, patients should be considered for cyclophosphamide, prostacyclin, and/or fibrinolytics. Defibrotide, an investigatory thrombomodulator, may prove a useful adjunct in recalcitrant catastrophic APS [164].

Table 35.7 Goodpasture disease

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	Autoantibodies against α3 chain of type VI collagen in alveolar and glomerular basement membranes lead to immune mediated destruction [166, 167]	Anemia
CNS vasculitis		Elevated blood urea nitrogen
Seizure		Elevated creatinine
Cardiac		Proteinuria
Pulmonary		Hematuria (microscopic or gross)
Alveolar hemorrhage		Red cell casts on urinalysis
Respiratory failure		Granular casts on urinalysis [166]
Gastrointestinal		Hemosiderin-laden macrophages on broncho-alveolar lavage [167]
Renal		
Glomerulonephritis		
Oliguric renal failure		
Hematological		
Iron deficiency anemia		

Goodpasture Disease

Goodpasture disease (Table 35.7) is a rare autoimmune disease characterized by the presence of autoantibodies directed against the GBM. These circulating antibodies may attach to GBM, alveolar basement membrane (ABM), or both depending on the individual. Why the GBM, ABM, or both are affected in different individuals remains unclear [168]. Approximately 10 % of patients with anti-GBM antibodies will have pulmonary disease alone, 20–40 % will have renal disease alone, and 60–80 % will have both, termed Goodpasture's disease or Goodpasture's syndrome [168]. Unlike systemic vasculitides, the ESR is seldom significantly elevated. ANA and RF are usually negative as well [168].

In patients with pulmonary disease, almost all will have hemoptysis at some point during their disease [168]. Alveolar bleeding is usually minute in volume, however massive bleeding may occur leading to respiratory failure and death. Massive pulmonary hemorrhage is the most common cause of death in patients with anti-GBM disease [168]. As discussed briefly with HSP, management of severe pulmonary hemorrhage consists of general supportive measures, aggressive ventilatory support, and immunosuppressives. Extra corporeal life support (ECLS) may be required in extreme cases.

Central nervous system involvement has been reported in two adolescents with Goodpasture's disease. The patients presented with generalized seizures and abnormalities consistent with vasculitis on MRI. Both patients improved with intensification of immunosuppressive therapy and plasmapheresis [169].

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is an antineutrophil cytoplasm antibody positive necrotizing granulomatous vasculitis affecting the lower and upper respiratory tracts, often associated with renal disease [170]. WG predominately affects adults; Hoffman and colleagues found that 15 % of WG patients seen at their referral center over a 24 year period were under age 19 [171], while other authors have reported much lower rates in children and adolescents [170, 172]. Children usually present with fever, anorexia, weight loss, cough, hemoptysis, and pain (chest pain, myalgia, arthralgia) [172]. Sinusitis, proteinuria, and hematuria are found nearly universally during initial evaluation [172].

Pulmonary disease with WG is rapidly progressive in children. Four of the ten patients in a Swedish study required admission to the PICU as a result of pulmonary dysfunction, and two required mechanical ventilation [172]. Pulmonary hemorrhage has been reported during the course of the disease, with severity enough to warrant mechanical ventilation, and the successful use of ECMO has been reported [49]. Isolated subglottic stenosis has also been associated with WG, more commonly in children than adults, which may require dilatation [173].

Therapy for WG consists of supportive medical care and immunosuppression [172]. A high dose pulse steroid (methylprednisolone) is given acutely, followed by an oral regimen. Usually cyclophosphamide is given in conjunction with steroids, and plasma exchange has been used [172]. In adults, steroids plus cyclophosphamide is considered standard of care [173]. With widespread use, steroid and cyclophosphamide therapy has changed the prognosis from universally fatal to quite good. Adult patients are able achieve disease remission in more than 90 % of cases, and relapse is declining with newer maintenance treatment protocols [174].

Churg-Strauss Syndrome

Churg Strauss Syndrome (CSS) is an antineutrophil cytoplasm antibody positive small vessel vasculitis much like Wegener's Granulomatosis, which usually presents with fever, pulmonary infiltrates, and respiratory distress in a patient with asthma [173]. Among pediatric patients, CSS is most commonly seen in adolescent patients, but remains rare. In 1984, Lanham published clinical criteria, which require only asthma, peripheral eosinophilia (>1.5 × 10^9/L), and evidence of systemic vasculitis involving two or more extrapulmonary organs to make the diagnosis of CSS [175]. However, the diagnostic criteria for CSS, according to the American College of Rheumatology, requires the presence of asthma, blood eosinophilia (>10 %), mono- or polyneuropathy, infiltrates on CXR, paranasal sinus abnormalities, and extravascular eosinophils on blood vessel biopsy [176]. Published reports have implicated a causative role for leukotriene modifiers in CSS, while others have found no such link [177]. A post-marketing analysis confirmed an association between leukotriene modifier therapy (alone or in combination with other asthma therapies) and CSS, but could not speculate on causality [178].

Cardiac Complications of CSS

Pericarditis or cardiomyopathy and congestive heart failure may also be present at diagnosis of CSS [173, 179, 180]. Cardiomyopathy secondary to coronary artery vasculitis is common in adult CSS patients, occurring in 22–26 % of patients, and corresponds to advanced disease [179].

Pulmonary Complications of CSS

The literature contains multiple reports of serious pulmonary hemorrhage in patients with CSS [181, 182]. Without treatment CSS is fatal within months, secondary to pulmonary disease. Widespread use of corticosteroids has significantly improved survival and become accepted as first-line therapy [183]. While some authors consider a combination of corticosteroids with another immuno-suppressive (cyclophosphamide) to be first-line [179], others reserve cyclophosphamide for those patients who fail corticosteroids alone or have severe disease [183].

Gastrointestinal Complications of CSS

While abdominal complaints are common, serious abdominal involvement is rare. Small bowel perforation and peritonitis in association with CSS has been reported [184].

Juvenile Dermatomyositis (JDM)

Juvenile dermatomyositis (JDM) (Table 35.8) is a rare autoimmune inflammatory muscle disease with an incidence of 1.7–3.1 per million children, affecting twice as many females

Table 35.8 Juvenile dermatomyositis

Selected manifestations	Pathophysiology	Laboratory abnormalities
Central nervous system	Endothelial activation by the class II HLA antigen DQA1*0501 and/or circulating immune complexes activates complement leading to microvascular occlusion and local ischemia [185]	Elevated creatine kinase
Seizures		Elevated aldolase
Pseudoseizures		Elevated lactate dehydrogenase
		Elevated ESR
Psychosis		Elevated CRP
Infarction		Lymphopenia [185]
Cardiac		
Myocarditis		
Pericarditis		
Congestive heart failure		
Cardiac tamponade		
Myocardial infarction		
Arrhythmia		
Pulmonary		
Restrictive lung disease		
Interstitial lung disease		
Recurrent aspiration		
Gastrointestinal		
Hemorrhage		
Esophageal dysmotility		

as males [185–188]. JDM is characterized by proximal muscle weakness, heliotrope rash, and elevated serum levels of skeletal muscle enzymes such as creatinine phosphokinase (CPK), aldolase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) [186, 189]. Muscle biopsy specimens reveal complement-mediated microvascular endothelial damage, which leads to local hypoperfusion and perifascicular atrophy [187]. Overall mortality rate among children with JDM is approximately 1.5 % [185].

CNS Complications of JDM

Although extremely rare, CNS complications of JDM are serious and life threatening. CNS involvement likely represents manifestation of severe, uncontrolled disease [188, 190]. Reported manifestations include visual disturbances, seizures, pseudoseizures, psychosis, and brainstem infarction [186, 190]. Seizures are likely the most common manifestation, but are much less common in JDM than in other vasculitides such as SLE [186]. Immunosuppressive therapy has been used with these complications, and has improved symptoms [190].

Pulmonary Complications of JDM

The most common pulmonary manifestations of JDM are those secondary to muscle weakness. Asymptomatic restrictive lung disease has been reported in up to 40 % of JDM patients at presentation [188]. Decreased ventilatory capacity may occur in up to 78 % of JDM patients throughout the course of the illness secondary to respiratory muscle weakness and decreased chest wall compliance [186]. Dysphagia secondary to esophageal dysmotility and pharyngeal weakness is a common symptom in JDM [186, 188], and may lead to pathologic aspiration severe enough to require parenteral nutrition and tracheostomy [186, 191].

Interstitial lung disease (ILD) is a well known complication of dermatomyositis, occurring in up to 65 % of adults [189, 192]. In children, interstitial lung disease has been less well described in association with JDM, however, it has been associated with anti-Jo-1 antibody positive patients [188], and may be detected early as a decrease in diffusion capacity [188]. Unfortunately, JDM-associated interstitial lung disease is often severe and rapidly progressive, with a high mortality [192]. Interstitial lung disease in children with JDM has been reported to occur early in the illness, particularly in patients whom the biochemical markers of ongoing disease (AST, ALT, aldolase, etc.) do not normalize with steroid therapy [189, 192]. Interstitial lung disease associated with DM has been treated with cyclosporine in both adults and children with promising results [192, 193]. Currently, however, the pediatric literature is limited to a few case reports and small series [192]. Cyclosporine is generally reserved for steroid resistant ILD or rapidly progressive ILD [189, 192].

Cardiac Complications of JDM

Clinically important cardiac involvement is rare; however, reports have been published of fatal cardiac vasculitis and cardiac tamponade with JDM [186]. Non-specific ECG abnormalities and pericarditis have also been reported in conjunction with JDM, although all of these are primarily associated with adult DM [188].

Systemic Sclerosis

Juvenile scleroderma is an autoimmune disease of unknown etiology characterized by hard skin with an onset before the age of 16 years. Two broad categories have been defined,

morphea (localized skin sclerosis), and systemic sclerosis (skin sclerosis with diffuse internal organ involvement) [194]. Systemic sclerosis (SSc) is rare in children, with only 10–17 % of patients with SSc patients accounted for by those less than 20 years of age [194, 195].

Mononuclear cell infiltration is a key component of the lesions of scleroderma. Cytokine liberation by these mononuclear cells leads to immune activation, increased collagen production, and endothelial damage. Ultimately fibrosis occurs and microvascular disease results in localized tissue ischemia [194].

Management of SSc has been challenging, and no therapy as yet has been shown to have significant benefit without significant risk [194, 196]. Methotrexate trials have had mixed results and steroids have generally been ineffective. Stem cell transplantation has been studied in adults, with disease improvement in 70 % of patients, but 19 % of patients had further disease progression and 17 % died from complications of the transplant itself [194]. One series describing the use of etanercept in ten adults with SSc published in abstract form showed no clinically important improvements [196].

Cardiopulmonary Complications of Systemic Sclerosis

Clinically insignificant cardiac disease is common in SSc, but severe cardiopulmonary involvement may be a major cause of morbidity and mortality among SSc patients [194, 195]. Involvement may come in the form of myocardial fibrosis leading to cardiomyopathy or arrhythmia, valvar insufficiency, or pericardial disease [194, 197]. Systolic [198] and diastolic [197, 199] dysfunction have been reported with SSc. Pulmonary hypertension with or without pulmonary fibrosis is another well-known complication of SSc [194, 200].

Autopsy series including both children and adults have shown myocardial fibrosis to be common in patients with SSc [201]. Myocardial fibrosis may lead to cardiomyopathy and arrhythmias including atrioventricular block, supraventricular tachycardia, and ventricular tachycardia [194, 197]. Frank cardiomyopathy is uncommon in pediatric systemic sclerosis, although dilated cardiomyopathy may be more common in children who have myositis in addition to systemic sclerosis [202]. Rokicki reported finding diastolic dysfunction among SSc patients without cardiac symptoms, as well as increased left ventricular mass without overt hypertrophy [197].

Steroid therapy has proven generally ineffective for the management of SSc, except in early muscle involvement or the edematous phase of cutaneous disease, and may be associated with renal crisis [194]. Nevertheless, given the autoimmune component of this disease, authors have reported the use of glucocorticoids in SSc cardiomyopathy [203]. In 32 adult patients with scleroderma and secondary myocardial dysfunction, prednisolone treatment was shown to increase LVEF, particularly in patients with the SSc form [198].

Subclinical pericardial disease has been reported as a common occurrence in autopsy series of SSc patients, found in 33–72 % of specimens [201]. Clinical pericardial involvement has been reported in 7–20 % of patients during the disease course [201]. However, Rokicki and colleagues evaluated 43 children with various forms of scleroderma and found no pericardial disease by clinical exam or echocardiography [197]. Rokiciki implied that pericardial disease may be a component of adult SSc as opposed to juvenile SSc [197].

Conduction abnormalities may occur in up to 60 % of adult patients with SSc, particularly in patients with concurrent myositis [204]. These patients are at high risk for sudden death; Follansbee and colleagues found retrospectively that 12 of 25 adult patients with SSc and myositis experienced sudden cardiac deaths [204]. Conduction system disease is often asymptomatic with the first manifestations being slight resting tachycardia and a decrease in heart rate variability attributable to dysautonomia [205].

Pulmonary fibrosis with pulmonary vascular disease has been reported as the most common cause of death among adult patients with SSc [200]. In adults, these two entities generally occur in simultaneously. While this may be the case in children, isolated pulmonary vascular disease is more common in young patients with scleroderma, in particular with SSc [194]. Unfortunately, this isolated pulmonary vascular disease has a much worse prognosis [194]; also, for reasons that remain unclear, pulmonary arterial hypertension (PAH) in scleroderma patients carries a higher risk of death than similarly affected patients with primary pulmonary hypertension [206]. In SSc patients as a whole, PAH likely has a prevalence of 12–15 %, but values as high as 50 % have been published [207–209]. The pulmonary vascular disease associated with SSc is similar in pathology and management to primary pulmonary hypertension [206, 209, 210]. Pathologic evaluation shows prominent intimal proliferation, medial hypertrophy, and adventitial fibrosis [206].

Prostacyclin analogues iloprost [Ventavis®, CoTherix] [211], epoprostenol [Flolan®, GlaxoSmithKline] [209], and treprostinil [Remodulin®, United Therapeutics] [212] have all been evaluated in adults with pulmonary hypertension secondary to the scleroderma. Improvements in exercise tolerance were seen with all; however the greatest improvement in pulmonary hemodynamics was seen with epoprostenol. Epoprostenol is currently considered the

"gold standard" for management of pulmonary hypertension unresponsive to acute vasodilators [213]. Further studies with treprostinil at optimal doses may show similar efficacy with greater ease of administration (subcutaneous infusion) and elimination of the need for indwelling venous catheters. Systemic sclerosis patients with pulmonary hypertension which does not respond to prostacyclin analogues have been treated with concurrent burst cyclophosphamide with marked improvement in hemodynamic measurements [214].

Endothelin-1 is a potent vasoactive peptide which acts through two receptors, "A" and "B", and has been implicated in various forms of pulmonary hypertension. Bosentan (Tracleer®, Actelion Pharmaceuticals) is the first orally available non-selective endothelin receptor antagonist approved for use in severe pulmonary hypertension. Channick and colleagues [215] reported significant improvements in pulmonary hemodynamics and exercise tolerance in adults with scleroderma and pulmonary arterial hypertension after 3 months of bosentan therapy. The same group reported after 1 year of treatment that these improvements had been sustained with ongoing bosentan therapy [216]. Initial monotherapy for pulmonary hypertension complicating SSc in adults is generally endothelin blockade [210] and successful use of endothelin blockade in pediatric SSc associated pulmonary hypertension has been reported [217].

In adult patients with systemic sclerosis and severe lung disease unresponsive to medical management, lung transplantation has been performed. Several case series have found that the outcomes of patients with scleroderma who undergo lung transplantation for severe pulmonary disease (both with and without pulmonary hypertension) have similar outcomes to individuals with primary lung disease in the absence of rheumatologic disease [218–220].

Scleroderma Renal Crisis

Scleroderma renal crisis is the abrupt onset of severe hypertension and rapidly worsening oliguric renal failure occurring in the setting of scleroderma [221]. It is usually accompanied by left ventricular failure and microangiopathic hemolytic anemia [221]. The pathophysiology is as yet unclear; however it likely involves vascular disease of the small arteries and arterioles of the kidney. This vascular disease causes decreased perfusion, which in turn leads to angiotensin-II mediated hypertension [221]. Some authors have implicated the recent addition of high dose steroids or non-steroidal anti-inflammatory medications in the development of scleroderma renal crisis [221].

Scleroderma renal crisis occurs in 14–18 % of adult patients with SSc during the course of their disease [221, 222]. With a mortality rate approaching 35 % despite aggressive antihypertensive management [221, 222], Scleroderma renal crisis is the most common cause of death in adult patients with SSc. Survivors usually have permanent renal damage, and may be dialysis dependent [221]. Management consists of aggressive antihypertensive therapy, and the use of ACE inhibitors (specifically captopril) has proven to improve survival in adult patients [221].

Behcet's Disease

Behcet's disease (BD) is a multisystem vasculitis of unknown etiology characterized by recurrent oral ulcers, genital ulcers, and uveitis [223, 224]. A positive pathhergy test (formation of a papule or pustule 48 h after skin pinprick or intradermal saline injection) supports the diagnosis of BD but is not required [223]. In Japanese and Middle Eastern patients, HLA-B51 has been associated with BD, although this association does not hold true for Western patients [223, 224]. Behcet's disease is uncommon in childhood, generally diagnosed in adults in the third decade of life, and is most prevalent in Japan, Turkey, Iran, and Mediterranean countries [223].

Systemic involvement with BD includes nearly all organ systems, and a wide range of severity. Central nervous involvement associated with BD includes headaches, aseptic meningitis, mild intracranial hypertension [225], organic psychiatric disturbances, seizures, hemiparesis, and sinovenous thrombosis [223]. Pulmonary involvement may include pleuritis [225], hemoptysis, parenchymal infarction, and pulmonary vasculitis with inflammatory aneurysms [223, 226]. Rupture of pulmonary artery aneurysms has resulted in hemorrhage and death [223, 226]. Cardiac involvement can include myocarditis, arrhythmia [223], myocardial fibrosis, or endocardial fibrosis [226]. Arterial and venous vascular thromboses are associated with BD, although more commonly in adult patients [225]. Multiple thromboses may be present and can lead to death [223]. Gastrointestinal manifestations of BD include colicky abdominal pain, diarrhea, bloody stools, and ulcerative colitis [223, 225]. Supportive medical care with corticosteroids is the mainstay of therapy for acute exacerbations or complications of BD [227].

Conclusion

Children with rheumatologic diseases require admission to the PICU for a multitude of diagnoses, affecting all organ systems. In addition to the broad spectrum of disease, the limited number of pediatric trials makes caring for these patients challenging. Supportive care remains the cornerstone of therapy in these patients while disease specific therapies (Table 35.9) continue to evolve. Continuing research into the pathophysiology of these diseases and new therapies will improve patient care and patient outcomes.

