Pediatric Critical Care

Current Controversies

Christopher W. Mastropietro
Kevin M. Valentine
Editors

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Foreword

Guided by controversy to deliver "a little of a lot of therapies" to the critically ill child

In the period surrounding the origin of our specialty of pediatric critical care medicine, life was simpler. We often had an approach that could be characterized with the phrase "pour it like you don't own it!" With time, however, our zeal to cure has tempered, on and off, often as the result of controversies that were created by our approach. This has led to eras across which a given therapy has been the subject of a veritable roller-coaster ride. For example, regarding fluids, I vividly remember periods in time where one attending physician would say that "a full patient is a stable patient," while another attending later in my career said, "make them pee dust." Indeed, we are now in an era of very judicious fluid administration. Similar controversies have evolved surrounding many of our so-called standard interventions such as corticosteroids administration in septic shock, optimal oxygen use in the critically ill, nutritional assessment and delivery, sedation practices, timing of the institution of ECMO in acute lung injury, and the application of hypothermia in acute brain injury, among others. This textbook, *Pediatric Critical Care: Current Controversies,* is thus timely if not overdue. Drs. Mastropietro and Valentine have assembled an outstanding group of experts in our field including Drs. Paul Checchia, Ira Cheifetz, Kanwaljeet Anand, Nilesh Mehta, David Askenazi, Gail Annich, Leticia Castillo, Joseph Carcillo, Kasum Menon, Hector Wong, Ericka Fink, Chani Traube, and Thomas Nakagawa, among many others, to address a number of key controversies that have challenged, if not plagued, our field for decades. This textbook also features a clinical case embedded within each chapter to highlight situations where many of these controversies are most daunting—adding a special and practical component for the reader. The textbook offers a great deal to caregivers in our field from trainees to senior faculty, both for bedside care and to spearhead and direct future investigations. Often I have found that the solution to optimal care in the PICU is one where we bring "a little of a lot of therapies" to critically ill infants and children. Get the right dose

of the optimal therapies to tackle the big problems that we face while limiting toxicity and other unwanted side effects, some of which we do not even (yet) recognize. I believe that this textbook will help us to achieve that important goal.

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Preface

Controversy as a Cornerstone of Pediatric Critical Care

Controversy is as much a part of pediatric critical care medicine as physiology, pharmacology, and microbiology. Controversy surrounding the diagnosis and management of critically ill children can be seen throughout the medical literature, as well as in plenaries and debates at professional national and international meetings, and at the bedside of many of our patients, where physicians within the same institutions can have difficulty agreeing on one strategy or another. Though these controversies are the source of frustration for many of us, they also motivate us to attempt to answer the questions and settle the debates and, in doing so, move our specialty forward.

For this textbook, we have enlisted experts in the field of pediatric critical care medicine to scour the medical literature and, along with their own individual experiences and expertise, present a comprehensive assessment of many of the controversial scenarios that we face in our daily practice. The chapters of the textbook have been organized by sections based on the organ systems on which the controversies are focused. For each chapter, the authors have been tasked to focus more on what we know rather than what we do not know, an approach that should prove more helpful to the readers and their patients. Through case scenarios, data from the most important and most recent published studies, and a wealth of personal experiences, the authors of these chapters have provided excellent resources filled with knowledge and guidance for current and future members of our field, including not only physicians but advanced practice providers, bedside nurses, respiratory therapists, and others who comprise contemporary multidisciplinary pediatric ICU teams.

Flaws can be detected in any research study, no matter the quality of the methods or the stature of the journal. Moreover, in many cases, our perception of flaws within the current literature is often enhanced or minimized, depending on our inherent biases. I would argue that, despite their flaws, value can be found in most of the published works that encompass our current ever-expanding body of literature. With this notion in mind, we hope that, as readers progress through this textbook, they will appreciate the valuable contributions that have been made to our field thus far and be inspired to build upon the foundation that have been provided by the authors as we continue to evolve as a specialty and vocation.

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Part I

Respiratory Controversies

1 Ventilator Management for Pediatric Acute Respiratory Distress Syndrome

Travis P. Vesel and Ira M. Cheifetz

Clinical Case

A 2-year-old child presents to the emergency department (ED) with poor feeding, fussiness, and tachypnea. His mother reports that he is otherwise healthy, but yesterday he started coughing and developed a fever. The child has been breathing faster than normal over the past 12 hours and has had poor oral intake. In the ED, vital signs include temperature 39.0 C, heart rate 150, respiratory rate 55, blood pressure 90/55, and oxygen saturation 82% on room air. The child is awake but somewhat somnolent. On physical examination, he has nasal flaring, supraclavicular and subcostal retractions, and mild wheezing and rhonchi on auscultation.

- What is the likely diagnosis?
- Does this child meet the definition of pediatric ARDS (PARDS)? If not, what additional data are required to make this diagnosis?
- What is the severity of the child's illness?

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Pathogenesis of Acute Respiratory Distress Syndrome

The clinical presentation of PARDS includes dyspnea, tachypnea, decreased lung compliance, pulmonary edema, and hypoxemia. Acute respiratory distress syndrome (ARDS) is characterized by two major modes of pathogenesis: direct lung injury and indirect lung injury [1]. In pediatric patients, the most common causes of direct lung injury are pneumonia, aspiration, and near drowning, with sepsis as the most common cause of indirect lung injury [2].

The three phases of ARDS are exudative, proliferative, and fibrotic. The exudative phase of lung injury is dominated by direct or indirect lung injury causing an increase in permeability of the alveolar-capillary barrier, with an influx of protein-rich edema fluid, neutrophils, macrophages, erythrocytes, and cytokines into the airspaces causing further damage to the alveolar and bronchial epithelial cells, as well as deactivation of surfactant. This pathophysiologic cascade results in intrapulmonary shunt physiology and arterial hypoxemia.

The flat type I pneumocytes are most sensitive to injury during the acute phase. During the proliferative phase, the cuboidal type II pneumocytes proliferate and differentiate into type I pneumocytes, re-epithelializing the denuded alveolar epithelium to repair the damaged lung segments. Although many patients recover, some

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survivors progress to a chronic fibrosing alveolitis, characterized clinically by chronic hypoxemia, increased alveolar dead space, and decreased pulmonary compliance.

Definition of Pediatric ARDS

In 2015, members of the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed the first reported pediatric-specific definition of ARDS (Fig. 1.1) [3]. Earlier definitions of acute respiratory distress syndrome include the American European Consensus Conference [4] and Berlin [5] definitions and do not include pediatric-specific criteria. The pediatric definition created by PALICC sought to include the unique pathophysiology of PARDS and include consideration of the developmental factors that may influence lung pathology in children. It is important to note the term "acute lung injury" (ALI) was eliminated from the stratification scheme in the 2015 PALICC definition.

The disease severity of PARDS is initially stratified based on noninvasive mechanical ventilation or invasive mechanical ventilation. Considering the increased use of noninvasive mechanical ventilation (i.e., CPAP or BiPAP), the PALICC definition includes patients supported in this manner; however, these patients are not stratified as mild/moderate/severe. In patients supported with invasive mechanical ventilation, disease severity is stratified using oxygenation index (OI) and oxygen saturation index (OSI). Considering pediatric patients are less likely to have arterial catheters as compared to adult patients, diagnostic criteria and disease severity stratification were expanded to include saturation by pulse oximetry. Previous definitions of ARDS relied on PaO_2 by arterial blood gas to make the diagnosis of ARDS. By expanding this definition,

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	**Mild**	**Moderate**	**Severe**
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20[2] PF ratio ≤ 300 SF ratio ≤ 264[1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
	Special Populations			
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing, and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Fig. 1.1 2015 PALICC pediatric acute respiratory distress syndrome (PARDS) definition. [1]Use PaO_2-based metric when available. However, if PaO_2 is not available, wean FiO_2 to maintain $SpO_2 \leq 97\%$ to calculate oxygen saturation index or SpO_2:FiO_2 ratio. [2]For non-intubated patients. [3]Stratification of disease severity by oxygen index or oxygen saturation index should not be used for children with chronic lung disease supported with invasive mechanical ventilation at baseline or children with cyanotic congenital heart disease [3]. (Used with permission)

more patients can be diagnosed with PARDS for treatment and research study purposes.

Other diagnostic criteria similar to previous definitions include chest imaging findings of new infiltrates consistent with acute pulmonary parenchymal disease. The definition was expanded to include unilateral radiographic findings, although this has been debated whether underlying disease pathology in PARDS can cause unilateral lung disease [3]. Timing of onset of PARDS symptoms of hypoxemia and radiographic changes must occur within 7 days of known clinical insult and is used to distinguish from existing chronic lung disease.

Although excluded from previous definitions of ARDS, the 2015 PALICC definition sought to include patients with chronic lung disease (with acute exacerbation), cyanotic congenital heart disease, and left ventricular dysfunction (left atrial hypertension). Diagnosis of PARDS and disease severity is difficult to define in children with chronic lung disease as some of these children are supported with mechanical ventilation and/or supplemental oxygen at baseline. They may also have radiographic findings that meet ARDS criteria at their clinical baseline. Similarly, patients with cyanotic congenital heart disease have low oxygen saturations by definition with a wide spectrum of baseline saturations. Patients with left ventricular dysfunction may develop pulmonary edema with less severe lung injury, considering an elevated baseline left atrial pressure.

It is recommended that all of these at risk populations be considered for diagnosis of PARDS when there is an acute clinical insult, a new finding or change in chest imaging consistent with parenchymal lung disease, and an acute deterioration in oxygenation not explained by changes in cardiac disease. It is important to include these patient groups in the definition of PARDS to allow for earlier diagnosis and therapeutic intervention and to improve the ability to include these patient populations in future research. Limitations to stratification in these patient populations of disease severity based on OI and OSI must be taken into consideration due to the variable, and below normal, baseline.

Clinical Case (Continued)

The child is started on 2 liters per minute (lpm) nasal cannula in the ED with improvement in oxygen saturations to the low 90% range as well as improvement in work of breathing. He is admitted to a pediatric unit but has worsening oxygen saturations over the next 12 h despite increasing oxygen flow. A rapid response is called by the bedside nurse, and the team arrives to find the patient on 4 lpm nasal cannula of 100% oxygen, significant respiratory distress, and oxygen saturation 78%. He is placed on a non-rebreather mask and is transferred to the PICU where he is intubated and started on a conventional ventilator.

- What are the options to improve hypoxemia in this child?
- Are there other less invasive respiratory support options available?
- What ventilator management strategies would you consider in this situation?

Noninvasive Respiratory Support

Although this chapter is focused on current controversies in invasive ventilator management for PARDS, it is important to mention noninvasive respiratory support. Noninvasive respiratory support has had increased use over the last decade, potentially preventing some of the adverse effects caused by invasive mechanical ventilation. These support modalities include high-flow nasal cannula and noninvasive mechanical ventilation devices, including nasal and full-face continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP). As with invasive mechanical ventilation, the benefits of these noninvasive modalities include delivery of high-oxygen concentration to the alveoli and decreased energy expenditure of the respiratory muscles with the added benefit of preserving natural

airway clearance mechanisms. CPAP helps maintain airway and alveolar patency, thereby preventing and/or improving atelectasis, a significant cause of shunt physiology and arterial hypoxemia. Additionally, adding inspiratory pressure with BiPAP helps increase tidal volume delivery in lungs with low compliance, improving alveolar ventilation and reducing $PaCO_2$ [6].

For most patients, noninvasive support devices are well tolerated, reduce the need for sedation, and possibly prevent intubation and mechanical ventilation, generally in patients with more mild disease. Currently, there are only a few studies to support the use of noninvasive respiratory support in children. In one study of 50 children with acute hypoxemic respiratory failure, predominantly secondary to bronchiolitis, supported with BiPAP or standard treatment (face mask oxygen), the patients supported with BiPAP showed a significantly decreased rate of intubation (28%) over those receiving standard therapy (60%, $p = 0.045$) [7]. This study showed noninvasive ventilation improved hypoxemia, tachycardia, and tachypnea as well as prevented some patients from endotracheal intubation and invasive mechanical ventilation. However, another study comparing noninvasive positive-pressure ventilation to inhaled oxygen post-extubation in children 28 days to 3 years of age showed no difference in re-intubation rates (9.1% vs 11.3%, $p > 0.05$) [8]. These studies did not include selection criteria or stratification by ARDS criteria and highlight the need for further studies in the benefits and potential adverse events related to the use of noninvasive respiratory support in the PARDS population.

In light of the current lack of data in patients with PARDS, noninvasive positive-pressure ventilation may be a safe alternative for pediatric patients with mild PARDS and can be considered to prevent intubation in some patients. It could be debated that noninvasive ventilation should only be considered in patients with less severe disease and not used in patients with moderate to severe lung disease. The clinician must understand potential risks associated with these modalities, including the risk of providing inadequate and untimely respiratory support with subsequent cardiopulmonary deterioration in patients with more severe disease. As noninvasive ventilation is trialed, careful and rapid assessment of the patient's response to therapy is necessary. Patients who will respond to therapy will likely show improvement in respiratory distress and oxygenation within the first 30–60 minutes. Clinical vigilance is required to determine if a patient is adequately supported with noninvasive ventilation and whether invasive mechanical ventilation should be pursued.

Lung-Protective Strategies

In the modern era of mechanical ventilation, much attention has been focused on what has been coined "lung-protective strategies" to prevent ventilator-induced lung injury (VILI). The major focus of these strategies is reduction of mechanical stresses on the alveoli, mainly overdistension (volutrauma), cyclic opening and closing of alveoli (atelectrauma), and excessive plateau pressure (barotrauma). Bedside goal-directed strategies, including tidal volume 5–8 ml/kg, positive end-expiratory pressures (PEEP) 10–15 cm H_2O, inspiratory plateau pressure < 28 cm H_2O [9], permissive hypercapnia (pH > 7.25 without a specific target $PaCO_2$), and permissive hypoxemia (SpO_2 > 88%, PaO_2 55–80), are the mainstay of lung-protective ventilator management strategies.

Tidal Volume Delivery: Volutrauma

Prior to the early 2000s, the general approach to mechanical ventilation targeted tidal volumes of 10–15 ml/kg, normal $PaCO_2$, and normal oxygen saturations. It should be noted that the normal resting tidal volume in humans is generally 6–8 ml/kg. In 2000, a landmark study by the ARDS Network showed a significant decrease in mortality in adult ARDS patients with targeted tidal volumes of 6 ml/kg (31%) as compared to "traditional" tidal volumes of 12 ml/kg (39.8%, $p = 0.007$) [10]. The results of this large adult study provided the basis for a significant shift in

the mechanical ventilation management strategies of ARDS patients. In practice, to achieve low tidal volumes and lower inspiratory pressures, a deviation from the goals of normal $PaCO_2$ and PaO_2 (SpO_2) was developed and coined permissive hypercapnia and permissive hypoxemia, respectively.

Although no pediatric study has confirmed a mortality benefit to low tidal volume ventilation in PARDS, pediatric critical care clinicians, in general, have been keen to adopt this strategy for its potential benefit. However, in contrast to the outlined adult findings, it must be noted that observational pediatric studies have shown a relationship between higher tidal volumes and lower mortality [11] or no relationship between tidal volume and mortality [12, 13]. Although they did not find a relationship with mortality, Khemani and colleagues showed higher tidal volumes were associated with increased ventilator-free days. It is important to note these pediatric studies were performed in the era of "lower than traditional" targeted tidal volumes (i.e., <10 ml/kg); thus, a comparison group to the "traditional" ARDS Network tidal volume group of >12 ml/kg is not available. Considering the limitations of observational studies, it is likely these findings represent a heterogeneous severity of disease, with higher tidal volumes seen in patients with better lung compliance (less severe lung injury) with the use of pressure-control ventilation mode. Additionally, in patients with more severe lung injury, physicians likely targeted lower plateau pressures to avoid barotrauma, resulting in lower tidal volumes.

Predicted body weight as compared to actual body weight is recommended when targeting a specific tidal volume as lung capacity is more closely related to height than weight [14]. Targeting predicted body weight may decrease the risk of over distension and volutrauma in obese patients.

The current recommendation for tidal volume management for PARDS, as described by PALICC, is to target tidal volumes of 5–8 ml/kg predicted body weight and as low as 3–6 ml/kg in patients with poor respiratory system compliance [9]. This recommendation is based largely on the findings of the initial adult studies, which have guided the clinical practice of ARDS with lower tidal volume goals. The studies in pediatrics that show lower mortality related to higher tidal volumes have suggested further study is likely warranted to assess a causal relationship between tidal volume and outcome in those with PARDS.

PEEP Titration: Atelectrauma

During normal respiration, the vocal cords close at the end of expiration to maintain a low level of positive pressure in the airways and alveoli to prevent atelectasis. In ARDS, the functional residual capacity of the damaged alveoli decreases, causing atelectasis unless higher mean airway pressure is applied. The use of higher positive end-expiratory pressure (PEEP) may help to avoid repetitive collapse-opening-collapse injury (atelectrauma).

Determining the optimal PEEP at the bedside can to be a difficult task, with methods including incremental increases (decreases) in PEEP while monitoring lung compliance (estimated using tidal volumes, drive pressure, and pressure/volume loops) and radiographic findings. During PEEP adjustment, especially at higher pressures, cardiopulmonary interactions and hemodynamic monitoring must be considered as elevated PEEP (i.e., intrathoracic pressure) may adversely affect central venous return and right ventricular afterload, therefore decreasing cardiac output.

It should be noted that atelectrauma has only been shown in experimental studies [15]. In the era of targeted low tidal volume, three adult trials in ARDS patients evaluating low PEEP vs. higher PEEP showed no significant difference in mortality [16–18]; however, two systematic reviews and meta-analyses suggested a small survival benefit of higher PEEP in patients with severe ARDS [19, 20]. Interesting to the pediatric critical care provider, a pediatric multicenter, retrospective analysis of 1134 patients with PARDS showed that 26% of pediatric patients were managed with lower PEEP than suggested by the ARDSnet protocol based on FiO_2. The investigators found an

increased mortality in that group as compared to the patients in which PEEP was within the protocol (OR 2.05, 95% CI 1.32, 3.17) [21].

PALICC guidelines suggest maintaining elevated levels of PEEP (10–15 cm H_2O) with consideration of higher titration in severe ARDS with attention to limiting the plateau pressure [9]. Considering no pediatric PEEP titration protocol has been studied prospectively, controversy remains as to whether the ARDSnet adult PEEP/FiO_2 titration chart is optimal for both adult and pediatric patients with ARDS.

Plateau Pressure and Drive Pressure (ΔP): Barotrauma

Plateau pressure refers to the equilibrated static pressure at the end of inspiration during an inspiratory hold, which is a result of the tidal volume delivered above PEEP without influence of airways resistance (flow). In pressure control mode of mechanical ventilation, peak inspiratory pressure (PIP) is controlled by the clinician, and ΔP (drive pressure) = PIP − PEEP. The drive pressure is influenced by: (1) airways resistance, (2) chest wall elastance, and (3) alveolar compliance, whereas the plateau pressure reflects the compliance of the alveoli. The tidal volume is then dependent on the compliance of the lung, with worsening lung compliance resulting in lower tidal volumes at the same inspiratory/plateau pressure.

Elevated peak airway pressures may cause trauma simply by pressure injury to the lung parenchyma. Another mechanism suggested for barotrauma is linked to the heterogeneous nature of ARDS, with some alveolar units more affected than others, resulting in different compliance of different lung segments. This may lead to low tidal volumes in poorly compliant lung segments and overdistension in more compliant (and potentially healthier) lung segments. This concept supports the use of pressure control ventilation modes in patients with PARDS, decreasing the risk of over distension of healthier lung segments, although the debate of volume control vs pressure control is more complex than this single point.

Pediatric observational studies have shown both an association between high inspiratory pressures and increased mortality [11, 12] and a lack of association between inspiratory pressure and mortality [13]. None of these studies were randomized or powered to determine the relationship between inspiratory pressure and mortality. A recent adult study in ARDS patients showed the drive pressure to be most predictive of mortality [22]. Whether there is a relationship between peak inspiratory, plateau, and/or drive pressures and mortality in PARDS is yet to be determined.

Based on the available data and clinical expertise, the PALICC recommendation is to maintain plateau pressures <28 cm H_2O, with consideration to increased pressure (28–32 cm H_2O) in patients with increased chest wall elastance (i.e., decreased chest wall compliance), such as those with obesity, chest wall edema, or severely increased abdominal pressure [9]. This recommendation may be considered controversial to some clinicians who argue that a higher plateau pressure (30–32 cm H_2O) in those without decreased chest wall compliance may be safe. Further studies are needed to delineate a "safe" plateau pressure in those with PARDS with the shared goal to decrease secondary lung injury caused by barotrauma.

Clinical Case (Continued)

The patient has been in the PICU for 72 h and continues to have worsening hypoxemia and progressive bilateral infiltrates on chest radiograph. His viral panel is positive for influenza. Despite attempts at lung-protective ventilator strategies including increased PEEP, plateau pressure < 28 cm H_2O, and tidal volume 5–8 ml/kg ideal body weight, his oxygen saturations are consistently ~80–85%. He is on the conventional ventilator in pressure control mode with FiO_2 0.80, PEEP 14 cm

H_2O, and PIP 34 cm H_2O, and now tidal volumes are consistently 3–4 ml/kg. The most recent arterial blood gas is pH 7.31, PCO_2 55 torr, PO_2 50 torr, and SO_2 83%.

- What is the child's P/F ratio, oxygenation index (OI), oxygen saturation index (OSI), and ARDS disease severity?
- What alternative modes of ventilation could you consider at this point?
- What adjunctive therapies would seem reasonable options?

High-Frequency Oscillatory Ventilation

Despite many studies investigating the use of high-frequency oscillatory ventilation (HFOV) for the management of ARDS, this continues to be a topic of significant controversy and debate. Research findings range from showing benefit to causing harm, leaving the clinician without guidance whether to use the modality in their pediatric patients. HFOV works on the principle of lung-protective ventilator management strategy: targeting reduction of atelectrauma, volutrauma, and barotrauma. In this mode, the patient's lungs are inflated using a constant distending pressure, the mean airway pressure (MAP), which helps to decrease cyclic opening and closing of the alveoli, i.e., atelectrauma. High-frequency (5–15 Hz) small tidal volumes may decrease lung injury caused by volutrauma. Disadvantages of HFOV include increased use of sedation and neuromuscular blockade [23], decreased airway clearance and suctioning due to loss of recruitment with circuit disconnections, and decreased ability to transport patients for studies and interventions. Another likely disadvantage due to physician management style, and not the HFOV per se, is slower weaning of mean airway pressure as compared to conventional ventilator due to clinician hesitancy and concern for loss of alveolar recruitment [24].