Table 35.9 Selected rhematologic medications

Medication	Class	Potential adverse effects	Reported use
Abciximab (Reopro®, Lilly, Eli and Company)	Platelet inhibitor	Serious bleeding Intracranial hemorrhage Alveolar hemorrhage Thrombocytopenia Hypotension [228]	Kawasaki disease Acute disease with large coronary aneurysms [147]
Azathioprine (Imuran®, Prometheus Inc.; others)	Immunosuppressive	Leukopenia Thrombocytopenia Bone marrow suppression Bacterial infections Fungal infections Viral infections Hepatotoxicity Malignancy-AML and lymphoma Interstitial pneumonitis [228]	Systemic lupus erythematosus Myocarditis [13, 44] Pericarditis [229] Peripheral neuropathy [230] Catastrophic antiphospholipid syndrome [164] Juvenile dermatomyositis Interstitial lung disease [231]
Cyclophosphamide (Cytoxan®, Bristol-Myers Squibb; others)	Alkylating agent, chemotherapeutic agent	Urinary bladder malignancy Lymphoproliferative malignancy Myeloproliferative malignancy Leukopenia Hemorrhagic cystitis Hemorrhagic myocarditis Hemorrhagic colitis Congestive heart failure Opportunistic infections Interstitial pneumonitis Interstitial pulmonary fibrosis [228]	Systemic lupus erythematosus Neuropsychiatric lupus [16, 39, 43, 232] Peripheral neuropathy [230] Transverse myelitis [44] Alveolar hemorrhage [44] Myocarditis [13, 44, 64, 229] Pneumonitis [229] Interstitial lung disease [229] Wegener's granulomatosis Central nervous system vasculitis [233] Kawasaki disease Treatment resistance [234] Henoch-Schonlein purpura Severe nephritis [173] Antiphospholipid syndrome Catastrophic antiphospholipid syndrome [164] Behcet's disease Inflammatory aneurysms [235] Juvenile dermatomyositis Interstitial lung disease [231, 236] Churg-Strauss syndrome Steroid resistance [237] Cardiac disease [237] Gastrointestinal disease [237] Central nervous system disease [237] Wegener granulomatosis Acute therapy [173] Maintenance therapy after remission [237] Goodpasture's syndrome Central nervous system vasculitis [169] Glomerulonephritis [167, 169]
Cyclosporine (Sandimmune®, Novartis; others)	Immunosuppressive	Nephrotoxicity Hepatotoxicity Lymphoma Hypertension Seizures Sepsis [215]	Juvenile rheumatoid arthritis Macrophage activation syndrome [95, 99] Catastrophic antiphospholipid syndrome [95, 164] Behcet's disease Uveitis [238, 239] Vascular complications (aneurysm, obstruction, etc.) [238] Juvenile dermatomyositis Acute fibrinous organizing pneumonia [240] Interstitial lung disease [192, 193]

(continued)

Table 35.9 (continued)

Medication	Class	Potential adverse effects	Reported use
Etanercept (Enbrel®, Immunex)	TNF modulator	Serious bacterial infections-including sepsis Demyelinating disorders	Treatment resistant associated uveitis [240]
		Lymphoma	Behcet's disease
		Aplastic anemia [215]	Uveitis [241]
Infliximab (Remicade®, Centocor)	TNF modulator	Demyelinating disorders	Kawasaki disease [149]
		Tuberculosis (including disseminated)	Treatment resistance
		Upper respiratory infections [215]	Behcet's disease
			Neruo-Behcet's [242]
			Uveitis [241, 243, 244]
IVIG	Immune globulin	Transmitted blood borne disease	Catastrophic antiphospholipid syndrome [164, 245]
		Acute renal failure	Kawasaki disease [135]
		Acute tubular necrosis	Henoch-Schonlein purpura [108]
		Proximal tubular nephropathy	Juvenile dermatomyositis
		Volume overload	Interstitial lung disease [192]
		Congestive heart failure [228]	Juvenile rheumatoid arthritis
			Macrophage activation syndrome [99]
Methylprednisolone (Solu-Medrol®, Upjohn; others)	Corticosteroid	Sodium retention	Systemic lupus erythematosus
		Congestive heart failure	Neuropsychiatric lupus [15, 16, 26, 39, 232, 246]
		Hypertension	Myelopathy [247]
		Fluid retention	Peripheral neuropathy [230]
		Potassium loss	Carditis/myocarditis [13, 16, 64]
		Gastric ulcer	Pericarditis [50, 56, 229]
		Pancreatitis	Pneumonitis [44, 229]
		Ulcerative Esophagitis	Alveolar hemorrhage [44, 45]
		Hepatotoxicity	Abdominal vasculitis [44]
		Hyperglycemia	Juvenile dermatomyositis
		Glaucoma	GI ulceration [50]
		Negative nitrogen balance [228]	Interstitial lung disease [192, 193, 231]
			Henoch-Schonlein purpura
			Severe nephritis [173]
			Kawasaki
			Treatment resistance [135]
			Antiphospholipid syndrome
			Catastrophic antiphospholipid syndrome [164, 165, 245]
			Churg-Strauss syndrome
			Acute therapy [237]
			Juvenile rheumatoid arthritis
			Macrophage activation syndrome [99]
			Wegener granulomatosis
			Acute therapy [173, 237]
			Goodpasture's syndrome
			Nephritis [167]

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Infectious Disease-Associated Syndromes in the PICU

36

Isaac Lazar and Clifford W. Bogue

Abstract

In this chapter, we discuss some of the more serious syndromes associated with infectious diseases that are encountered by clinicians in the PICU. The syndromes discussed include necrotizing fasciitis, hemorrhagic shock and encephalopathy, Rocky Mountain spotted fever and Lemierre's syndrome. All of these conditions are serious, potentially life-threatening syndromes for which early recognition and treatment is critical to obtaining a positive outcome for the patient. We discuss the history and epidemiology, pathogenesis, clinical manifestations and management of each condition with the goal of providing clinicians with the most current information about each syndrome.

Keywords

Necrotizing fasciitis • Hemorrhagic shock and encephalopathy • Rocky Mountain spotted fever • Lemierre's syndrome • Erhlichiosis

Introduction

There may be no more common trigger of pathology in pediatric critical care than that initiated by an offending pathogen. Numerous pathogens – bacterial, viral, fungal, and rickettsial – are responsible for a myriad of infectious diseases, often resulting in multi-organ disease necessitating supportive critical care. While a comprehensive review is beyond the scope of this current chapter, herein we review some of the more common and important infectious diseases faced by practicing intensive care personnel. By highlighting the epidemiology, pathogenesis, clinical presentations, and treatment principles of these important entities, we hope to arm the practitioner with the knowledge to rapidly diagnose and provide timely therapy for these most challenging infectious diseases.

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Necrotizing Fasciitis

Necrotizing fasciitis (NF) is a progressively destructive infectious process that involves the deep fascia and its surrounding fat. If left untreated, or if a prompt aggressive surgical debridement is not done, the mortality rate is extremely high.

History and Epidemiology

NF was first clinically described in the USA in 1871 by Jones who called it "hospital gangrene." Wilson first used the term NF in 1951, and the term has remained in use since that time [1]. Although medical and surgical treatment has improved over the years, NF remains a true surgical emergency. NF carries a high mortality and survivors frequently suffer from the disfiguring results of extensive surgical debridement. Skin grafting and reconstructive plastic surgeries are often needed to improve a patient's quality of life. NF can be classified into two

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subgroups based on the microbiological etiology of the disease [2]. *Type I* includes infection caused by mixed species of anaerobes, most commonly Bacteroides and Peptostreptococcus species, facultative anaerobes such as non-group A [beta]-hemolytic streptococci, and enteric gram negative species. Type I is most commonly seen in patients with predisposing medical conditions such as immune deficiencies (primary and secondary), morbid obesity, and diabetes mellitus. *Type II* NF is caused by Gram positive aerobic bacteria – almost exclusively Group A Streptococcus (GAS) and Staphylococcus Aureus [3]. Some authors also mention a *Type III* NF that is caused by a marine vibrio (gram negative organism) entering the fascial space through a sharp fish bone injury, sting, infected wound or insect bite [4]. Overall, a wide range of different bacteria have been isolated from NF patients [3]. Review of the pediatric NF literature reveals many individual case reports and small case series with few publications that include large numbers of patients. Because the disease is relatively rare in the pediatric population (0.5–2.9/1,000,000/year) [2, 5, 6], some of the data described in this chapter is taken from the adult medical and surgical literature where the disease is more common.

Pathogenesis

Understanding the pathophysiology of necrotizing fasciitis may prompt early diagnosis. The disease process starts at the superficial fascia and, although the portal of entry for bacterial infection can vary, direct invasion of the offending pathogen occurs in most pediatric cases. Minor blunt or penetrating trauma, a surgical wound or instrumentation site, or a secondary varicella lesion infection, are among the most commonly associated injuries [7, 8]. The bacterial inflammatory process spreads within the superficial fascia and to the surrounding adipose tissue. Enzymes and toxins elaborated by the bacteria enable the organisms to spread through the fascia causing thrombosis, further microbial invasion and liquefaction necrosis of the superficial fascia. Histologically, areas of necrosis are seen within the superficial fascia with leukocytes (mainly polymorphonuclear neutrophils) infiltrating the deep dermis and fascia. Thrombosis of blood vessels within and surrounding the fascia is accompanied by suppuration and destruction of the fascia. As this process progresses, occlusion of perforating nutrient vessels to the skin causes skin ischemia responsible for the cutaneous manifestations of necrotizing fasciitis. As the condition evolves, ischemic necrosis of the skin ensues with gangrene of the subcutaneous fat, dermis and epidermis [9].

Diagnosis

Establishing the diagnosis of NF can be difficult and a high index of suspicion is necessary. Patients who present with chronic, debilitating medical conditions (e.g. diabetes mellitus, complications of premature birth, immune suppression, or morbid obesity) or who present with the breakdown of skin integrity (e.g. IV drug abuse, recent varicella disease, trauma or surgery), together with non-specific soft tissue complaints, should be carefully evaluated for NF. One of the largest studies published on pediatric NF was published by Fustes-Morales et al. [7]. Their 30-year retrospective review of 39 NF pediatric patients admitted to a single medical center in Mexico found a similar disease distribution between boys and girls with the mean age of onset being 4.4 years (range 10 days–15 years). Presenting symptoms were mostly non-specific and non-localizing and included fever (92 %), vomiting (54 %), hypotension and irritability (33 %), physical exhaustion (28 %), altered mental status (15 %), and impaired peripheral perfusion (13 %). Interestingly, in this series, more than 20 % of the patients with NF had no predisposing conditions that would identify them as having increased risk of developing NF [6].

Certain clinical signs can help raise the index of suspicion of a diagnosis of NF. Initial signs and symptoms may include local erythema and swelling with disproportionate pain over the site. Signs of systemic inflammatory such as fever, tachycardia, hypotension and shock may develop. Once the infection progresses, more typical signs and symptoms can be observed, including tense edema outside the area of compromised skin, discoloration (ecchymosis), blisters/bullae and necrosis. Crepitus and/or subcutaneous gas can often be palpated.

Because NF is hard to diagnose, even in the hands of an experienced clinician, clinical and laboratory tools have been used to help differentiate NF from other soft tissue infections. Wong analyzed the results of laboratory tests routinely performed for the assessment of a wide range of severe soft tissue infections from cellulitis to NF [9]. The laboratory results they analyzed included complete blood count, electrolytes, erythrocyte sedimentation rate and C-reactive protein. A numerical score based on the relative contribution of the laboratory parameters for distinguishing necrotizing fasciitis from other soft tissue infections was established. This laboratory-based risk score predicting the presence of necrotizing fasciitis was termed the "LRINEC Score" (Table 36.1). The score is calculated by totaling up each of the six predictive factors. A score of six or greater was found to have a positive predictive value of 92.0 % (95 % CI 84.3–96.0) and negative predictive value of 96.0 % (95 % CI 92.6–97.9). A score of eight or more is strongly predictive of necrotizing fasciitis (positive predictive value 93.4 %, 95 % CI 85.5–97.2) [9]. Unfortunately, the LRINEC Score has not been validated in children.

Plain radiography, ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) all have been used to help diagnose NF. Plain radiographs

Table 36.1 Laboratory Risk Indicators for Necrotizing Fasciitis (LRINEC score)

Value	LRINEC score points
C- reactive protein, mg/L	
<150	0
>150	4
WBC count, cells/mm^3	
<15	0
15–25	1
>25	2
Hemoglibin level, g/dl	
>13.5	0
11–13.5	1
<11	2
Sodium level, mmol/dl	
>135	0
<135	2
Creatinine level, mg/dl	
<1.6	0
>1.6	2
Glucose level, mg/dl	
<180	0
>180	1

can detect gas in the soft tissues, thus raising the possibility of NF. Ultrasonography may show thickening of the deep fascia with soft tissue distortion and free fluid along the fascia. CT scan may show fascial thickening, tissue enhancement, free fluid and gas along the fascia. MRI findings include fascial thickening, free fluid collection around the fascia and T2W enhancement of the inflamed tissue. Unfortunately, all of these imaging study modalities have high sensitivity but low specificity. Surgical intervention should not be delayed waiting for an imaging study [1, 9].

A definitive diagnosis is made by pathological specimen – either micro- or macroscopic. Frozen section studies are usually diagnostic. The "finger test" – the exploration of the suspected fascia though a small incision and looking for easily dissecting tissue, foul smelling "washwater pus", grey avascularized fascia and surrounding tissue, and poorly compliant muscular tissue – is considered by many authors to be the preferred mode of clinical diagnosis [1, 8, 9].

Clinical Manifestations

When lesions are left untreated, they show a characteristic progression. Over 24–48 h, the erythema that initially developed changes to a bruised-like purple lesion and ultimately progress to an ischemic, blue-colored lesion often associated with overlying blisters or bullae. Finally (by days 4–5) the affected area may become gangrenous if left untreated. The historical reports of necrotizing fasciitis differ from those in the recent era since necrotizing fasciitis is now more commonly associated with streptococcal TSS [10]. The first difference is that recent cases have tended to occur in previously healthy children who had sustained minor trauma to an extremity or other break in the integument. Second, in contrast to older reports, recent cases of necrotizing fasciitis caused by GAS are frequently associated with severe manifestations of systemic illness and result in a high morbidity. These observations have led some to speculate that the high mortality rate in cases of streptococcal necrotizing fasciitis may be due to the emergence of virulent streptococci [10]. Moss et al. observed that prompt surgical consultation and early aggressive intervention were associated with better outcomes than late surgical intervention or medical treatment alone, which frequently ended in patient demise [8]. Admission to the intensive care unit, with efforts aimed at achieving hemodynamic and respiratory stability, are recommended while awaiting definitive surgical treatment [8].

Management

Antibiotic therapy should be started as soon as clinical suspicion arises. Broad-spectrum coverage for gram-positive, gram-negative, and anaerobic organisms should be considered. Possible treatment combinations include monotherapy with antimicrobials such as meropenem or piperacillin/tazobactam. Multi-drug regimens have also been described, including high-dose penicillin, high-dose clindamycin, and an aminoglycoside for coverage of gram-negative organisms. Vancomycin should be included until methicillin-resistant staphylococcal infection has been ruled out. The use of protein synthesis inhibitors, such as clindamycin, may help by inhibiting toxin production, which can be crucial for controlling the inflammatory response in patients with NF, particularly in those with clostridial and streptococcal infections [1]. One should consult an Infectious Disease specialist for determining optimal antibiotic coverage based on the local community's microbial resistance and sensitivity as well as for determining the optimal length of antibiotic treatment.

Though antibiotic selection is critically important, prompt, aggressive exploration and debridement of deep-seated infection are indicated. Surgical excision should be extensive, removing all necrotic tissue. Aggressive hemodynamic resuscitation should follow in the peri-operative period. Re-exploration of the operative site and removal of any remaining necrotic tissue should be delayed until the infected material has been completely removed. Gram stain of surgically-obtained specimens should be performed to provide additional insight to the etiologic diagnosis and may help to narrow the antibiotic treatment. Antibiotic administration should continue until no further debridement is needed and the patient's physiological condition has

improved. Prolonged treatment with antibiotics is not necessary and may predispose the patient to wound colonization with drug-resistant organisms [1]. As for other modalities, anecdotal reports have suggested that hyperbaric oxygen may be used. However, the use of this treatment remains speculative and no controlled studies have been conducted to examine the efficacy of this treatment option.

Hemorrhagic Shock and Encephalopathy

History and Epidemiology

Hemorrhagic Shock and Encephalopathy Syndrome (HSES) is a rare syndrome that strikes babies in the first few months of life. It was first described by Levin in 1983 in a group of ten infants who presented with high fever, shock, encephalopathy, loose or bloody diarrhea, renal and hepatic failure and disseminated intravascular coagulopathy (DIC) [11]. This was considered a newly-described syndrome at the time and since its initial description, about 200 cases have been reported worldwide. A clinically similar syndrome, the Influenza Associated Encephalopathy (IAE), has been described and is characterized by patients who present with encephalopathy, high fever, hemorrhagic shock, and multi-system organ failure. The initial cases of IAE were primarily from Japan with a few case reports from other parts of the world [12]. IAE is thought to be a different disease, though, as it usually has viral etiology (mainly influenza virus, including cases of newly emerging N1H1 Influenza [13]) and affects an older patient population. IAE will not be discussed in this chapter.

Pathogenesis

The etiology of HSES remains unclear, but has been related to various triggers [11, 14, 15]. Most published reports have been unable to link the syndrome to a specific infectious pathogen. Levin suggested abnormally low α-1 antitrypsin and α-2 macroglobulin levels with abnormally high trypsin and amylase levels may play a role in the etiology [11, 16]. Beacon et al. summarized data from UK from 1982 to 1988 in a case-control study comparing 31 cases of HSES in patients aged 6 months and younger to 124 matched controls [17]. The authors identified a strong association between head wrapping and environmental over-heating in HSES cases, raising the hypothesis that hyperthermia plays a key role in the pathogenesis of this syndrome. While this hypothesis has been suggested by a few authors [15, 18], others have rejected it [16]. To date there is no consensus regarding the etiology of HSES.

Table 36.2 Hemorrhagic shock and encephalopathy diagnostic criteria

Clinical	Shock
	Coma and seizures
	Bleeding or laboratory evidence of DIC
	Diarrhea
	Oliguria
Laboratory	Falling hemoglobin levels (>3 mg/dl below admission value)
	Falling platelet count ($< 150 \times 10^9$/L)
	Prolonged prothrombin time, partial thromboplastin time and thrombin time
	Low fibrinogen level
	Elevated fibrin degradation products
	Elevated urea and creatinine plasma concentration
	Elevated alanine aminotransferase and aspartate aminotransferase plasma concentrations
	Metabolic acidosis
Exclusions	Known infection or metabolic disorder.
	Reye's syndrome
	Toxic shock syndrome

Clinical Manifestations

The diagnosis of HSES is difficult to make because there is no single laboratory test to confirm diagnosis. Diagnosis is based on a combination of clinical and laboratory data along with the exclusion of etiologies that can give a similar clinical presentation. Levin et al. published the case definition criteria in 1989 (Table 36.2) based on their large population study [16]. The usual age at presentation varies from infants (2 months) to children (14 years) [16, 19] and most affected children had a history of an upper respiratory tract infection or gastroenteritis 2–5 days prior to admission. The disease course is illustrated in Fig. 36.1 [20]. In most reported cases, the child was found, within a few hours of being put to bed, with severe neurological impairment such as coma and/or seizures. HSES usually presents abruptly with high fever (above 39 °C), hypovolemic shock, coma, seizures, watery diarrhea that develops into bloody lower GI bleeding, profound coagulopathy and oliguria. The hallmark of the disease is severe neurologic deterioration beyond what would be expected from the shock. Brain imaging studies show diffuse cerebral edema and areas of focal bleeding and infarcts. In the report, all patients were admitted to the pediatric ICU and were intubated and ventilated for long periods of time. Based on the constellation of clinical findings, a number of other diseases/syndrome should be considered, including viral hemorrhagic fever, sepsis syndrome, hemolytic uremic syndrome, Reye's syndrome or toxic shock syndrome.

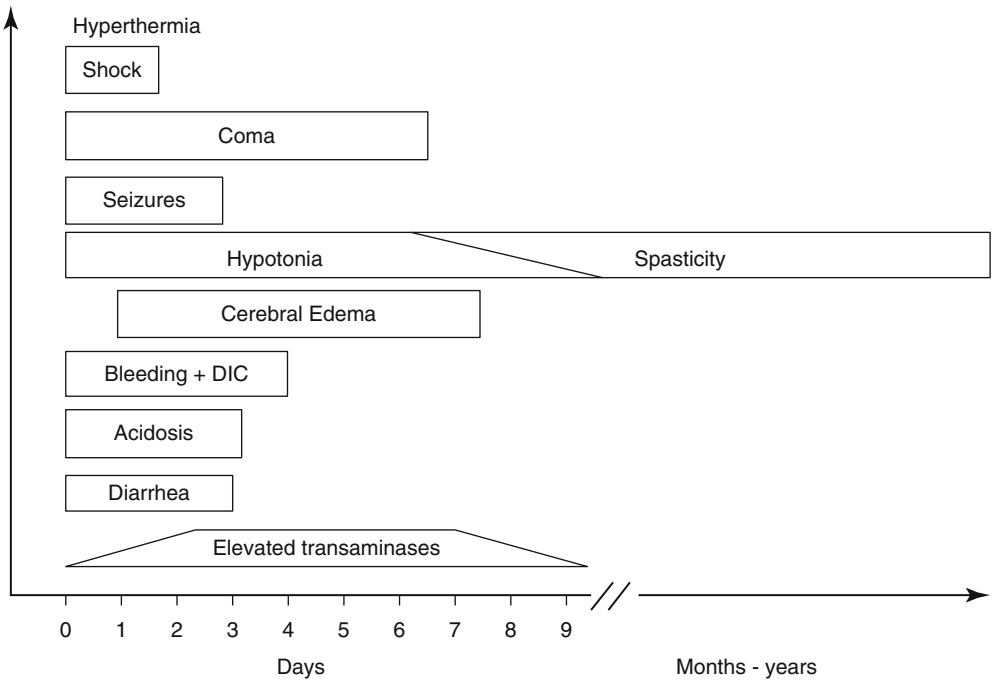

Fig. 36.1 Clinical picture and time course of symptoms of HSES (Adapted from Ince et al. [20]. With permission from Wolter Kluwers Health)

Laboratory Findings

Laboratory studies are consistent with a clinical diagnosis of shock and hypoperfusion. Metabolic acidosis and decreased hemoglobin and platelet levels develop within a few hours of hospital admission and are associated with shock and DIC. Hypernatremia and hyperkalemia are common and are due to renal injury. Altered liver function is evidenced by markedly increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels; however, there are usually only mild elevations in bilirubin and ammonia. Serum CPK may be disproportionately elevated. In general, the laboratory abnormalities peak at 24–48 h after presentation and return to normal level by 7 days [21].