Although HFOV has been available since the 1970s, there are relatively few studies in pediatrics that help guide the clinician caring for the critically ill child with ARDS. Initial pediatric studies showed improvement in oxygenation parameters [25, 26] but no difference in 30-day mortality [27]. The general consensus at this time was HFOV was safe to use in pediatric patients; however, long-term survival benefit was still to be determined. It is important to note that in these early studies, HFOV was compared to conventional ventilation with high tidal volumes. In subsequent years, adult and pediatric data began to support the use of HFOV, and these data are summarized in a meta-analysis by Sud et al. [28]. Eight randomized controlled trials (two pediatric) from 1994 to 2007 were reviewed in this meta-analysis, with the majority during the era of low tidal volume conventional ventilation strategy. The authors concluded that HFOV might improve survival for hospital or 30-day mortality (risk ratio 0.77, $p = 0.03$, six studies with low bias, 365 patients, 160 deaths). Only one study with five subjects in the final analysis included children.

Two large, randomized controlled studies in adults have helped shape the current management strategies regarding HFOV in adult patients with moderate to severe ARDS. The OSCAR trial [29] showed no significant effect on 30-day mortality between HFOV and conventional ventilation with low tidal volumes and high PEEP. Further, the OSCILLATE trial [23] was stopped prematurely for increased mortality in the HFOV group as compared to the control group (47% vs 35%, relative risk of death with HFOV 1.33, $p = 0.005$). However, results of the OSCILLATE study have come into question, considering the HFOV group had higher mean airway pressures, increased use of vasoactive drugs, sedatives, and neuromuscular blockers.

The most recent data regarding the use of HFOV in children has shown similarly inconclusive results. A secondary propensity score analysis was performed on the subgroup of patients in the RESTORE trial supported with early HFOV as compared to those treated with conventional mechanical ventilation and late HFOV [24].

Of the 2449 subjects enrolled in the trial, 353 patients (14%) were supported with HFOV. After adjusting for risk category, the authors concluded early HFOV was associated with longer duration of mechanical ventilation but no association with mortality. It is important to note this study was not controlled or randomized to these groups, so minimal definitive conclusions can be gained from this analysis.

No conclusive evidence exists that high-frequency oscillatory ventilation is a superior mode of ventilation as compared to "lung-protective" conventional ventilation, with a large randomized controlled adult trial showing it may be more harmful. Despite this HFOV remains a commonly used modality in the respiratory management of PARDS patients and a source of controversy and debate. Inconsistent results supporting negative effects, equipoise, and positive benefit to its use leave the pediatric critical care clinician without guidance as no definitive trial of HFOV has yet been completed in the PARDS population. A randomized, controlled trial of HFOV in patients with severe PARDS is currently being initiated. Hopefully, the role of HFOV for PARDS will be known in the coming years. The PALICC recommendations at this time support "consideration" of HFOV in patients with hypoxemic respiratory failure in patients whose plateau pressure exceeds 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance [9] or 32 cm H_2O in the presence of reduced chest wall compliance.

Adjunctive Therapies

Recruitment Maneuvers

Recruitment maneuvers refer to intermittent increases in airway pressure with the intent of opening collapsed lung units. ARDS patients with predominant lung pathology of diffuse alveolar collapse (as compared to focal consolidation) and inflammatory edema [30] and those without impairment of chest wall mechanics [31] may benefit most from recruitment maneuvers. Pediatric and adult studies have shown recruitment maneuvers to be safe [32, 33] and improve oxygenation [34] in patients with ARDS. No data exist on the effect of recruitment maneuvers on clinically relevant outcomes, such as mortality, morbidity, length of stay, or duration of mechanical ventilation in pediatric patients [35].

In practice, there are several variations to performing recruitment maneuvers. In the authors' opinion, manual recruitment maneuvers are not recommended as the pressure delivered via the bag can be highly variable and difficult to control even with a manometer, risking the negative effects of volutrauma and barotrauma on the lungs as well as decreased cardiac output (decreased venous return, increased right ventricular afterload). Additionally, derecruitment is likely to occur when converting from the manual bag back to the ventilator circuit. Current recommendations support careful recruitment maneuvers to improve severe oxygenation impairment by using slow incremental and decremental PEEP adjustment and recommend not using sustained insufflation maneuvers [9].

Prone Positioning

Prone positioning may improve ventilation-perfusion matching due to shunt physiology related to atelectasis by promoting blood flow to the more open anterior segments (i.e., creating zone 3 conditions) and by mobilizing secretions. The PROSEVA trial, a large adult randomized controlled trial including 466 adults with severe ARDS, showed improvement in 28-day (16.0% vs 32.8%, $p < 0.001$) and 90-day mortality (23.6% vs 41.0%, $p < 0.001$) with prone positioning for at least 16 h/day [36]. Pediatric trials showed improvement of oxygenation while in the prone position [37–39]; however, no change in mortality has been seen [40]. The largest pediatric randomized controlled trial was stopped early due to futility, showing no change in ventilator-free days (primary outcome) or secondary endpoints: time to recovery of lung injury, organ failure-free days, cognitive impairment, overall functional health at hospital discharge or on day 28, or mortality [41]. Systematic reviews showed

improved oxygenation in patients with acute hypoxemic respiratory failure [42] and improved mortality in severe ARDS (PaO_2/FiO_2 ratio < 100) [43], supporting consideration to prone positioning in this specific patient population.

Considering the only large pediatric randomized controlled trial terminated early due to futility, prone positioning is not routinely recommended for PARDS by PALICC [44]. However, this recommendation is debatable when considering the recent adult data showing significant improvement in mortality in adults with severe ARDS. Prone positioning could be considered in severe PARDS patients (with P/F ratio < 100) based on extrapolation from the available adult-based data. A randomized controlled trial of prone positioning in severe PARDS is currently being initiated and will, hopefully, provide greater insight into this management strategy.

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) is a potent pulmonary vasodilator which has been evaluated for use in patients with ARDS. The mechanism of action is relaxation of smooth muscle by increasing intracellular cyclic guanosine monophosphate. In ARDS, delivery of iNO should theoretically preferentially vasodilate and increase perfusion to well-ventilated healthy alveoli, thus possibly decreasing intrapulmonary shunt physiology. Pulmonary vasodilation also results in decreased pulmonary vascular resistance (i.e., right ventricular afterload) when elevated due to hypoxic pulmonary vasoconstriction. Randomized controlled trials in PARDS patients showed transient improvement in oxygenation [45] but no effect on mortality [46]. In 2011 a meta-analysis evaluating the use of iNO in 14 adult and pediatric studies showed transient improvements in oxygenation but no reduction in mortality. The authors noted that iNO may be harmful due to an increased rate of renal failure [47].

Considering the data, iNO is not recommended for routine use in the management of children with ARDS [44, 48]. Inhaled nitric oxide may be considered in patients with pulmonary hypertension and right ventricular dysfunction or, as a temporizing measure, while extracorporeal membrane oxygenation is mobilized in the severely ill patient.

Surfactant

Surfactant is a mixture of protein and lipid produced by type II pneumocytes which helps maintain alveolar patency by decreasing surface tension. Proposed mechanisms for surfactant deficiency in ARDS are direct damage to type II pneumocytes and inactivation of surfactant by protein-rich pulmonary edema fluid during the acute phase of ARDS. With the success of surfactant in the neonatal respiratory distress syndrome population, much excitement has surrounded the potential for restoration of the surfactant system to improve outcomes in the PARDS patient. Early studies and randomized controlled trials showed acute increases in oxygenation [49–52]. One of three larger pediatric randomized controlled trials showed an improved mortality [53], whereas two others showed no effect on mortality [54, 55]. Interestingly, one study showed no improvement in oxygenation with surfactant administration [55]. Current recommendations do not suggest the use of surfactant in the management of PARDS [44].

Clinical Case (Continued)

The patient was transitioned to HFOV on PICU admission day 4 with a mild hypotension that responded to fluid resuscitation. He showed a sustained improvement in both oxygen saturation and the bilateral infiltrates over the following days. After discussions about adjunctive therapies for PARDS, prone positioning was trialed; however, no improvement in oxygenation was seen. Five days later, our patient was transitioned to conventional ventilation and was successfully extubated several days later to 2 lpm via *nasal cannula.*

Important Topics for Further Discussion

Any chapter discussing current controversies in mechanical ventilation for pediatric acute respiratory distress syndrome would not be complete without acknowledging important topics reviewed elsewhere in this book. These topics include extracorporeal support, weaning and extubation readiness assessment, corticosteroid therapy, and sedation management.

Future Directions

Pediatric ARDS continues to be a commonly managed disease with a high mortality [56]. As highlighted in this chapter, significant controversy and uncertainty exist in the critical care management of these patients. Changes in approach to the clinical management of these patients have occurred over the last two decades with a resultant increased trend in survival rate. However, there is still significant controversy and opportunity for research to evaluate benefit and harm of current management modalities and/or combinations of approaches as well as to determine the specific patient populations that may benefit the most from each management strategy. At the same time, it is also important for investigators and clinicians to accept that some treatment modalities may already have sufficient scientific data to support discontinued use in the management of ARDS.

Exciting new lines of research, including biomarkers of lung injury [57], may shed light on goal-directed therapies to identify specific patients that may benefit the most from a particular therapy. Advances in the understanding of the immune system and pharmaceutical modulation will likely benefit the PARDS patient in the future. Also, considering the significant advances in material science and technology over the past few decades, alternative modalities and devices for oxygen delivery [58–60] other than mechanical ventilation should be developed with hope of decreasing the detrimental effects of ventilator-induced lung injury and sequelae of other therapies associated with mechanical ventilation.

Take-Home Points

- Lung-protective mechanical ventilator strategies have significantly reduced mortality in ARDS.
- Current recommendations support consideration of HFOV and recruitment maneuvers but do not currently support the use of inhaled nitric oxide or exogenous surfactant administration. The use of prone positioning remains uncertain.
- There remains significant opportunity for research in the management of PARDS.

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2 Extracorporeal Membrane Oxygenation for Acute Pediatric Respiratory Failure

Matthew Friedman and Michael Hobson

Case Presentation

A 2-year-old girl has developed hypoxemic respiratory failure, severe pediatric acute respiratory distress syndrome, and sepsis secondary to influenza and Staphylococcus aureus pneumonia. On day 4 of mechanical ventilation, she is supported with high-frequency oscillatory ventilation with mean airway pressure set at 30 cmH_2O. Her inspired oxygen requirement is 70%, and she has been unable to be weaned over the past 12 h. Her arterial blood gas shows pH 7.26, $PaCO_2$ 65 mmHg, PaO_2 58 mmHg, and base deficit − 2. Epinephrine (0.06 mcg/kg/min) and dopamine (5 mcg/kg/min) infusions are required for hemodynamic support. Relevant clinical questions for the care of this child include:

- *What clinical criteria can be utilized to determine if extracorporeal membrane oxygenation is indicated to support this child's hypoxemic respiratory failure?*
- *Which extracorporeal modality and cannulation approach is most appropriate in this clinical scenario?*
- *Which mechanical ventilation strategies and other respiratory therapies can help to optimize her chances of recovery?*

Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of extracorporeal life support utilized to rescue neonatal, pediatric, and adult patients with respiratory, cardiac, or combined cardiopulmonary failure that is refractory to conventional supportive and therapeutic measures. As a modified form of cardiopulmonary bypass, modern-day ECMO circuitry utilizes either a semi-occlusive roller pump or a centrifugal pump combined with a hollow fiber membrane oxygenator for gas exchange. As a supportive modality, ECMO can provide extended physiologic respiratory and cardiac support for days to weeks, thereby allowing the clinical team time to diagnose and treat the patient's underlying disease process. To date, the Extracorporeal Life Support Organization registry contains more than 87,000 ECMO runs in its history, of which approximately 10% are children supported for a pulmonary indication [1].

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Despite the growing use of ECMO across critical care settings, a discrepancy exists in the available data regarding the effectiveness and benefit of ECMO for various patient populations. For neonates with refractory respiratory failure, clinical trials have shown that ECMO decreases mortality and is cost-effective [2–4]. Likewise, ECMO has been demonstrated to be a valid treatment option for critically ill adults with refractory respiratory failure, [5] yet no clinical trials evaluating the efficacy of ECMO have been performed for children with respiratory failure. Current evidence for use of ECMO for children with respiratory failure relies mostly on registry reports and single-center experiences. A recent secondary analysis of the RESTORE trial [6] utilizing matching techniques to compare patients who did and did not receive ECMO showed no mortality benefit from ECMO as compared to ventilation management strategies [7]. This report, while thought provoking, was a secondary analysis of a study designed to evaluate a nurse-driven sedation protocol, and thus the results should be interpreted with caution. Examining ECMO in children with respiratory failure is further limited by the heterogeneity of this patient population; variations in patient age, disease processes, and patient comorbidities all contribute to this heterogeneity. Lastly, the clinical management of ECMO varies greatly across pediatric centers.

Without reliable data by which to guide clinical decision-making, pediatric intensivists managing respiratory failure often must resort to their "gut feeling" when initiating and managing ECMO. The stakes are high – acuity of illness and rapid deterioration often do not allow much time for these life-saving decisions. Prognostication of outcome is difficult, and the costs (e.g., patient morbidity, financial burden, resource utilization) are potentially immense. Given these constraints, we attempt to summarize the available literature regarding ECMO support for pediatric respiratory failure and provide an organized framework by which clinicians can make logical decisions for these challenging patients.

Indications for ECMO

Indications for initiating ECMO in the setting of pediatric respiratory failure can be divided into two general frameworks (Table 2.1). The first clinical scenario is one of progressive hypoxemia and associated hemodynamic instability that remains refractory despite escalation in ventilatory support and other ancillary therapies. Quite simply, the child will die without ECMO, and the decision to initiate ECMO is not a difficult one. The second scenario is one in which the toxicities of medical therapy may begin to outweigh their clinical benefit. In the setting of respiratory failure and severe lung disease, the concept of ventilator-induced lung injury (VILI) becomes pertinent. Mechanical ventilation (MV) has been shown to initiate or worsen lung injury through the mechanisms of volutrauma, barotrauma, oxygen toxicity, and atelectrauma [8]. Current recommendations to limit VILI in children with acute respiratory failure (ARF) include a low tidal volume strategy (5–8 mL/kg predicted body weight), limiting plateau pressures to <28 cmH_2O, and titration of positive end-expiratory pressure (PEEP) in an effort to achieve alveolar recruitment and reduce fraction of inspired oxygen concentration (FiO_2) to non-toxic levels [9]. Permissive hypercapnia (maintaining a pH > 7.25) and mild hypoxemia (PaO_2

Table 2.1 Indications for initiation of ECMO for respiratory failure

Rapidly progressive or severe hypoxemia resulting in hemodynamic instability and risk of cardiovascular collapse despite maximizing medical therapy
An oxygenation index sustained above 25 and not improving, combined with one sign of impaired tissue oxygenation:
1. Rising serum lactate
2. Widening arterial-venous saturation gradient
3. Diminishing urine output
4. Decreasing near-infrared spectroscopy (NIRS)
5. Increasing need for vasoactive support
6. Worsening metabolic acidosis
Hypercarbia and respiratory acidosis causing cardiovascular compromise
Presence of refractory or severe air leak syndromes compromising gas exchange or hemodynamic stability

40–50 mmHg) are acceptable consequences of these maneuvers, provided adequate systemic oxygen delivery and hemodynamics are maintained [9]. In children with severe lung disease, these lung-protective strategies may have to be exceeded to provide adequate ventilation and oxygenation, with progressive VILI as an untoward consequence. Initiating ECMO provides respiratory support allowing for reduction in ventilator settings to non-toxic levels and possibly to avoid further VILI. In either scenario, the most important principle when deciding upon ECMO suitability is to identify those children with a high probability of mortality yet having potentially reversible lung disease.

Hypoxemic Respiratory Failure and Pediatric Acute Respiratory Distress Syndrome

Pediatric acute respiratory distress syndrome (pARDS) is a clinical syndrome characterized by decreased lung compliance and difficulties with oxygenation. Mortality from pARDS ranges from 18% to 35% [10, 11]. Clinical predictors of mortality from pARDS could help clinicians identify children who would benefit from ECMO support for refractory hypoxemic respiratory failure. Candidate predictors include alveolar dead space fraction (utilized in the studies below as [$PaCO_2$ – end tidal CO_2]/$PaCO_2$), the PaO_2/FiO_2, and the oxygenation index (OI). Nuckton et al. prospectively measured dead space fraction in adult patients with ARDS early in the course of their illness and found increasing dead space fraction to be an independent risk factor for mortality [12]. From a pediatric perspective, in a retrospective review of 217 children requiring mechanical ventilation for acute hypoxemic respiratory failure, the dead space fraction at disease onset and day one both correlated with mortality, though not independently associated when controlled for severity of illness, 24-h maximal inotrope score, and oxygenation index [13]. On the other hand, in a cohort of 266 children with pARDS, Yehya et al. recently showed that the alveolar dead space fraction at the onset of pARDS was significantly higher in non-survivors (0.31 vs 0.13), was independently associated with mortality, and functioned better as a predictor of mortality than the initial PaO_2/FiO_2 ratio or oxygenation index [14]. This predictive value of dead space fraction however was not observed at 24 h. Functionally, a single numerical value at disease onset may not be practical from the standpoint of clinical decision-making, as intensivists may attempt other modalities and therapies (e.g., high-frequency oscillatory ventilation, prone position, inhaled nitric oxide, etc.) before proceeding with ECMO.

The PaO_2/FiO_2 (PF) ratio and the oxygenation index (OI = [(mean airway pressure × FiO_2 × 100)/PaO_2]) have both served as markers of lung disease severity in children with hypoxemic respiratory failure, but the OI has become preferred in contemporary pediatric critical care practice, as it incorporates the mean airway pressure (MAwP) required to maintain oxygenation goals [15]. Over the past decade, many retrospective and prospective studies have demonstrated an association between higher OI and mortality in children with hypoxemic respiratory failure [16–19]. Historically, an OI of greater than 20 has been used as an indication to transition from conventional mechanical ventilation to high-frequency oscillatory ventilation (HFOV) [20, 21]. In these studies, an OI greater than 20 is associated with mortality rates of more than 40%. The trend in OI value is likely more informative than any single data point, as pARDS is an evolving disease process. For example, utilizing data from preexisting cohorts with pARDS, the Pediatric Acute Lung Injury Consensus Conference evaluated the following variables as predictors of mortality: initial PF ratio, initial OI, worst PF ratio during the first 3 days of mechanical ventilation, and worst OI values during the first 3 days of mechanical ventilation. The worst (highest) OI value during the first 3 days of ventilation was the best discriminator for non-survival, with an area under the receiver operating characteristic curve of 0.75 [15]. Recent data suggests that incorporating an inflammatory cytokine profile alongside the oxygenation index is superior in predicting outcomes in pARDS compared to the oxygenation index

alone [22]. These data are intriguing, as they suggest the possibility of a future biomarker array that could help identify patients with pARDS at risk for mortality and thus stratify those candidates who should be considered for earlier ECMO support. Until then, it can be concluded that for patients with pARDS that progress to ECMO, higher pre-ECMO oxygenation index is at higher risk of mortality [23, 24].

Currently, the Extracorporeal Life Support Organization recommends an OI sustained above 40 as the indication for initiation of ECMO in children with respiratory failure [25]. However, there are likely children with hypoxemic respiratory failure and OI values below this threshold that could benefit from ECMO's potential ability to mitigate further VILI. For example, in an analysis of a cohort of children in our institution with hypoxemic respiratory failure who were ventilated with HFOV, an OI greater than 25 at 48 h following the onset of pARDS conferred a significantly higher odds of mortality (odds ratio: 5, 95% CI 1.3 to 16.7, $p < 0.05$) [19]. While the predictive value of the oxygenation index continues to grow in the arena of pediatric critical care, to date, no definitive OI threshold exists above which pediatric intensivists can be 100% certain regarding the optimal time point for the initiation of ECMO for pARDS. The Pediatric Acute Lung Injury Consensus Conference from 2015 states that "it is not possible to apply strict criteria for the selection of children who will benefit from ECMO in pARDS" [26].

In the absence of strict numerical criteria surrounding oxygenation, intensivists are left to rely on the gestalt clinical picture when deciding upon the initiation of ECMO to support children with hypoxemic respiratory failure. Key components within this framework include trends in ventilator support and oxygenation measures over time, hemodynamic stability, organ function, and acid-base status. First, with regard to the trajectory of respiratory support and oxygenation, serial assessments serve more valuable than an evaluation at a single time point [26]. It is our practice to obtain arterial blood gases and calculate the oxygenation index every 4 h. Concurrently, we also track trends in peak inspiratory pressures as a marker for the potential of evolving ventilator-induced lung injury. Second, children with evolving hypoxemic respiratory failure can develop hemodynamic instability. Etiologies for this instability can be multifactorial, including impaired oxygen delivery to the myocardium, impaired right ventricular preload from increased intrathoracic pressure, increased right ventricular afterload from hypercarbia and acidosis, and concurrent sepsis. Next, the cascade of inflammatory cytokines released during ARDS as well as with VILI has been demonstrated to result in direct organ dysfunction, fluid retention, and subsequent fluid overload [27]. All of the above factors may culminate in a progressive metabolic acidosis, the effect of which is noteworthy in critically ill children. In a retrospective cohort of children with hypoxemic respiratory failure supported with HFOV, the presence of a metabolic acidosis was independently associated with a higher risk of mortality [19]. Likewise, studies examining pre-ECMO variables in this patient population have shown that the presence of acidosis is associated with worse survival [23, 24]. For example, in a study by Dimico and colleagues containing data from 1325 children within the ELSO registry, odds of survival to hospital discharged increased by 15% for every 0.1 increase in pre-ECMO pH.

Hypercarbic Respiratory Failure

Though severe refractory hypoxemia is the most common indication for pediatric respiratory ECMO, there are patients who require ECMO due to severe ventilation impairment leading to hypercarbia. Acute hypercarbic respiratory failure is defined as a P_aCO_2 greater than 50 mmHg, typically associated with respiratory acidosis. Modern ventilation strategies are focused on limiting VILI and allowing for permissive hypercarbia [28, 29]. The possible detrimental effects of moderate hypercarbia (50–75 mmHg) have been debated, but they are inconsequential compared to the risks associated with ECMO [30]. Thus, ECMO is not advised for moderate hypercarbia (i.e., $PaCO_2$ up to 75 mmHg). However, as P_aCO_2 rises and respiratory acidosis becomes more severe, dysfunction of other organ systems

becomes more significant, particularly that of the cardiovascular system. Therefore, severe hypercarbic respiratory failure with acidosis and hemodynamic instability is an indication for initiation of ECMO [30]. ECMO can correct hypercarbia rapidly with a resultant improvement in acidosis and organ function. During this process, clinicians must be aware of possible detrimental consequences of rapid correction of $PaCO_2$, which includes cerebral vasoconstriction and the development of alkalosis.

Status asthmaticus is the most common disease causing severe hypercarbia requiring ECMO, but patients with status asthmaticus only represented 3% of the pediatric respiratory cases reported to ELSO from 2009 to 2015 [31, 32]. Patients who require ECMO for status asthmaticus typically have severe acidosis (pH < 7.0) and severe hypercarbia (P_aCO_2 > 100 mmHg) despite maximal medical therapies [32]. Children with status asthmaticus on ECMO have very good survival, with 88% surviving to hospital discharge. Moreover, status asthmaticus improves relatively quickly, with an average duration of ECMO of 92 h [32].

Cystic fibrosis (CF) with pulmonary exacerbation is another patient population that can require ECMO for severe hypercarbic respiratory failure. There were 73 ECMO runs in the ELSO registry for cystic fibrosis from 1998 to 2013, with 52% survival [33]. There has been debate if patients with CF are candidates for ECMO due to the progressive nature of their disease. Each patient must be evaluated individually. First, the reversibility of their respiratory failure should be assessed. The primary determination in this regard is if the child has a pulmonary infection that is potentially amenable to antibiotic therapy. If lung disease is not thought to be reversible, then candidacy for lung transplantation should be considered. Cystic fibrosis should only be considered an absolute contraindication to ECMO if the patient is deemed not to have the potential for recovery from the acute process and is not a candidate for lung transplantation. Candidacy should be considered for any intubated cystic fibrosis patient to help inform decisions of whether or not to pursue ECMO. This candidacy should be determined by working with your local pulmonologist and, if necessary, a regional lung transplant center.

Airway Disorders

Patients with significant air leaks may not meet typical oxygenation or ventilation criteria for ECMO. Indications for ECMO support in patients with air leak syndromes include recurrent pneumothoraces causing life-threatening events or persistent air leaks not improving with chest tube thoracostomy. Patients with broncho-pleural fistulae from pulmonary infection or surgery that do not heal spontaneously on mechanical ventilation can also be successfully managed with ECMO, which allows for reduction of peak airway pressure [34, 35]. ECMO can also be used intraoperatively for major airway surgeries and postoperatively to allow for healing of surgical sites without the effects of high positive airway pressures [36, 37].

Our recommendations are a general framework to utilize when deciding upon ECMO support for children with refractory respiratory failure who have a potentially reversible lung disease and no absolute contraindication to ECMO (Table 2.1).

Case Presentation

OI was calculated to be 36 without improvement over 12 h despite medical therapy and use of high-frequency oscillatory ventilation. Her inspired oxygen concentration could not be weaned below 70%. At this point, her refractory hypoxemic respiratory failure secondary to influenza and Staphylococcus aureus pneumonia was considered refractory to conventional therapy with no trajectory of improvement. There was also concern that her potentially injurious ventilator support and high inspired oxygen concentration would continue to worsen her underlying lung disease. Based on these data, cannulation for ECMO was being considered.

Patient Selection

Diagnosis

Critically ill children may develop respiratory failure from a wide array of infectious or noninfectious and direct or indirect etiologies [38]. Successful use of ECMO support for children with refractory lung injury from a broad variety of noninfectious causes has been reported, including burn injuries [39], trauma [40, 41], hydrocarbon aspiration [42], and rheumatologic diseases [43, 44]. In an analysis of factors associated with pediatric ECMO survival, Zabrocki et al. reviewed 3213 children supported with ECMO for a primary pulmonary indication from the years 1993 through 2007 [24]. In this review, diseases associated with the best survival rates include asthma (83%), aspiration pneumonia (71%), and RSV bronchiolitis (70%). As infection is the most common etiology of pARDS [45], the remainder of the focus in this section will be on specific infectious pathogens. Overall survival for children with bacterial and viral pneumonia who require ECMO is approximately 56–59% [24]. Infectious agents that portend worse outcomes include *Bordetella pertussis,* herpes simplex virus (HSV), fungal pneumonia, and methicillin-resistant *Staphylococcus aureus* (MRSA).

Over the past two decades, the overall survival for children with pertussis who are supported with ECMO is 39%, considerably lower as compared to children requiring ECMO for other viral and bacterial etiologies [24]. In a retrospective analysis, children with pertussis who survived their ECMO course were found to have higher pre-ECMO PEEP (11 cmH_2O vs. 7 cmH_2O, $p = 0.006$) and significantly higher pre-ECMO pH values (7.31 vs. 7.14, p 0.002) when compared to non-survivors [46]. Lung pathology obtained from young infants who died from fulminant pertussis shows necrotizing bronchiolitis with necrosis of the alveolar epithelium [47]; thus, an open-lung strategy achieved with high PEEP (i.e., 10–11 mmHg) may help to offset the pathophysiologic ramifications of this process. Refractory pulmonary hypertension and severe leukocytosis are two additional pathophysiologic mechanisms which contribute to the severity of fulminant pertussis infections. Significantly leukocytosis is observed in infants with the most severe infections, with white blood cell (WBC) counts in excess of 100,000/mm^3 associated with increased mortality risk [48]. Postmortem examinations of these patients show leukocytes obstructing the pulmonary blood vessels [47]. This severe leukocytosis leads to vascular hyperviscosity and pulmonary arteriole thromboses and, when combined with the reactive pulmonary vasculature of the young infant, pulmonary hypertension refractory to conventional therapy. Given the role of leukocytosis in the pathology of this disease, an interesting single-center case series explored the utility of leukodepletion in infants with fulminant pertussis [49]. Implementation of a clinical protocol for leukodepletion for children with WBC count of greater than 50,000/mm^3 resulted in improved survival, with a reduction in mortality from 44% to 10%. Leukofiltration for patients receiving ECMO support was accomplished by placing a WBC filter sited in the bridge of the ECMO circuit. While this report was a single-center study with a small volume of patients, a case-mix adjustment accounting for age, WBC count, and ECMO referral time revealed a significantly better observed mortality following the implementation of leukodepletion than predicted. Thus, while the prognosis for infants with fulminant pertussis requiring ECMO remains guarded, implementation of leukodepletion can be considered to help offset the pathologic consequences of severe leukocytosis and subsequent pulmonary hypertension.

Case reports exist which describe the use of ECMO to support both neonates [50] and adults [51] for HSV infections. ECMO was successful in the cases of isolated respiratory infection leading to ARDS. Conversely, the outcomes for use of ECMO with disseminated HSV infection remain quite poor. Disseminated neonatal HSV is a rapidly progressive infection, which leads to multiple organ failure and has a high mortality rate despite aggressive care. A 2010 review of 40 neonates with HSV infection supported with

ECMO showed an overall survival to hospital discharge of 25% [52]. Survival remained constant across all decades, suggesting that the fulminant nature of this particular infection should cause one to approach initiating ECMO with caution.

Patients with active fungal infections prior to the initiation of ECMO are at risk of persistent seeding and contamination of the ECMO circuit. *Candida* was the predominate fungal species acquired both pre- and during ECMO in a study of the ELSO registry. While the presence of a fungal infection significantly increased the odds of mortality in all age groups, 82–89% of patients with fungal infections prior to the initiation of ECMO became culture negative at some point into their ECMO course [53]. Similarly, the presence of a fungal infection did not lead to an increase in circuit complications or circuit failure. Thus, the authors of this review concluded that while a fungal infection remains an important comorbidity to consider when initiating ECMO support, it, in and of itself, should not be considered an absolute contraindication to ECLS. However, caution must be exercised for pediatric patients with respiratory failure secondary to fungal infections. In the aforementioned review by Zabrocki et al., fungal pneumonia was the single diagnosis independently associated with the highest risk of mortality [24]. It is likely that the fungal infection alone does not portend to a grim prognosis but rather is a surrogate marker for patients with other diagnoses associated with poor outcomes on ECMO, such as patients with oncological diagnoses.

Community-acquired MRSA is an invasive bacterium that can cause skin and soft-tissue infections in previously healthy children. The invasive nature of this bacterium may lead to severe necrotizing pneumonia and ARDS in some children. Concurrent with the rise of invasive MRSA infections in the community over the past 25 years, the use of ECMO to support children with hypoxemic respiratory failure secondary to MRSA pneumonia has also risen [54]. Mortality from this pathogen remains high, with an approximate mortality rate of 50% for children who require ECMO; children older than 5 years seem to be particularly at risk. MRSA pneumonia and sepsis may result in thrombocytopenia-associated multiple organ failure (TAMOF), and there is some evidence which shows benefit from plasmapheresis performed during ECMO to reverse the sequelae of this disorder [55]. Combining plasmapheresis to the ECMO circuit adds a layer of technical complexity, and there is also increased heparin clearance during the procedure, thus necessitating careful monitoring of anticoagulation. Despite these challenges, recent data have shown that therapeutic plasma exchange can improve organ function in children with sepsis-induced multiorgan dysfunction who require ECMO support [56].

Duration of Mechanical Ventilation

As late as the 1990s, children with respiratory failure were not considered candidates for extracorporeal support after 7–10 days of mechanical ventilation due to a significant reduction in survival when ECMO was initiated beyond this timeframe [57, 58]. In this era, lung-protective ventilator strategies had not yet become standard practice, and, perhaps, significant VILI that had accrued in these children prior to ECMO initiation was irreversible. More contemporary data suggests that the optimal timing for ECMO initiation still lies within the first week of mechanical ventilation [59–61], but outcomes for children ventilated beyond 7 days prior to ECMO have improved such that these children should still be considered appropriate candidates for extracorporeal support. Domico et al. reviewed the relationship of pre-ECMO mechanical ventilation duration and the outcomes of 1352 pediatric patients who required ECMO for respiratory failure from 1999 to 2008 [23]. In this analysis, a significant reduction in survival was not observed until the pre-ECMO duration of ventilation exceeded 14 days. Similarly, in Zabrocki's review of pediatric respiratory failure, analysis of pre-ECMO mechanical ventilation revealed that survival remained 56% or higher for children who had ECMO initiated within the first 14 days of mechanical ventilation but declined to 38%

beyond this timeframe [24]. Fourteen days is now often considered a "cutoff" for duration of ventilation prior to ECMO; however, the outcomes for patients with certain diagnoses, such as viral pneumonia, can be good even when ECMO is initiated after 2 weeks of ventilation [21, 22]. Careful patient selection is therefore paramount to successful use of when ECMO if extracorporeal support is initiated after an extended course of mechanical ventilation. Factors that should be considered are the number of comorbidities, the number of non-pulmonary organ failures, and the primary cause of pARDS.

Patient Comorbidities

Historically, the ideal ECMO candidate was one with a known reversible illness, had single-organ failure and minimal comorbidities, was neurologically intact and not developmentally delayed, and had minimal bleeding risk. Practically speaking, very few children cared for in modern-day pediatric intensive care units fit this description. Over the past two decades, the use of ECMO for respiratory support in children with comorbidities has increased markedly. In 1993, 19% of children placed on ECMO had underlying comorbidities, compared to 47% in 2007 [24]. Not surprisingly, children with comorbidities have lower survival rates when compared to previously healthy children [24]. Comorbidities which have been shown to significantly increase mortality on ECMO include acute kidney injury, liver failure, cancer, primary immunodeficiency, and pre-ECMO cardiac arrest [24].

Acute kidney injury is a common occurrence in the intensive care setting, and its impact on outcomes of children requiring ECMO is notable. Recently, the Kidney Intervention During Extracorporeal Membrane Oxygenation Study Group showed that approximately 60% of children requiring ECMO support have acute kidney injury, and this comorbidity is associated with a longer duration of ECMO and an increased risk of mortality [62]. Closely related to acute kidney injury is fluid overload, which also impacts ECMO patient outcomes. In a recent analysis of 756 neonatal and pediatric ECMO patients, peak fluid overload, fluid overload at ECMO discontinuation, and the change in fluid overload during ECMO were significantly higher in patients who suffered mortality either while on ECMO or later during their hospitalization [63].

The status of a patient's immune system is a significant consideration when deciding upon a child's suitability for extracorporeal support. Historically, an immunocompromised condition was a relative contraindication for ECMO for several reasons:

- Leukopenia from chemotherapy or the disease process itself confers a risk for subsequent super-infection.
- Concurrent thrombocytopenia and coagulopathy place patients at a higher risk for hemorrhagic complications.
- Multiorgan failure is often present prior to the initiation of ECMO.
- Doubt or uncertainty may exist regarding the patient's long-term prognosis with respect to their underlying disease.

A recent review examined the outcomes of 107 children with underlying malignancies (73 hematologic, 34 solid tumors) who received ECLS for various disease processes (the majority of which were acute respiratory failure) over a 13-year period [64]. Overall survival to hospital discharge was 35% (36% for respiratory failure, 29% for cardiac failure), which is worse than for other children receiving ECLS. Despite their immunosuppressed state, only 19% of these children acquired a new infection while on ECMO. Children with malignancies did have a higher rate of hemorrhagic complications, including cannula site bleeding, disseminated intravascular coagulation, and CNS hemorrhages when compared to children without cancer. Currently, most pediatric ECMO centers offer ECMO support for this patient population. Of 118 centers surveyed, 78% did not view the presence of a malignancy as a contraindication, and 17% considered pediatric cancer as only a relative contraindication to ECMO [64]. The support for the use of ECMO in this patient population, despite only

a 35% overall survival, likely stems from the notion that these patients, the majority of whom have leukemia, have a good prognosis with regard to their underlying malignancy if their acute respiratory failure can be overcome. In this cohort, the median OI prior to initiation of ECMO was 52, reflecting that these patients likely have a higher degree of lung injury prior to ECMO initiation, relative to other patient populations. It remains to be seen if earlier initiation of ECMO within this patient population could potentially result in improved outcomes. Regardless, malignancy should not be considered an absolute contraindication from ECMO. Close communication with the child's oncology team regarding the long-term prognosis from their underlying malignancy is an additional essential piece of information to be considered in this decision-making process.

Children undergoing hematopoietic stem cell transplantation (HSCT) are another immunosuppressed patient population where the decision to implement extracorporeal support may be controversial. These children can develop life-threatening complications in the immediate posttransplant period (e.g., diffuse alveolar hemorrhage, idiopathic pulmonary syndrome, various infections) and in the later stages following transplantation (e.g., graft versus host disease, bronchiolitis obliterans), all of which can lead to respiratory failure refractory to conventional care. Historical mortality rates for children requiring mechanical ventilation following HSCT are well over 50% [65–67]. More recent data suggests that an earlier transition from conventional ventilation to HFOV may improve survival, but mortality remains high [68]. With regard to the use of ECMO in this patient population, there are sparse case reports documenting the successful use of ECMO to support HSCT patients through posttransplant complications, including diffuse alveolar hemorrhage, [69] idiopathic pulmonary syndrome, [70] and sepsis secondary to neutropenic enterocolitis [71]. However, in an ELSO registry review of 19 children undergoing ECLS following HSCT, 79% died during the ECMO course: seven developed multiorgan failure, three had refractory hemorrhage, and five had support was withdrawn for others reasons [72]. Furthermore, only one of the four remaining children alive after ECMO survived to hospital discharge. A more recent ELSO registry review of children placed on ECMO support following hematopoietic stem cell transplant also showed poor outcomes, with only 10% of patients surviving to hospital discharge [73]. Based on this experience, it can be concluded that, at the present time, children undergoing HSCT are unlikely to survive refractory respiratory failure requiring ECMO. Broadly speaking, this population of children has had dismal outcomes when requiring intensive care admission, particularly if mechanical ventilation is necessary, and thus ECMO should be avoided.

In summary, while the historical approach may have been to reserve ECMO for previously healthy "salvageable" patients, contemporary ECMO utilization has shown that there are in fact very few conditions completely incompatible with ECMO. In the setting of pediatric respiratory failure, extracorporeal support serves as either a bridge to patient recovery or a bridge to consideration for lung transplantation in the event of non-recovery. Unless a disease process is deemed irreversible or the child is not a candidate for lung transplantation, ECMO remains a realistic option to support most critically ill children with refractory respiratory failure.

ECMO Modality and Cannulation Strategy

Once the decision has been made to initiate extracorporeal support for the child with worsening respiratory failure, the next determination is choice of ECMO modality. Venovenous (V-V) ECMO involves the removal of deoxygenated blood from the patient's right atrium, oxygenation and ventilation as the blood traverses through the ECMO circuit, and then return of oxygenated blood into the child's central venous circulation through a different port, often within the same cannula. V-V ECMO provides gas exchange but no direct cardiac support. In contrast, with veno-arterial (V-A) ECMO, oxygen-

ated blood returning to the patient enters the arterial circulation, commonly through a different cannula in the carotid or femoral artery. Completely bypassing the patient's native heart and lungs, V-A ECMO can provide complete cardiopulmonary support [74].

The inherent risks between these two ECMO modalities should be considered. With V-A ECMO, cannulation of the femoral artery incurs the risk of lower extremity ischemia [74], while cannulation of the carotid artery carries a substantial risk of stroke (23%) [75]. In an analysis of pediatric patients with respiratory failure, the use of V-A ECMO was independently associated with an increased risk of neurologic injury when compared to V-V ECMO [76]. Other risks associated with V-A ECMO include embolism of air or thrombi into the patient's arterial circulation or increased systemic afterload leading to distension of the left ventricle, with subsequent risk of pulmonary hemorrhage. The primary disadvantage of V-V relative to V-A ECMO is its inability to provide cardiac support for patients with hemodynamic instability. However, there are important cardiac benefits that indirectly result from initiation of V-V ECMO for respiratory failure. First, with the ability to wean mechanical ventilation, intrathoracic pressure decreases, thereby improving preload to the right ventricle. Second, the ability of V-V ECMO to correct hypercarbia and acidosis can lead to a reduction in pulmonary vascular resistance and a corresponding decrease in right ventricular afterload. Lastly, oxygenated blood returning from the ECMO circuit passes through the pulmonary vasculature, eventually making its way into the left ventricle. A portion of this blood will enter the coronary circulation as it exits the aortic valve, providing a previously oxygen-deprived myocardium with a rich source of oxygen and a resultant improvement in ventricular function and hemodynamics.

In a single-center review of children requiring ECMO for acute respiratory failure from 1991 through 2002, Pettignano et al. illustrated the hemodynamic benefits of V-V ECMO [77]. In this cohort, 35% of patients required at least one vasopressor, and 41% required at least one inotropic infusion at the time of ECMO cannulation. After initiation of ECMO support, there was a significant reduction in vasoactive medication requirements, and all patients were free from vasoactive infusions by day 6 of ECMO. Similarly, an analysis of 4332 ECMO runs for children with sepsis showed significantly better survival for children receiving V-V support when compared to those on V-A ECMO [78]. This study was unable to account for pre-ECMO severity of illness and also did not factor in the type of hemodynamic derangement that characterized each patient's type of sepsis (i.e., warm shock vs. cold shock). However, the fact that such a large number of children with sepsis were successfully supported with V-V ECMO gives credence to the ability of this modality to support critically ill children who have unstable hemodynamics.

The use of V-V ECMO in pediatric critical care is continuing to increase [79], and based on data from a large retrospective review, V-V ECMO appears to confer a survival advantage relative to V-A ECMO [24]. To date, there is no definitive formula or inotrope score by which to guide intensivists in choice of ECMO modality for children with acute respiratory failure and associated hemodynamic instability. Our own institutional practice relies greatly on echocardiogram imaging of myocardial performance to aid in this decision. A child with mild to moderately depressed right ventricular function, which is most often due to a combination of high pulmonary vascular resistance induced by lung disease and respiratory acidosis, is a candidate for V-V ECMO, even if requiring a moderate amount of vasoactive medications for hemodynamic support. V-V ECMO is recommended for these patients, even in the setting of hemodynamic instability, as correction of respiratory acidosis and an increase in right ventricular preload that occur after ECMO initiation often improve ventricular function. In contrast, a child with an echocardiogram showing significantly depressed left ventricular or biventricular function due to sepsis-induced myocardial depression should be cannulated for V-A ECMO.

ECMO cannula selection and configuration is an essential decision made in the process of initiating V-V ECMO support. One option for V-V cannulation is a multisite configuration with single-lumen ECMO catheters, the first being placed within the right internal jugular vein and extending into the right atrium and the second inserted into a femoral vein and extending upward into the inferior vena cava. The alternative cannulation option utilizes a dual-lumen venovenous (VVDL) catheter inserted into the right internal jugular vein, with both drainage and reinfusion lumens of the cannula residing within the right atrium. One disadvantage of the two-cannula technique includes the need to access multiple venous sites, thus being a more invasive and time-consuming procedure, along with increasing the sites for potential bleeding and infectious complications. Second, children weighing less than 15 kg typically do not have large enough femoral veins to accommodate the necessary-sized ECMO catheters. Given these constraints of the two-site cannulation technique, the application of the VVDL cannulation strategy to provide ECMO support to children with respiratory failure has increased significantly over the past decade [24, 80]. Zamaro et al. analyzed the performance and complication rates of these two cannulation strategies from 1323 pediatric V-V ECMO runs [80]. Compared to multisite cannulation, VVDL cannulation achieved greater weight-adjusted ECMO flow but had a slightly higher rate of mechanical (26.2% vs. 22.5%, p 0.004) and cardiac (24.4% vs. 21.7%, p 0.03) complications. Importantly, there was no significant difference in survival between the two cannulation techniques.

One drawback to early versions of VVDL ECMO catheters was their potential to bend and kink, thus raising the possibility of obstruction to blood flow and interruption of the ECMO circuit. The newer generation of VVDL catheters is manufactured with wire reinforcement to offset this potential complication. The only available pediatric literature comparing these two types of catheter designs was a single-center retrospective study of 25 neonates and infants, which found no difference in the incidence ECMO flow interruption between the wire-reinforced and non-wire cannulas within the first 72 h [81]. The two wire-reinforced VVDL ECMO catheters currently available for pediatric use are the OriGen® DL cannula (OriGen® Biomedical, Austin, TX) and Avalon® Elite Bicaval cannula (Avalon® Laboratories, LLC, Rancho Dominguez, CA). The OriGen® is placed in the right atrium and has a proximal drainage hole and distal reinfusion hole. The configuration of the bicaval Avalon® cannula places the drainage holes within the SVC and IVC, while the reinfusion port is located within the right atrium and is directed toward the tricuspid valve, offering the theoretical advantage of reducing the amount of recirculation. The use of bicaval ECMO cannulas has been shown to be effective and safe in the adult ECMO population [82, 83], but the smaller-sized venous and cardiac structures inherent to pediatric patients may raise concern regarding an increased rate of mechanical complications and increased need for catheter repositioning. Several pediatric ECMO centers have published their institutional experiences with the bicaval wire-reinforced cannulas and have noted minimal complications in both pediatric and neonatal patients [81, 84–86]. In an analysis of cannula complications by Zamaro and colleagues, there was no difference in rate of complications when wire-reinforced and non-wire-reinforced catheters were compared [80]. Proper imaging techniques during cannulation, including the combined use of echocardiography and fluoroscopy, have been shown to reduce complications and the need for catheter repositioning [86]. Lastly, successful and safe percutaneous ECMO cannulation of pediatric patients performed by intensivists has recently been described [87]. A single-center retrospective review of percutaneous ECMO cannulations performed by intensivists included 18 pediatric patients cannulated for V-V ECMO. In this cohort, the overall rate of successful cannulation was 98% [87]. In our current practice, we consider wire-reinforced VVDL ECMO catheters safe for pediatric patients and are the preferred modality by which to provide extracorporeal respiratory support.