Management

Unfortunately, there is no specific therapy available for this syndrome. General supportive measures should be undertaken until the disease process runs its course. Because of the uncertainty of the etiology and the possibility of viral or bacterial infection, bacterial and viral cultures should be drawn and broad-spectrum antibiotic treatment should be initiated. The patient should be placed in isolation and precautions for possible viral hemorrhagic fever should be employed until the diagnosis can be ruled out. Cardiovascular support is usually necessary and fluid resuscitation and/or inotropic medication was utilized in all reported cases. Anemia and coagulopathy usually necessitate frequent blood product replacement. Oliguria and renal failure are usually due to pre-renal azotemia and while traditional renal replacement therapy has been used, there is one case report suggesting there may be some benefit from plasma exchange with continuous hemofiltration [22]. Overall, disease outcome seems to be related to the severity of the neurologic impairment on admission and is worse if the patient has prolonged coma or status epilepticus. Aggressive attempts should be taken to control seizure activity and, if signs of increased intracranial pressure (ICP) are present, to control ICP as well. The majority of the patients showed early signs of cerebral edema that often progresses to diffuse brain injury. The theoretical advantage of invasive intracranial pressure monitoring should be weighed against the possible complications in a high-risk patient with systemic coagulopathy. No data regarding benefit from invasive ICP monitoring is present. Mortality is high and ranges between 50 and 80 % with severe neurological disability in the survivors [16, 19].

Rocky Mountain Spotted Fever

History and Epidemiology

Rocky Mountain spotted fever (RMSF) is a tick-borne disease that has been recognized in North America for more than a century. RMSF was first described in the Rocky Mountain region of the United States in the late 1800s and is caused by the obligate intracellular coccobacillus *Rickettsia rickettsii*. RMSF is the most common fatal tick-borne illness in the United States. An estimated 612 deaths were attributable to RMSF in the United States during 1983–1998, and

approximately 12 % of reported deaths occurred in children aged less than 10 years [23]. A recent publication summarizes the annual incidence of RMSF from 2000 to 2007 and shows a worrisome increase in the incidence of the disease from 1.7 cases to 7.0/1,000,000 person in the USA [24]. The authors speculate that some of the increase may be related to the newly-developed ELISA test that was introduced during the study period. Nearly two-thirds of RMSF cases occur in children younger than age 15 years (peak age, 5–9 years). The case-fatality ratio of untreated RMSF across all age groups combined approaches 25 % [25] and 3–5 % in treated patients [26, 27]. While RMSF was initially seen in the Northern Rocky Mountain and Pacific States, today it has been reported in almost every state in the continental United States except Maine and Vermont. Most cases that have been reported are from the South Atlantic Region, Pacific Region, and the West South Central Region. From 1994 to 2003, 54 % of the reported cases were from five states: North Carolina, Tennessee, Oklahoma, South Carolina, and Arkansas. The disease is transmitted by the American dog tick (*Dermacentor variabilis*), a relatively common and broadly distributed tick in the Eastern United States, and by the wood tick (*Dermacentor andersoni*) in the Rocky Mountain States. A clear spring-summer distribution of cases is an invariant feature of this illness and attests to the association of RSMF with peak occurrences of *Dermacentor* tick bites. Currently, the disease is in the midst of its third resurgence since 1920, following epidemiologic peaks from 1939–1949 to 1974–1984. The reasons for the cyclical waxing and waning are not understood but it does underscore the fact that little is known about the virulence mechanisms associated with *R. rickettsii* and that it remains an important and prevalent disease [28]. It is possible that the new resurgence of the disease is secondary to changes in the vectors of the tick-borne disease as suggested by a recent report of *R. rickettsii* being transmitted by a new vector, the common brown dog tick *R. sanguineus* [29].

Pathogenesis

Ticks become infected with *R. rickettsii* either transovarially or by feeding on infected mammals. Once infected, the ticks are not killed by the infection, thus allowing them to serve as both a reservoir and a vector of *R rickettsii*. The organisms are usually transmitted to humans through the saliva of a tick while it is feeding, although infections may occur following exposure to crushed tick tissues, fluids, or feces. Following the bite of an infected tick, *R. rickettsii* multiply within the endothelial cells of the small blood vessels, which then become widely disseminated resulting in the pathologic lesion of widespread vasculitis of the small blood vessels. The precise mechanism of the invariant endothelial injury is not known. However recent in vitro studies suggest that NF-κB activation may play a prominent role [30, 31]. Focal areas of endothelial proliferation and perivascular mononuclear cell infiltration lead to thrombosis and leakage of red blood cells into the surrounding tissue. These latter changes create the characteristic petechial rash. These vascular lesions also appear to account for most of the prominent clinical manifestations including fever, headache, rash, myalgias, and central nervous system changes.

Clinical Manifestations

In its early stages, RMSF can resemble many other infectious and non-infectious conditions and can be difficult to diagnose. A history of tick bite is elicited in only 50–60 % of patients, especially in rural areas where children often remove ticks without telling their parents. The incubation period after a tick bite is approximately 7 days, with a range of 2–14 days. The larger the initial inoculum, the shorter the incubation period is. The initial symptoms of infection are non-specific and may mimic a number of conditions, including viral syndrome. These symptoms include high fever, nausea, vomiting, severe headache, anorexia and malaise. Other non-specific signs or symptoms include myalgia (especially bilateral calf pain), photophobia, and abdominal pain. Meningoencephalitis, myocarditis, and pulmonary involvement are all integral aspects of the syndrome that are also seen in other vasculitis syndromes such as toxic shock syndrome and toxic strep syndrome.

While the classic triad of RMSF symptoms is fever, rash, and headache, this combination is not always present when the patient initially presents. The rash usually appears between the second and fifth day of illness and is a blanching, erythematous macular rash that initially begins on the wrists and ankles and typically involves the palms and soles. The rash quickly spreads to the trunk and head within hours and usually transforms into the characteristic petechial rash of RMSF somewhere between the days 6 and 10 of illness. However, rash occurs in only 35–60 % of patients and as many as 10–15 % of patients with RSMF never develop a rash [32].

Other manifestations of the disease are related to the extensive vasculitis that occurs and include changes in mental status and/or meningismus. There are reports of disease progression in the central nervous system that includes coma, seizures, cranial nerve palsies, central deafness, and cortical blindness. Other manifestations of the vasculitis include conjunctivitis, periorbital edema, congestive heart failure, myocarditis, shock, hepatosplenomagly, and jaundice. The respiratory system is also frequently involved and patients can develop severe pneumonia and/or acute respiratory distress syndrome.

Table 36.3 Case definition from the centers for disease control and prevention for Rocky Mountain spotted fever

Laboratory criteria for diagnosis
Fourfold or greater rise in antibody titer to *R rickettsii* in acute- and convalescent-phase specimens ideally taken >3 weeks apart, or
Positive polymerase chain reaction assay to *R rickettsii*, or
Demonstration of positive immunofluorescence of skin lesion (biopsy) or organ tissue (autopsy), or
Isolation of *R rickettsii* from a clinical specimen
Case classification
Probable: a clinically compatible case with a single indirect immunofluorescence assay serologic titer >64 or >16 with single complement fixation titer or other supportive serology (eg, >128 by latex agglutination, microagglutination, or indirect hemagglutination test)
Confirmed: a clinically-compatible case that is confirmed by laboratory findings

Laboratory Findings

The classic laboratory abnormalities that help increase the index of suspicion for this diagnosis include hyponatremia (≤ 130 mEq/l) and thrombocytopenia ($<150\times10^3$/ml). Hyponatremia appears in approximately 20 % of patients while thrombocytopenia occurs in approximately 33 % of patients. Other laboratory findings that may be seen include leukopenia, anemia, increased serum liver transaminases, and elevated BUN. If a lumbar puncture is performed, many patients have normal findings; however, in approximately one-third of the cases patients will have a mononuclear pleocytosis.

Criteria for the diagnosis of RMSF include the presence of a clinically compatible illness plus at least one of the following (Table 36.3) [33]: (1) serologic evidence of a significant change (fourfold increase or greater) in antibody titer reactive with *R. rickettsii* antigens between paired serum specimens; (2) demonstration of *R. rickettsii* antigen by immunohistochemistry in a clinical specimen such as a skin biopsy or other tissues; (3) detection of *R. rickettsii* DNA by PCR in a clinical specimen, such as whole blood or tissue; or (4) isolation of *R. rickettsii* from a clinical specimen with growth in culture. Probable cases have a clinically compatible illness and serologic evidence of antibodies reactive with *R. rickettsii* in a single serum sample at a titer considered indicative of current or past infection. At the Centers for Disease Control, reciprocal IFA IgG titers ≥64 are considered to be evidence of current or past infection. Because rapid laboratory confirmation of RMSF infection is not available, clinicians should strongly consider initiating empiric therapy in patients with a compatible clinical presentation and epidemiologic circumstance (e.g. recent recreational or occupational activities during spring and summer months that could result in exposure to ticks) to reduce morbidity and mortality resulting from delayed diagnosis [34]. The classic triad of fever, headache and rash should make the clinician consider RMSF but these symptoms are not specific for the diagnosis and there are many common diseases that mimic RMSF (Table 36.4). The diseases most likely to be confused with RMSF include disseminated meningococcal disease, measles, and human monocytic ehrlichiosis.

Table 36.4 Common diseases that mimic Rocky Mountain spotted fever

Human monocytic ehrlichiosis
Meningococcemia
Enterovirus infection
Staphylococcal sepsis
Toxic shock syndrome
Adenovirus infection
Drug hypersensitivity
Immune thrombocytopenic purpura
Henoch-Schoenlein purpura
Infectious mononucleosis
Kawasaki disease

Management

The treatment of choice for RMSF is doxycycline therapy for at least 7 days [32]. Doxycycline is preferred because it has a broad spectrum of coverage that includes coverage of other tick borne illnesses, including the ehrlichioses and other rickettsial infections, which are frequently in the differential diagnosis. Appropriate antimicrobial therapy should be started immediately when the diagnosis of RMSF is suspected. It is imperative that treatment not be delayed pending laboratory confirmation. Historically, tetracyclines and chloramphenicol were the only two antimicrobial agents that had clinically-proven efficacy against *R. rickettsii*. However, chloramphenicol is considered second line therapy because its use is associated with a higher percentage of fatal outcomes then treatment with tetracycline. Therefore, doxycycline therapy is indicated, even in children, whenever RMSF or an erhlichiosis is suspected. The risk of tooth-staining is not significant for short term therapy and it appears that it requires up to five or six courses before any teeth staining occurs. Doxycycline has the advantage that it is effective against human monocytic ehrlichiosis while chloramphenicol may not be. Doxycycline (100 mg twice daily for adults); 4 mg/kg per day orally or intravenously for patients up to 45 kg, is administered in two divided doses and is continued for 3 days after defervescence and demonstration of clinical improvement. The most effective ways to reduce the risk for

RMSF are to limit children's exposure to ticks during peak spring and summer months (April to September), thoroughly inspect children for ticks after time spent in wooded or grassy areas, and if discovered, immediately remove attached ticks. As with other systemic illnesses that cause a toxic vasculitis, aggressive and anticipatory management of multiple system organ involvement is critical. RMSF carries a mortality rate of 2–4 % with the risk of death increasing significantly when therapy is delayed for more than 5 days.

Ehrlichiosis as a Mimicker of RMSF

As mentioned above, the other rickettsial-borne illness that can be nearly indistinguishable from RMSF is human monocytic ehrlichiosis (HME) [35]. Slightly different in presentation from RMSF, the rash associated with HME, which can be macular, maculopapular, petechial or a combination of these, is usually distributed on the trunk, but can also involve the extremities. Common laboratory abnormalities present in HME include thrombocytopenia and leukopenia, although anemia can also be noted. Other findings can include nonspecific elevations in liver transaminases and hyponatremia. If CSF is examined, typical findings include a lymphocytic pleocytosis with an elevated protein level. While the distinction between RMSF and HME may be difficult, it is fortunate that antimicrobial therapy is similar. Thus, doxycycline remains the antibiotic of choice in children, with either tetracycline or rifampin as acceptable alternatives. It is recommended that antimicrobial therapy be continued for at least 3 days after the patient becomes afebrile for a minimum course of 5–10 days. Alternative infectious causes or clinical syndromes (e.g. vasculitis) should be considered in the setting where clinical improvement on doxycycline is not observed.

Lemierre's Syndrome

Though initially described in 1900 by Courmont and Cade, this syndrome was named after Dr. Andre Lemierre who reported on a series of patients with anaerobic septicemia in the mid-1930s [36]. In this classic report, most patients presented with either pharyngeal or tonsillar infection or a peritonsillar abcess. However, this seemingly innocuous presentation was followed by the onset of ipsilateral swelling and pain of the neck that rapidly progressed to bacteremia and metastatic infections, usually of the lungs. Prior to the introduction of antibiotics, this syndrome was a relatively frequent complication of pharyngitis with an almost uniformly fatal outcome. The most frequently identified causative agent remains the obligate anaerobic gram-negative rod, *Fusobacterium necrophorum* cultured in over 80 % of cases. Other notable pathogens less commonly identified in this clinical presentation include: other *Fusobacterium* sp., *Bacteroides* sp., *Peptostreptococcus*, group B and C *Streptococcus, Streptococcus oralis* and *Eikenella corrodens* [37]. Furthermore, it should be noted that polymicrobial bacteremia is present in 10–30 % of cases. Following the development of antibiotics, there was a dramatic decrease in both the incidence and mortality of Lemierres syndrome. Nevertheless, because of its persistent occurrence and rapid progression, intensive care personnel should be aware of this rare and potentially fatal disease since a delay in the recognition and initiation of appropriate therapy will increase the associated morbidity and mortality.

Lemierre's syndrome is now recognized as a severe complication of lateral oropharyngeal infections that leads to a suppurative thrombophlebitis of the ipsilateral internal jugular vein. Septic thromboembolism of this site contributes to the invariably ensuing septicemia and metastatic infections, most commonly of the lungs and joints [38]. The usual interval between the primary infection and suppurative thrombophlebitis with sequelae is usually 3–7 days. Interestingly, patients are typically healthy adolescents or young adults with an estimated three-quarter of cases occurring in 16–25-year olds [38].

The pathogenesis of Lemierre's syndrome remains incompletely understood. It has been hypothesized that a preceding bacterial or viral pharyngitis may reduce the local host immune response allowing commensurate bacterial penetration into the soft tissue. In support of this, there have been reports of Lemierre's disease in association with Epstein-Barr virus pharyngitis. Once the fusobacterium has penetrated the site of infection, numerous virulence factors may mediate the subsequent pathogenesis including hemolysin, lipoprotein lipase, leukocidin and lipopolysaccharide. Local spread an oropharyngeal space infection (e.g. parotitis, sinusitis, mastoiditis, otitis and dental infection) leads to thrombophlebitis of the internal jugular vein. This can also result from an anterograde extension of thrombophlebitis of the peri-tonsillar veins into the internal jugular vein.

Presenting symptoms include sore throat, fever, painful swelling of the neck, dysphagia and trismus. The presence of infectious foci in the lungs may manifest as pleuritic chest pain or dyspnea, while joint pain can be associated with infection at these potential distant sites. Contrast-enhanced CT of the neck is the modality of choice for diagnosing thrombosis of the internal jugular vein. Additionally, CT can provide additional imaging of the surrounding soft tissues for assessing underlying abscesses, fasciitis and/or myositis. The spreading of soft tissue infection along fascial planes of the neck can progress to the carotid sheath and into the mediastinum and chest, resulting in mediastinitis, lung abscess, or pneumonia detectable with the additional CT scanning of the chest. The differential diagnosis can include cervical necrotizing fasciitis, suppurative odontogenic infections or trauma so consultation with experienced otolaryngology and dental colleagues is often needed.

Treatment for Lemierre's disease generally remains supportive. *Fusobacteria* are generally exquisitely sensitive to numerous antibiotics: penicillin, clindamycin, metronidazole and cephalosporins. The disease occurs too infrequently

to have thoroughly tested combined strategies, but most infectious disease experts recommend either combined therapy employing high-dose penicillin and metronidazole or monotherapy with clindamycin. Infrequently, surgical drainage of an isolated abscess or debridement of true fasciitis may be necessary. Most often however, an ill-defined, underlying phlegmon is observed that is not amenable to surgical approach. Finally, while it may be instinctively intuitive that anticoagulation in Lemierre's disease would be indicated, it clinical utility remains unproven except in the case of thrombotic extension to the cavernous sinus [39]. Recently reported experience suggests that many authors recommend anticoagulation during the acute phase of illness in order to prevent clot progression and potentially decrease the risk for septic pulmonary emboli. This indication is balanced by additional concerns regarding the risk for hemorrhage and thus, potential extension of the infection. Despite this controversy [40], current literature suggests that most reported patients are started on anticoagulation and maintained on it for several weeks [41].

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Life Threatening Tropical Infections

37

Gabriela I. Botez and Lesley Doughty

Abstract

Infectious diseases are among the most common pediatric illnesses and are frequently encountered in the pediatric intensive care unit. Tropical infections, on the other hand, are relatively uncommon in children in developed countries, except those with pertinent travel histories or recent immigration. Clinicians who participate in mission work and disaster relief work also encounter these diseases as they are endemic in many developing nations. For the most part these infections do not result in critical illness however some do and this chapter will focus on a few of the more common infections with potential to be acutely life threatening. The epidemiology, pathophysiology, clinical manifestations, and current clinical management are presented for severe malaria, dengue fever, typhoid, and leptospirosis.

Keywords

Severe malaria • Dengue fever • Typhoid • Leptospirosis • Critical illness • Pediatric

Introduction

Infectious diseases are among the most common pediatric illnesses and are frequently encountered in the pediatric intensive care unit (PICU). Tropical infections, on the other hand, are relatively uncommon in children in developed countries, except those with pertinent travel histories or recent immigration. With a few notable exceptions, most tropical infections seen in developed countries are likely to cause illnesses that do not result in the need for critical care. As a result, many pediatric intensivists have minimal exposure and training related to these diseases. There are two scenarios in which life-threatening tropical diseases are likely to be encountered in developed countries: (1) *Imported diseases* seen in returned travelers or immigrant children and (2) *Locally prevalent diseases* seen during mission trips to tropical countries. Of course, clinicians working in developing countries are likely to see many of these diseases and conditions almost daily. These clinicians likely will have a different level of experience and expertise with these diseases. As such, the chapter will be geared towards those clinicians working in developed countries, focusing on those diseases that either present in developed countries after travel/immigration or those that are encountered by healthcare providers who engage in disaster relief and/or mission work.

Imported Diseases

Millions of children travel internationally every year [1] to many developing countries. While most return home healthy, travel acquired illness should be included on the differential diagnosis of the acutely ill child, especially if presenting less than 30 days after returning from abroad. The largest multinational study to date [2] reporting on the clinical and epidemiological characteristics of 1,591 children who were ill after international travel

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Table 37.1 Incubation periods for potentially life-threatening tropical infections

<14 days
Bacterial diarrhea
Dengue
Malaria (falciparum)
Typhoid fever
Leptospirosis (average 1–2 weeks)
Rickettsial infection
Avian influenza
Viral hemorrhagic fever
Chikungunya
Yellow fever
14–30 days
Malaria (falciparum)
Typhoid fever (average 7–21 days)
Hepatitis A and E (2–6 weeks)
Acute schistosomiasis
Tuberculosis
>30 days
Malaria (ovale, vivax)
Hepatitis A, B and E
Acute schistosomiasis
Tuberculosis

found that the most common syndrome categories were diarrhea (28 %), dermatologic disorders (25 %), systemic febrile illnesses (25 %), and respiratory disorders (11 %) [2]. The group with the highest rate of hospitalization (36 %) was the systemic febrile illness group. Apart from the nonspecific viral illness syndrome, this group included malaria, typhoid fever, and dengue fever – two thirds of children presenting with these conditions required hospitalization. This finding is in keeping with previous observations that almost all life-threatening infections after travel present with fever [1, 3, 4].

In the approach to the pediatric febrile returned traveler, knowledge of incubation periods can give critical clues to the etiology of the underlying fever (Table 37.1) [3, 5–7].

In this chapter we will focus our discussion on the three most common tropical infections that may present with critical illness in the United States, which include malaria (there are approximately 225 pediatric cases every year in the US), dengue (there were 23 reported cases in children between 1999 and 2009, though dengue was not a reportable disease to the CDC until 2009, so this is likely a gross underestimation), typhoid fever (there were 21 pediatric cases reported to the CDC between 1999 and 2009 [8]), and leptospirosis. In addition, the practitioner should include rickettsial diseases and tuberculosis in their differential diagnosis of the sick febrile child returning from the tropics. Although these diseases have worldwide prevalence and specific risk factors related to various exposures, they are more commonly encountered in the tropical regions.

Locally Prevalent Diseases

In addition to the conditions listed above, the following is an abbreviated list of potentially life-threatening infectious diseases that are likely to be encountered while working overseas:

1. Severe diarrheal syndromes, notably cholera, amebiasis, *Clostridium perfringens*
2. Other hemorrhagic fevers, including yellow fever, Congo-Crimean fever, Lassa fever
3. Tuberculosis including meningoencephalitis, pericarditis, disseminated pulmonary disease leading to acute respiratory failure or a sepsis-like picture
4. Tetanus
5. Acute liver failure due to parasitic infestations or viral hepatidites
6. Heart failure due to Chagas disease (Trypanosoma infections)
7. Meningococcal disease
8. AIDS

Due to space limitations, we will not discuss these conditions, and the reader is referred to other textbooks on Tropical Medicine and Medical Microbiology/Parasitology as well as MMWR Geosurveillance Reports.