Case Presentation

In addition to her persistently elevated OI, her relatively short duration of illness thus far and her potentially reversible viral influenza and Staphylococcus aureus pneumonia were determined to be characteristics of a good candidate for ECMO. The patient was receiving relative modest doses of vasoactive support – epinephrine 0.06 mcg/kg/min and dopamine 5 mcg/kg/min. These infusions were likely necessary due to the combination of hypoxemia, respiratory acidosis, and high MAwP, conditions that were considered amenable with venovenous ECMO. The decision was therefore made to cannulate the patient with a wire-enforced VVDL cannula in her right internal jugular vein for V-V ECMO support. Following successful cannulation, vasoactive medications were able to be easily weaned to off over the first 12 h on ECMO.

Pulmonary Management

Ventilator Management

There have been major strides in the study of mechanical ventilation in ARDS over the past decades [29]. The result of these studies has been the low tidal ventilation strategy, which consists of low tidal volumes (V_T) (6–8 mL/kg), PEEP titrated to keep $F_iO_2 < 0.6$, and permissive hypercarbia. However, for patients who fail this strategy and are cannulated for ECMO, the optimal ventilator management strategy has not been well studied. The ideal mechanical ventilation strategy would limit VILI without lengthening ECMO duration due to lung collapse.

Traditional ventilator management on ECMO has been a "lung-rest" strategy to limit VILI. Current ELSO guidelines suggest low rate, moderate PEEP (5–15 cmH_2O) and low plateau pressure [25]. Few published studies describe mechanical ventilation practices while on ECMO in the pediatric population. A recent survey found most pediatric intensivists (87%) employ a strategy of "lung rest" while on ECMO [88].

According to a recent review, most adult patients have V_T, FiO_2, and plateau pressure significantly reduced after initiation of ECMO, while PEEP is minimally reduced from their pre-ECMO support, being maintained on average between 12 and 13 cmH_2O [89]. In this review, the proportion of patients with ventilator settings considered to be injurious (defined as TV > 8 mL/kg, plateau pressure > 30 cmH_2O, peak inspiratory pressure >35 cmH_2O or $F_iO_2 \geq 0.8$) decreased from 90% pre-ECMO to 18% after initiation of ECMO [89].

The goal of the historical practice of "lung rest" is to limit the risk of VILI, but this strategy often leads to lung collapse. In a recent survey of mechanical ventilation practices during ECMO, most pediatric intensivists (76%) target a PEEP of ≤10 cmH_2O [88]. This level of PEEP in the setting of pARDS will frequently lead to total lung collapse and the need for re-recruitment of the lung later in the ECMO course. The need for re-recruitment may prolong the ECMO course and contribute to VILI. Given this concern, some intensivists no longer practice strict "lung rest" while on ECMO for ARDS [90]. The most popular new ventilation practice is an open-lung strategy on ECMO, similar to the adult ARDS low V_T ventilation strategy [91].

While attempting aggressive lung recruitment in the acute inflammatory stage of ARDS is discouraged, as it can exacerbate VILI, maintaining lung recruitment with relatively high MAwP while on ECMO may be advisable. On conventional ventilation, this goal is achieved by maintaining high PEEP with a long inspiratory time. Airway pressure release ventilation (APRV) is a mode of ventilation, which utilizes a high distending pressure with brief intermittent releases of pressure to improve ventilation, and patients are able to spontaneously breathing during the periods of high distending pressure [92]. APRV can also be used to achieve a high MAwP without high plateau pressures, similarly to a high PEEP and long inspiratory time strategy with conventional ventilation, which maintains recruitment with potentially less risk of VILI. The ELSO rec-

ommendations regarding PEEP offer a wide acceptable range – 5–15 cmH_2O [25]. The use of PEEP at the higher end of this range in neonates with respiratory failure has been shown to lead to shorter duration of ECMO [93, 94]. Similarly, in adults on V-V ECMO, higher PEEP during the first 3 days on ECMO has been associated with improved survival [95]. Conversely, higher PEEP over the whole ECMO course has been shown to be associated with increased mortality [96]. It is hard to reconcile these seemingly incongruous findings. However, one could hypothesize that PEEP later in the ECMO course is more related to patient factors than ventilator strategy. In other words, patients with improving lung disease will have PEEP decreased over the course on ECMO, while patients who do not improve and ultimately die will remain on higher PEEP throughout their course. Additionally, high PEEP in the first 3 days on ECMO is more likely to be a conscientious strategy of maintaining lung recruitment and less so reflective of the patient's severity of lung disease.

The risks of maintaining a higher MAwP must be weighed against the risks of allowing lung collapse. High MAwP will cause elevated intrathoracic pressure which may impair hemodynamics due to impaired venous return. Elevated static pressures, like those used in an open-lung ventilation strategy or in APRV, do not to contribute significantly to VILI [97]. There are also risks to a lung-rest approach resulting in complete lung collapse. Hemodynamically, lung collapse will lead to increased right ventricular afterload by way of increased pulmonary vascular resistance. On V-V ECMO, lung collapse will also lead to severe pulmonary venous desaturation, and systemic arterial saturations will suffer. Additionally, there is emerging evidence of the damaging effects of recurrent atelectasis, often called atelectrauma [8, 98, 99]. If there is complete lung collapse, the lungs will need to be re-recruited later in the ECMO course, which often can only be accomplished with high driving pressure, which is the biggest contributor to VILI [97]. Lastly, the time necessary to re-recruit the lungs may prolong the ECMO course. Neonatal data shows that higher PEEP (i.e.,12–14 cmH_2O vs 4–6 cmH_2O) leads to shorter ECMO runs and fewer complications [93, 94]. Identifying the ideal PEEP for a patient is a multifactorial decision that includes evaluation of lung expansion on chest x-ray, hemodynamics, oxygenation, lung compliance, and other factors. In a recent study, the use of electrical impedance tomography for adult patients with respiratory failure on ECMO showed that an optimal PEEP of 15 cmH_2O best balanced overdistension and lung collapse [100].

The one consistent finding from the limited data published about mechanical ventilation for adults on ECMO is that higher driving pressure (peak inspiratory pressure minus PEEP) or plateau pressure is associated with increased mortality [89, 101, 102]. Limiting peak or plateau pressure is advisable for adults on ECMO as it is for any adult with ARDS. However, the upper limit of what is reasonable for driving and plateau pressures in children has not been well established in pARDS and might be higher than in adults [17, 18, 103].

Secretion Clearance on ECMO

Invasive procedures on ECMO are avoided whenever possible due to the increased risk of hemorrhage associated with anticoagulation. Bronchoscopy, however, is an invasive procedure that may be necessary for some patients supported on ECMO. Though there are only a few reports of bronchoscopy on ECMO in the literature [98–101], it is commonly implemented in clinical practice. Routine bronchoscopy of patients on ECMO is performed in 55% of pediatric ECMO centers and 76% of adult centers [90]. While the benefits of bronchoscopy on ECMO have not been established in the literature, they are often seen at the bedside in patients with thick respiratory secretions that cannot be mobilized through traditional suctioning techniques. In the limited published data on pediatric bronchoscopies on ECMO to date, minor bleeding episodes occur in up to 35% of patients in some report, the risk of significant pulmonary hemorrhage is 0–1.5% [104–107]. Bronchoscopy

is therefore feasible and relatively safe in patients on ECMO, with a small risk of pulmonary hemorrhage.

HFPV is a combination of high-frequency ventilation and conventional mechanical ventilation principles. HPFV consists of high-frequency sub-physiological tidal volumes superimposed on low-frequency conventional tidal volume ventilation [108]. One institution published their experience with the use of high-frequency percussive ventilation (HFPV) and increased frequency of bronchoscopy to target secretion clearance for pediatric respiratory ECMO. They showed an increase in ECLS-free days when compared to historical controls [106]. It is not clear if the benefit was due to HFPV, increased bronchoscopies, the combination of the two, or other changes to practice that were not measured. The use of HFPV and frequent bronchoscopy promotes secretion clearance and is most likely to be beneficial in diseases that cause excessive secretions such as bronchiolitis.

Extubation on ECMO

The practice of extubation on ECMO has becoming increasingly utilized in the past several years. In a 2015 survey, only 10% of centers reported extubating patients on ECMO, while a 2017 survey reported 41% of centers extubate patients [90, 91]. ECMO is employed to allow for oxygenation and ventilation without the risk of VILI. It has been suggested, therefore, that the best way to limit VILI would be to remove the "V" or ventilator. Extubating patients on V-V ECMO has been shown to be feasible and safe in selected patients [90, 109]. In one retrospective study, extubation on ECMO was associated with improved survival [109]. If extubation is feasible, there is the benefit of reducing sedation once the noxious stimulus that is the endotracheal tube is removed. Patients who are extubated and not sedated will also be able to participate in more aggressive rehabilitation while on ECMO. Not all patients will be candidates for extubation on ECMO. Younger patients, for instance, may require paralysis or heavy sedation to prevent mechanical complications, obviating any possibility of extubation. It should also be noted that extubated patients might require reintubation for procedures including bronchoscopy and decannulation from ECMO.

Recommendations

Maintenance of lung aeration with modest ventilator settings may be advantageous to their recovery. Lung aeration will facilitate higher arterial oxygen saturations (SaO_2), allow for some oxygenation if there is an emergency requiring separation from the circuit, and possible shorten ECMO course by eliminating the time needed to re-recruit collapsed lung. Our usual strategy is to maintain lung aeration with high PEEP (10–14 mmHg) or APRV when possible. Due to our concerns that strict adherence to the historical "lung-rest" settings with low driving pressure (e.g.. 10 cmH_2O) and complete lung collapse may not be optimal and may prolong the ECMO course, we often use slight higher MAwP (15–20 mmHg) and driving pressure (12–18 mmHg) than historical "lung rest." On the other hand, when there is complete lung collapse despite these moderate MAwP, we do not advise trying to re-recruit alveoli in the acute inflammatory phase of pARDS.

Some patients will have complete lung collapse in the face of high MAwP. In patients with lung collapse and who are likely to have prolonged ECMO courses, extubation is an option. Patients that are most likely to be able to be extubated and benefit from extubation are school-aged or older children in whom a short ECMO run (<7 days) is not expected. Further, to successfully extubate patients on ECMO, the circuit must be able support oxygenation without the aid of mechanical ventilation, which requires high flow rates without significant recirculation issues.

We support aggressive airway clearance with bronchoscopy for pediatric respiratory ECMO, particularly in patients with disease processes that lead to mucous plugging. Bronchoscopy is likely most beneficial when performed early, such as within the first week on ECMO, with the

goal of lung recruitment when the inflammatory stage of pARDS is resolving. The need for further bronchoscopy can be determined by the secretion burden noted during the first bronchoscopy and the subsequent clinical course. Diagnostic bronchoscopy can also be performed to assess for infectious complications. Routine reduction or interruption anticoagulation for bronchoscopy is not suggested due to low risk of significant bleeding.

Case Presentation

After cannulation for venovenous ECMO, the 2-year-old child with influenza and Staphylococcus pneumonia was managed with a high PEEP strategy (i.e.,10–12 mmHg) and modest driving pressure (i.e., pressure above PEEP 12–16 mmHg). Daily chest x-rays demonstrated modest lung aeration. During the initial portion of her ECMO course, she was receiving only relatively small tidal volumes (~2–3 mL/kg) with this approach. Over the next 2 weeks, with the assistance of an aggressive pulmonary toilet that included multiple bronchoscopies, her tidal volumes gradually increased to 6–7 mL/kg, and she tolerated weaning of ECMO support. She was successfully decannulated after 20 days of ECMO support with no detectable complications.

Centralization of ECMO and the Effect of Center Volume

The relationship between ECMO volume and the quality of ECMO care delivered at individual centers are active topics of discussion and study. There are theoretical benefits of centralization of this highly complex care. ECMO is relatively rare, even in the largest centers, and centralization of care allows for a concentration of expertise. ECMO requires a team approach between ECMO technicians, bedside nurses, respiratory therapists, surgeons, intensivists, and other medical personnel. All members of the team must have an understanding of the special needs of a patient on ECMO. Centers that perform a high volume of ECMO develop an institutional knowledge that can only develop over many years and many ECMO runs.

There have been multiple studies done to evaluate if center volumes affect outcomes. Children treated at sites with 20–49 ECMO runs per year and greater than 50 ECMO runs per year (pediatric and neonatal combined) have been shown to have lower odds of mortality compared to centers with less than 20 runs per year [110]. The single cut-point that produced the most significant difference in mortality was 22 cases per year [110]. In another study, there was a strong relationship between center volume and mortality for pediatric cardiac patients [111]. Lastly, when survival was assessed based on age-specific center ECMO volumes, neonatal and adult volumes were significantly associated with survival, and there was a nonsignificant trend toward improved survival in higher-volume centers for pediatric patients [112]. The effect of center volume is particularly difficult to answer concerning pediatric respiratory ECMO. A medium-to-large sized pediatric ECMO program may only have five respiratory cases per year, and few centers perform more than ten pediatric respiratory ECMO runs annually. A recent international position paper on ECMO for acute respiratory failure in adults argues for centralization of ECMO and a minimum of 20 ECMO cases per year, with 12 of them being for respiratory support [113]. This recommendation is based on the pediatric data discussed above and expert opinion.

In the CESAR trial, adult patients with severe ARDS were randomized to staying at community hospitals or being transferred to a center capable of ECMO [5]. Patients who were transferred had improved survival (63% vs. 47%), even though only 75% of transferred patients were cannulated for ECMO [5]. Therefore, early transfer from centers that do not provide ECMO can be recommended for patients with severe ARDS with high OI. Volume alone however does not ensure quality care; education, training,

and ongoing quality improvement must be combined with clinical expertise. It is recommended that all personnel caring for patients on ECMO are familiar with the circuit function and potential complications [26]. Given the relative rarity of ECMO, particularly pediatric respiratory ECMO, hands-on clinical experience can be limited. Simulation is a tool that can increase familiarity to ECMO and its complications. Simulation has been shown to be a beneficial educational tool in ECMO [114, 115]. A simulation program for all personnel caring for ECMO patients should be pursued, especially at low-volume centers, to augment orientation and ongoing learning.

In summary, though the minimum number of cases needed to provide adequate ECMO care is not clear, center volume likely plays a role in the quality of ECMO care and outcomes. Furthermore, in pediatrics, there may be indication specific and age specific minimums since cardiac, neonatal, and pediatric respiratory ECMO have distinct differences that require different knowledge and skill sets. Centralization of ECMO is likely beneficial to patients.

Prolonged ECMO and Lung Transplantation

Long-Term ECMO

The average for duration of ECMO support for pediatric respiratory failure is slightly less than 13 days [1]. However, there are some patients who require ECMO longer for lung recovery. In a study of prolonged ECMO published from the ELSO database in 2012, pediatric respiratory ECMO runs lasted ≥21 days in 12% of cases [116]. ECMO continues to be employed for increasingly sicker and more complex patients, which has likely led to more prolonged ECMO courses [24]. The current rate of prolonged ECMO may therefore be higher than 12%.

Children on ECMO for more than 21 days for acute respiratory failure have significantly worse survival, 38%, compared to 61% for less than 14 days and 53% for 2–3 weeks [116] (Fig. 2.1). Survival in pediatric respiratory ECMO patients steadily decreases as length of ECMO increases from 5 days to 37 days, and there is a late steep drop in survival after approximately 48 days on

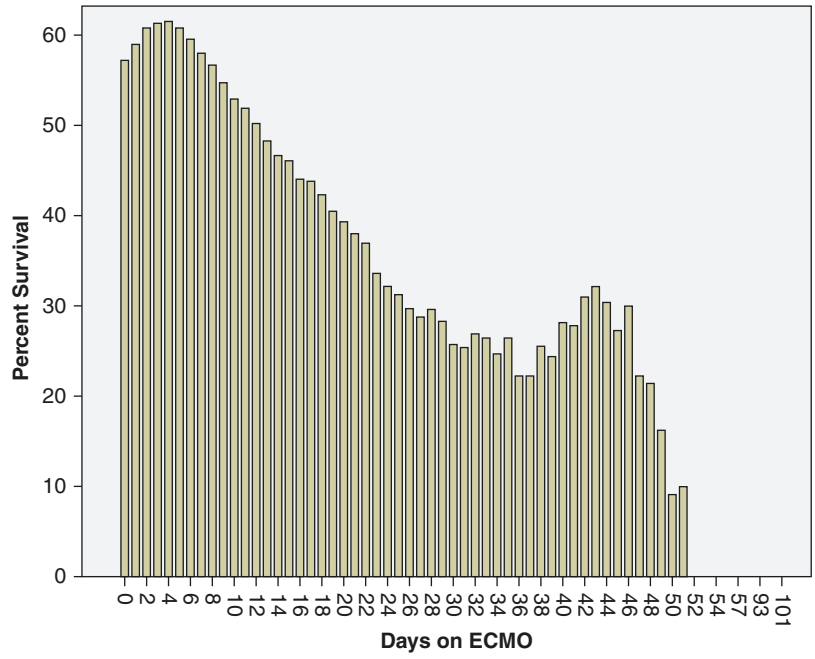

Fig. 2.1 Survival of patients to discharge as a function of days on ECMO ($n = 3160$). (Reproduced with permission from Brogan et al. [116])

ECMO [116]. From 1993 to 2007, there were no survivors of the nine patients supported on ECMO for 52 days or more in the ELSO database [116]. More recently, there have been many cases reported of long-term respiratory ECMO in both children and adults with good outcomes, including lung transplant or late lung recovery after up to 265 days of ECMO [116–121]. These reports are remarkable as, historically, it has been thought that if native lung function was not improving or restored at 2–4 weeks of ECMO support, the chance of recovery was remote [119]. As evidenced by these case reports of successful prolonged ECMO, there may be previously underappreciated regenerative capacity of the lungs. The paradigm for lung recovery may be more similar to recovery of kidney function after acute kidney injury, where the chances of recovery of native function decrease over time, but there is still potential for return to normal function in some patients even weeks to months after injury.

The decision of when lung recovery becomes remote is difficult. There is a paucity of data to help physicians prognosticate which patients on prolonged ECMO may recover. Despite the lack of many survivors after 8 weeks on ECMO, reports of successful outcomes beyond this time frame suggest there should be no absolute cutoff for length of ECMO duration in pediatric respiratory failure. It is therefore imperative to carefully assess patients on prolonged ECMO support in regard to proximate cause of respiratory failure, premorbid lung function, potential for lung recovery, presence of other organ dysfunctions, and the goals of the patient or decision-makers.

ECMO as a Bridge to Lung Transplant

Patients who are on prolonged ECMO without recovery of native function may be candidates for lung transplant. The evaluation process for lung transplantation should be considered for patients on ECMO for greater than 3 weeks without a trajectory toward improvement or early in the ECMO course for patients with known progressive lung diseases such as CF. While consensus guidelines state that ECLS is a relative contraindication to lung transplantation, 1.5% of lung transplant recipients are bridged to transplant on ECMO [122, 123]. Patients bridged to lung transplant on ECMO may have worse short-term survival, but adult lung transplant recipients who are spontaneously breathing on ECMO have similar 3-year survival to patients on no support and better survival than patients on mechanical ventilation alone or on ECMO with mechanical ventilation [123, 124].

Considerations on Prolonged ECMO

When a patient is supported on prolonged ECMO, other important considerations are rehabilitation and tracheostomy. Tracheostomy on ECMO is not common practice in pediatrics, with only 13% of pediatric centers reporting performing tracheostomies in these patients [90]. The placement of tracheostomy while on ECMO is more frequently performed in adults [90]. To our knowledge, the largest report of tracheostomy on ECMO at a pediatric institution contains nine patients ages 7–25 years [125]. Two of nine survived without lung transplantation, and four survived with lung transplantation. All patients had decreased sedation needs within 72 h. The biggest concern with performing tracheostomy on ECMO is bleeding due to anticoagulation. Practices for anticoagulation vary from holding of anticoagulation around the time of procedure to varying reductions in heparin dosing [90, 125]. In two adult case series of 168 ECMO patients in total, minor bleeding after tracheostomy was common (approximately 30%), while major bleeding occurred in only 2% and 8% of cases. No deaths were attributed to complications of tracheostomy [126, 127]. If tracheostomy is to be considered, the timing of tracheostomy remains a difficult decision. The average time on ECMO to tracheostomy in the pediatric study of nine patients was 10 days [125]. Older pediatric patients with longer than average expected ECMO durations or those on

ECMO as a bridge to lung transplant are most likely to benefit. These patients may be able to tolerate decreases in sedation and actively participate in rehabilitation due to developmental stage. These patients are also the same subset of children that may benefit from extubation on ECMO. Tracheostomy is a higher risk than extubation due to bleeding complications but would be preferred when the ECMO circuit cannot support oxygenation without positive-pressure ventilation.

The other major consideration for patients on prolonged ECMO is rehabilitation. Patients on ECMO often have multiple risk factors for ICU-related neuromuscular weakness including corticosteroids, neuromuscular blockade, systemic inflammation, immobility, hyperglycemia, and multiorgan failure [128]. Physical therapy with mobilization is common on ECMO, but ambulation of patients on ECMO is rare [125, 129, 130]. Ambulation on ECMO is a difficult process but can be accomplished safely with a coordinated team approach and either extubation or tracheostomy to eliminate the precarious endotracheal tube.

Children on ECMO as a bridge to lung transplantation who participate in rehabilitation have shorter length of ventilation after transplant and shorter length of ICU stay compared to those who do not participate in rehabilitation [130]. Additionally, patients ambulated on ECMO have lower hospital costs than those who do not ambulate [131]. In a survey of 208 adult ECMO centers, major barriers to ambulation identified included concerns about hemodynamic instability, hypoxemia, and femoral cannulation [132]. In pediatrics, these barriers are present, but there is additional concern for cannula movement. Pediatric patients have a smaller margin for error in the location of cannula, especially when a bicaval cannula is being used for V-V-ECMO.