Malaria

Epidemiology

Malaria is the most important parasitic disease of man. Recognized since antiquity, it has a huge global impact – approximately 5 % of the world population is infected with malaria and almost two thirds of the world's population is exposed to malaria annually. In 2008, there were an estimated 243 million clinical cases globally and 863,000 deaths, mostly in children aged <5 years living in sub-Saharan Africa [9]. According to the CDC [10], from 1999 to 2008 there were 8,117 cases of travel-associated malaria with 43 fatalities among US residents. The majority of these infections (66 %) were acquired in sub-Saharan Africa with similar proportions of remaining cases from Asia (14 %) and Central/South America (12 %).

In its latest MMWR report [11], the CDC received reports of 1,484 cases of malaria in 2009, including two transfusion-related cases, three possible congenital cases, one transplant-associated case, and four fatal cases among persons in the United States. Sixteen percent of these – 225 cases – occurred in children (age <18 years). Of the 86 children for whom chemoprophylaxis information was known, 27 (31 %) were reported as having taken chemoprophylaxis – 18 of these (67 %) had taken an appropriate regimen, though only four (22 %) reported adherence. Physicians practicing in the US

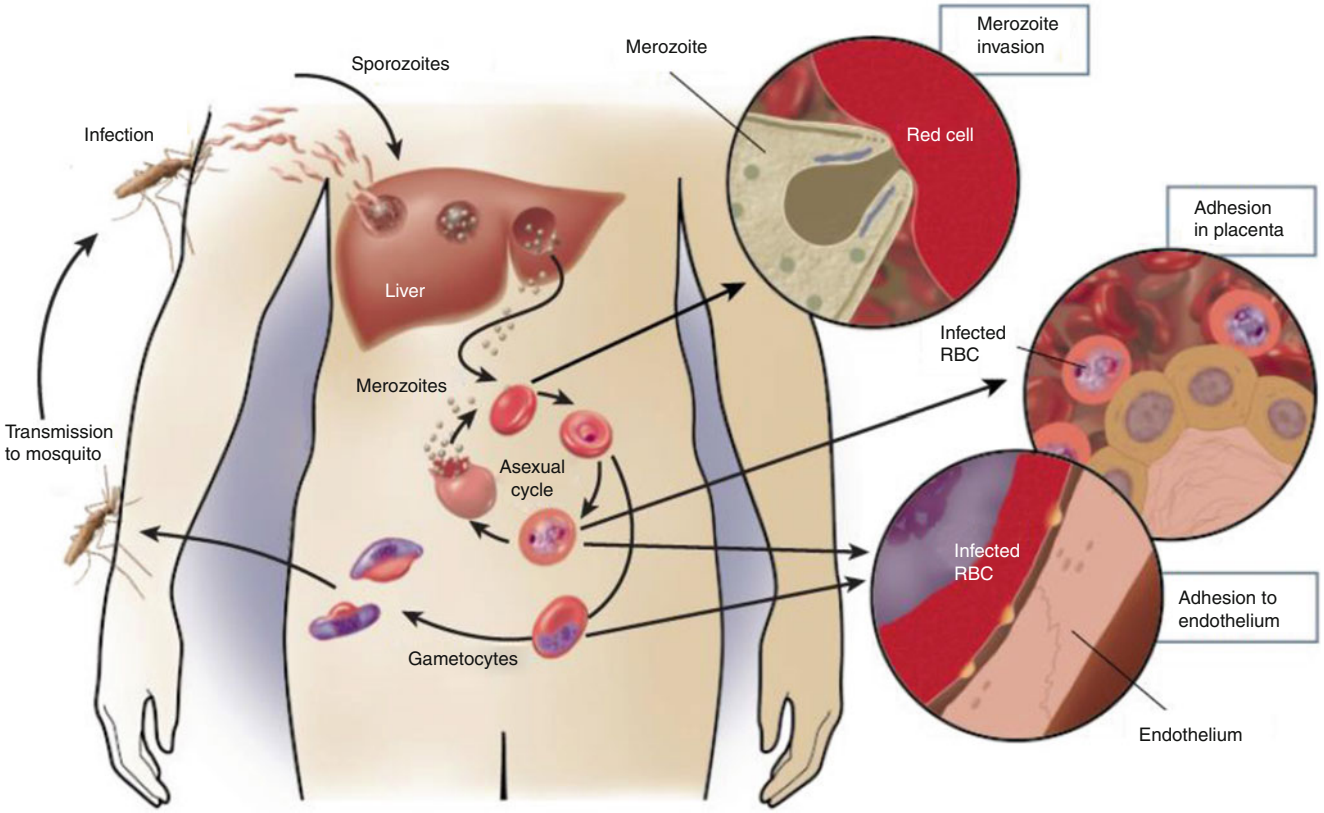

Fig. 37.1 Parasite life cycle and pathogenesis of falciparum malaria. The molecular and cellular events during the parasite life cycle influence the severity of the disease. Disease occurs only as a result of the asexual blood stage after the parasite leaves the liver and begins to invade and grow inside red blood cells (*RBCs*). All human Plasmodium spp. invade by the same mechanism, but P. falciparum reaches high parasitemia because of greater flexibility in the receptor pathways that it can use to invade all RBCs. RBCs infected with P. falciparum must bind to endothelium or placenta for the parasite to avoid spleen-dependent killing mechanisms, but this binding also leads to much of the pathology (Reprinted from Ref. [16]. With permission from Nature Publishing Group)

are unlikely to encounter malaria frequently, which can make it more difficult to include it in the differential diagnosis of fever. However, failure to consider a diagnosis of malaria in a febrile child returning from an endemic area can lead to significant delays in diagnosis – in different series, between 35 % [12] and 90 % [13] of pediatric cases were initially misdiagnosed. In children, acute malaria is often mistaken for a viral illness or acute gastroenteritis due to associated nausea, vomiting and diarrhea. This delay in recognition, compounded with lack of immediate availability of antimalarial drugs in some US hospitals, can contribute to significant morbidity and mortality.

Etiology

The malaria parasite, *Plasmodia*, is a sporozoan parasite of red blood cells (RBCs) transmitted to mammals by a mosquito vector. Human malaria is caused by five species of *Plasmodium*, namely *falciparum*, *ovale*, *vivax*, *malariae* and the recently characterized species *knowlesi* ("monkey malaria" – malaria of long-tailed and pig-tailed macaque monkeys, found on the island of Borneo and peninsular Malaysia, though it can also infect humans [14]). All of the species of *Plasmodium* causing malaria in humans are transmitted by mosquito species of the genus *Anopheles*. Only female mosquitoes bite, and the sporozoites are transmitted to the skin from the saliva of a biting female mosquito, after which they eventually make it into the bloodstream through the network of capillaries in the subcutaneous tissue. After the sporozoites are introduced to the blood through the mosquito bite, they remain in the circulation for approximately 45 min before infecting a hepatocyte [15]. For the next 6–15 days, the parasites develop in hepatocytes (the incubation period) (the sporozoites at this stage are known as schizonts) and are then released into the circulation as merozoites, where they infect RBCs. The life cycle of the *P. falciparum* is shown in Fig. 37.1 [16]. The sporozoites of both *P. vivax* and *P. ovale* can become dormant in the hepatocyte in a form referred to as a hypnozoite. The hypnozoite may emerge months to years after initial infection to cause the relapses that characterize infections with these two species [15].

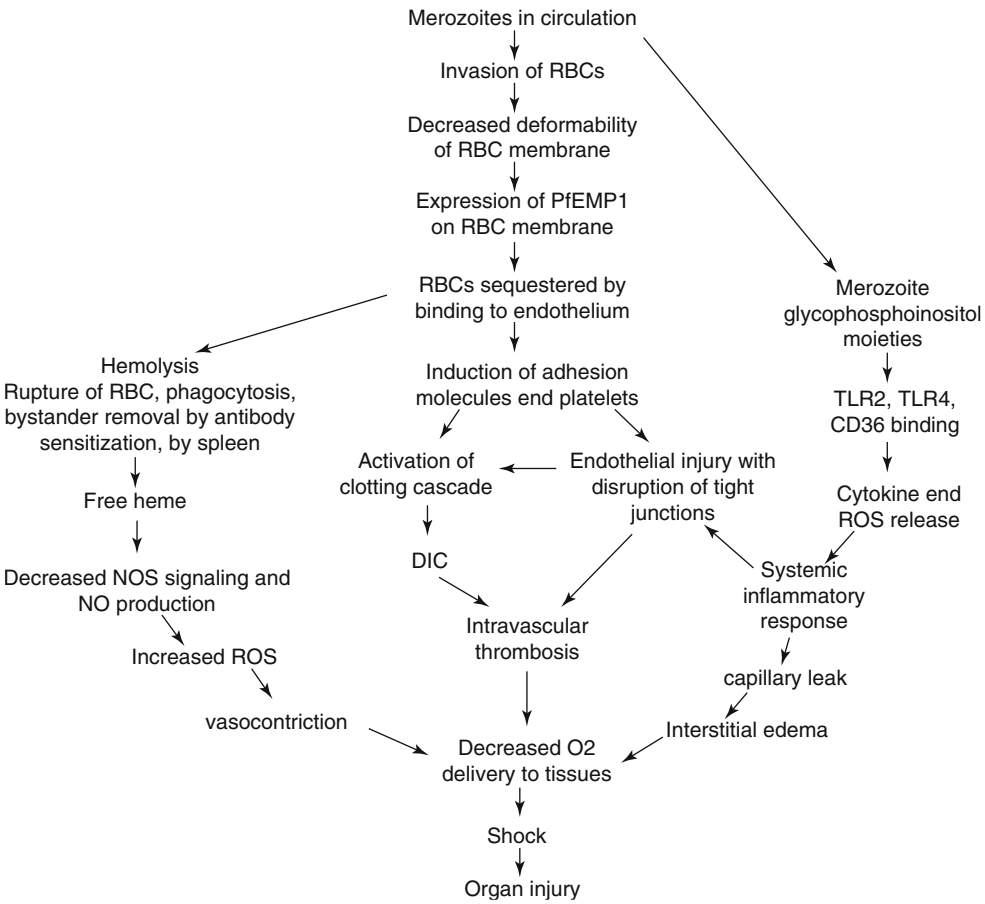

Fig. 37.2 Pathogenesis of malaria (Based on data from Ref. [23])

Within the RBCs, the sporozoites grow to form a trophozoite, dividing several times to produce new merozoites. The merozoites are released into the bloodstream, where they are free to invade new RBCs. The parasites feed on hemoglobin and other RBC materials, which causes damage and eventual destruction of the RBCs. Infection caused by *P. falciparum*, is associated with the worst morbidity and mortality due to the ability to sequester itself in the capillaries and cause major organ dysfunction [17]. Although classically viewed as "benign", infections with *P.vivax* and *ovale* can have severe clinical manifestations, such as acute respiratory distress syndrome (ARDS), severe anemia, spleen rupture [18], and in chronic untreated infections, severe malnutrition [19]. *P. malariae* can result in long-lasting infections and if untreated can persist asymptomatically in the human host for years, even a lifetime [9].

Pathophysiology of Severe Malaria

Plasmodia are parasites of RBCs, and as such the pathophysiology of malaria results from destruction of RBCs (both infected and uninfected [16]), followed by liberation of the parasite and its metabolic byproducts into the circulation, which can trigger the excessive production and release of pro-inflammatory cytokines [20–22]. As mentioned briefly above, a mechanism of disease specific to *P. falciparum* is sequestration of infected RBCs to the endothelium of various tissues, in a manner somewhat similar to sickling, leading to microvascular obstruction with decreases in the regional blood flow and perturbation of tissue metabolism. In spite of a growing body of literature on the pathophysiology of severe malaria, opinion is divided over which of these mechanisms – inflammation versus sequestration – represents the main driving force leading to disease and death in severe *P. falciparum* malaria (see Fig. 37.2) [23].

Inflammation

The idea that the characteristic febrile paroxysms of malaria are induced by parasite products released at the time of schizont rupture originated in the nineteenth century [24]. Malaria parasites induce the release of cytokines in a similar way as bacterial endotoxin [15], although they are much less potent. Merozoites contain (and release upon rupture) many glycophosphoinositol moieties that can activate the host inflammatory response in macrophages and dendritic cells via Toll like receptor 2 (TLR2) and to a lesser extent TLR4 as well as scavenger receptors such as CD36 [16, 20–22].

Tumor necrosis factor (TNF), interleukin (IL)-1 and gamma interferon (γ-IFN) are produced and, in turn, induce release of a cascade of other pro-inflammatory cytokines including IL-6, IL-8, IL-12, and IL-18. These are balanced by production of anti-inflammatory cytokines, notably IL-10 [15]. Cytokines are responsible for many of the signs and symptoms of infection, particularly fever and malaise. In addition, cytokines upregulate the endothelial expression of adhesion molecules such as intercellular adhesion molecule 1 through which *P. falciparum*-infected RBCs promoting cytoadherence, providing a pathogenic link between inflammation and adherence/sequestration. Some investigators have suggested that severe malaria and bacterial septicemia may have a common cytokine-mediated pathology [15, 24, 25]. Several studies have shown a positive correlation between blood cytokine levels and prognosis in severe *Falciparum* malaria, although the relationship is far from linear. For example, some authors [26] have found that appropriate levels of TNFα exhibit antiparasitic effects, and a high TNFα production capacity protects from severe malaria [27]. On the other hand, excessive TNFα levels are associated with complications such as severe anemia [28], and a low ratio of plasma levels IL–10/TNFα is associated with severe malarial anemia [29].

Interaction Between Malaria Parasites and RBCs

Parasite entry into erythrocytes is the key to the establishment of blood stage infection and thus is central to both acute and severe malaria. Infected RBCs have reduced deformability and altered surface characteristics and can be sequestered and destroyed by the spleen. In addition, once the parasites successfully complete the erythrocytic stage of their life-cycle, they replicate, and are released as merozoites with rupture of their host RBCs, leading to intravascular hemolysis [30]. In a recent study [31] from Mali, children with severe malarial anemia and markers of active intravascular hemolysis also demonstrated reduced whole blood levels of nitrite and increased NO consumption relative to controls, which is evidence of NO depletion. It is likely that the mechanism is similar to other hemolytic anemias, where free plasma hemoglobin reacts with NO produced by NO synthases to form biologically inactive nitrate. Because NO plays a critical role in downregulating the expression of adhesion molecules [32] and maintaining blood flow and vascular tone, the catabolism of NO and arginine from intravascular hemolysis in malaria likely promotes inflammation and endothelial activation [33], thus increasing the cytoadherence of abnormal RBCs.

Due to its complexity, erythrocyte invasion is an inefficient process and may be completed in only a small fraction of erythrocytes targeted for infection. Parasite antigens are shed during RBC entry, and many of these parasite encoded erythrocyte-adhesive proteins are present at high levels in plasma. They adhere to uninfected erythrocytes and resulting in IgG or complement binding to erythrocytes, leading to their clearance from circulation [34]. As a result of this binding, the direct Coombs test for immunoglobulins and/or complement deposited on the surface of the RBCs is frequently positive. The antibodies giving rise to the positive test are not autoimmune, but rather directed against adsorbed malarial antigens [35]. In addition to destruction of infected and uninfected erythrocytes, decreased erythrocyte production and/or suppression of the erythropoietic response contributes to the severe malarial anemia [34]. Although the cumulative data strongly support that there is imbalance of cytokines in malarial anemia, the cytokine pathways have not been fully characterized.

Sequestration

An important difference between *P. falciparum* and other human malarias is the way in which *P. falciparum* modifies the surface of the RBCs so that parasitized RBCs can adhere to the endothelium [16]. This phenomenon is called "cytoadherence" and it protects the parasite from destruction, as non-adherent, mature parasitized RBCs are cleared rapidly in the spleen [16]. As a result, only young forms ("ring") are found in the bloodstream, the rest of the parasite burden is "sequestered" in the microvascular beds of many organs. Sequestration occurs predominantly in the venules of vital organs, being greatest in the brain, heart, eyes, liver, kidneys, intestines, and adipose tissue [15]. This explains why some patients with heavy parasitemia are minimally symptomatic, whereas patients with less impressive bloodstream parasite numbers can be gravely ill, as blood parasitemia is an inaccurate marker of total body parasite burden in *P. falciparum* infections.

The mechanics of cytoadherence involve interaction between parasitized RBCs, endothelial cells, other RBCs, platelets and leukocytes. Parasitized RBCs express an adhesion molecule on their membrane, *P. falciparum erythrocyte membrane protein 1* (PfEMP1) [16]. This protein mediates adhesion to various membrane receptors, most importantly CD36 and ICAM 1, but also chondroitin sulphate A (CSA), vascular cell adhesion molecule 1 (VCAM 1), E selectin, platelet endothelial cell adhesion molecule 1 (PECAM 1), and integrins and selectins [15]. Parasitized red blood cells (pRBCs) and unparasitized RBCs (uRBCs) become less deformable during *P. falciparum* malaria and, consequently, plug the 3–7 μm-diameter capillaries with stiff RBCs, which have an average diameter of 7.5 μm [36]. The altered surface membrane of RBCs leads to micro-agglutination of parasitized RBCs as well as clumping of unparasitized RBCs around parasitized RBCs to form micro-thrombi ("rosettes") [36]. A role of complement receptor 1(CR1) in RBC rosette formation has been postulated as individuals with polymorphisms in the CR1 gene, who express low levels of CR1, show greatly reduced rosette formation, and are protected against

severe disease [37]. While the mechanisms responsible for cytoadherence and agglutination are well described, their pathologic consequences are less clear. Several mechanisms that might cause damage to host endothelium have been proposed, including mechanical obstruction of blood flow, with vascular leak and subendothelial hemorrhage, activation of endothelium, platelets and leukocytes [38], followed by systemic or local production and deposition of pro-inflammatory cytokines [16] that further upregulate the expression of the adhesion receptors, thus closing the loop between inflammation and sequestration.

The pathophysiology of severe malaria is therefore quite complex. Infection results in destruction of both infected and uninfected RBCs leading to anemia and decreased O2 carrying capacity, microvascular obstruction, and inflammation, all of which result in decreased tissue perfusion [16]. Parasite antigens are thought to activate platelets [38], which in turn provide adhesion receptors to microvascular beds originally devoid of these receptors [39]. The activated platelets contribute to the activation of the inflammatory response, increased levels of endothelial cell adhesion molecules, and sequestration. These events lead to disruption of the local microvasculature with ensuing vascular leak, potentially hemorrhage in various tissue beds.

Clinical Manifestations

The clinical manifestations of malaria are dependent on the previous immune status of the host, which varies with the age of the patient and the epidemiological context in which the infection is acquired. Holo-endemic areas (i.e. areas where essentially every individual in the population is infected) have high intensity, constant malaria transmission. Hypo-endemic or unstable transmission areas have a low, erratic, and markedly seasonal transmission pattern. In holo-endemic areas, infection is most severe in children between 1 and 3 years old. The severe manifestations, such as cerebral malaria, severe anemia, and shock are encountered in this age group and explain the high mortality rate in the pediatric population. Children less than 1 year of age are protected by passive maternal antibodies and by a higher percentage of hemoglobin F, which retards parasite development [40]. As children age, constant exposure to infection leads to a boost in immunity and a situation called "premonition", where infections cause little to no problem to the host and parasitemia may either be eradicated or continue asymptomatically. As a consequence, an individual may be parasitized, but not ill. In a symptomatic and parasitized individual, the parasites may be causing the fever or may be a "red herring" – there is no definitive means of distinguishing between malarial disease and incidental malarial infection as indicated by relative quantities of parasitemia. As a result, in endemic settings, a positive malaria test does not necessarily mean that malaria is the cause of the illness. In contrast, in hypo-endemic areas where transmission is too sporadic to promote "premonition", symptomatic infections are more common and the severe forms of disease, such as cerebral malaria, severe anemia, may be encountered at any age [15].

Malaria encountered in the United States follows similar patterns, according to the immune status of the patient. Imported malaria in travelers without previous exposure is much more likely to be symptomatic, and severe forms can be encountered in all patients irrespective of their age [15]. Conversely, children who are partially immune (e.g., newly arrived immigrants or refugees from areas where malaria is highly endemic) frequently present with signs of chronic infection, such as hepatosplenomegaly, anemia, and jaundice. It is not unusual for these patients to have very minimal symptoms, such as anorexia or decreased activity, or even to be asymptomatic [41]. A study [42] of Liberian children immigrating to Minnesota found that smears of blood from 28 to 43 patients were positive for malaria parasites. Of children with positive test results, one third were asymptomatic, and splenomegaly was the only manifestation of disease in one-third.

In most children, the first symptoms begin 10 days to 4 weeks after transmission by an infected mosquito. In exceptional cases presentation can be as early as 8 days or as late as 1 year, particularly in malaria caused by *P vivax*, *P ovale*, or *P malariae* or in children who have taken prophylaxis [43]. The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness [44]. Signs and symptoms include headache, fatigue, abdominal discomfort, muscle and joint aches, usually followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. This leads to frequent over-diagnosis in endemic areas and conversely, under-diagnosis in non-endemic areas where many other more commonly encountered illnesses are considered first. If the infection continues untreated, the fever in *P. vivax* and *P. ovale* may regularize to a 2-day cycle (tertian malaria) and *P. malariae* to a 3-day cycle (quartan malaria). *P. falciparum* remains erratic for longer and usually doesn't regularize to a tertian pattern or, conversely, may turn into a daily fever cycle (quotidian malaria) [15] Older textbooks used to emphasize the diagnostic importance of these "fever charts", however many clinical studies have showed that these are neither sensitive nor specific for a diagnosis of malaria and reliance on the fever periodicity may miss a significant number of cases [30].

In a host without immunity and in the absence of effective treatment, the parasite burden continues to increase and severe malaria may ensue. The WHO definitions for severe malaria are listed in Table 37.2 [45]. This progression may occur within a few hours, although the risk factors and the specific pathogenic mechanisms of development of severe

Table 37.2 WHO definition of severe malaria is one or more of the following features

Clinical features
Cerebral malaria: coma/altered mental status/more than two seizures in 24 h
Respiratory distress (more likely from metabolic acidosis than true ARDS)
Circulatory collapse or shock, SBP <70 mmHg in adults and <50 mmHg in children
Cinical jaundice plus evidence of other vital organ dysfunction
Hemoglobinuria
Abnormal spontaneous bleeding
Pulmonary edema
Laboratory findings
Hypoglycemia (blood glucose <40 mg/dl)
Metabolic acidosis (plasma bicarbonate <15 mmol/l)
Severe normocytic anemia (Hb <5 g/dl, Ht <15 %)
Hyperparasitemia (>2 %–100,000/μl in low or >5 %–250,000/μl in high intensity transmission areas
Serum lactate >5 mmol/l
Renal impairment

Based on data from Refs. [44, 45]

malaria are still subject to controversy. Hyperparasitemia as a marker of disease severity should be interpreted with caution. Two patients with the same peripheral parasitemia may have as much as a 100-fold difference in the total number of parasites in the body. In "benign" malarias (non-falciparum) where there is no sequestration, blood parasitemia is a reliable estimate of total parasite biomass. However in *P. falciparum* malaria, only the first third of the asexual life cycle can be seen and the remaining two-thirds of the parasitized cells are sequestered. As a consequence there might be large discrepancies between the number of parasites in the peripheral (circulating) blood and the number of parasites in the body (the parasite burden) – sequestration "hides" the parasites causing harm. As such, some patients appear to tolerate high parasitemia with little adverse effect, whereas others die with low parasite counts [15] (notwithstanding the role of covert co-infections). The predominance of more mature parasites on the blood film suggests greater sequestered parasite biomass and carries a worse prognosis for any parasitemia than a predominance of younger forms. The presence of intra-neutrophilic phagocytosed malaria pigment (more than 5 % of the neutrophils) also reflects the degree of previous schizogony and is also a valuable prognostic index. Measurement of proteins released by the parasite such as Pf HRP2 in plasma provides a good method of assessing this hidden pathogenic sequestered biomass [46] – a useful addition in cases where the severity of the disease seems discrepant with the measured parasitemia. The case fatality in people receiving treatment for severe malaria is typically 10–20 % [44]. However, if left untreated, it is fatal in the majority of cases.

Cerebral Malaria

Cerebral malaria is one of the deadliest complications of severe malaria. It is defined by the WHO as "unarousable coma in a patient with *P falciparum* parasitemia in whom other causes of encephalopathy have been excluded" [44]. Although the term implies a distinct disease entity, the clinical syndrome is highly variable, with most cases falling into one of three main categories [20] characterized by coma with (or due to) (1) marked physiological derangement (severe anemia, metabolic acidosis, hypoglycemia, respiratory distress, shock; (2) protracted or multiple seizures, where unconsciousness might be caused by a long (>1 h) postictal state or by subclinical or subtle seizure activity; (3) a pure neurological syndrome of coma and abnormal motor posturing, which might be complicated by raised intracranial pressure and recurrent seizures.

The differential diagnosis of fever and encephalopathy in children is quite broad, including many infectious, metabolic, and oncologic processes. However, the positive predictive value of malarial parasitemia for cerebral malaria in the appropriate clinical context is quite high in a hypo-endemic or non-endemic area such as the US or Europe. On the other hand, as discussed above, in holo-endemic areas the presence of malaria parasitemia can be an incidental finding. In addition, "exclusion of other causes of encephalopathy" as required in the WHO definition of cerebral malaria may call for investigations that are not routinely available in developing countries. Without a standard diagnostic criterion for cerebral malaria, a useful clinical indicator is the presence of malarial retinopathy, which consists of retinal whitening – as a consequence of retinal ischemia, vessel changes (whitening, "tramlining"), retinal hemorrhages, and papilledema as seen in Fig. 37.3 [47]. In a prospective autopsy study [48] from Malawi, 24 % of the children who fulfilled the usual criteria for cerebral malaria before death had evidence at post mortem of an alternative cause for the coma. The presence of malarial retinopathy had a positive predictive value of 95 % and a negative predictive value of 90 % for fatal cerebral malaria in comatose parasitemic patients from Malawi [48, 49]. The absence of malarial retinopathy, or finding isolated papilledema or retinal hemorrhages should alert the clinician to the possibility of other causes of coma, particularly if the coma is prolonged.

Almost all patients with cerebral malaria present with fever, rigors, chills, headache, and vomiting. Altered sensorium might be present from the outset, or might develop slowly over a period of several days. Signs of irritability, restlessness or psychotic behavior can be the initial manifestations of cerebral involvement. In children with cerebral malaria, coma usually develops rapidly, and often follows seizures. In children with cerebral malaria, seizures occur in approximately 60–70 % of cases [50]. In a study [51] of 65 Kenyan children with cerebral malaria, 40 (62 %) had

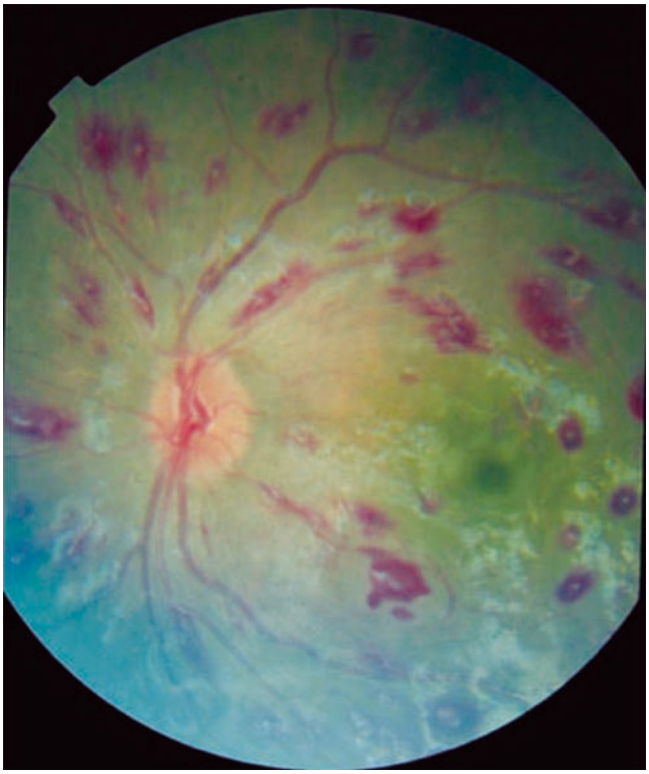

Fig. 37.3 Malarial retinopathy. Photograph of the retina in a patient with cerebral malaria, which shows exudates (i.e. retinal "whitening"), hemorrhages and changes in the color of the blood vessels (Reprinted from Ref. [47]. With permission from Nature Publishing Group)

seizures after admission and ten (15 %) had subtle seizures, manifesting as nystagmoid eye movements, irregular breathing, excessive salivation, and conjugate eye deviation. Seizures were often repetitive and prolonged, and 18 children (28 %) had an episode of status epilepticus. Brainstem signs are common and are associated with other features of high intracranial pressure [50]. Common signs include changes in pupillary size and reaction and disorders of conjugate gaze and eye movements. Other signs include abnormal respiratory patterns, motor abnormalities of tone and reflexes (usually upper motor neuron), posturing (decerebrate, decorticate, or opisthotonic posturing) – the latter usually associated with cerebral edema.

Intracranial hypertension occurs in virtually all children with cerebral malaria [47, 52]. While the etiology is multifactorial, the most likely cause is increased cerebral blood volume as a result of sequestration of infected and noninfected erythroctyes [50], coupled with an alteration of the blood – brain barrier [48]. Focal disruptions in the barrier at sites of sequestration could result in the exposure of sensitive perivascular neuronal cells to plasma proteins and increased concentrations of cytokines and metabolites caused by abnormalities in microcirculation. Although most children with cerebral malaria regain consciousness within 48 h and seem to make a full neurological recovery, approximately 20 % die and 10 % have persistent neurological sequelae [50].

Severe Malarial Anemia

Severe malarial anemia, defined as hemoglobin concentration <5 g/dL in the presence of *P. falciparum* parasitemia, is more common in children than in adults, with a peak incidence between 1 and 3 years of age [35]. The underlying causes of severe malarial anemia are multifactorial and involve both direct and indirect destruction of parasitized and nonparasitized erythrocytes, ineffective erythropoiesis, and dyserythropoiesis [34]. Mortality of children with asymptomatic severe malarial anemia is low (around 1 %), but rises to more than 30 % when anemia is complicated by severe respiratory distress and metabolic acidosis [53]. "Blackwater fever" is a rare, but feared complication. A rapid and massive intravascular hemolysis of parasitized and nonparasitized red blood cells results in hemoglobinuria and acute onset anemia and is accompanied by high fever, hepatic involvement, and renal failure. Unfortunately, even with aggressive treatment, this complication is often fatal [23]. Activation of the coagulation cascade and platelets has been widely reported in malaria [39]. Typical disseminated intravascular coagulation (DIC) with the presence of bleeding is reported in 5–10 % of severe malaria cases [23] – 1 % of all cases – probably less frequently in children. Thrombocytopenia is a common finding and is attributable to sequestration in the spleen or increased consumption secondary to activation of coagulation system.

Severe malaria is a complex syndrome affecting many organs and metabolic acidosis is both an important component of the syndrome and the major predictor of a poor outcome [54]. Table 37.3 lists some uncommon manifestations of severe malaria in children [45]. The etiology of the metabolic acidosis in this case is multifactorial and includes increased lactate production from the parasite, decreased hepatic metabolism [15], recent seizure activity, hypovolemia, cardiac dysfunction and sequestration obstructing the microvasculature causing tissue hypoxia. While the relative contribution of each of these factors is still subject to debate, it is likely that hypovolemia, by causing a volume concentrated and sluggish circulation, acts synergistically with other factors leading to cytoadhesion, increasing the likelihood of microvascular obstruction. In children, respiratory distress (deep breathing, Kussmaul's respiration, tachypnea) is usually a clinical sign of metabolic acidosis [15]. It can be misinterpreted as cardiac failure and circulatory overload, which rarely occurs in children [55].

A less common pulmonary manifestation of severe malaria is ARDS. Its pathogenesis includes cytoadherence with sequestration followed by changes in endothelial permeability, as well as immune/inflammatory mediated lung injury [23]. In addition, bacterial pneumonia or aspiration caused by impaired mental status may be aggravating factors of lung injury.

Hypoglycemia (blood glucose concentration <45 mg/dL) is associated with a poor outcome in children with malaria [24]. It results from impaired hepatic gluconeogenesis [15], however it can be compounded by quinine induced hyperinsulinemia. Severe hypoglycemia can lead to altered mental status and seizures. Current guidelines [44] recommend monitoring serum glucose concentration every 4 h, especially in unconscious patients.

Acute renal failure caused by acute tubular necrosis is a fairly frequent complication of severe malaria especially in non-immune European or US adults, but is rare in children. The postulated mechanism is thought to be sequestration of parasitized and nonparasitized RBCs with consequent microvascular ischemia leading to acute tubular necrosis [23], although other factors such as hypovolemia, intravascular hemolysis with hemoglobinuria, superimposed bacterial sepsis with DIC may also contribute. In some cases, immune complex deposition and/or autoimmune reactions to glomerular structures induced by the parasite are thought to result in glomerulonephritides or nephrotic syndrome, especially in children.

Table 37.3 Less frequent manifestations of severe malaria in children

CNS
Spontaneous subdural empyema
Subdural hemorrhage/intracranial hemorrhages
Central pontine myelinolysis
Acute disseminated encephalomyelitis
Pulmonary
Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)
Secondary bacterial pneumonia
Pleural effusion
Gastrointestinal and hepatic
Malarial hepatitis and jaundice
Acute liver failure
Spontaneous splenic rupture (especially with *P. vivax* and *P. ovale*)
Acute pancreatitis
Hematologic
Thrombocytopenia
Anemia
Purpura fulminans
Acquired hemophilia A
Hemophagocytic syndrome

Based on data from Ref. [23]

Laboratory Findings and Diagnosis

There are several methods for detecting malaria parasites in the blood, including direct microscopy, rapid antigen detection testing (RDT), and polymerase chain reaction (PCR). Light microscopy has long been considered the gold standard for making the diagnosis of malaria. Parasites are directly observed in thick or thin blood smears as seen in Fig. 37.4 [56]. The thick film preparation is more sensitive, but is more difficult to interpret by inexperienced examiners [30]. The thin smear is used to identify the *Plasmodium* species and to perform a quantitative assessment of parasite burden. While considered a "gold standard", the sensitivity and specificity of direct microscopy is variable. In resource poor settings, a study [57] found 25–100 % sensitivity and 56–100 % specificity of microscopy done at rural health centers in Zambia compared with reference laboratory microscopy. In non-endemic areas, where access to equipment is less of a concern, lack of experienced microscopists and the relative rarity of the diagnosis also can result in significant delays and errors in diagnosis [58].

"Rapid Diagnostic Tests" (RDTs) are immunological antigen detection tests in a dipstick or cassette format that can give a diagnosis in minutes. The sensitivity and specificity of the RDT's vary with the species and the antigen targeted [59]. In a recent meta-analysis comparing performance of RDTs with the reference standard – microscopy – with or without PCR, the average sensitivities of the most commonly used RDTs were 93–95 %, while the average specificities where 95–98 % [60]. Caution needs to be exercised when translating these performance characteristics from an

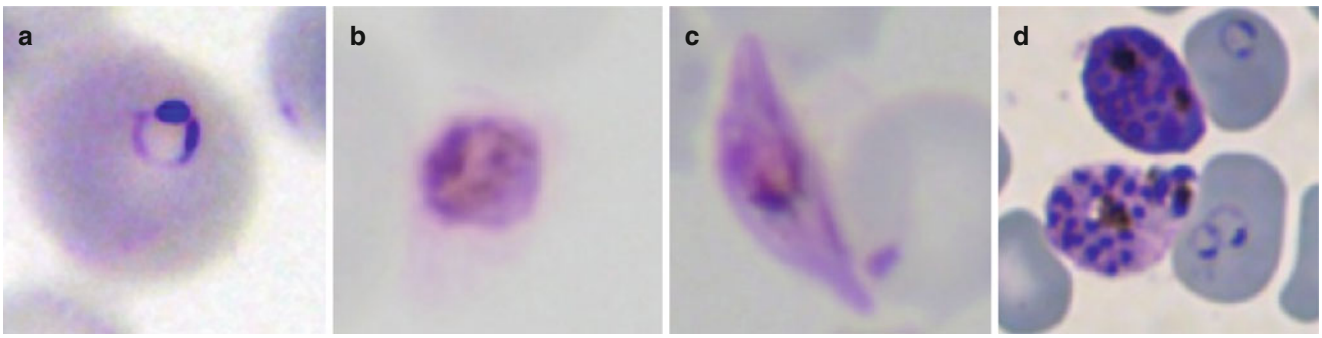

Fig. 37.4 Direct microscopic diagnosis of malaria. (**a**) *P. falciparum* ring, (**b**) trophozoite, (**c**) gametocyte, (**d**) schizont (Reprinted from Ref. [56]. With permission from BioMed Central, Ltd)

Table 37.4 Parenteral treatment options for malaria by severity

Uncomplicated malaria
Atovaquone plus proguanil (once a day for 3 days)
Artemether plus lumefantrine
Dihydroartemisinin plus piperaquine
Quinine plus doxycycline or clindamycin
Severe malaria
Artesunate 2.4 mg/kg IV or IM is given on admission (time = 0), then at 12 h and 24 h, then once a day for a minimum of 24 h or until clinical improvement occurs.
Artemether or quinine are acceptable alternatives if parenteral artesunate is not available:
Artemether 3.2 mg/kg IM is given on admission then 1.6 mg/kg per day
Quinine 20 mg salt/kg on admission loading dose (IV infusion or divided IM injection), then 10 mg/kg/dose every 8 h; infusion rate should not exceed 5 mg salt/kg/h

endemic to a non-endemic area, because the sensitivity of the RDTs decreases sharply when parasite density is below 200/μl, as may be the case with imported malaria. A positive test is useful, though a negative test should be confirmed by serial microscopy [61]. In the US, there is only one RDT approved by the FDA, *Binax Now*®. Its use is unlikely to become widespread, because the manufacturer requires that the laboratory prepare a positive test with known malaria infected blood for quality assurance each time a sample is tested with the RDT and malaria infected blood is not routinely stocked in most laboratories [59]. While potentially useful in the acute setting where an urgent diagnosis is needed, the RDTs cannot be used to monitor response to therapy as the malarial antigens persist up to 3 weeks in spite of successful treatment [61].

Polymerase chain reaction (PCR) is increasingly being used as the "gold standard", being capable of detecting parasites below the threshold for microscopic identification [62]. PCR is particularly advantageous in patients who have very low parasite levels, have taken chemoprophylaxis with consequent alteration in the morphology of the parasites, or in non-endemic settings where experience with direct microscopy is not as extensive. Other ancillary tests supporting a diagnosis of malaria include an elevated C-reactive protein, an elevated procalcitonin, thrombocytopenia, anemia, neutropenia, elevated liver function tests, and albuminuria [17].

Treatment

The first step in managing a child with suspected malaria is to determine whether the infection is uncomplicated, in which case the patient may be managed on a general pediatric ward or even as an outpatient. Alternatively, if the infection is a severe case (cerebral malaria or severe malarial anemia), treatment in a closely monitored setting is usually recommended. Additional factors to consider in triaging children towards admission to a closely monitored or ICU setting include evidence of dehydration, inability to take or comply with oral medications requiring parenteral antimalarial treatment, or coexistence of malaria and sickle cell anemia [43]. In holo-endemic areas in particular, with high rates of asymptomatic malarial infections, coexisting or alternative illnesses causing a clinical picture suggestive of severe malarial anemia should be aggressively pursued. The most common differential diagnoses include meningoencephalitis, pneumonia, infectious or metabolic encephalopathy, other causes of severe anemia, and septic shock. In this epidemiological context, falciparum malaria is a diagnosis of exclusion, in which three negative blood smears at 8–12 h intervals are required before the diagnosis can be ruled out. In the meantime, the systemically ill patient is started on empiric parenteral antimalarial therapy as detailed below, in addition to broad-spectrum antibiotic therapy as clinically indicated. The WHO guidelines for therapy and particularly parental treatment options for malaria by severity are listed in Table 37.4 [44, 45].

Severe malaria is a medical emergency because the mortality of untreated severe malaria (particularly cerebral malaria) is thought to approach 100 %. Death from severe malaria often occurs within hours of admission, so it is essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible. According to the WHO guidelines, after rapid clinical assessment and a strong suspicion of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with *any effective antimalarial first available* [44, 45]. The mainstay of therapy was intravenous quinine or quinidine until the results of a randomized controlled trial comparing standard therapy – parenteral quinine versus artesunate were published in 2011 [63]. This study recruited 5,425 participants in an open-label randomized trial. Artesunate treatment was shown to significantly reduce the risk of death from severe malaria compared to intravenous quinine: RR 0.76, 95 % CI 0.65–0.9. No difference was found in the risk of serious neurological sequelae at day 28. Artesunate therapy was also associated with a lower risk of hypoglycemia compared to quinine. Artesunate also

Table 37.5 Parenteral to enteral options for full treatment course of severe malaria

Severe malaria options for parenteral to enteral transition
Artemether plus lumefantrine,
Artesunate plus amodiaquine
Dihydroartemisinin plus piperaquine
Artesunate plus sulfadoxine-pyrimethamine
Artesunate plus clindamycin or doxycycline
Quinine plus clindamycin or doxycycline

has the advantage of not requiring rate controlled infusion or cardiac monitoring during administration and no need for dose modification in renal failure [23]. Conversely, administration of parenteral quinine is fraught with the potential dangers of cardiac arrhythmias – cardiac telemetry is mandatory. If the QRS becomes prolonged more than 50 % its baseline value, or QTc > 600 msecs or >25 % baseline, the infusion should be stopped [23]. As mentioned above, quinine can also cause hypoglycemia through direct stimulation of insulin secretion. The loading dose of quinine should not be given if the patient has received quinine, quinidine, or mefloquine during the previous 24 h [44]. Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if no other effective parenteral drugs are available. Parenteral chloroquine is no longer recommended for the treatment of severe malaria, because of widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended [44]. Parenteral antimalarials should be administered for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, a 7 day treatment course should be completed with the enteral combinations listed in Table 37.5 as described by the WHO [44, 45]. Treatment should be monitored closely. Along with clinical improvement, parasite clearance should also be demonstrated by following daily parasite counts. In the first 24–36 h of therapy, it is possible for the parasite count to rise and this does not indicate failure of therapy [23]. However if the counts do not start to fall by 48 h and/or do not clear by day 7, resistance to the chosen course of chemotherapy is likely.