We suggest physical therapy in all patients on ECMO for acute respiratory failure if oxygenation and hemodynamics tolerate it. Patients who are likely to be on prolonged ECMO, if able to be extubated or has a tracheostomy in place, may benefit from more aggressive rehabilitation such as ambulation.

Termination of Extracorporeal Support

ECMO is a resource-intense, high-risk technological modality that can provide extended respiratory support for children with respiratory failure. Within this framework, ECMO serves as a bridge to a destination for each child it supports. Potential pathways include bridge to a diagnosis, bridge to recovery, and bridge to lung transplantation. Making diagnostic determinations and outlining criteria for lung transplantation are typically concrete decisions within the medical team's grasp. Likewise, the development of a catastrophic complication (e.g., massive hemorrhagic stroke) on ECMO renders the decision to terminate ECMO support, in most instances, straightforward. But in the absence of such a complication, our ability to predict pulmonary recovery is fraught with difficulty and uncertainty. Much of this complexity is related to the tremendous amount of heterogeneity within our patient population in the pediatric ICU, including diagnosis, age, comorbidities, and many of the other factors discussed in the preceding sections. Decision-making around prolonged ECMO support is challenging due to these limitations, and the clinical team may find uncertainty as to whether pulmonary recovery is still possible or if continuing ECMO now reached the point of futility. A multidisciplinary discussion of prognosis and probability of lung recovery should be initiated by 3 weeks of support, when the chance of survival begins to decline [116]. Current recommendations in the ethics literature suggest a careful analysis for potentially inappropriate care ECMO when respiratory support reaches 2–3 months [133].

Importantly, the potential for non-recovery and the possibility of termination of ECMO support should be introduced and communicated to the child's family during the initial informed consent process prior to commencement of ECMO. However, several issues make true informed consent difficult, if not sometimes impossible, during these conversations such as complex and unfamiliar technology, uncertainty regarding diagnosis and prognosis, limited time

for discussion due to acuity of the clinical situation, and a sense of urgency conveyed by the medical team [134]. The specific necessity of withdrawal of ECMO support in cases of futility is recommended as a standard component of the consent form for ECMO [133]. Second, P-PREP [135] and Ped-RESCUER [136] are recently validated prediction models that help pediatric intensivists estimate the mortality risk for children with respiratory failure at the time of initiation of ECMO (Table 2.2). Both models consider patient diagnosis, several pre-ECMO variables, and accompanying comorbidities. While not perfect tools, P-PREP and Ped-RESCUERS can provide the clinical team guidance when counseling families regarding their child's risk of dying on ECMO.

Table 2.2 Components mortality scores for children with respiratory failure on ECMO

	PPREP[a]	Ped-RESCUERS[b]
V-A ECMO	×	
Time from admit to ECMO		×
Length of MV	×	×
P/F ratio	×	
pH	×	×
pCO_2		×
Mode of ventilation		×
Mean airway pressure		×
Primary diagnosis:		
Asthma		×
Aspiration	×	
Bronchiolitis		×
Pertussis	×	×
RSV	×	
Sepsis-induced ARDS	×	
Comorbid conditions:		
Pre-ECMO arrest	×	
Cancer	×	×
ARF	×	
Acute liver necrosis	×	
Year of ECMO	×	
Milrinone infusion		×

[a]Pediatric pulmonary rescue with extracorporeal membrane oxygenation prediction
[b]Pediatric risk estimate score for children using extracorporeal respiratory support
https://www.elso.org/Resources/ECMOOutcomePredictionScores.aspx

Conclusion

In summary, ECMO continues to be an available modality to support children with the most severe forms of hypoxemic and hypercarbic respiratory failure. Ideal candidates for ECMO are those patients with reversible lung injury or those whom could be considered for lung transplantation in the event of non-recovery. V-V ECMO is the ideal extracorporeal modality to support these patients if left ventricular function is not depressed. Single-site cannulation utilizing double-lumen ECMO catheters is becoming the standard technique by which to obtain vascular access for V-V ECMO. Once on ECMO, ideal strategies for mechanical ventilation include a moderate-to-high degree of PEEP to maintain alveolar recruitment while minimizing plateau pressures to avoid further lung injury. As clinical experience with ECMO for pediatric respiratory failure continues to increase, we will have a better understanding of the optimal means of using this technology as well as its limitations.

Take-Home Points

- ECMO candidacy evaluation requires holistic approach to the patient, including evaluation of the cause of respiratory failure, the trajectory of disease, and comorbidities.
- Venovenous ECMO support is the preferred configuration for pediatric respiratory failure when feasible.
- The goal of mechanical ventilation on ECMO is to limit ventilator-induced injury; however, the best strategy is yet to be determined.
- Prolonged ECMO for respiratory failure in children has an increased risk of mortality, with the risk consistently rising after the first few weeks on ECMO.
- Center ECMO volumes may play a role in patient outcomes, but these are likely age- and disease-specific. Centers with low ECMO volumes should use other methods to maintain competency, such as simulation.

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3 Weaning and Extubation Readiness Assessment in Pediatric Patients

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Introduction

Mechanical ventilation is a lifesaving intervention that is used to support patients with acute respiratory failure. Mechanical ventilation however is not without risk. Complications such as ventilator-induced lung injury, ventilator-associated pneumonia, prolonged exposure to narcotics and sedatives, airway trauma, and consequent respiratory muscle weakness have been well described in the literature [1–5]. Because of these risks as well as the associated costs of prolonged intensive care unit (ICU) care, one of the most important goals of pediatric critical care teams is to decrease the duration of mechanical ventilation while concomitantly avoiding extubation failure. Extubation failure has also been associated with increased duration of mechanical ventilation, ICU length of stay, ventilator-associated pneumonia, hospital cost, and mortality [6–8]. In contrast to current adult ICU models of care, ventilator weaning and extubation readiness assessment in pediatric ICU populations has not been standardized [9–11]. We aim to present a summary of recent literature focused on pediatric ventilator weaning and extubation readiness assessment that can be used as the foundation for the discussions and collaborative research needed to improve our understanding of this crucial issue in pediatric critical care medicine and the eventual creation of pediatric-specific guidelines.

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Definitions

One of the challenges encountered by pediatric critical care teams is the lack of clear definitions for the terms commonly used when discussing pediatric ventilator weaning and extubation readiness.

Ventilator Weaning Versus Extubation Readiness

These two definitions are often used interchangeably in clinical practice and research. Weaning is the gradual decrease of ventilator support, during which a patient assumes a steadily increasing proportion of the responsibility for effective gas exchange. Extubation readiness assessments, on the other hand, are conducted by placing patients on minimal ventilator support for a predetermined period of time to assess their ability to maintain gas exchange spontaneously. Further, the primary goal of ventilator weaning protocols is to decrease the duration of mechanical ventilation, whereas extubation readiness assessments aim to minimize the risk of extubation failure.

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Extubation Failure

The definition of extubation failure is not consistent between the studies. Most studies have used reintubation within 48 h of the first extubation attempt as their definition, though some have included patients who receive noninvasive positive-pressure ventilation (NIPPV) or high-flow nasal cannula (HFNC) as extubation failures. The time frame during which reintubations are considered extubation failures has also varied across studies, ranging between 24 and 72 h after extubation [7, 12–14]. To avoid confusion and be able to compare studies in the future, extubation failure should be defined as the need for reintubation for cardiopulmonary distress within 48 h of the first planned extubation attempt. Moreover, the timing of extubation failure can be subdivided into three categories: (1) immediate, occurring less than 6 h after extubation; (2) early, occurring between 6 and 24 h after extubation; and late, occurring between 24 and 48 h after extubation. The majority of extubation failures however occur within the first 24 h of extubation [7, 12, 13, 15].

Post-Extubation Stridor and Upper Airway Obstruction

Post-extubation stridor signifying upper airway obstruction is one of the more common causes of extubation failure in children. Airflow resistance is inversely proportional to the fourth or fifth power of airway radius. Since children have smaller baseline airways when compared to adults, even minimal edema can cause significant increase in airway resistance and work of breathing. Definitive criteria for what constitutes post-extubation stridor have also not been standardized; rather, it is a clinical diagnosis [16]. Most often, physicians use the presence of audible stridor with respiratory distress requiring therapeutic interventions such as racemic epinephrine, systemic corticosteroids, inhaled helium-oxygen gas mixture, or reintubation as a surrogate definition of post-extubation stridor [16, 17]. A more physiologic approach using calibrated respiratory inductance plethysmography and esophageal manometry to identifying upper airway obstruction after extubation and differentiate between subglottic and supraglottic types has been used in a recent study [18].

Ventilator Weaning

Case Study

A 12-year-old boy is recovering from septic shock and pediatric acute respiratory distress syndrome secondary to streptococcus pneumoniae pneumonia. The child has spent 7 days on high-frequency oscillation ventilation and then transitioned to conventional mechanical ventilation 5 days ago. Ventilator settings have been weaned gradually. Currently, the child is receiving synchronized intermittent mechanical ventilation with pressure-regulated volume control (SIMV-PRVC) with the following ventilator settings: tidal volume 8 ml per kg, rate 16 breaths/min, inspiratory time 1.2 seconds, pressure support (PS) 12 cmH_2O, positive end-expiratory pressure (PEEP) 8 cmH_2O, and fraction of inspired oxygen (FiO_2) 65%. Chest x-ray shows lung expansion to 10th rib posteriorly. He is breathing spontaneously without distress, and his respiratory rate is 24 breaths/min. His oxygen saturation as determined by pulse oximetry (SpO_2) is 100% and end-tidal CO_2 ($EtCO_2$) 55 mmHg. A curious pediatric resident on the team asks which ventilator setting should be weaned first, how quickly can the child be weaned, and when can the child be extubated.

The course of mechanical ventilation begins with intubation and can be divided into the following phases:

- ***Acute or escalation phase:*** this phase starts with initiation of mechanical ventilation and

continuing escalation of ventilator support until reaching gas exchange goals.

- ***Plateau phase:*** this phase is when gas exchanges goals are met and there is no significant increase of ventilator settings.
- ***Weaning phase:*** this phase starts when the disease leading to respiratory failure starts to improve and gradual decrease of ventilator settings occur.
- ***Extubation readiness assessment:*** in this phase patient is placed on minimal ventilator support for a predetermined period of time to assess their ability to maintain gas exchange spontaneously.
- ***Extubation or liberation from mechanical ventilation:*** this phase happens after patient passes extubation readiness assessment and then discontinued from mechanical ventilation by removal of artificial airway or separation for mechanical ventilation if patient has tracheostomy tube in place.

During the plateau phase of mechanical ventilation, clinicians should begin planning the patient's ventilator weaning strategy. Standardized strategies to wean off mechanical ventilation in pediatric population are limited. In general, as a patient's disease process improves and gas exchange can be maintained, pediatric critical care teams initiate ventilator weaning, usually starting with the most potential injurious ventilator settings (see Chap. 1: *Ventilator Management for Pediatric Acute Respiratory Distress Syndrome*). As ventilator support is weaned, the patient is gradually allowed to assume more of the breathing spontaneously and tolerate reductions in the doses of sedative medications. As the minute ventilation provided by the ventilator is reduced (i.e., ventilator rate and tidal volume (V_T) are weaned), work of breathing and $EtCO_2$ should be monitored closely. Additionally, the accuracy of $EtCO_2$ measurements depends on appropriate ventilation-perfusion matching and the absence of leak around the endotracheal tube and within the ventilator circuit. Arterial, capillary, or venous partial pressure of carbon dioxide (PCO_2) measurements should be occasionally checked and compared to $EtCO_2$ measurements during the weaning process.

Pediatric studies showed that manual ventilator weaning protocols have the potential to decrease duration of mechanical ventilation [19–22]. The protocols used in these studies differed in regard to the sequence of parameters weaned and rapidity of which each parameter was adjusted. In addition, some protocols were physician directed, while others were respiratory therapist directed, and only a portion of protocols included an extubation readiness assessment [21–22]. An example of a weaning protocol is provided in Fig. 3.1 [22].

Closed-loop ventilation has been proposed as a method of standardizing the ventilator weaning process. In closed-loop ventilation, the ventilator would decrease or increase the PS above a patient's set PEEP based on mathematical algorithms utilizing available information such as the patient's respiratory rate, V_T, and $EtCO_2$. In a small pilot pediatric study, this approach showed a trend toward decreasing the duration of mechanical ventilation without increasing the risk of extubation failure [23, 24]. The effectiveness of closed-loop ventilation is dependent upon the accuracy of input data from the bedside monitoring devices and ventilator itself, especially V_T [25]. Current closed-loop ventilation protocols also lack the ability to assess and incorporate patients' work of breathing in their algorithm.

Causes of Ventilator Weaning Failure

The causes of ventilator weaning failure can be divided into the following categories: residual lung disease, respiratory muscle weakness, cardiac dysfunction, pulmonary hypertension, fluid overload, and neurologic issues (e.g., sedation, central or peripheral nerve injury, and congenital or acquired neuromuscular disorders).

Respiratory Muscle Weakness

Respiratory muscles, most important of which is the diaphragm, can develop atrophy and

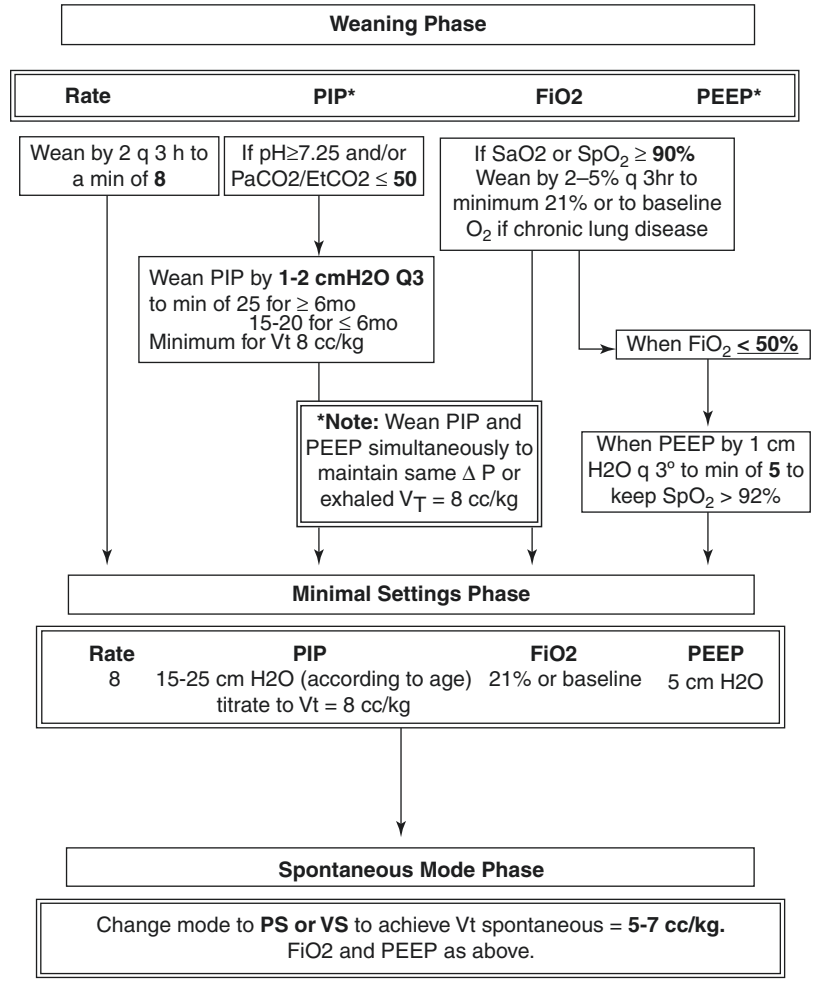

Fig. 3.1 An example of a pediatric ventilator weaning protocol. *PIP* peak inspiratory pressure, FiO_2 fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, $PaCO_2$ arterial partial pressure of carbon dioxide, $EtCO_2$ end-tidal carbon dioxide, SaO_2 oxygen saturation, SpO_2 pulse oximetry, V_T, tidal volume, ΔP difference in pressure, *PS* pressure support, *VS* volume support

weakness during the course of mechanical ventilation [26–28]. Respiratory muscle weakness can be part of critical illness polyneuropathy/myopathy and is usually complex and multifactorial. These factors can be related to the critical illness itself (like brain or spine injury, sepsis, acute respiratory distress syndrome, and burns) but also can be related to disuse, protein catabolism, electrolytes imbalance (especially hypophosphatemia and hyperglycemia), and medications like neuromuscular blockers, corticosteroids, and aminoglycosides [29, 30].

For patients who are suspected to have respiratory muscle weakness, many intensivists will use periods of time during which the patient receives only continuous positive pressure (CPAP) with PS from the ventilator. These "sprints" are employed to strengthen or retrain the respiratory muscles. The duration and frequency of CPAP with PS are somewhat arbitrary, at the discretion of the bedside clinician. While these sprints are commonly used in clinical practice, there are no published studies or guidelines on their effectiveness in the pediatric population. At most institutions, periods of CPAP with PS ranging between 30 min and 2 h are ordered to be performed 2–4 times a day and are discontinued early if signs of respiratory distress are observed.

Cardiac Dysfunction and Pulmonary Hypertension

Underlying cardiac dysfunction can be unmasked during ventilator weaning. As mean airway pressures decrease, left ventricular afterload will increase, and signs and symptoms of cardiac failure may become apparent (e.g., pulmonary edema, decreased urine output, poor peripheral perfusion). In patients with pulmonary hypertension, hypercarbia or atelectasis that can occur as ventilator support is reduced could increase pulmonary vascular resistance and precipitate pulmonary hypertensive crises. In these clinical scenarios, ventilator weaning must be halted, or ventilator support may have to be increased. Vasoactive support and pulmonary hypertensive therapies should then be optimized before weaning is reattempted.

Fluid Overload

Fluid overload is common in critically ill children. Many children requiring mechanical ventilation can have increased total body water due to capillary leak, fluid resuscitation, and acute kidney injury. Fluid overload will result in edema of the upper airway, lungs, diaphragm and chest wall, all of which impact respiratory dynamics and impair gas exchange. Indeed, recent evidence has associated fluid overload with an increased duration of mechanical ventilation in critically ill pediatric patients [31–34]. Fluid status should therefore be assessed carefully before and during the weaning process using daily weights and meticulous review of daily fluid balance. When fluid overload is thought to be hindering ventilator weaning, fluid removal strategies such as diuretic administration, pleural or peritoneal drainage, or renal replacement therapy should be considered.

Sedation Optimization

During mechanical ventilation, pediatric patients commonly require sedative medications to minimize pain and anxiety, though these medications often decrease their ability to spontaneously breathe during the weaning process. Excessive sedation will lead to prolonged duration of ventilator weaning [21], yet under-sedation and agitation will increase airway trauma and the risk of post-extubation stridor, especially in younger patients [17, 18, 35]. The optimal manner in which this balance is achieved has yet to be determined. At a minimum, sedation should be managed carefully during the entire ICU course with a focus on minimizing pain and recognizing and treating delirium (see Chap. 18: *Optimizing Sedation in the Pediatric ICU*).

Mucociliary Clearance

Impaired mucociliary clearance resulting in an excessive burden of secretions can also detrimentally affect ventilator weaning. Impaired mucociliary clearance during mechanical ventilation can be caused by decrease of ciliary function due to inflammation; excessive mucus production or increased viscosity of mucous; impaired cough due to immobility, sedation, neuromuscular blockade, and muscle weakness; and the endotracheal tube itself. Several pulmonary hygiene therapies are available and commonly provided to mechanically ventilated pediatric patients. Mucolytics such as nebulized hypertonic saline and dornase alpha may be able to thin endotracheal tube secretions and thereby aid in their mobilization. The effectiveness of these therapies in expediting ventilator weaning and decreasing mechanical ventilation duration in critically ill pediatric populations is unclear and requires more investigation [36–38]. Chest physiotherapy (CPT) is also used in mechanically ventilated children with atelectatic lung regions, but it can cause oxygen desaturation, hemodynamic changes, an increase in intracranial pressure, and patient discomfort [39]. Intrapulmonary percussive ventilation (IPV), which is a form of airway clearance technique that loosen and mobilize secretions toward the upper airways by delivering mini bursts of gas into the lungs at rates between 100 and 300 breaths per minute, might be an

effective alternative [40]. Until more data are available, practitioners must weigh the balance of the potential benefits of these therapies against the risks and expense, which includes the resources, personnel, and time necessary to administer these therapies.

Extubation Readiness Assessment in Pediatric ICU

Extubation readiness assessment is a prerequisite for extubation in most modern pediatric critical care, but parameters for this practice have yet to be standardized [41]. Extubation readiness assessment can be divided into the following components: screening for entry criteria into an extubation readiness trial (ERT), respiratory support during the ERT, the duration of ERT, criteria for what constitutes a successful ERT, and anticipation of post-extubation respiratory support needs.

Screening for Entry Criteria into the ERT

Data from pediatric studies of unplanned extubation have reported that up to half of these patients remain extubated [42–44]. These data likely reflect, in part, our ability to support patients with noninvasive respiratory modalities but also likely contain missed opportunities for earlier extubation. Many institutional quality improvement efforts have attempted to address this opportunity by establishing extubation readiness assessment protocols that mandates daily screening to determine in patients meet criteria for entry into an ERT (Table 3.1) [14, 21, 45, 46].

Table 3.1 Entry criteria for extubation readiness trial

Presence of spontaneous breathing
Adequate cough and gag reflex
No planned procedures requiring general anesthesia within the next 24 h
Cardiopulmonary stability with no increase of vasoactive drips for at least 12 h
No increase of ventilator support for at least 12 h
Adequate lung compliance and gas exchange

Respiratory Support during the ERT

There are three reported ways to conduct an ERT in critically ill pediatric patients: CPAP trials with PS, CPAP trials without PS, and T-piece trials (i.e., oxygen provided without positive pressure). A survey of pediatric critical care physicians working in the United States found that 95% of physicians use PS augmentation (or simply called PS/CPAP trials) during ERTs [41]. A prospective, randomized study of 257 mechanically ventilated patients comparing a PS-augmented ERT to T-piece ERT showed similar success rates between the two types of ERT and no statistical difference in the rate of extubation failure [47]. In this study, however, entry criteria to initiate an ERT were at the discretion of the attending physician rather than predetermined objective clinical parameters. In other words, clinicians may have had a higher threshold to initiate an ERT in patients who were to be placed on a T-piece, which could have overestimated the success of T-piece ERT. While current adult guidelines recommend using 5–8 cmH_2O of PS [48], the amount of PS to be used in a pediatric ERT is still under debate. In some studies, PS used for the ERT is set based on endotracheal tube size; 10 cmH_2O for 3 and 3.5 mm diameter tubes, 8 cmH_2O for 4 and 4.5 mm diameter tubes, and 6 cmH_2O for 5 mm and larger diameter tubes [14, 21, 45]. Recently published data however has suggested that using PS during an ERT underestimates post-extubation effort of breathing, regardless of endotracheal tube size, and may contribute to a higher extubation failure rate (Fig. 3.2) [49, 50]. Based on these data, children who experience any concerning symptoms (e.g., tachypnea, diaphoresis, tachycardia, increased $EtCO_2$) during an ERT using CPAP with PS are likely at high risk for extubation failure.