Adjuvant Management

Initial management is based on that of any acutely and severely ill patient. A rapid clinical assessment should focus on airway patency, early recognition of impending respiratory failure and shock, and neurological assessment. Hypoglycemia should be ruled out or treated empirically. The following discussion will focus on specific complications of severe malaria.

Cerebral Malaria

Children presenting with fever and altered mental status, even with a positive malaria parasitemia, should have further investigations performed in parallel with starting parenteral antimalarial treatment. Most authorities [23, 44, 45, 52, 64] recommend obtaining a lumbar puncture and starting empiric antibiotics at meningitic dosing, pending culture results. The cerebrospinal fluid (CSF) findings in cerebral malaria are generally unremarkable – mild pleocytosis, slightly elevated protein, and a normal glucose level [41]. In a child with neck stiffness or a full fontanel, other infections of the CNS or intracranial hemorrhage should be considered rather than cerebral malaria [43]. Other investigations, such as head imaging, viral studies, tuberculosis testing, toxic or metabolic screening should be performed as clinically indicated. Given the high incidence of seizures in cerebral malaria and the possible occurrence of subclinical status, EEG monitoring should be strongly considered.

Supportive treatment of cerebral malaria follows the general management principles of non-traumatic intracranial hypertension – support of the airway with mechanical ventilation as needed, maintenance of normocapnia, isotonic fluids, seizure control, aggressive fever control (preferably avoiding NSAIDS), avoidance of hypoxia, hypotension and hypoglycemia. Given that most cases of cerebral malaria in children are cared for in severely limited resource settings, there is scarce literature on using advanced therapies such as controlled mechanical ventilation, use of osmolar agents, or intracranial pressure monitoring. In a small study from Kenya [52], mannitol was successful in transiently reducing intracranial pressure but no convincing clinical evidence emerged supporting its use. However patients in this study were not ventilated and they were supported with hypotonic fluids (1/8 saline in Dextrose 4 % solution according to the local protocol), hence the results are difficult to evaluate in reference to the standard management of intracranial hypertension in resource-rich ICUs.

Severe Malarial Anemia

In the sickest children with severe malarial anemia and lactic acidosis, early transfusion, preferably of whole fresh blood, is indicated [15]. In children with severe malarial anemia but no signs of decompensation, the indications for transfusion are less well defined. The WHO recommends using a cutoff of Hb < 5 g/dL in high transmission settings and less than 7 g/dL in low transmission settings [44]. However, these general recommendations still need to be tailored to the individual, as the pathological consequences of rapid development of anemia are worse than those of acute on chronic anemia, where there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

Exchange transfusion has been initially tried for patients with hyperparasitemia and multi-organ failure in adult ICU

settings. The rationale [44] for exchange blood transfusion has been proposed as:

- removing infected RBCs from the circulation and, therefore, lowering the parasite burden (although only the circulating relatively non-pathogenic stages are removed; this is also achieved rapidly with artemisinin derivatives);
- reducing rapidly both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host; and
- replacing the rigid unparasitized red cells by more deformable cells, therefore alleviating microcirculatory obstruction.

A meta-analysis of 12 studies concluded that adjunct RBC exchange transfusion did not improve survival as compared to antimalarial chemotherapy alone [65]. The current WHO guidelines [44] do not make any recommendation about exchange transfusion for management of severe malaria. Some authors of a proposed guideline [43] for the management of imported pediatric malaria in the UK suggested that exchange transfusion might be considered in patients with persistent acidosis and multi-organ impairment who are not responsive to resuscitation and adequate anti-infective treatment. The authors caution that exchange transfusion remains an experimental treatment and there is no consensus on the indications, benefits and dangers involved, or on practical details such as the volume of blood that should be exchanged.

Metabolic acidosis is a consistent feature of severe malaria but differs fundamentally from that associated with sepsis [15]. The relative importance of hypovolemia versus microvascular obstruction in the pathophysiology of acidosis is controversial. Small studies [54] have found evidence for hypovolemia in children with severe malaria. Standard fluid resuscitation (20 mL/kg aliquots rapid infusion as typically used in pediatric septic shock) resulted in improvement in hemodynamic parameters and clinical condition in small series. These findings are contradictory to classical teachings that urge caution with vigorous intravenous volume expansion in severe malaria, specifically with concerns of precipitating pulmonary edema and/or intracranial hypertension.

In an effort to address the controversies surrounding fluid resuscitation in severely ill children with malaria and other conditions, a recent large randomized trial – the Fluid Expansion As a Supportive Therapy (FEAST) trial [66] included 3,141 children in Uganda, Kenya and Tanzania with febrile illnesses and signs of poor perfusion. Importantly, 57 % of the patients in this study had severe malaria. The investigators found that bolus fluid resuscitation consisting of 20–40 mL/kg of either albumin or saline, as compared with controls – 2–4 mL/kg/h maintenance fluids (i.e. no fluid bolus), increased the absolute risk of death at 48 h by 3.3 % and the risk of death, neurologic sequelae, or both at 4 weeks by 4 %. In the subgroup of children with severe malaria, fluid resuscitation increased mortality as well – OR 1.59 (1.10–2.31). The trial included children with malaria, sepsis, pneumonia and meningitis, randomizing all children across treatment arms, even though recommendations for fluid resuscitation are different among these conditions. The authors argue that in sub-Saharan Africa, where resources are very limited, positive diagnosis is not possible at the time of admission to the hospital, and a uniform approach has to be employed for treating severely ill children with very different clinical conditions that present in a similar manner. While the results of this study caution against liberal fluid resuscitation where facilities for advanced diagnostics and monitoring are unavailable, their applicability is probably somewhat limited to those same settings. Conversely, at least for now, in more resource-rich settings, it seems reasonable to identify and treat hypovolemia and/or distributive shock according to the usual Pediatric Advanced Life Support (PALS) guidelines and employ the usual parameters to guide treatment (restoration of peripheral perfusion and urine output, central venous pressure, artificial ventilation as necessary). In children presenting with coma, a more cautious approach to volume expansion should be employed [43], maintaining the fine balance between risk of aggravating cerebral edema and the necessity of an adequate cerebral perfusion pressure.

In cases of refractory shock or unexplained clinical deterioration, "algid malaria" which is a bacterial infection superimposed on acute malaria should be aggressively searched for and treated. In a recent study [67] from rural Kenya, the prevalence of bacteremia was 11.7 % among children presenting with malaria, the most frequent isolate being non-typhoidal salmonella, followed by *Staphylococcus aureus* bacteremia. Broad-spectrum antibiotic therapy should be used, especially for severely ill children, until a bacterial infection is excluded. In addition, nosocomial infections such as UTIs or ventilator-associated pneumonias can occur and should be treated according to the local guidelines.

Dengue

Epidemiology

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, the incidence of dengue has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. The rising incidence over the last 50 years can be seen in Fig. 37.5 [68]. The reasons for the global resurgence of epidemics of dengue include large scale population growth and migration of viremic humans to new geographic settings with a suitable vector and susceptible population [69]. In addition, the uncontrolled urbanization that has occurred in the last 30 years, as well as the tremendous growth in international trade have facilitated transmission and increased densities of *Aedes* – borne disease [70, 71].

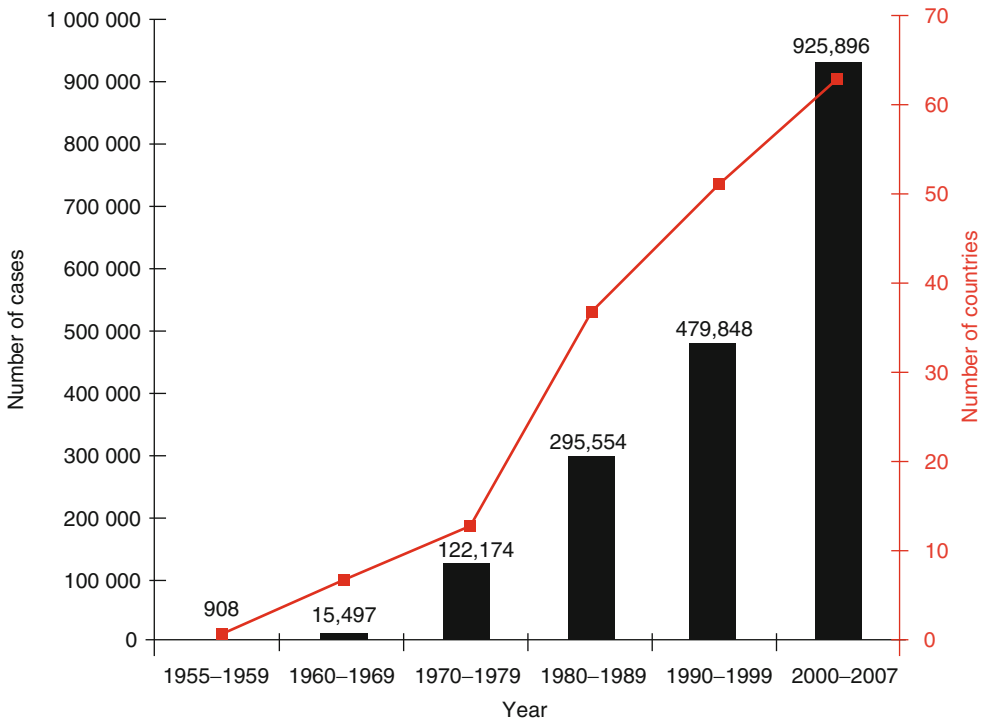

Fig. 37.5 Average annual number of dengue fever and dengue hemorrhagic fever reported to WHO and of countries reporting dengue, 1955–2007 (Reprinted from Ref. [68]. With permission from World Health Organization (WHO))

Dengue infections span a spectrum of illness ranging from asymptomatic to life-threatening severe dengue which also is known as Grade III-IV DHF and in the past has been referred to as dengue shock syndrome (DSS) [72]. Each year there are an estimated 50–100 million dengue infections worldwide, of which 500,000 are cases of DHF with 20,000 deaths, mainly in children [15]. Case fatality rates vary from 1 to 5 % but can be less than 1 % with appropriate treatment [68]. An important detail in the reported epidemiology of this disease is that the cases reported likely represent only a percentage of the true incidence, as in many countries dengue only became a reportable disease since 2000. For instance, in the USA dengue fever first became a reportable disease in 2009.

Dengue is a worldwide condition spread through the tropical and subtropical zones, where environmental conditions are optimal for dengue virus transmission by the highly "domesticated" *Aedes* mosquitoes, classically *Aedes aegypti*. The most seriously affected regions are South East Asia and the Western Pacific region, followed by Central and South America, Africa and the Eastern Mediterranean regions. According to the WHO [68], the majority of notified cases of dengue in Canada and the US are persons who had travelled to endemic areas. From 2001 to 2007, 796 cases of dengue were reported in the US, the majority imported. The diagnosis should be considered in any patient developing fever within 14 days after even a brief trip to the tropics or subtropics, including those regions where dengue has not traditionally been considered an endemic disease [69].

It is important to note however that not all US cases of dengue are imported. Outbreaks of dengue in Hawaii and southern Texas have been reported [68]. A serological survey [73] in Brownsville, Texas a city on the border with Mexico, found that 38 % of surveyed residents had IgG antibodies to dengue, indicating that a substantial proportion of the city population had been infected with the dengue virus transmitted locally. The introduction and spread of a secondary dengue virus vector into the US in 1985, the *Aedes albopictus* mosquito, means that wide-spread appearance of dengue in the continental US could be a real possibility [74].

Etiology

Dengue is an acute, febrile infection caused by one of four dengue viruses (DENV-1, DENV-2, DENV-3 and DENV-4), members of the family Flaviviridae (same genus as yellow fever virus, West Nile virus, St. Louis encephalitis virus, and Japanese encephalitis virus), belonging to the Arboviruses. Dengue virus is transmitted from human to human by mosquito bites – the vector is the female *Aedes* mosquito, which, once infected, remains infective for life (30–45 days). Man is the main reservoir of the virus [15]. Viremia in susceptible humans begins between 3 and 6 days after subcutaneous injection, lasts for another 3–6 days, and ends as the fever resolves [71, 75]. Dengue can essentially be excluded as the cause of symptoms in a traveler who develops an illness more than 14 days after returning from a tropical or subtropical country [76]. Lifetime immunity follows infection by one serotype, but immunity to the other serotypes is short-lived [15] and is actually involved in the pathogenesis of severe

dengue when reinfection with a different serotype occurs (see below). Infectious virus and the virus-encoded non-structural protein 1 (NS1) are present in the blood during the acute (febrile) phase, and high-level early viremia and NS1 antigenemia have been associated with more severe clinical presentations [15, 77, 78].

Pathophysiology

All four dengue serotypes are capable of causing a clinical spectrum of illness ranging from undifferentiated febrile illness (dengue fever) to severe DHF/DSS, depending on the immune status and age of the host, primary vs. secondary infection, and an array of other putative factors. DHF/DSS occurs predominantly in children under the age of 16 years and is generally associated with secondary dengue infections [15]. Both the undifferentiated viral syndrome, seen in young children (from first-time infection) and the classic dengue fever or "breakbone fever" seen in older children and adults (from secondary infections), are self-limited diseases that require minimal supportive therapy and have with excellent prognosis [15]. The focus of our discussion will therefore be severe dengue also known as DHF/DSS in the old classification scheme (see further discussion below).

The major pathophysiological processes that distinguish severe DHF from mild dengue are an abrupt onset of vascular leakage, with effusions, ascites and ensuing hypovolemic shock, accompanied by thrombocytopenia and a hemorrhagic diathesis [79]. The acute onset of hypovolemic shock – usually due to low plasma volume and less frequently due to hemorrhage – and the often dramatic clinical recovery with fluid resuscitation, argue in favor of a transient functional increase in plasma vascular permeability that results in plasma leakage [15]. A characteristic feature of severe DHF is that it manifests clinically between days 4 and 6 of the illness, a time when the viremia is in steep decline and the host immune response is well established. The timing of these events suggests the host proinflammatory response, rather than direct virus-mediated effects, mediates the vascular permeability syndrome leading to DSS [80]. However, in spite of extensive research, little is known of the exact mechanisms underlying the change in vascular permeability. The prevailing view is that dengue infection triggers an immunopathogenic cascade that alters microvascular structure or function in some as yet undefined way, resulting in a transient, spontaneously-reversible increase in permeability [81].

In the first few days of clinically apparent infection, there is an innate immune response in all patients [69, 82]. Gene expression studies have shown that blood leukocytes in the early acute phase of dengue relative to the late convalescence phase overexpress genes related to antiviral responses, innate immune responses and inflammatory pathways [80]. Overproduction of cytokines by dengue virus-infected cells or by activated lymphocytes is believed to be critical in pathogenesis [83, 84]. In addition, NS1, the major nonstructural dengue virus protein, which can be either expressed on the surface of infected cells or released in the plasma, is an important trigger for complement activation [79]. Together, complement activation products and cytokines may act synergistically to produce vasoactive and cytotoxic effects by directly targeting the vascular endothelium, resulting in vascular leakage.

Serologic-epidemiological studies in Cuba [85] and Thailand [86] consistently support the role of secondary infection with a different serotype as a risk factor for severe dengue, which is also regularly observed during primary infection of infants born to dengue-immune mothers. This immunopathogenic model hypothesizes that low circulating antibody titers from a primary infection bind to epitopes on the heterologous infecting virus and facilitate its entry into Fc-receptor-bearing cells [68]. This paradoxically results in an increased number of infected cells, a higher viral burden, and induction of a "cytokine storm" that will contribute to the syndrome of increased capillary permeability that characterizes severe dengue.

There is still controversy as to whether direct infection of endothelial cells with the dengue virus contributes to the pathogenesis of the increased vascular permeability. Infection of endothelial cells by dengue virus has been studied *in vitro* but has resulted in conflicting findings; the role of endothelial cells in dengue disease pathogenesis remains incompletely understood [87]. A postulated mechanism includes activation and apoptosis of human microvascular endothelial cells, with disruption of the inter-endothelial cell junctions [88]. Other studies have suggested a role for vascular endothelial growth factor (VEGF) [82] or alterations in β integrin expression on the surface of the infected endothelium [89]. Another plausible pathophysiological mechanism for the increased vascular permeability characteristic of severe dengue is a transient disruption in the function of the endothelial gylcocalyx layer [69]. This layer covers the luminal surface of vascular endothelium throughout the body and is composed of a hydrated mesh, rich in carbohydrates and in dynamic equilibrium with plasma constituents. The endothelial glycocalyx has important roles in transduction of shear stress, regulation of leukocyte-endothelial cell interactions, regulation of clotting and complement cascade and it contributes to the permeability of the capillary wall [90]. Supporting the hypothesis of increased systemic permeability due to damaged glycocalyx is the observation that urinary clearance of albumin and other macromolecules is increased in children with active dengue infection [91]. In addition, both the virus itself and dengue non-structural protein (NS1) are known to adhere to heparan sulfate, a key structural element of the glycocalyx [69], and increased urinary

heparan sulfate excretion has been detected in children with severe infection [92, 93]9392.

In spite of its name (DHF), hemorrhage is not the major determinant of shock in severe dengue hemorrhagic fever. Self-limited muco-cutaneous hemorrhage is common, while overwhelming hemorrhage occurs less often. When it does occur, it can involve the gastrointestinal tract, skin, heart (pericardium), pleura, lungs or periadrenal tissue [94]. The pathogenesis of hemorrhage includes vascular changes, including capillary fragility (the basis of the tourniquet test), thrombocytopenia – due to both decreased marrow production and increased consumption, platelet dysfunction and disseminated intravascular coagulation (DIC) [95], the latter usually in the setting of prolonged shock. While all these changes have been noted, they are seldom severe enough to cause the overwhelming hemorrhage that can occur in DHF [96]. An alternative explanation comes from studying the Ebola virus, another arbovirus belonging to the Filoviridae family. Recent work has demonstrated that Ebola virus produces a viral glycoprotein that infects endothelial cells and causes vascular cytotoxicity, leading to entothelial loss and vascular leak and hemorrhage [97]. Some authors speculate that this mechanism may be shared by other arboviruses causing viral hemorrhagic fevers, including dengue [96]. Others are circumspect, given the lack of direct evidence [98, 99].

Disease Classification and Clinical Course

Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness, dengue fever (DF), or dengue hemorrhagic fever (DHF). In addition, a few patients experience unusual manifestations that are grouped under the name of "expanded dengue syndrome". The clinical course of the infection is often unpredictable in an individual patient, although certain risk factors have been identified. The classification of dengue infections has undergone many revisions, all with the same goal of proper triage of cases that are potentially life threatening and thus require more intensive monitoring and therapeutic management in areas with limited resources. In 2012 the WHO differentiated dengue fever into uncomplicated dengue and severe dengue. Warning signs were described to help identify clinical changes indicative of a transition to the severe classification. This WHO classification is shown in Table 37.6 [72].

Most cases of dengue fever have no signs of bleeding, except a positive tourniquet test (also known as the Rumpel-Leede Capillary-Fragility Test – a blood pressure cuff is inflated to the midpoint between systolic blood pressure and diastolic blood pressure for 5 min), which is defined by the presence of 10–20 petechiae per a 1 in. diameter circle, as seen in Fig. 37.6 [100]. Despite the name DHF and DF is not hemorrhage but rather the presence of capillary leak.