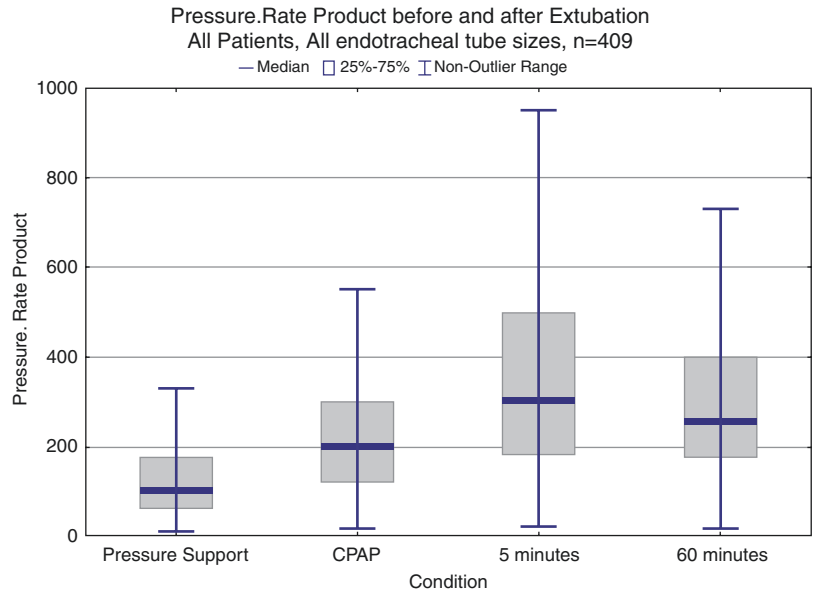

Fig. 3.2 Pressure rate product as a function of peri-extubation respiratory support. (1) Pressure support of 10 over continuous positive airway pressure (CPAP) of 5 cmH_2O. (2) CPAP of 5 cmH_2O. (3) Spontaneously breathing at 5 min post-extubation. (4) Spontaneously breathing at 60 min post-extubation

Duration of the ERT

The duration of ERTs in pediatric populations has most commonly been reported to be 2 h [14, 21, 35, 45–47]. Though shorter periods of ERT have been used, there is concern that these short trials might mask some respiratory insufficiency. In a prospective study, a 15 min ERT using CPAP of 5 cmH_2O was found to be successful in predicting extubation success [51]. In this study the physicians determined whether or not to proceed with ERTs by their standard clinical assessment which may have delayed initiation of ERTs, raising concerns for selection bias. This may have overestimated the success of such short ERTs.

Criteria for What Constitutes a Successful ERT

The main criteria for passing an ERT is maintaining adequate spontaneous gas exchange, which is typically considered to be maintaining an SpO_2 within a targeted range (usually ≥92%) with modest FiO_2 (≤ 0.4), maintaining $V_T \geq 5$ ml per kg of ideal body weight, and no signs of cardiopulmonary compromise. Accurate measurement of V_T depends on the absence of a significant leak around the endotracheal tube or within ventilator circuit and the location at which V_T is measured, at the end of ETT vs. at the ventilator [25]. Leak percentage can be calculated as follows: [(inspired V_T – expired V_T)/inspired V_T) × 100]. Leak percentage less than 20% is required to accurately assess V_T.

Level of consciousness or sedation must be adequate to promote spontaneous breathing. As previously discussed in ventilator wean section, both oversedation and under-sedation can contribute to failure of an ERT. Tachypnea, tachycardia, and diaphoresis often associated with excessive agitation will compromise cardiopulmonary reserve [14]. Use of peri-extubation medications that can keep patients calm without suppressing their respiratory drive can be helpful in this scenario. Specifically, the use of dexmedetomidine has become relatively commonplace at some centers to facilitate extubation readiness assessment and extubation [52]. Subjective assessment of the quantity and quality of endotracheal and oral secretions is also required during an ERT, as an excessive secretion burden, especially in a child with underlying neurologic injury, can lead to extubation failure [41]. Anticholinergic drugs such as scopolamine and

Table 3.2 Extubation readiness trial passing criteria

Respiratory assessment	
Exhaled tidal volume ≥ 5 ml/kg of ideal body weight	
Oxygen saturation (SpO_2) within target range	
No increase work of breathing or diaphoresis	
Respiratory rate within target range:	
Age	**Respiratory rate**
<6 months	20–50
6 months–2 years	15–45
2 years–5 years	15–40
>5 years	10–35
Cardiovascular assessment	
No increase work of breathing or diaphoresis	
No poor perfusion	
No increase in heart rate > 40 beats per minute from baseline	
No hypotension defined as value below minimal systolic blood pressure:	
Age	**Minimal systolic blood pressure**
Term infant <1 month	60
1–12 months	70
1–10 years	70 + (age in years x 2)
≥10 years	90
Sedation assessment	
No apnea or bradypnea	
Exhaled tidal volume ≥ 5 ml/kg of ideal body weight	

glycopyrrolate can be used to decrease the amount of secretions in this patient population [53, 54]. If a patient is deemed to have failed an ERT due to cardiopulmonary, sedation, or airway protection concerns, the patient is placed on pre-ERT ventilator settings and screened again the next day for extubation readiness [14, 21, 45, 46]. ERT passing criteria are listed in Table 3.2.

Anticipation of Post-Extubation Respiratory Support

Theoretically, most patients should be able to be extubated to room air or oxygen via traditional nasal cannula (NC) if they passed an ERT. In reality, respiratory support provided to patients upon extubation varies markedly across centers [14, 15, 46]. In general, pediatric ICU population post-extubation support using HFNC ranges between 21 and 36% [46, 55], while NIPPV use ranges between 7 and 14% [14, 46]. Further, in regard to extubation failure, no clear benefit could be gleaned from one modality as compared to the others. HFNC has increasingly been used to support pediatric patients with respiratory distress and failure with a resultant decreased rate of intubation [56, 57]. However, the prophylactic use of HFNC after extubation to prevent extubation failure has yet to be studied in general pediatric ICU population. In a recent single-center prospective randomized trial of 108 mechanical ventilated children, NIPPV was not superior to traditional oxygen therapy via NC in preventing reintubation [58]. NIPPV is likely useful in preventing reintubation when applied electively for patients at increased risk of extubation failure, including children with cerebral palsy, severe kyphoscoliosis, neuromuscular disorders, brain injury, and cardiac dysfunction [59–62].

The use of NIPPV provides an alternative to invasive ventilation with the advantage of

decreasing ventilator-associated pneumonia and sedation requirements, but all of these potential benefits are not without risk. NIPPV can cause considerable agitation and anxiety and can increase the risk of aspiration. Though current interfaces (e.g., nasal prongs, face masks) are well tolerated by many patients, collaboration is needed between medical professionals and industry to design more pediatric appropriate NIPPV interfaces that minimize leak while also providing patient comfort, preventing skin breakdown, and minimizing aspiration risk [63]. It's also important to note that patients must be monitored for early signs of NIPPV failure such as tachypnea or tachycardia and, when present, should prompt reintubation, as delay in the recognition of these signs can lead to increased morbidity [61].

Establishing a Respiratory Therapist-Driven Extubation Readiness Assessment Protocol

The majority of studies examining the effectiveness of ERTs rely upon physician-driven protocols [14, 21, 45]. These protocols are often impractical, as the ability of physicians at busy tertiary care pediatric ICUs to regularly screen patients for ERT eligibility is usually limited. Respiratory therapist-driven protocols have been effectively applied at several institutions to standardize extubation readiness assessment [46, 64]. Respiratory therapists may represent the optimal personnel to perform each phase of the ERT, given their expertise and 24-h availability. At our institution, we successfully established a respiratory therapist-driven extubation readiness assessment protocol utilizing input from a multiprofessional team of pediatric intensivists, nurses, respiratory therapists, and informational technologists [46]. Through frequent education and feedback of respiratory therapists, we were able to achieve a protocol compliance of 92% and decrease extubation failure rate from 7.8% to 4.5% without increasing the duration of mechanical ventilation or the use of HFNC or NIPPV post-extubation [46].

Potential Adjuncts to Extubation Readiness Assessment

The compliance, resistance, oxygenation, pressure (CROP) index, and rapid shallow breathing index (RSBI) have been used in some studies to predict extubation success.

$$\text{CROP Index} = \frac{C_{dyn} \times MIP \times \left(\frac{PaO2}{PAO2}\right)}{RR}$$

C_{dyn}: Dynamic compliance; MIP: Maximal negative inspiratory pressure; PaO2: Arterial partial pressure of oxygen; PAO2: Alveolar partial pressure of oxygen; RR: Respiratory rate.

RSBI = respiratory rate divided by spontaneous V_T (calculated per body weight)

In older studies, CROP index cutoff of ≥ 0.1 or ≥ 0.15 and RSBI cutoff of ≤ 8 or ≤ 11 breaths/ml/kg had been used as predictors for extubation success [65, 66]. These indices, while useful in adult ICUs, incorporate respiratory rate as part of their equation and, as a result, have limited utility in pediatric ICUs with different age groups with different ranges of what are considered to be normal respiratory rates. These measurements also require accurate measurement of V_T, which is not always available.

Maximum inspiratory pressure (MIP) or more commonly known as negative inspiratory force (NIF) has been used for many years to assess the strength of respiratory muscles, especially in patients with congenital or acquired neuromuscular disorders [67–69]. NIF is obtained by asking the patient to breathe out to residual volume (so lung volume would be at the functional residual capacity) and then take a maximal inspiratory effort against an occluded airway. NIF can be done in intubated and extubated patients using an uncalibrated manometer which can affect its validity. NIF values depend on patient coordination, motivation, and cooperation with the test. NIF measurements are usually trended over time, and patients are deemed ready for extubation when NIFs are consistently lower than negative 30 cmH_2O.

On the other hand, patients with NIF values consistently greater than negative 15 cmH_2O are less likely to be successfully extubated.

Neurally adjusted ventilatory assist (NAVA) and maximum airway pressure during occlusion (aPiMax) are emerging as potentially useful means of assessing respiratory muscle strength. NAVA catheters are used to assess electrical diaphragmatic activity using a multiple-array esophageal electrode catheter placed in the esophagus as a feeding tube. Pediatric patients who passed their ERT had a lower V_T to delta electrical diaphragmatic activity, indicating better diaphragm strength [26]. The accuracy of this method depends on the accurate positioning of the NAVA esophageal catheter. In a more recent study, maximum airway pressure during occlusion (aPiMax) was used to assess respiratory muscle strength prior to extubation using calibrated esophageal manometry and respiratory inductance plethysmography. Patients with aPiMax $\leq$30 cm H_2O were found to have higher rate of extubation failure when compared to patients with less muscle weakness, i.e., aPiMax >30 cm H_2O [70]. The utility of using these measures outside clinical research depends on availability of the technology and personnel needed to obtain such readings.

Volumetric capnography has been used to calculate physiologic dead space to tidal volume ratio (V_D/V_T) as a possible predictor of extubation success or failure. In a prospective pediatric study of 45 mixed medical and surgical patients, $V_D/V_T \leq 0.50$ was found to predict extubation success, while $V_D/V_T > 0.65$ was associated with extubation failure [71]. In pediatric cardiac ICU, dead space correlated with duration of mechanical ventilation and predicted extubation success in two ventricle, but not single-ventricle patients after cardiac surgery [72]. Volumetric capnography requires specialized exhaled CO_2 monitors for its calculations, which are not yet used routinely in many contemporary pediatric ICUs.

Extubation Failure

Extubation failure is associated with increased duration of mechanical ventilation, ventilator-associated pneumonia rates, intensive care and hospital length of stay, hospital cost, and mortality [6–8, 15]. The rate of extubation failure ranges between 2% and 20% depending on the study population, time period of the study, and the definition used for extubation failure [10]. The rate of extubation failure also varies across institutions [12, 15, 73, 74]. Extubation failure causes are not well defined but commonly divided into the following categories: upper airway obstruction, pulmonary insufficiency, respiratory muscle weakness, cardiac dysfunction, neurological impairment, and oversedation. In many cases, the etiology can be multifactorial. Upper airway obstruction is frequently reported as the most common cause of extubation failure in general pediatric critical care population, accounting for one- to two-thirds of extubation failure [14, 18, 74]. Risk factors for extubation failure are young age (less than 48 months), longer duration of mechanical ventilation prior to the first extubation attempt, underlying airway disorders, genetic conditions, neurological disease, chronic respiratory disease, and patients receiving chronic NIPPV [7, 21, 70, 75].

Strategies to Prevent Post-Extubation Upper Airway Obstruction

Because upper airway obstruction is the most common cause of extubation failure in general pediatric critical care populations, pediatric critical care team should use an airway insertion and maintenance bundle to decrease the risk. The insertion bundle should focus on decreasing injury to the airway during endotracheal tube placement by choosing an age-appropriate endotracheal tube size according to the Pediatric Advanced Life Support (PALS) guidelines and limit the number of intubation attempts [76–78]. Recommended sizes of endotracheal tubes by age are provided in Table 3.3 [76, 77]. If notable resistance to endotracheal tube advancement occurs during placement, an endotracheal tube that is 0.5 mm smaller in diameter should be used. Smaller endotracheal tubes should also be used for patients with suspected airway narrowing such as patients with croup, thermal or chemical injuries, or previous history of subglottic

Table 3.3 Airway insertion and maintenance bundle

Airway insertion
Use endotracheal tube (ETT) size according to pediatric advanced life support (PALS) guidelines*:
$\text{Uncuffed ETT size} = 4 + \frac{\text{age}}{4}$
$\text{Cuffed ETT size} = 3.5 + \frac{\text{age}}{4}$
Infants up to 1 year of age: 3.5 uncuffed or 3.0 cuffed ETT
Children 1–2 years of age: 4.0 uncuffed or 3.5 cuffed ETT
**Cuffed ETT is preferred*
Airway maintenance
Monitor cuff pressure and keep inflation pressure less than 20 cmH_2O

stenosis or tracheal surgical interventions. Patients with trisomy 21 have smaller subglottic diameter and are considered to be increased risk for post-extubation stridor; practitioners should therefore use an endotracheal tube 0.5 to 1 mm smaller in diameter than what would typically be used for a genetically normal child of the same age [79].

Contrary to what many clinicians have thought, data have shown that cuffed endotracheal tubes are not associated with an increased risk of post-extubation stridor as compared to uncuffed tubes [80]. In fact, using uncuffed endotracheal tube might increase the risk of upper airway obstruction due to injury of the subglottic epithelium that can occur when larger uncuffed endotracheal tube is inserted to minimize leak [15, 81]. Indexing endotracheal tube size to body surface area may help avoid this scenario. In a study of neonates recovering from cardiac surgery, patients who failed extubation had significantly larger inner diameter endotracheal tubes (mean 16.3 mm/m^2) compared to patients who were successfully extubated (mean 15.3 mm/m^2), and this difference was largely due to the size of the uncuffed tubes used in patients who failed extubation (mean 17.6 mm/m^2). Based on these data, we recommend using endotracheal tubes with inner diameters less than 16 mm/m^2. For example, in a neonate with body surface area of 0.2 mm^2, we would recommend a 3.0 cuffed endotracheal tube (15 mm/m^2) rather than a 3.5 uncuffed endotracheal tube (17.5 mm/m^2).

Cuffed endotracheal tubes have many advantages. They minimize air leak around the endotracheal tube, especially in patients requiring higher peak and mean airway pressure due to poor respiratory system compliance. Cuff tubes can also provide a seal that should reduce aspiration risk and improve the accuracy of V_T and $EtCO_2$ monitoring. Further, with the of ability to change cuff volume using a simple small volume syringe, cuff volume and pressure can be adjusted if subglottic diameter is affected by fluid balance or subglottic edema and inflammation, thereby avoiding further airway injury. Specifically, in an airway maintenance bundle, endotracheal tube cuff pressure should be monitored regularly to ensure that the inflation pressure is less than 20 cmH_2O, which may help decrease the risk of post-extubation stridor [80]. As an alternative, leak pressure can be monitored regularly such that there is only enough cuff inflation to allow audible air leak at 25 cmH_2O [76, 82].

Data on the value of assessing cuff leak pressure prior to extubation and peri-extubation corticosteroids administration in predicting or preventing extubation failure, respectively, are conflicting. To obtain an accurate leak pressure, the patient ideally should be neuromuscularly blocked with the neck in neutral position and an appropriately sized endotracheal tube for age in place. If no leak can be detected, especially when higher airway pressures are used (>30 cmH_2O), caution regarding extubation should be exercised, especially in neonates with small airway diameters (where only a small amount of subglottic edema can result in upper airway obstruction) and patients with underlying airway anomalies. The caveat to the leak test is that secretions around endotracheal tube can affect the ability to detect a leak and can therefore cloud its interpretation. For patients without a detectable leak at reasonable airway pressures or patients with underlying airway anomalies, use of systemic corticosteroids within 6–24 h prior to the planned extubation attempt may decrease the rate of post-extubation stridor [18, 83–85]. Routine use of peri-extubation corticosteroids, on the other

hand, based on current data, cannot be recommended.

Extubation in Special Patient Populations

Congenital or Acquired Cardiac Disease

Case Scenario

A 2-year-old girl recently diagnosed with idiopathic dilated cardiomyopathy is admitted to the pediatric ICU on mechanical ventilation. Her respiratory status improves gradually with diuretic therapy and systemic afterload reduction using a milrinone infusion. After 72 h of mechanical ventilation, she passes a 2 h extubation readiness trial, which used 10 cmH_2O of pressure support and 5 cmH_2O of continuous positive airway pressure. She was extubated to traditional nasal cannula without any audible stridor. Her milrinone infusion was stopped 12 h after extubation. Within the next 24 h, she was noted to have increase work of breathing and hypoxemia that did not respond to escalating respiratory support to high-flow nasal cannula. She was reintubated, and post-intubation chest x-ray showed cardiomegaly and increased pulmonary edema. The bedside respiratory therapists ask if there are any tools available that could have alerted the team to the risk of extubation failure in this patient.

Current data suggest that extubation failure in cardiac critical care patients is around 6%, though extubation failure is higher in neonates recovering from cardiac surgery (around 12%). Similar to general pediatric ICU patients, most extubation failures occur within the first 24 h after extubation, and there is considerable variation in extubation failure rates across centers [12, 15].

While post-extubation stridor and upper airway obstruction do frequently occur in children with underlying cardiac disease, other causes of extubation failure are more common. In two studies of neonates recovering from cardiac surgery, cardiac insufficiency was the most common cause of extubation failure [13, 15]. Moreover, risk factors for extubation failure in these studies were more specific to these neonates with cardiac disease. For example, hypoplastic left heart syndrome, postoperative infection, prolonged open sternotomy (greater than 4 days), and use of uncuffed endotracheal tubes have been found to be risk factors for extubation failure. Risk factors for extubation failure in general pediatric ICU populations are also relevant to children with cardiac disease. In two studies from the Pediatric Cardiac Critical Care Consortium, one of which included a heterogeneous population of children with medical and surgical cardiac disease; prolonged duration of mechanical ventilation and underlying airway anomalies were identified as independent risk factors for extubation failure [12, 73]. Children who undergo cardiac surgery are also at risk for recurrent laryngeal nerve injury and phrenic nerve injury, though vocal cord and diaphragm paresis, respectively, are not typically apparent until after extubation [86, 87]. For patients who fail extubation secondary to post-extubation stridor and upper airway obstruction following aortic arch intervention, where the recurrent laryngeal nerve is located, evaluation for vocal cord paresis via direct laryngoscopy should be pursued [88]. Likewise, for patients with an elevated hemidiaphragm on chest x-ray following extubation failure or have no other discernible causes for their extubation failure, evaluation of diaphragm motion with ultrasound or fluoroscopy is warranted.

Though cardiac insufficiency commonly contributes to ventilator weaning and ERT failure in children with cardiac illness, interpretation of standard monitoring information such as changes in vital signs and peripheral perfusion as surrogates of adequate cardiac output during an ERT can be misleading. More objective measures such as arterial and venous blood gas measurements can be helpful, but these data are not always

obtainable (e.g., malfunctioning or discontinued arterial line, incorrect tip location of central venous catheter for accurate systemic venous oxygen saturation measurement). For these reasons, near-infrared spectroscopy (NIRS) monitoring shows promise as an objective mean of evaluating the success or failure of an ERT [89]. NIRS provides real-time noninvasive data about cerebral and somatic (most often renal) tissue oxygen delivery and has become commonplace at many institutions. In one study, a 12% drop in somatic NIRS during an ERT was associated with an increased risk of extubation failure in this population [89]. Though bedside clinicians should not rely solely on NIRS measurements when assessing extubation readiness in children with cardiac disease, decreasing NIRS trends should give clinicians pause and prompt thorough reassessment prior to extubation (Fig. 3.3).

Multiple respiratory modalities are being used in pediatric cardiac ICU post-extubation. In one study of 283 neonates who underwent cardiac surgery, 55% were extubated to HFNC, 31% were extubated to room air or NC, and 14% were extubated to NIPPV (Fig. 3.4) [15]. In a randomized, controlled trial of 89 patients (younger than 18 months of age) who underwent cardiac surgery found that patient who were placed on HFNC post-extubation had lesser use of NIPPV when compared to patients who placed on conventional nasal cannula, but there was no difference of extubation failure between the two groups [90].

Over the past decade, early extubation of patients who undergo surgery for congenital or acquired heart disease in the operating room or shortly after arrival to the ICU has become standard at many institutions. Benefits of early extubation include decreased exposure to mechanical ventilation and its associated complications including sedation requirements; early initiation of oral feeding; and decreased utilization of ICU and hospital resources [91]. Additionally, spontaneous breathing and early extubation have physiologic benefits as well, as negative intrathoracic pressures are advantageous to most children with cardiac disease, especially those with cavopulmonary connections [92, 93]. The benefits of early extubation must be weighed against the costs of extubation failure, which has been associated with increased duration of mechanical ventilation, hospital length of stay, and mortality

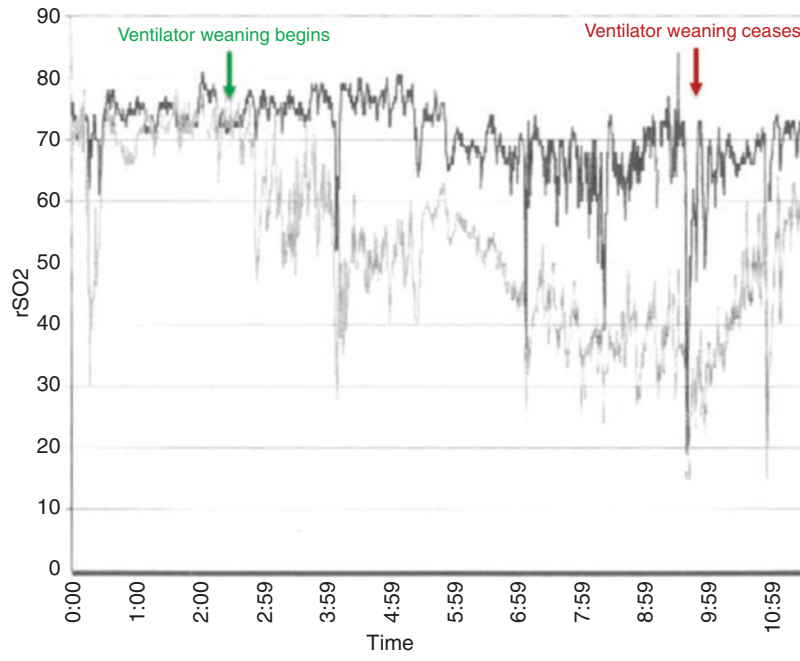

Fig. 3.3 An example of near-infrared spectroscopy (NIRS) trends during mechanical ventilation weaning. Cerebral (black) and renal (gray) NIRS measurements during ventilator weaning in a neonate recovering from cardiac surgery. The renal NIRS measurements steadily decrease during ventilator weaning and only begin to increase after ventilator weaning is aborted and ventilator support is increased. Based on this concerning trend, inotropic support for adjusted extubation was delayed for 24 h

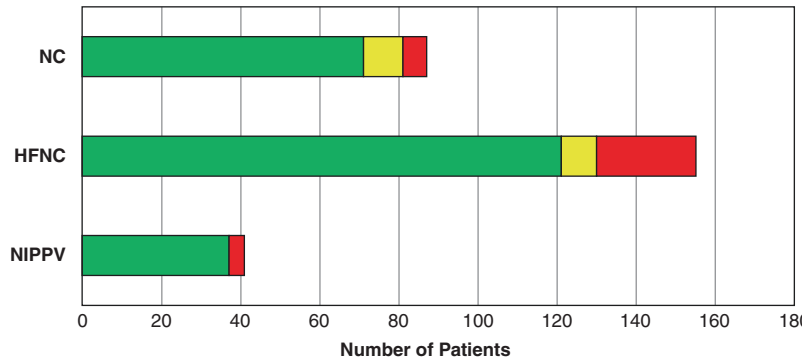

Fig. 3.4 Respiratory support provided upon extubation. Number of neonates extubated to room air or oxygen via nasal cannula (NC), oxygen via high-flow nasal cannula (HFNC), and noninvasive positive-pressure ventilation (NIPPV). Each bar represents neonates successfully extubated (green), neonates in which support was escalated to HFNC or NIPPV but not reintubated (yellow), and neonates who required reintubation (red)

[7, 94]. In a recent report from the Virtual PICU Systems (VPS), LLC, database, 6810 (25%) of 27,398 children from 62 centers between 2009 and 2014 who underwent cardiac surgery were extubated in the operating room [94]. Of the children extubation in the operating room, 395 (6%) required reintubation, and 44 patients (0.6%) died. Likewise, in a prospective observational single-center study of 1000 infants and children who underwent surgery over an 8-month period between 2012 and 2013, 45 of 871 (4.5%) of children extubated in the OR required reintubation, and 9 (1%) of these patients died [95].

To identify optimal candidates for early extubation, we recommend a multi-professional approach that can include pediatric cardiac intensive care providers, anesthesiologists, perfusionists, cardiologists, cardiothoracic surgeons, nursing, and respiratory therapists [95, 96]. Caudal analgesia; short-acting pain and sedative agents like fentanyl, remifentanil, midazolam, or medications that minimally suppress respiratory drive like dexmedetomidine; and careful intraoperative attention to fluid balance (i.e., modified ultrafiltration) may help prepare patients for successful extubation [91, 95–98]. At our institution, we utilized a multi-professional approach to develop a list of evidenced-based relative contraindications for extubation in the operating room, which are listed in Table 3.4 [91, 94, 95, 97–102].

Table 3.4 Relative contraindications for extubation in the operating room after pediatric congenital heart surgery

Neonatal age < 1 month
Cardiopulmonary bypass time > 150 min
STAT mortality category 4 or 5
Use of deep hypothermic circulatory arrest
Preoperative mechanical ventilation
Open sternotomy
History of airway anomalies
Intraoperative respiratory issues (excessive secretions/hypoxemia)
History of difficult intubation
Significant postoperative bleeding
Trisomy 21 with laryngomalacia
Nonelective and emergent surgeries
Inotropic support (dopamine >5 mcg/kg/min, any dose of epinephrine)

Though this list is by no means absolute, we encourage individual institutions to develop similar protocols to, at the very least, maintain a consistent approach to the practice of early extubation after cardiac surgery.

Traumatic Brain Injury

Patients with traumatic brain injury are at risk for bulbar dysfunction, which can affect their ability to protect their airway, manage oropharyngeal secre-

tions, and effectively cough. Traditional ERTs might fail to predict extubation success in this patient population, as these issues will not manifest until the endotracheal tube is removed. A weak or absent cough has been found to be the most significant predictor for extubation failure in this population [103], though level of consciousness and secretion burden (quality and quantity) can be used as a surrogates to assess the risk of upper airway problems after extubation during ERT.

Neuromuscular Disease

Patients with neuromuscular disorders can require mechanical ventilation under many circumstances including: the initial acute presentation of their disease; an acute exacerbation or worsening of their underlying disease; an intercurrent infectious illness; after an aspiration event; or postoperatively following elective or urgent surgery. In some disorders such as Duchenne's muscular dystrophy or Pompe disease, concurrent cardiomyopathy can also lead to intubation and mechanical ventilation. Because of their often weak or impaired cough, in-exsufflator, also referred to as cough-assist device, simulates cough and is commonly used as chronic pulmonary hygiene therapy in these children. Studies have reported the benefits of this treatment, with improvement of atelectasis and decreases in the frequency of developing pneumonia and requiring mechanical ventilation [104–106]. Though data are lacking on the use of these devices in acute respiratory failure, they are often used to improve secretion clearance, expedite recovery, and decrease the duration of mechanical ventilation.

The general principles of weaning and extubation readiness assessment discussed in this chapter thus far can be applied to those children, but physicians may need to modify their extubation practices to avoid extubation failure [103]. Specifically, extubation to continuous NIPPV in conjunction with aggressive use of an in-exsufflator can be a successful strategy to prevent reintubation in these patients, even if they have previously failed an ERT [62, 69, 107].

Patient with Chronic Respiratory Support

Patient with complex chronic conditions are an increasing population in the pediatric ICU and have a disproportionate use of healthcare resources [108, 109]. Children with complex chronic conditions are known to be at increased risk for extubation failure [7]. Moreover, many children chronically receive NIPPV or invasive mechanical ventilation via tracheostomy at home, which puts them at risk for aspiration and recurrent infection. Many of these children will also have severe obstructive sleep apnea or restrictive lung disease due to progressive scoliosis. When these patients are admitted to the pediatric ICU with acute on chronic respiratory failure, previously discussed general ventilator weaning and extubation practices can be applied. Patients who receive NIPPV chronically are typically extubated to continuous NIPPV with higher pressures, and FiO_2 than their baseline support and respiratory support is then weaned gradually. For patients on long-term invasive ventilation via tracheostomy, the goal of the pediatric ICU team is to wean them to their level of pre-illness support.

Future Directions

Ventilator weaning and extubation readiness assessments represent fundamental and often time-consuming practices in pediatric critical care, yet no consensus on standardized ventilator weaning and extubation readiness assessment guidelines in the pediatric ICU has been published to date. Urgent work is needed to establish a multi-professional, multicenter quality improvement working group to establish pediatric-specific guidelines that can advance practice in this area. If pursued, these efforts have the potential to reduce the morbidity and mortality that has been consistently associated with delays in ventilator weaning and extubation failure in the pediatric ICU.

Key Points

- Pediatric ventilator weaning and extubation readiness assessment definitions and practices are not standardized.
- Patients with congenital heart disease, traumatic brain injury, neuromuscular disease, and complex chronic illness are at higher risk for weaning and extubation failure and thus may need alternative approaches to ventilator weaning and extubation readiness assessment to optimize their chance of extubation success.
- Multi-professional multicenter quality improvement collaboration is needed to reach pediatric-specific ventilator weaning and extubation readiness assessment guidelines.

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4 Management of Status Asthmaticus in Critically Ill Children

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Introduction

Asthma remains as one of the most common chronic, noncommunicable diseases in childhood, generally associated with variable respiratory symptoms from variable limitations in airflow. Asthma manifests as the consequence of complex genetic and environmental interactions, presenting with extreme heterogeneity in the clinical signs and symptoms, their frequency and severity, as well as significant heterogeneity in the types and extent of airway inflammation and airway remodeling over time. Historically, the prevalence of asthma in children (and adults) has been under recognized. Our understanding has improved in the last 40 years through survey-based prevalence studies that estimate asthma affects as many as 334 million people worldwide [1, 2]. With the current global prevalence estimated at 4.85%, asthma remains the 14th leading cause of years lived with disability (YLDs) [1]. The Global Asthma Network formed in 2012 plans to continuously monitor the global burden of asthma to better understand how it is changing, improve diagnosis, and reduce risk factors for its occurrence [3].

Asthma prevalence has generally remained the highest in developed countries (e.g., 21% in Australia) and lowest in developing countries (e.g., 0.2% in China) [4], although its prevalence is increasing in developing countries as they modernize and may be substantially underestimated in some resource-poor countries. Children show greater variability in asthma symptoms, in early childhood ranging from 2.8% in Indonesia to 37.6% in Costa Rica, and in early adolescence, ranging from 3.4% in Albania to 31.2% in Isle of Man [2, 5]. The CDC reported increases in the prevalence of asthma among US children from 5.8% in 2003 to 9.6% in 2007, currently affecting more than seven million US children [6]. Asthma prevalence is much higher in boys than in girls, but it changes around puberty such that prevalence is almost 20% higher in adult women than in men [7]. This pattern is likely related to gender differences in airway development – male children have smaller airways relative to lung size as compared to female children, while adolescent females have smaller airways relative to lung size as compared to adolescent males. Therefore, remission in childhood asthma is more likely among boys than in girls, except in patients with severe asthma or those with sensitization to fur [8]. Gender differences in obesity, cigarette smoking, or environmental exposures may also increase the prevalence of asthma [9].

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Asthma exacerbations not only produce frequent symptoms and increase medical resource utilization but are also associated with substantial disability, impaired quality of life, and avoidable deaths in children. Surveys from the International Study of Asthma and Allergies in Childhood (ISAAC) found positive correlations between the prevalence of wheezing in childhood (6–7 years of age) with national mortality rates ($r = 0.32$, $p < 0.05$) and hospital admission rates ($r = 0.73$, $p = 0.003$) among 13–14-year-old children, whereas *severe* wheezing at 6–7 years of age had stronger correlations with mortality at 13–14 years ($r = 0.42$, $p < 0.025$) [10]. Given the strong positive correlations between asthma symptom prevalence, hospital admissions, and mortality, it is not surprising that status asthmaticus is a leading source of critical illness in children and the most common medical emergency [6]. While evaluating these patients, clinicians must maintain a high index of suspicion and greater vigilance, since 13% of patients with near-fatal asthma present with their first-ever attack of status asthmaticus [11]. Among those with a previous history of asthma, 63% had no prior hospital admissions for asthma in the year preceding their presentation with near-fatal status asthmaticus, and 86% had no prior admissions to the pediatric intensive care unit (PICU) [11].

Pathophysiology: A Brief Précis

The National Institutes of Health (NIH) define asthma as a chronic inflammatory disorder of airways in which many cells including mast cells and eosinophils contribute to symptoms associated with variable airflow obstruction that is reversible either spontaneously or with medications [12]. Although the detailed immunology of asthma is beyond the scope of this chapter, clinicians must recognize that eosinophilic asthma may include patients with allergic and non-allergic eosinophilic inflammation, whereas non-eosinophilic asthma may include patients with paucigranulocytic and neutrophilic inflammation. Some patients may also present with a mixed granulocytic inflammation, carrying features of eosinophilic asthma and non-eosinophilic asthma (see recent reviews [13, 14]).

The key pathophysiologic feature of status asthmaticus is inflammation of small airways leading to increased airway resistance and dramatically extending the time required for full exhalation. Residual air remains "trapped" in alveoli at the time of the next inhalation, thus alveolar volumes may increase progressively with each breath and lead to increased end-alveolar and intrathoracic pressures. Consequently, the end-expiratory alveolar pressures are often two- to threefold higher than normal, increasing the required changes in pressure to reach the negative alveolar pressures necessary to generate airflow by the patient [15, 16]. For example, continuous positive airway pressure (CPAP) functionally normalizes this gradient and has been shown to reduce the respiratory load in the spontaneously breathing asthma patient [15]. Although changes in the respiratory system mainly reduce dynamic lung compliance due to increased airway resistance [17, 18], atelectasis develops around the overdistended alveoli to reduce static lung compliance as well. Greater resistance to airflow increases work of breathing, presenting initially as increased distress and expiratory effort. Later, worsening lung hyperinflation limits full diaphragmatic relaxation, thus reducing the efficiency of diaphragmatic function and calling into play the use of accessory respiratory muscles with increased work of breathing during inhalation and exhalation [19, 20].

The progressively increasing lung volumes seen in status asthmaticus can also affect cardiac ventricular function. Alveolar hyperinflation-associated airway obstruction, increasing micro-atelectasis, hypoxia-induced pulmonary vasoconstriction in atelectatic areas, β-agonist and/or dehydration-induced metabolic acidosis, and respiratory acidosis from impending respiratory failure all contribute to increases in right ventricular afterload. Moreover, spontaneously breathing patients during an asthma exacerbation can have peak inspiratory pressures as extreme as -35 cm H_2O [21]. This negative intrathoracic

pressure directly accentuates left ventricular afterload, with increasing likelihood of pulmonary edema and worsening gas exchange [22]. *Pulsus paradoxus* is a physiological manifestation of the exaggerated variation in systolic blood pressure associated with high intrathoracic pressures during inspiration [23, 24]. Therapy with β_2-agonists increases heart rate, contributing to progressively diminished ventricular filling time and consequently lower cardiac output. Switching from negative pressure ventilation to positive-pressure ventilation in patients who require intubation is likely to result in acute hypotension secondary to decreased venous return [22]. In addition, many of the sedative agents used for intubation also have vasodilatory and myocardial depressant effects, particularly among children, further affecting cardiac output and increasing the risks of cardiac arrest during or immediately after tracheal intubation.

Clinical Assessment

Patients suffering from status asthmaticus require rapid and frequent assessments, watching for signs of respiratory distress or impending respiratory failure. A focused approach both for positive and negative findings on the physical exam will ensure that children are treated with the required escalation of care as necessary. The level of alertness is particularly important in their neurological assessment, since lethargy may be due to fatigue or due to hypercarbia, and this observation may be confused with their natural sleep cycle during nighttime hours. Children who are lethargic due to fatigue or hypercarbia very likely have impending respiratory failure and warrant close attention in the PICU.

Children may also exhibit profoundly increased work of breathing as demonstrated with retractions or paradoxical thoracoabdominal breathing. A prompt evaluation of the patients' general appearance, airway patency, effectiveness of respiratory effort (including both inhalation and exhalation), adventitious breath sounds, and adequacy of circulation form the foundations of their clinical assessment. The most vital aspect of clinical assessment in asthmatic patients is serial physical exams by bedside clinicians at least hourly or every couple of hours to appreciate changes in their clinical trajectory.

Presenting symptoms usually include a history of cough, increased respiratory rate, increased work of breathing and disordered breathing patterns. Auscultation of the chest will demonstrate turbulent airflow with diffuse wheezing and a prolonged expiratory phase due to air trapping by their hyper-reactive small bronchial airways. Children with mild-to-moderate status asthmaticus present with wheezing during the expiratory phase only, those with moderate-to-severe status asthmaticus manifest wheezing during both inhalation and exhalation phases, and patients with critical status asthmaticus may present with a "silent chest" since wheezing is only appreciated if there is adequate airflow in the small bronchi [24]. All patients with status asthmaticus must be monitored closely in a pediatric ICU, with serial physical exams being supplemented with continuous cardiorespiratory monitoring and intermittent arterial blood gas sampling.

Diagnostic Evaluation

The evaluation of children with status asthmaticus is mostly based on clinical findings, biplanar chest radiographs, an arterial blood gas to evaluate gas exchange, a complete hemogram to exclude eosinophilia or other abnormalities, tests to exclude viral or atypical pneumonitis, and a basic metabolic profile to rule out dehydration or β_2-agonist-induced hypokalemia. More advanced testing is rarely required but may be indicated to exclude parasitic, toxic, or environmental triggers for status asthmaticus. Bedside asthma scores may facilitate communication between members of the pediatric ICU team, though most clinical asthma scores lack sufficient validation and are limited by the subjective evaluation of the variables comprising these scores [25, 26].

Fiberoptic Bronchoscopy

Bronchoscopy may be indicated to rule out foreign body aspiration and bilateral bronchomalacia or diffuse bacterial bronchitis, but the vast majority of patients can be managed without bronchoscopy. The risks versus benefits of bronchoscopy must be weighed carefully because instrumenting hyper-reactive and inflamed airways may lead to significant clinical deterioration, life-threatening hypoxemia, and cardiac arrest. In a single-center case series of 44 ventilated asthmatic patients, bronchoscopies revealed thick mucus plugs, secretions, and bronchial casts. Saline lavage of obstructive airways was well tolerated with demonstrable improvements in pulmonary compliance, reduced duration of mechanical ventilation, but no differences in the PICU length of stay [27]. Occasionally, fiberoptic bronchoscopy can be used to instill human recombinant DNase or other mucolytic agents into plugged airways, but this practice is not routine at most centers [28].

Xenon Ventilation Computed Tomography

Recent studies have examined the usefulness of xenon ventilation computed tomography in asthmatic patients [29]. This technique is a relatively new method to evaluate pulmonary functions and ventilation defects in asthmatic patients by examining alteration in xenon trapping following administration of methacholine and salbutamol [30]. Although this testing may potentially unmask airway abnormalities contributing to ventilation-perfusion mismatch, its application to pediatric patients with status asthmaticus remains controversial. The potential usage of xenon is considered relatively benign since it is nonreactive in the body and disposed of from the lungs without any systemic effects in critically ill patients [29, 31].

Exhaled Nitric Oxide

Inhaled nitric oxide is not indicated for the treatment of status asthmaticus [32], but measurements of exhaled nitric oxide may estimate the extent of inflammatory airways in asthmatic patients. An increase in exhaled nitric oxide is known to accompany eosinophilic inflammation [32]. Although measured concentrations of exhaled nitric oxide may help gage the pathophysiologic trajectory of patients with status asthmaticus, the accuracy and prognostic value of this investigational test has not been established in clinical studies as of yet [33]. Exhaled nitric oxide is increased in steroid-naïve asthmatic subjects during status asthmaticus, although this returns to baseline after appropriate anti-inflammatory treatment is administered [33]. Additional studies are needed before testing for exhaled nitric oxide demonstrates its effectiveness to bedside clinicians.

Case Scenario

An 11-year-old female with a history of moderate-to-severe asthma presents to a local emergency department with wheezing progressing to severe respiratory distress over the previous 24 h. Her respiratory rate is 40 breaths per min, her heart rate is 125 breaths per minute, and her oxygen saturation as determined by pulse oximetry is 96%. She receives three consecutive albuterol nebulization treatments (2.5 mg each), one nebulization treatment with ipratropium bromide (500mcg), and one dose of intravenous methylprednisolone (1 mg/kg). One hour later, she is assessed by a pediatric intern, who notes that her vital signs and her respiratory effort have not improved, and persistent prolonged expiration and wheezing are apparent on auscultation of her chest. After this assessment, the pediatric intern asked her attending physician what the next best step in the management would be.

Pharmacological Management

In a study including 13,552 children critically ill with asthma, marked clinical variability in pharmacological management and mechanical support was noted (21% were treated in Collaborative Pediatric Critical Care Research Network (CPCCRN) PICUs, 79% were treated in non-CPCCRN PICUs). Wide variations occurred in the frequency of medication use in CPCCRN centers – ipratropium bromide 41–84% patients, terbutaline 11–74% patients, magnesium 23–64% patients, and methylxanthines 0–46% patients – implying a lack of consensus with regard to the pharmacological management of children with status asthmaticus [34]. We present the following sections recognizing that different clinicians may choose different elements from this menu based on the clinical features of specific patients, local institutional practices, resource availability, and personal preference. We have also summarized a suggested algorithmic approach to the management of status asthmaticus in Fig. 4.1.

Inhaled β-Adrenergic Agonists

β-Agonists cause smooth muscle relaxation by activating the β_2-adrenergic receptor and increasing cyclic adenosine monophosphate (cAMP) concentrations in smooth muscle cells, which inhibits the release of calcium ion from intracellular stores and reduces the membrane calcium entry and its intracellular sequestration [35].