Table 37.6 WHO 2009 dengue classification

Dengue fever	Reside or travel to endemic area
	Fever and 2 of the following:
	Nausea, vomiting
	Headache
	Rash
	Myalgias, arthralgias
	Tourniquet test positive
	Leukopenia (<5,000 cells/mm^2)
	Mild thrombocytopenia (<150,000 cells/mm^2)
	Mild elevation in HCT (5–10 %)
	No other evidence of plasma leakage
Warning signs	Abdominal pain
	Persistent vomiting
	Edema, other fluid accumulation
	Mucosal bleeding
	Lethargy or restlessness
	Hepatomegaly (>2 cm)
	Increase in HCT and decreased platelet count
Severe dengue	Severe plasma leakage
	Shock (DSS)
	Edema, pulmonary edema, effusions, ascites, hypoalbuminemia
	Severe bleeding
	Severe organ dysfunction including:
	Altered mental status
	Transaminitis (AST or ALT >1,000)
	Multiple organ failure

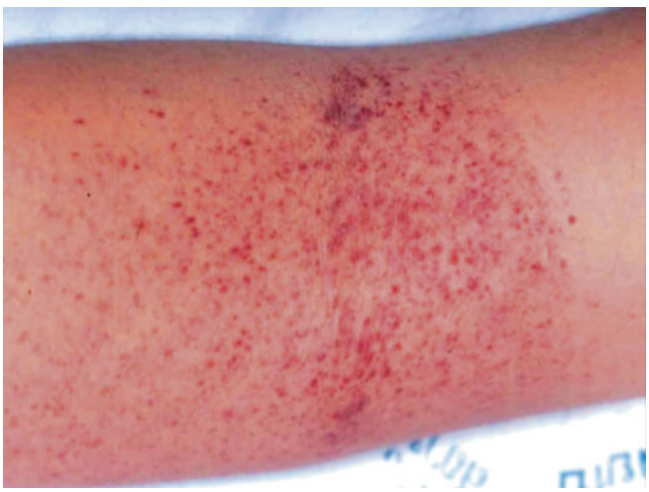

Fig. 37.6 Positive tourniquet test (Reprinted from Ref. [100]. With permission from Oxford University Press)

Evidence of plasma leakage includes hemoconcentration (10–20 % from baseline (if available), hypoproteinemia, and/or pleural effusion and ascites which are the most objective signs of plasma leakage [101]. Severe plasma leakage will result in shock and DHF III, IV are characterized by

Table 37.7 WHO classification of dengue hemorrhagic fever severity

DF/DHF	Grade	Signs and symptoms	Laboratory
DHF	I	Fever	Platelets <100,000 cells/mm^2
		Positive tourniquet test	HCT rise by ≥20 %
		Evidence of plasma leakage	
DHF	II	Grade I and spontaneous bleeding	Platelets <100,000 cells/mm^2
			HCT rise by ≥20 %
DHF[a]	III	Grade II and shock	Platelets <100,000 cells/mm^2
			HCT rise by ≥20 %
DHF[a]	IV	Grade III and profound shock (moribund)	Platelets <100,000 cells/mm^2
			HCT rise by ≥20 %

[a]DHF III and IV are DHF with shock, formerly called dengue shock syndrome

Table 37.8 Complications of severe dengue fever

Expanded dengue syndrome	Dengue hemorrhagic fever with shock with complications due to co-infection, severe shock, or pre-existing conditions
	Single organ dysfunction including
	CNS: encephalitis, encephalopathy, CNS bleed, ADEM
	GI: hepatitis, acute liver failure, pancreatitis, parotitis
	Renal: hemolytic uremic syndrome
	Cardiac: dysrhythmia, myocarditis, pericarditis
	Respiratory: ARDS, pulmonary hemorrhage
	Musculoskeletal: rhabdomyolysis
	Opthalmic: macular hemorrhage, optic neuritis
Immune dysregulation syndromes	Hemophagocytic histiocytosis syndrome
	Immune thrombocytopenia
Shock without capillary leak	Unclear etiology

shock in addition to the other criteria. Previously, DHF with shock was referred to as DSS however this terminology has been eliminated from the current classifications. The WHO classification of DHF by severity (Grades I–IV) is shown in Table 37.7 [101].

Most patients infected with dengue experience a self-limited, mild illness and only about 5–10 % [102] progress to severe disease, mostly characterized by hypovolemic shock due to plasma leakage, with or without hemorrhage [68]. In some cases however, the clinical course of dengue is beyond that of typical severe dengue. Other features of severe dengue that have been reported include those listed in Table 37.8. Such entities may occur either as a complication of severe shock, preexisting conditions, or possibly co-infections [103, 104]. Typically, the clinical course is characterized by three well-defined phases: febrile, critical and recovery.

Febrile Phase

The *febrile phase* lasts 2–7 days and is characterized by sudden onset, high-grade fever. The clinical manifestations are relatively similar to many other viral syndromes – making the early diagnosis of dengue challenging. Common signs and symptoms include facial flushing, skin erythema/rash, generalized body aches, myalgia, arthralgia, headache, conjunctival injection, and pharyngeal erythema. Anorexia and nausea are common and lead to dehydration. Young children and infants can develop febrile seizures and they present more often with encephalopathy than older children [105]. There is often tender hepatomegaly [100].

A positive tourniquet test in this phase increases the probability of dengue. In a prospective study in Thailand, the positive predictive value of a positive tourniquet test done during the febrile phase was 57 % in distinguishing dengue from nonspecific viral infection [106]. The combination of a positive tourniquet test plus leukopenia (WBC <5,000/mm^3) increases the positive predictive value to 70–83 % [100]. Mild mucocutaneous hemorrhage can be seen – reported frequencies vary between 9.7 % of serologically confirmed cases in a retrospective study in Puerto Rico [107] to 68 % in a prospective study in Thailand [106]. Leukopenia is one of the first laboratory abnormalities observed, while thrombocytopenia usually ensues shortly thereafter.

Critical Phase

Defervescence occurs between day 3 and 7 of illness, accompanied by worsening thrombocytopenia and the onset of plasma leakage, as evidenced by a rising hematocrit level. This *critical phase* lasts 24–48 h [108]. It is postulated that patients without a marked increase in capillary permeability will improve, while those with increased permeability will progress onto severe dengue which is essentially DHF Grade III–IV [68]. Since it is difficult to know which patients will progress onto this critical phase, it is important for the clinician to be aware of warning signs that clinically significant vascular leakage may be developing [69, 72]. Although rare, true hemorrhage can occur, and is more often seen in adult patients [109].

Hypovolemic shock occurs when a critical volume of plasma is lost through leakage, although less commonly it might occur due to severe hemorrhage. Before intravenous fluid therapy, it may be difficult to detect objective signs of plasma leakage such as pleural effusions and ascites. During the initial stage of shock, the usual compensatory mechanisms come into play, with tachycardia, peripheral vasoconstriction and cool extremities. These mechanisms maintain a "normal" or even elevated diastolic blood pressure with a narrow pulse pressure (less than 20 mmHg). As opposed to many cases of bacterial septic shock, DSS is reversible and

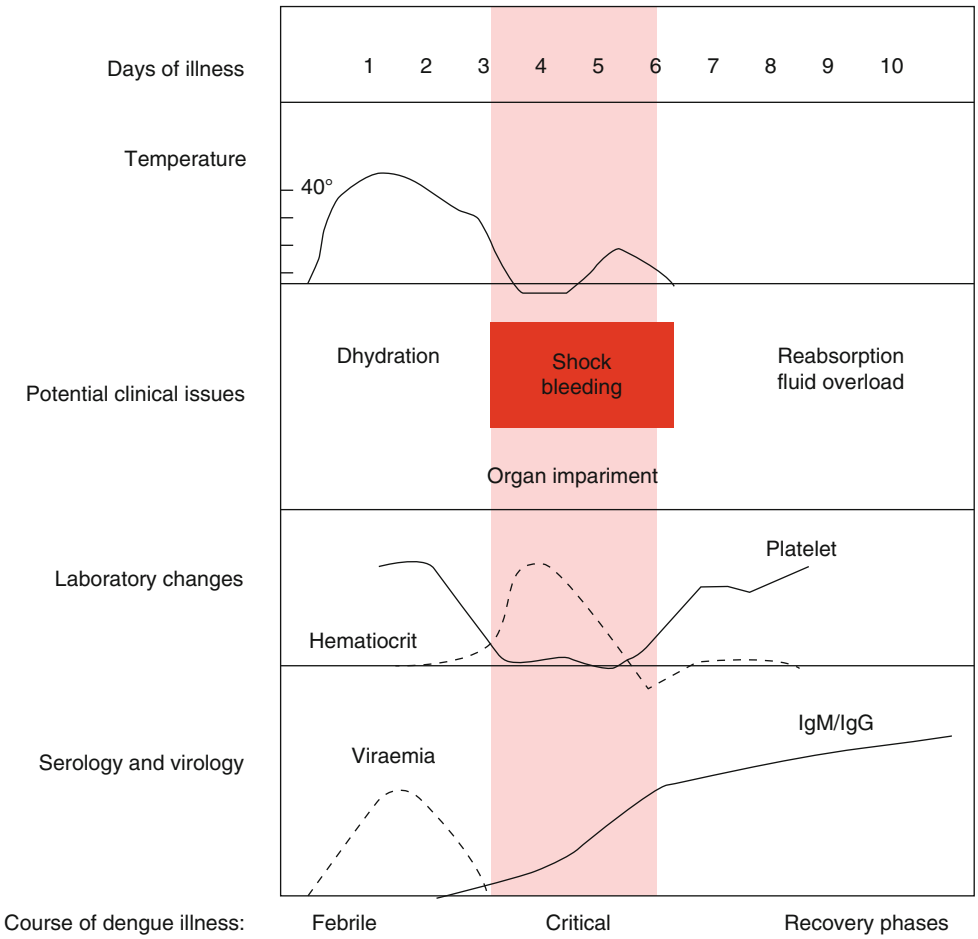

Fig. 37.7 The clinical course of dengue illness and laboratory studies (Reprinted from Ref. [68]. With permission from World Health Organization (WHO))

of short duration if timely and adequate volume resuscitation is administered [101]. Prolonged uncorrected shock progresses in the usual fashion, with hypoperfusion leading to multiorgan failure, metabolic acidosis and DIC and a high mortality rate.

Respiratory distress may be due to diffuse capillary leak or it may result from massive pleural effusions. Ascites may progress to abdominal compartment syndrome [110]. In addition, excessive administration of intravenous fluids, especially during the transition period from critical to recovery phase may lead to pulmonary edema and potentially to congestive heart failure. Clinical observations [105] have suggested that the degree and duration of plasma leakage is shorter in infants than in children, thus predisposing them to iatrogenic fluid overload with its attendant complications.

Recovery Phase

If the patient survives the 24–48 h *critical phase*, the capillary leak resolves, followed by a gradual reabsorption of edema fluid in the next 48–72 h [68]. Brisk diuresis ensues, with decrease of hematocrit towards baseline level, followed by stabilization of hemodynamic parameters and improvement in the general condition. Some patients may have a particular rash, described as "isles of white in the sea of red" [111], that may be pruritic. Even cases with profound shock that receive adequate and timely treatment recover within 2–3 days, however those who have prolonged shock and multiorgan failure will take longer to recover [101].

The typical course of dengue infection is summarized in Fig. 37.7 [68].

Diagnosis

Early in its course, dengue infection is often indistinguishable from other viral syndromes, parasitic infections, or bacterial sepsis. In addition, other conditions leading to a systemic inflammatory response should be considered in the differential diagnosis. Laboratory methods for confirming dengue vary depending on the stage of the illness. In the early stages – the first 4–5 days of illness – diagnosis relies on detection of the virus, viral nucleic acid or viral antigens (especially non-structural antigen 1 – NS1) that can be detected within the first 24 h to 5–7 days. These are called "direct" methods and although they provide an early and accurate diagnosis, they are not widely available in resource-limited countries. As the patient

Table 37.9 WHO guidelines for dengue laboratory diagnosis

Probable dengue	Clinical features
	Positive IgM or IgM
	Occurrence at same location/time as confirmed dengue cases
Confirmed dengue	Isolation of whole virus, detection of genomic sequence by RT-PCR or antigen from serum, CSF or autopsy samples
	Fourfold increase in serum IgG or increase in IgM between paired sera

Based on data from Ref. [101]

progresses into the critical/recovery phases, serology becomes the method of choice [68] – while serology is widely available, it is also less accurate. The antibody response varies according to the immune status of the host. A first dengue infection in a person who has not been infected with or immunized against another *Flavivirus* (e.g. yellow fever, Japanese encephalitis, etc.) leads to the appearance of specific IgM antibodies in the serum between day 5 and 10 of illness. These IgM antibodies disappear after 2–3 months. Anti-dengue serum IgG becomes detectable at the end of the first week of illness, increasing slowly thereafter, with levels detectable for months and possibly longer. During a secondary dengue infection, or in a person previously infected with or immunized against another *Flavivirus*, antibody titers rise rapidly but cross-react with many viruses from the *Flavivirus* group. The predominant antibody type of secondary dengue infection is IgG, which rises as early as day 5 of illness and persists from months to life. Early IgM levels are much lower than in the primary infection and may even be undetectable [69]. Given these intricacies and the variable performance characteristics of commercially available ELISA tests, studies have shown that combining a direct method such as NS1 detection (day 1 to 7–9) with a serologic method such as IgM/IgG detection (after day 4–5) allows for dengue diagnosis throughout the normal temporal spectrum of patient presentation [112] (Table 37.9).

Treatment

Management of dengue is centered around careful fluid administration and supportive management, as no effective antiviral agents to treat dengue infection are available [69]. After making a presumptive diagnosis of dengue, management priorities include [102]:

- Establish the phase of the disease – febrile, critical or convalescence
- Recognize the presence of warning signs that prompt the need for hospitalization
- Recognize and reverse the shock state, using iv fluids and blood as needed
- Titrate fluid administration aiming to preserve an effective circulating blood volume but simultaneously avoiding fluid overload

Management of Dengue Hemorrhagic Fever Grade 1 and 2 (Without Shock)

The goal of therapy is to judiciously match the ongoing losses due to plasma leakage that occur during the 24–48 h of the critical phase. Clinical experience, synthesized in the most current guidelines [101], has shown that fluid needs during this period are about maintenance plus 5 % deficit, without the need for more aggressive fluid boluses [101]. Isotonic, dextrose-containing fluids are recommended. The hourly fluid administration rate is titrated according to the projected stage of the illness, i.e. a slower initial rate if the plasma leakage is just beginning. A useful clinical correlate is the severity of thrombocytopenia – a platelet count of 50–100,000/mm^3 is usually seen in the "initial" stages of leakage, whereas a platelet count <50,000 usually indicates that it has been ongoing for some time [108]. The rate of iv fluid should be adjusted according to the clinical vital signs, hematocrit – measured at least every 4–6 h during the critical phase – and urine output (target at least 0.5 mL/kg/h). Worsening of the clinical condition and/or inability to decrease the rate of iv fluids as predicted should prompt consideration of:

- Accelerated plasma leak with transition to DHF Grade III–IV – management described below
- Occult bleeding: whole blood or PRBCs are indicated, 10 ml/kg aliquots
- Liver or kidney dysfunction
- Myocardial dysfunction – one study [113] notes an incidence of systolic dysfunction from 14 % in pediatric patients with DHF non-shock to 36 % in DHF with shock. The clinical significance of these findings is not clear, as this seems to be a different phenomenon than the myocardial depression in septic shock [102]. The use of inotropes and vasopressors is rarely employed in clinical practice, outside of the situation of late presenting, decompensated shock [101]

- Presence of co-infections, such as bacterial sepsis, meningitis, malaria or underlying medical conditions
- Expanded dengue syndrome: occurrence of unusual manifestations, such as myocarditis or pericarditis, pancreatitis, encephalopathy, HLH, etc.

Management of DHF Grades 3 and 4 (Dengue Shock Syndrome)

More aggressive fluid strategy, with initial boluses of 10 mL/kg/h for the first 2–3 h is the mainstay of treatment for patients with grades 3 and 4 DHF (DSS). In case of low blood pressure/critically decreased perfusion of vital organs, the guidelines do recommend larger fluid boluses of 20 mL/kg, but only until blood pressure is restored. The hematocrit should be checked before and after the fluid boluses [101]. The presence of hypotension should alert the practitioner to the possibility of concealed hemorrhage. After the initial resuscitation, fluid administration is titrated according to the clinical response and gradual return of the hematocrit towards baseline levels. A suggested algorithm is presented in Fig. 37.8 [68].

The choice of resuscitation fluid – colloid versus crystalloid – has been the subject of many controversies. A few prospective, randomized controlled trials have been performed in the last decade [114, 115] and have shown that that neither crystalloids nor colloids had a distinct advantage over the other in terms of recurrence of shock, the need for rescue colloids after initial resuscitation, the subsequent need for diuretics, or mortality. The guidelines currently recommend crystalloid for the initial resuscitation of DHF Grade III and a choice between crystalloid or colloid for the initial resuscitation of DHF Grade IV [101].

As discussed in the management of grades 1 and 2 DHF, changes in hematocrit are a useful guide to treatment. A rising or persistently high hematocrit in an unstable patient indicates ongoing plasma leakage and the need for a further bolus of fluid. The same hematocrit in a patient who is improving clinically and has good urine output only calls for continuation of the current regimen and the expectation that the plasma leakage will stop in the next 24 h. Conversely, a decrease in hematocrit in an unstable patient indicates major hemorrhage [68] and the need for urgent transfusion. The same hematocrit in an improving patient indicates relative hemodilution due to reabsorption of extravasated edema fluid, signaling transition into convalescence, so in this case intravenous fluids should be discontinued to avoid iatrogenic fluid overload.

In contrast to the PALS guidelines for pediatric septic shock that emphasize early and aggressive fluid resuscitation, often with more than 60 mL/kg of fluid in the first few hours, the strategy for dengue shock is quite different and many authors and guidelines call attention to the need for hourly titration of iv fluids. While the pathophysiology of the two shock states may be different, it is important to note that in western countries mechanical ventilation is easily accessible if patients develop signs and symptoms of fluid overload and respiratory compromise. However in countries where dengue is endemic, respiratory compromise secondary to fluid overload is a major contributor to mortality in settings with poor resources, few personnel, and limited equipment [115]. It is thus incumbent upon critical care physicians to adjust their practice to the appropriate setting and keep parenteral fluid therapy to the minimum required to maintain cardiovascular stability, until plasma leakage ceases [69]. Patients with severe dengue shock, especially if presenting late in the course, should also receive supportive care as clinically indicated, to include renal replacement therapy, use of inotropes and vasopressors, management of liver failure or encephalopathy.

Typhoid and Paratyphoid Fever

Epidemiology

Typhoid fever has an estimated annual incidence of 20 million cases worldwide, causing 200,000 deaths. Paratyphoid fever contributes about five million cases annually [116], with fewer deaths. The regions with the highest incidence of typhoid fever (>100/100,000 cases/year) include South-Central and South-East Asia. Regions with medium incidence (10–100/100,000 cases/year) are the rest of Asia, Africa, Latin America and the Caribbean, while countries in the "developed" world – North America, Europe, Australia and New Zealand have a low incidence of typhoid fever (<10/100,000 cases/year) [116]. In regions with an increased burden of disease, the highest incidence of typhoid fever is observed in children less than 5 years of age [117], whereas in low incidence regions, where the disease is primarily travel- acquired [118], children and young adults are equally affected, with the incidence gradually decreasing in people above 30–40 years of age [116].

Since typhoid fever is an exclusively human disease, with a fecal – oral mode of transmission, the improvement in food hygiene and water sanitation in developed countries that took place in the twentieth century led to a marked decline in the incidence of the disease. For example, in the US the annual incidence dropped from 7.5/100,000 in 1940 to 0.2/100,000 in the 1990s [119]. In addition, the proportion of cases related to foreign travel increased from 33 % in the 1960s to

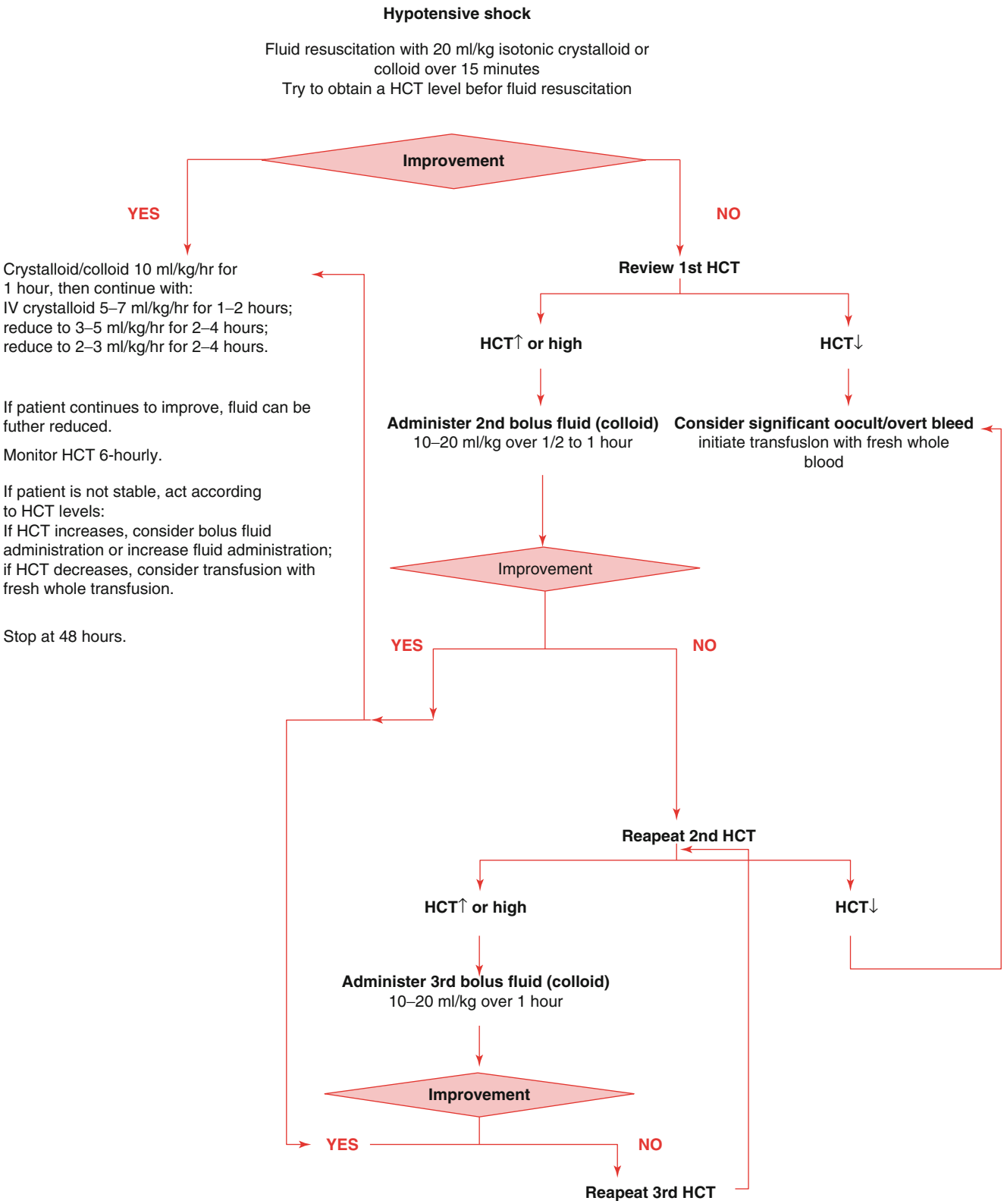

Fig. 37.8 Algorithm for fluid replacement in severe dengue with hypotensive shock (Reprinted from Ref. [68]. With permission from World Health Organization (WHO))

80 % in the 1990s. In the latest surveillance study from the US [120], during 1999–2006 there were 1,902 typhoid fever cases. Less than half of the patients were children – 4 % were younger than 2 years old, 12 % were between 2 and 5 years old, and 25 % between 6 and 17 years of age. Three quarters of these patients were hospitalized, with a case fatality rate of 0.2 %. About 80 % of cases were travel related (mostly to the Indian subcontinent) – notably, only 5 % of the travelers had received typhoid vaccine. Of the domestically acquired cases, the illness was traced either to a typhoid carrier or to food related outbreaks.

Etiology

Typhoid fever and its close cousin, paratyphoid fever, constitute the "enteric fever" group. They are systemic bacterial illnesses caused by the bacterium *Salmonella enterica*, serotype Typhi and respectively, Paratyphi A, B and C. These pathogens are exclusively human and the infection is transmitted through food or water contaminated with feces or urine of a patient or a carrier [15]. Typhoid fever is therefore primarily a disease of overcrowding, poor sanitation, and undertreated water. In highly endemic countries the ratio of typhoid to paratyphoid fever is about 8–10 to 1 [116], whereas, among travelers, the incidence of the disease caused by *S. paratyphi* may be more important, probably due to a vaccine effect, which gives protection only for *S. typhi* [119].

Pathophysiology

Typhoid bacilli are ingested and then penetrate the intestinal mucosa. In order to produce disease in healthy individuals, the infectious dose has to be large, between 1,000 and one million organisms in volunteers. The infectious dose is decreased in the presence of the capsular Vi antigen, decreased stomach acidity, and food (which protects the bacterium) [121]. Once in the small intestine, the organisms penetrate the mucosa – likely through the specialized epithelial M cells – and are taken up by the macrophages resident in the submucosa and travel to the local lymph nodes [122]. In contrast to the non-typhoidal Salmonella serotypes resulting in gastroenteritis, which cause a significant neutrophil influx in the intestinal mucosa and localized infection, the typhoidal Salmonella evade this local defense mechanism. Recent evidence suggests that typhoidal strains evade pattern recognition receptors and induce a less vigorous inflammatory response [123]. A short bacteremic phase ensues, which carries the Salmonella to the reticuloendothelial system of the liver and spleen, where massive multiplication of the organisms occurs. The incubation period lasts 7–14 days, followed by a severe secondary bacteremia which marks the onset of clinical illness [122]. During this phase, virtually all organs can be invaded, but of particular importance are the infection of the Peyer's patches and the gallbladder. The Peyer's patches become hyperplastic, with superficial necrosis that leads to superficial ovoid ulcers, a hallmark of typhoid fever. Located along the longitudinal axis of the gut, these do not heal with stricture formation, however when such an ulcer erodes into a mural vessel, severe hemorrhage and/or perforation leading to peritonitis can occur [122]. Infection of the gallbladder can result in a chronic, subclinical cholecystitis with persistent fecal carriage.

Clinical Manifestations

The incubation period averages 10–20 days (range 3–56 days) and is dependent on the infecting dose and the virulence of the Salmonella serotype. Paratyphoid fever has a shorter incubation period and has a similar, sometimes milder clinical course [122]. The classic description of the untreated typhoid fever of average severity is a protracted illness spanning about 4 weeks. The first week is characterized by non-specific, flu-like symptoms, a "coated" tongue, intermittent or low grade fevers, constipation in adults, diarrhea in children or HIV positive adults [124]. During the second week, the overall condition of the patient declines, with sustained high fevers and a characteristic "relative bradycardia." Patients appear systemically ill with abdominal distention and splenomegaly. In about 30–50 % of cases "rose spots" appear – these are pink, maculopapular lesions, 2–4 mm in diameter that develop in crops over the upper abdomen and lower thorax. These are not specific for typhoid, as they may also occur in invasive non-typhoidal salmonellosis and shigellosis [122]. They may be difficult to see in dark skinned individuals and may also be difficult to differentiate from other bacterial or viral exanthems. During the third week, the overall condition of the patient declines further, with continuous sustained high fever, neuropsychiatric manifestations, worsened abdominal distention, and diarrhea. Significant complications occur in about 10–15 % of patients and include overwhelming septic shock, myocarditis, intestinal perforation or hemorrhage, and typhoid encephalopathy. Gastro-intestinal bleeding is the most frequent complication and is usually mild, however in about 2 % of cases the bleeding can be life threatening. Intestinal perforation is the most serious complication, occurring in about 2 % of cases and it doesn't always present with an acute abdomen but rather in a more subtle manner, with worsening abdominal pain, tachycardia and altered mental status. Encephalopathy and shock carry a high mortality [121]. Neuropsychiatric symptoms include apathy, severe agitation, and delirium, although deep coma is unusual. For unclear reasons, the incidence of encephalopathy varies by country, from 10 to 40 % of

Table 37.10 Antibiotic recommendations for typhoid fever

	Optimal treatment	Alternative treatment
Typhoid fever		
Sensitive	Fluoroquinolone	Chloramphenicol, Amoxicillin, TMP-SMX
MDR	Fluoroquinolone or Cefixime	Azithromycin, Cefixime
Quinolone resistant	Azithromycin or Ceftriaxone	Cefixime
Severe typhoid fever		
Sensitive	Fluoroquinolone	Chloramphenicol, Amoxicillin, TMP-SMX
MDR	Fluoroquinolone	Ceftriaxone or Cefotaxime
Quinolone resistant	Ceftriaxone or Cefotaxime	High dose fluoroquinolone, ceftriaxone, azithromycin[a]

[a]Unclear effectiveness however treatment for quinolone resistance is not well defined

patients in Indonesia [125] to less than 2 % of patients in Vietnam [126]. Patients who survive into the fourth week start to improve, defervesce, abdominal distention also improves slowly, although the danger of perforation and hemorrhage persists well into the fourth week. Variations from this classic picture are often seen and with the widespread use of antibiotics, the clinical course is much shorter. In fact, community-based studies in areas of endemic disease indicate that many patients, especially children less than 5 years of age, may have a non-specific febrile illness that is not recognized clinically as typhoid [124].

Relapse occurs in about 1.5–20 % of patients treated with antibiotics, usually 2–3 weeks after the resolution of fever. The blood culture becomes positive again and the isolate usually has the same antibiotic susceptibility pattern as the isolate from the original episode [121]. The relapse has a shorter and milder clinical course than the original episode and occurs in spite of high titers of O, H and Vi antibodies. Reinfection may also occur and can only be distinguished from relapse by molecular typing techniques [127].

Diagnosis

Laboratory diagnosis of typhoid fever has remained very challenging for decades. The clinical diagnosis can be difficult depending on the timing of presentation relative to the natural history of the clinical disease. The gold standard confirmatory test is a blood culture – however the sensitivity of a blood culture can be as low as 40–80 % early in the disease when bacteremia is highest and even lower later in the clinical course [128]. Stool and urine cultures become positive after the first week. However, sensitivity for stool and urine cultures is also low. Bone marrow culture is quite sensitive (55–67 %), though bone marrow aspiration is invasive and impractical in many cases. Multiple serologic tests are as widely used as microbiologic culture, but also with problematic performance. The Widal test is the classic test and is based on detecting antibodies to the O and H antigens of *S. typhi*. Other tests such as the Typhidot or Tubex tests directly detect IgM antibodies to multiple *S. typhi* antigens. These tests have also underperformed and overall show roughly a 70–90 % sensitivity and 70–90 % specificity. Despite their limitations they still are used clinically. Nested polymerase chain reaction is exquisitely sensitive and specific and remains promising as the next gold standard for diagnosis where laboratory resources are available. In the end, diagnosis of Typhoid is made largely on a clinical basis. Other common laboratory abnormalities are mild and nonspecific including leukopenia and thrombocytopenia in adults, whereas leukocytosis frequently occurs in children. Hepatic enzymes may also be mildly elevated [128, 129].

Treatment

Significant drug resistance issues have arisen with regard to the Salmonella serotypes responsible for typhoid and paratyphoid. Drug choices should be made based on the severity of illness, geographic resistance patterns, or laboratory sensitivities from clinical isolates. Historically, treatment with amoxicillin or trimethoprim-sulfamethoxazole was the standard of care for many years. Unfortunately, resistance to these agents has become very common. In some areas of China and India 50–80 % of isolates are multidrug resistant [119]. Fluoroquinolones have been an excellent alternative supported by multiple clinical trials. Unfortunately in many areas of central and South East Asia, decreased susceptibility to fluoroquinolones is as high as 75–80 % in Tajikistan and Vietnam in the late 1990s [119]. Many prospective trials have also demonstrated significant success with azithromycin and ceftriaxone, and treatment with these agents is becoming more widespread. Unfortunately, recently extended-spectrum beta-lactamases have been identified in typhoidal Salmonella serotypes that will greatly limit the therapeutic options for this widespread tropical disease [130]. At this point, for invasive infections fluoroquinolones or third generation cephalosporins are recommended empirically until sensitivities are available [121, 129, 130]. Table 37.10 contains some treatment options for resistant serotypes although in the case of quinolone resistance, multidrug regimens are being studied but data is lacking at this point [128, 131]. Other adjunctive therapy includes dexamethasone has been

used as an adjunctive therapy for severe disease characterized by shock and obtundation/coma. Reportedly, the use of dexamethasone reduced mortality in a severe cohort from 35–55 to 10 % [125, 132, 133].

Some reports have described different clinical features in multidrug resistant typhoid fever (MDRTF) and rising overall mortality up to 16 % in this cohort. These patients are more toxic in appearance, with a higher fever (up to 40 °C in some cases), more frequent (and more severe) abdominal distention and tenderness, and hepatomegaly and splenomegaly [134]. Several hypotheses have been suggested to explain this including delay in starting effective antibiotics, high bacterial load, and possibly higher microbial virulence.

Leptospirosis

Epidemiology

Leptospirosis is the most widespread zoonosis in the world and it is caused by a spirochete of the genus *Leptospira*. The annual incidence of leptospirosis in tropical endemic areas is 10–100/100,000 people whereas it is 0.1–1/100,000 people in temperate areas [135]. In the end there are more than 500,000 cases of leptospirosis reported per year with an overall mortality rate of 10 % [136]. Although leptospirosis is seen in tropical, subtropical, and temperate climates, it is endemic in much of the tropics, especially in South East Asia. The incidence of the disease is associated with the lack of proper sanitation, poor water quality, flooding, and the presence of maintenance hosts such as rats, dogs, cattle, and swine who excrete leptospira in the urine [137]. Infected rats shed the pathogen for life and most other animals shed for 6–12 months, thereby preventing pathogen eradication from the soil and water. In the past two decades the epidemiology of this disease is changing to include more poor urban settings, especially those with high rainfall and flooding. In addition, there have been multiple, limited outbreaks in nonendemic areas such as the USA, Canada, and continental Europe [138]. Many of these outbreaks were related to recreational contact with contaminated natural settings [137, 138]. The disease is contracted via contact with contaminated water or soil, as well as direct contact with infected animal urine. As such, the risk (and incidence) of leptospirosis is increased in many occupations, including farmers, butchers, and veterinarians because of direct contact with hosts. Also, sewer workers, construction workers, flood relief workers, and military personnel are at risk due to indirect contact with contaminated waters. In addition, recreational activities resulting in exposure to contaminated fresh water bodies (lakes, streams, ponds) are at risk for contracting the disease [139]. With increased incidence in endemic areas as well as nonendemic areas, leptospirosis is now considered an emerging global disease [137].

Etiology

Leptospira are spirochetes belonging to the same genus as *Borrelia* and *Treponema*, the pathogens responsible for Lyme disease and syphilis, respectively. Leptospira can be saprophytic or pathogenic and the pathogenic species are within the *L. interrogans* subgroup. There are many serogroups and serovars within this pathogenic category. The organism is morphologically unique with a thin and highly coiled shape with flagella present. The organism shares features with both Gram-positive and Gram-negative organisms in that its surface contains peptidoglycan, phospholipids, outer membrane proteins, and lipopolysaccharide [136, 137].

Pathophysiology

Leptospira are extracellular organisms and are highly invasive. The pathogen invades the body by contact with skin abrasions, mucous membranes (conjunctiva and nasopharynx), and possibly through intact skin [138, 140]. They invade tissues by adhering to a wide range of extracellular matrix components, endothelial cells, leukocytes, and kidney epithelial cells thereby gaining access to the bloodstream [136, 138]. Once the pathogen has invaded the entry point such as the conjunctiva, there is rapid penetration and dissemination of the organism throughout the body and particularly the kidney [141]. An early finding of diffuse endothelial injury or vasculitis is the main mechanism of tissue damage [142]. Although the exact cause of the vascular inflammation is not yet understood, there are many data showing evidence of small vessel disease in the lung and kidney, as well as the aorta, coronary arteries, and cerebral vessels. Other mechanisms of injury in addition to direct endothelial injury are parenchymal cell injury and increased vascular permeability [142]. Whether the vasculitis demonstrated in leptospirosis is of an autoimmune nature is controversial. Many of the features of common vasculitides such as immune complex deposition have not been shown in leptospirosis, leading some to maintain that the endothelial activation/injury is sepsis-like rather than autoimmune mediated [142, 143].

Acute kidney injury is common in leptospirosis and histopathologically the abnormality is an interstitial nephritis with interstitial edema and mononuclear infiltration. Large numbers of leptospires are found throughout the tubules, interstitium, and in some cases within glomeruli. Typically, AKI in this setting is non-oliguric and presents with evidence of tubular dysfunction with hypokalemia, hypomagnesemia, and hypophosphatemia. Rhabdomyolysis can add to the severity of AKI as well.

Severe lung injury and pulmonary hemorrhage is commonly observed in leptospirosis. By histopathology, the lung is edematous with moderate monocyte infiltration into the

Table 37.11 Clinical forms of leptospirosis

Anicteric	Fever, headache, chills, abdominal pain, conjunctival suffusion, severe myalgias, normal CSF
Aseptic meningitis	Can follow anicteric form, CSF pleocytosis, self limited, often mistaken for viral
Weil syndrome	Jaundice, severe renal dysfunction, hemorrhagic manifestations
Severe pulmonary form	Hemorrhagic pneumonitis, ARDS, massive pulmonary hemorrhage, +/− jaundice

alveolar septum. In addition, leptospiral antigen was demonstrated on the luminal surface and in the cytoplasm of endothelial cells in the alveolar septal capillaries. There are several experimental reports demonstrating Goodpasture's-like findings in the lung with linear deposits of immunoglobulin and complement along the alveolar septa. These findings suggest the presence of antiglomerular basement membrane antibodies, which could cross-react with lung septal matrix causing massive hemoptysis [142, 143]. In addition, experimentally abnormalities of multiple ion transporters are seen in leptospirosis models, and it is thought that these alterations of pulmonary permeability are important in ARDS seen in leptospirosis [141].

Clinical Manifestations

In most cases Leptospirosis is a mild nonspecific self-limited illness with initial symptoms presenting 2–30 days (average 10 days) after exposure to the bacteria [137, 139, 144]. There are four forms of leptospirosis. The *anicteric form* accounts for 85–90 % of cases and is a nonspecific febrile illness. The *aseptic meningitis form* can present concurrent with the anicteric form. *Weil's form* is characterized jaundice and the features are listed in Table 37.11 [142]. Lastly, the *severe pulmonary form of leptospirosis* (*SPFL*) may occur with or without jaundice. The mortality from Weil syndrome and SPFL is >10 and >50 % respectively [135, 141].

The clinical course is biphasic, with the initial phase lasting for 3–9 days characterized by leptospiremia and presenting with the sudden onset of high fever, headache, severe myalgias (lower limbs), chills, conjunctival suffusion, abdominal pain, nausea, vomiting, diarrhea, and malaise. At this point symptoms can resolve. In approximately 20 % of cases, after 1–3 days the second phase begins which is coincident with the appearance of circulating IgM and is thus called the "immune phase" [135, 140, 141, 145]. During this time fever is much less or absent. However, headache, myalgias, conjunctival suffusion, aseptic meningitis (80 % in children), hepatomegaly, and interstitial nephritis are the common during this phase, which can last up to a month. It is also called the leptospiruric phase because after the first week, leptospires are eliminated in the urine [141].

The severe form of leptospirosis – Weil's Syndrome can begin after an initial anicteric phase or the jaundice can be seen within the first 4–6 days. This presentation occurs in less than 10 % of leptospirosis patients. The liver is enlarged and tender and the jaundice is due to hepatocellular injury, cholestasis, and increased bilirubin load from tissue hemorrhage reabsorption. A hallmark of this disease is significantly elevated bilirubin out of proportion to the mildly elevated transaminases [138]. Despite this significant liver injury, it is recoverable and as such is rarely the cause of death in this disease. Renal failure can occur in 40–60 % with oliguria developing within the first 2 weeks. AKI can occur and can vary from urine sediment changes to anuric renal failure [141]. As stated above, the injury pattern is that of interstitial nephritis. Most develop nonoliguric AKI and those with some preservation of kidney function have better survival. Typically resolution of AKI in adults is near complete by 6 months. In one cohort of 43 children the incidence of AKI was 79 % however only two such children required dialysis and one died. These data show that children with AKI fare much better who also present mostly with nonoliguric AKI with hypokalemia [146].

Cardiac issues can arise with arrhythmias, myocarditis, and pericarditis. Coronary arteritis was found in 70 % and aortitis was found in 50 % of a reported cohort [139]. In addition, neurologic issues can be present, including altered mental status, meningoencephalitis, and cranial nerve palsy [135]. Severe hemorrhagic complications can occur in Weil's Syndrome, including ocular suffusion, petechiae, pulmonary hemorrhage, GI hemorrhage, and hematuria. Thrombocytopenia is present in up to 70 % of patients. In fact, hemorrhage has become the most serious manifestation of leptospirosis and the incidence of significant hemorrhage is increasing worldwide [141].

Severe pulmonary disease can manifest with or without jaundice. The incidence of pulmonary disease ranges from 20 to 70 % and has been increasing worldwide over the last two decades. There is no apparent relationship between the severity of lung disease and the severity of jaundice and liver injury. The spectrum of pulmonary disease can range from dyspnea, cough, tachypnea, chest pain, hemoptysis to ARDS and massive pulmonary hemorrhage. Recently, a cohort of Weil's Syndrome patients were described with a 69 % incidence of pulmonary hemorrhage at autopsy and pulmonary hemorrhage is now the leading cause of death from leptospirosis [135, 147]. A typical CXR is characterized by diffuse small opacifications that are disseminiated or coalesce [135]. Although the mortality for Weil's Syndrome is 10 %, the mortality for leptospirosis associated pulmonary hemorrhage is >50 % [148]. At autopsy, the lung reveals extensive pulmonary hemorrhage from numerous

sites, congestion, edema, and hyaline membranes [135]. In children the incidence of Weil's Syndrome and pulmonary hemorrhage is lower and mortality also is lower compared to adults. In a recent study of 139 pediatric cases the most common symptom was fever, headache, and myalgia. Jaundice was present in 18 % and renal failure in 2 %. Shock was present in 9 % and meningitis in 7 % [149].

Diagnosis

The most important aspect of this diagnosis is clinical suspicion followed by the limited laboratory studies available. Isolation of leptospira from the blood or CSF during the leptospiremic phase in the first 2 weeks is possible and from the urine thereafter for many weeks [144]. Serological methods rely on detection of IgM specific for leptospira in the early "immune phase" of the illness; however, false negatives can confound if obtained prior to 5–7 days. This serology is much more reliable in the second week of illness. The gold standard is the microscopic agglutination test (MAT) showing at least a fourfold rise in titers or a single titer of >1:800 [138, 139, 144]. Sensitivity for this test is not perfect and reaches 82 % after the second week and 96 % after the fourth week. PCR based diagnostics are being investigated.

Treatment

Antibiotic therapy is effective if initiated within 5 days of the onset of symptoms according to the WHO. Other clinicians report benefit from antibiotics started later in the course of illness [150]. Unfortunately given the nonspecific signs and symptoms and minimal laboratory diagnostic options, the diagnosis is often made as the disease is beginning to resolve. The antibiotics typically used are penicillin for severe disease and doxycycline for milder disease. Cephalosporins and macrolides can also be used. The Jarisch-Herxheimer reaction can occur shortly after starting any bacteriocidal antibiotic treatment of a spirochete. Typically it occurs within 1–2 h and is characterized by fever, tachycardia, rigors, and hypotension [139].

Because of the autoimmune-like findings, steroids have been tried in severe disease. The data remain conflicting and controversial.

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Index

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