Albuterol is a racemic mixture of R-albuterol and S-albuterol. The R-enantiomer is pharmacologically active, and the S-enantiomer is inactive. Levalbuterol is the pure R-enantiomer available as a preservative-free solution. In comparative trials, the use of equivalent doses of levalbuterol was not superior to albuterol [36]. Albuterol remains the drug of choice for treatment of status asthmaticus. Depending on different variables, approximately 10–20% of the albuterol dose will reach the lungs. The National Asthma Expert Panel recommends nebulized albuterol doses for asthma exacerbations in children younger than 12 years of 0.15 mg/kg (minimum dose 2.5 mg)

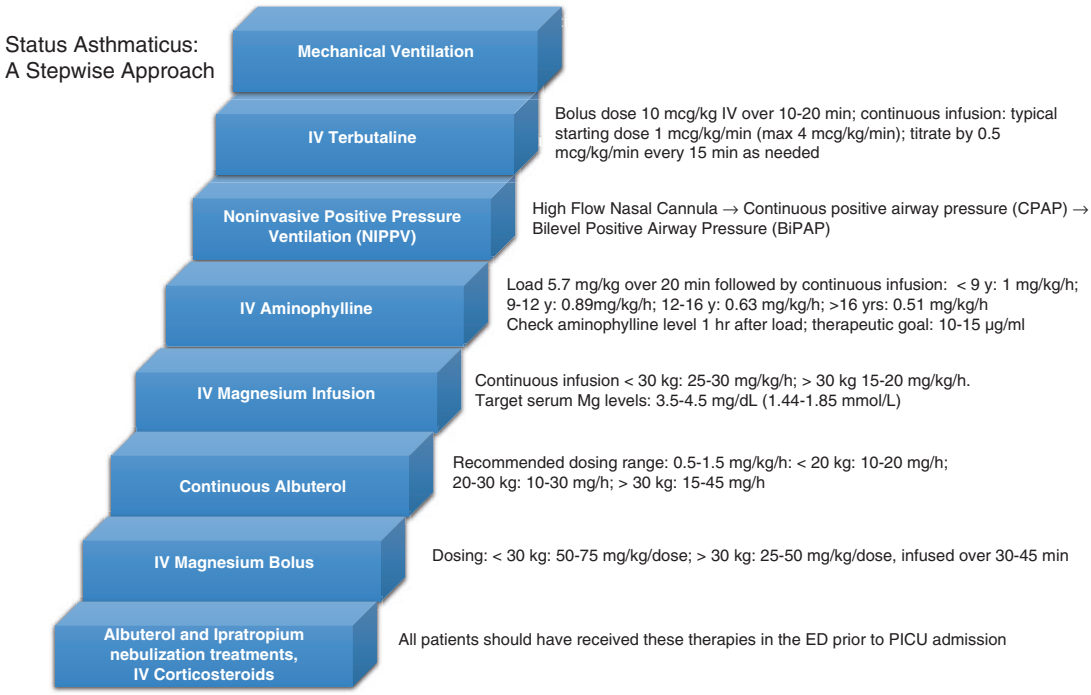

Fig. 4.1 An algorithmic approach to status asthmaticus

every 20 min for three doses, followed by 0.15–0.3 mg/kg (maximum 10 mg) every 1–4 h.

For patients not showing clinical improvement, continuous albuterol nebulization at 0.15–0.5 mg/kg/h is recommended. Larger doses, up to 30 mg/h, can be used for critical or near-fatal asthma. Existing evidence supports the use of continuous albuterol nebulization in pediatric patients with status asthmaticus and impending respiratory failure, leading to faster clinical improvement and decreased duration of hospital stay when compared with intermittent albuterol nebulization and decreased hospitalization rate when continuous albuterol regimen is used in the emergency department. Additionally, continuous albuterol treatment at these doses is safe and well tolerated [37]. Reported doses of albuterol used in pediatric patients often exceed the expert panel recommendations [38]. Data on the effectiveness and safety of these higher doses compared to traditional recommended doses are sorely needed.

Anticholinergic Agents

The parasympathetic nervous system contributes to airway resistance via acetylcholine-mediated airway smooth muscle contraction; regulation of mucus secretion, ciliary beat frequency, and mucus clearance via mucosal glands and epithelial cells; vasodilation by smooth muscle relaxation in blood vessels; and modulation of inflammation [39]. There are five subtypes of muscarinic receptors (M1-M5), which belong to the larger group of G protein-coupled receptors. Acetylcholine stimulates these receptors. M3-receptors located on the airway smooth muscle mediate bronchoconstriction, and M3-receptors located on the submucosal cells regulate glandular secretion. M2 muscarinic receptors are also on the bronchial smooth muscle, which indirectly cause smooth muscle contraction by reducing β-adrenoceptor-mediated relaxation through inhibition of adenylate cyclase. Blockade of both M2 and M3-receptors on airway smooth muscle should therefore inhibit bronchoconstriction.

On the other hand, parasympathetic nerves supplying the lungs also have muscarinic receptors. M2-receptors on postganglionic parasympathetic nerves limit acetylcholine release by a negative feedback mechanism. Thus, blocking the M2-receptors on parasympathetic nerves with muscarinic antagonist will increase acetylcholine release and potentiate vagally induced bronchoconstriction. Parasympathetic neuronal M2-receptors are susceptible to viral infections and exposure to ozone (which decreases their function) and are less functional in patients with asthma. The mechanism for this latter reduction in neuronal M2-receptor functions in multifactorial and involves the downregulation of receptor expression and blockade by endogenous antagonists [40]. Anticholinergic drugs block M2 and M3 muscarinic receptors on the airway smooth muscle, glands, and nerves with similar affinity, thereby impairing smooth muscle contraction and decreasing airway secretions while simultaneously augmenting acetylcholine release, supporting the rationale to develop selective M3-receptors medications [41].

Ipratropium bromide is a synthetic quaternary ammonium derivative with an isopropyl group at the N-carbon atom of atropine that limits its systemic absorption. Inhaled ipratropium targets the muscarinic receptors in the bronchial airways without the systemic effects of atropine, such as tachycardia. The low oral absorption of ipratropium is beneficial, since up to 90% of an aerosolized dose may be swallowed. Ipratropium is a nonselective muscarinic receptor inhibitor, which produces bronchodilation by the inhibition of acetylcholine-mediated bronchospasm without affecting the mucociliary clearance. Ipratropium has no impact on intraocular pressure or pupillary size even when up to four times the recommended dose is used; nevertheless, it can produce prolonged pupillary dilatation when sprayed accidently into the eyes [42]. The half-life of ipratropium is 3–4 h, the onset of action is 15 min, peak effects occur at 1–2 h after administration, and duration of action is 4–6 h.

Early administration of three or more repeated doses of inhaled ipratropium with β_2-agonists has been shown to decrease the rate of hospital

admission for pediatric and adult patients with moderate-to-severe status asthmaticus by 30% [43]. Improvements in spirometry and clinical scores have also occurred with the use of multi-dose protocols, without increasing side effects [43]. A double-blind, randomized study in adults with severe asthma found that those receiving ipratropium for 36 h or longer were discharged home earlier than those that receiving ipratropium for 12 h [44]. In another study, patients using fenoterol/ipratropium versus fenoterol or ipratropium alone were found to have greater bronchodilator effects in children with acute asthma [45].

Intermittent ipratropium therapy is recommended in hospitalized patients with acute asthma because of its high safety profile and documented beneficial impact [46]. The effect of ipratropium is dose-dependent, with the recommended dose range from 250 to 500 mcg [47]. In one case report, a 13-year-old patient with status asthmaticus refractory to β_2-agonist treatments showed improvement after starting continuous ipratropium at 1000 mcg per hour [48]. Despite this report, however, continuous ipratropium therapy has not been systematically investigated.

Anti-inflammatory Drugs

Corticosteroids are a cornerstone for both acute and long-term asthma management, as airway edema and inflammation are the most prominent pathological features of the disease. Indeed, use of systemic corticosteroids to treat status asthmaticus is not controversial and will therefore be discussed briefly. Methylprednisolone, dexamethasone, prednisone, and hydrocortisone are the traditional corticosteroids used for critically ill patients, but they differ in glucocorticoid potency, duration of onset, and mode of administration. For patients with mild-to-moderate asthma exacerbations, oral prednisone is the most common therapy prescribed. Oral dexamethasone has also been used to treat patients with asthma in the acute care setting. Dexamethasone is a long-acting corticosteroid that has traditionally been used for children with croup. In one study of patients 2–18 years of age who presented to the emergency department with mild-to-moderate acute asthma exacerbations, Qureshi et al. evaluated the efficacy of oral prednisone versus oral dexamethasone [49]. Compared to oral prednisone, oral dexamethasone did show similar efficacy with improved compliance and fewer side effects when compared with oral prednisolone [49]. The authors hypothesized that the improved compliance was observed because dexamethasone is more palatable than oral prednisone with shorter prescription duration. Hydrocortisone, a short-acting corticosteroid with relatively less anti-inflammatory potency than the other corticosteroids, is not commonly used for acute asthma exacerbations.

Corticosteroids that are highly potent with a fast onset are the most desirable for patients with status asthmaticus. Systemic corticosteroids are preferred and have also been shown to be superior to inhaled corticosteroids for status asthmaticus, with reduced need for hospitalization [50]. Intravenous methylprednisolone is the most commonly recommended due to its potent glucocorticoid effects and limited mineralocorticoid effects [51]. Patients presenting with status asthmaticus should receive intravenous methylprednisolone 2 mg/kg (maximum dose 80 mg) early in the course of their management, as its onset of action occurs approximately 4 h after administration. There are no significant added benefits from systemic corticosteroids at doses above 80 mg/day or 2 mg/kg/day with regards to pulmonary function, rate of hospital admission, or hospital length of stay [23].

Magnesium

Magnesium sulfate acts in the airway by blocking voltage-sensitive calcium channels, inhibiting calcium uptake and calcium-myosin interactions, thus producing smooth muscle relaxation [52]. Magnesium also stabilizes T-cells and inhibits mast cell degranulation, consequently decreasing histamine release and inflammatory mediators. Other mechanisms of action include inhibition of acetylcholine release by the cholinergic motor

terminals and stimulation of nitric oxide and prostacyclin production. When intravenous magnesium sulfate is added to β_2-agonists and systemic corticosteroids, it improves pulmonary function in children and adults and reduces hospital admissions by 30% in children and in a lesser degree in adults [53].

Magnesium has a rapid onset of action and its duration of action is limited by renal clearance. As serum magnesium concentrations increase, renal excretion of magnesium increases linearly, potential hindering achievement of goal serum concentrations. Specifically, serum magnesium concentrations of up to 4 mg/dL are thought to be required for airway smooth muscle relaxation. In a cohort study of children with status asthmaticus, using continuous magnesium infusions at 40 mg/kg/h for 4 h after a loading dose of 50–75 mg/kg was safe and attained magnesium levels of 4.4 mg/dL at the end of the infusion [54]. Pediatric patients receiving magnesium sulfate in this study improved clinically, with reductions in tachycardia and tachypnea. The optimal dose of magnesium sulfate is currently unclear, with recommended dose ranges of 25–100 mg/kg to a maximal dose of 2,000 mg, independent of weight. In obese patients, magnesium dose should be based on their ideal body weight. We recommend an initial bolus dose of 50–75 mg/kg for children weighing <30 kg and 25–50 mg/kg for those weighing >30 kg, infused over a period of 30–45 minutes to improve acute respiratory symptoms and avoid hypotension. In cases of life-threatening status asthmaticus refractory to standard treatment, a continuous infusion of 25–30 mg/kg/h for children <30 kg and 15–20 mg/kg/h for children weighing >30 kg, up to a maximum dose of 40 mg/kg/h can be added. Titration to the desired clinical effect should be based on target serum magnesium concentrations of 3.5–4.5 mg/dL and tolerability [55]. On the other hand, there is limited evidence that intravenous magnesium is beneficial in asthma exacerbations of less severity (i.e., moderate-to-severe asthma presentations) [56].

Nebulized inhaled magnesium sulfate has also been trialed as a therapeutic agent for asthma exacerbations. In a systematic review study including adult and pediatric patients, inhaled magnesium has shown some clinical benefit in patients with acute severe asthma attacks with no apparent serious adverse effects [57]. In another study containing adult asthma patients, treatment with nebulized magnesium sulfate improved pulmonary functions and reduced hospital admissions in adults by 37% [53]. In contrast, a study of pediatric patients with moderate-to-severe asthma using 800 mg of nebulized magnesium failed to reduce their time to discharge [58]. Similarly, a recent Cochrane review reported minimal clinical improvement and no reduction in hospital admissions when nebulized magnesium was used concomitantly with β_2-agonists and ipratropium therapy [59].

In conclusion, intravenous magnesium sulfate should be used in children, especially those with life-threatening critical asthma and those not responding to initial treatments, with low risk for severe adverse effects. Nebulized inhaled magnesium therapy, however, cannot currently be recommended.

Methylxanthine Drugs

The most commonly used methylxanthine in acute asthma exacerbation is theophylline. Theophylline brings relief to asthmatic patients due to its direct bronchodilator effect [23]. Parenteral form of theophylline is aminophylline, which is a 2:1 complex of theophylline and ethylenediamine (aminophylline is converted to theophylline systemically, such that 1 mg aminophylline = 0.8 mg theophylline). Aminophylline is FDA approved as an adjunctive treatment for acute asthma exacerbations in all age groups, including children older than 1 year.

Theophylline pharmacokinetics are age-dependent, which affects its pediatric dosing recommendations. The elimination half-life of theophylline gradually decreases during the first year of life from ~ 24 h in term neonates to between 2 and 10 h (mean 4 hs) in children 1 to 9 years old and between 3 and 16 h (mean 8 h) in

adults [60]. Theophylline's primary actions are dose-dependent, as lower serum concentrations result in anti-inflammatory and immunomodulatory effects, whereas higher serum concentrations show greater bronchodilator effects [61]. Due to potential toxicity, serum theophylline concentrations should be followed at least every 12 h, and repeated bolus doses or infusion rates should be adjusted based on the target steady-state serum concentrations, with a traditional goal range of 10–15 μ/mL. Obese patients should have their ideal body weight used for dosage calculation [23]. Theophylline dosing is summarized in Fig. 4.1.

In a prospective, randomized, controlled trial by Ream et al. published in 2001, 47 children admitted to a pediatric ICU with status asthmaticus receiving traditional β-agonist, anticholinergic, and corticosteroid therapy were randomized to receive IV theophylline or placebo [62]. Twenty-three patients who received theophylline were compared with 24 controls, with cohorts having similar clinical asthma scores (i.e., Wood-Downes score [63]) prior to study enrollment. Faster recovery times (defined by clinical asthma scores ≤ 3) were noted in both non-intubated and intubated patients receiving theophylline as compared to controls – 19 ± 3 h versus 31 ± 5 h for non-intubated patients and 66 ± 10 h versus 191 ± 33 h for intubated patients. Four years later, Wheeler and coworkers examined the effects of intravenous theophylline and terbutaline in a randomized controlled trial in 36 patients with status asthmaticus receiving traditional β-agonist and corticosteroid therapy [64]. More specifically, they randomized patients to receive adjunctive therapy with intravenous theophylline plus placebo, intravenous terbutaline plus placebo, or intravenous theophylline plus terbutaline. The authors observed no differences in clinical asthma score over time, length of pediatric intensive care unit stay, or incidence of adverse events between the three groups, with the exception of a higher incidence of nausea in children who received both theophylline and terbutaline. Importantly, in a cost analysis that included the cost of both drugs and the cost of theophylline levels, median hospital cost was significantly less in patients who received only theophylline: $280 US dollars compared to ~$4000 in each of the other two cohorts.

Prior to these two small but important trials, several studies were published suggesting lack of benefit from theophylline therapy for patients with acute asthma exacerbations. Most of the patients in these studies however were not critically ill [65–68]. Recently, a meta-analysis of 52 study arms from 42 trials involving theophylline, some of which included adults and others included children, involving intravenous theophylline concluded that, when given with bronchodilators and corticosteroids, theophylline can be helpful and represents a cost-effective and safe choice for patients with status asthmaticus [69]. We recommend initiation of intravenous aminophylline in patients who are not improving or worsening despite inhaled β-agonists, systemic corticosteroids, ipratropium bromide, and intravenous magnesium.

As previously concluded by Mahemuti et al. given the low cost of theophylline, and its similar efficacy and rate of side effects compared with other drugs, we suggest that theophylline, when given with bronchodilators and corticosteroids, is a cost-effective and safe choice for acute asthma exacerbations [69].

Intravenous Albuterol

One study examined the advantage of combining intravenous albuterol (salbutamol) to inhaled albuterol in children during the initial management of severe acute asthma in the emergency department. Children receiving a single dose of 15 μg/kg intravenous albuterol over 10 min with inhaled albuterol had a shorter recovery time and earlier discharge compared with a group of children who received inhaled albuterol alone. The intravenous albuterol cohort had increased incidence of tremors, but no other notable side effects [70]. These data support the use of a single-dose intravenous albuterol in addition to inhaled albuterol in the emergency department in children with severe asthma.

Intravenous Terbutaline

Use of intravenous albuterol in contemporary pediatric ICU is rare. Rather, terbutaline is typically used as an intravenous β-agonist for children with status asthmaticus who are failing traditional therapy. Terbutaline can be given as a subcutaneous dose of 10 mcg/kg, with a maximum dose of 250 mcg, and can be repeated every 20 min for a total of 3 doses. The recommended intravenous loading dose is 10 mcg/kg over 10–20 min, followed by continuous infusions of 0.1–10 mcg/kg/min. The usual starting dose is 1 mcg/kg/min, with an average maximum dose of ~4 mcg/kg/min [71]. Frequently reported side effects are tachycardia, arrhythmias, diastolic hypotension, tremors, and hypokalemia (which results from upregulation of sodium-potassium pumps on cell membranes, resulting in shifting of potassium from extracellular to intracellular space [71]).

The postulated failure of inhaled albuterol to enter through constricted airways led to the recommendation for intravenous β_2-adrenergic agonists in children with severe asthma exacerbation. Regardless of this rationale, there is little evidence showing clear benefits to support the use of intravenous β_2-agonists as a substitute for or in addition to inhaled β_2-agonists. One retrospective study found that early administration of intravenous terbutaline in the emergency department might decrease acute respiratory failure and the need for mechanical respiratory support in pediatric patients [72]. On the other hand, a prospective, randomized, double-blind, placebo-controlled trial in pediatric patients with status asthmaticus found no differences between patients randomized to receiving terbutaline and those receiving placebo infusions in clinical asthma severity scores, need for continuous nebulized albuterol, or length of stay in the PICU. Additionally, more patients who had received terbutaline had elevated serum troponin levels at 12 and 24 h, suggesting possible cardiotoxicity, compared to those who received placebo [73]. Three different meta-analyses have also failed to show a clinical advantage with intravenousβ_2-agonists compared to other therapies for status asthmaticus [74–76]. Based on these data and the aforementioned work by Wheeler and colleagues [64], there is not sufficient evidence supporting routine use of intravenous β_2-agonists. On the other hand, because of the conflicting nature of the available data and the sound physiologic rationale for its use, we consider a trial of terbutaline in patient's refractory to standard therapy and at risk for progressing to fulminant respiratory failure and mechanical ventilation to be reasonable.

Anesthetic and Other Gases

Helium

Helium-oxygen (heliox) is a gaseous mixture commonly utilized for patients with airway obstruction because of its lower density as compared to oxygen alone or room air [77]. The lower density of inhaled gas improves flow through high-resistance airways by reducing the degree of turbulent flow. As gas flow becomes less turbulent in the affected airways, the flow velocity is reduced, and the flow pattern may transition from turbulent to more laminar. Additionally, heliox can improve removal of carbon dioxide (CO_2), as CO_2 will diffuse into heliox four times as rapidly than in oxygen or room air [24]. The reduction in turbulent airflow may also aid with the delivery of aerosolized medications into distal lung segments [24]. Heliox is most commonly applied as a mixture of at least 70% helium (i.e., 70% helium/30% oxygen, 75% helium/25% oxygen, etc.), with mixtures containing lower concentrations of helium being relatively ineffective at improving airflow.

Heliox has been recommended by some as a means of avoiding endotracheal intubation in patients with status asthmaticus [78–80]. Several pediatric studies examining the use of heliox for acute asthma exacerbations or status asthmaticus however have failed to demonstrate consistent benefits, including its use as a carrier for albuterol nebulization [81–84]. At most, heliox may improve clinical asthma scores, but it has not been associated with a reduced rate of

hospitalization or other important clinical outcomes [78, 85]. Its role in mechanically ventilated asthmatics is also likely limited. In a very recent prospective study of 13 adults with severe asthma or chronic obstructive pulmonary disease exacerbations requiring mechanical ventilation, use of heliox led to only modest reductions in peak inspiratory pressure and partial pressure of CO_2 measurements and had little effect indices of dynamic hyperinflation (e.g., plateau pressure and total positive end-expiratory pressure) [86].

Use of heliox therapy is costly, has limited utility in patients with hypoxemia, and can be technically difficult to provide, especially in mechanically ventilated patients [87]. Many ventilators are not equipped to deliver heliox safely [88], and for mechanical ventilators that are capable of administering heliox, delivery of the appropriate fractional oxygen component, volume measurements, and valve functioning can also be adversely affected [87]. Routine use of heliox for patients with status asthmaticus can therefore not be recommended, and its use in mechanically ventilated patients should be avoided. On the other hand, it may be useful in select patients, such as children with status asthmaticus without significant hypoxemia, though clinicians should be prepared for endotracheal intubation and intervene quickly if no improvement or clinical worsening is noted.

Isoflurane

Inhaled isoflurane, a gaseous anesthetic, has been used outside of the operating room in some centers for status asthmatics and other conditions. Isoflurane is a potent bronchodilator and particularly attractive as a therapy for status asthmaticus due to its rapid onset and absence of cumulative toxicity [89]. Trained anesthesiologists have used inhaled anesthetics successfully in pediatric patients with life-threatening asthma exacerbation with favorable outcomes [89–93]. Unfortunately, its use is technically challenging in many facilities because of limited air scavenging systems. Cost, variability in physician and nursing credentialing and comfort with this class of drugs, and the logistical issues of administering an inhaled anesthetic gas for long periods of time outside of the operating room setting have also prevented widespread use. If the capabilities to administer inhaled isoflurane are available, close monitoring including invasive arterial pressure measurement is mandatory, as observational studies have described frequent side effects, the most common of which is hypotension requiring vasoactive infusions (77%) [74]. Other reported side effects include arrhythmias, neurologic abnormalities, accumulation of inorganic fluoride, tolerance during therapy, and abstinence syndrome after discontinuation [89, 94, 95].

Respiratory Support

Oxygen Therapy

The goals of treatment as outlined by the National Asthma Education and Prevention Program (NAEPP) are to treat significant hypoxemia, reverse the airflow obstruction, and reduce the likelihood of future episodes [96]. Oxygen should undoubtedly be applied to treat hypoxemia, but high inspired oxygen concentrations are infrequently required for patients with status asthmatics. Thus, the need for higher inspired oxygen concentrations should raise concern for other respiratory insults, most important and life-threatening of which are pneumothoraces [97, 98].

High-Flow Nasal Cannula (HFNC)

High-flow nasal cannula is often used to prevent respiratory failure by generating positive airway pressure [99], particularly in patients with status asthmaticus [100]. HFNC can also serve as a delivery method for albuterol nebulization or metered-dose inhaler (MDI) therapy and leads to rapid improvements in blood gas and clinical parameters within 24 h [101]. Preliminary outcome studies reported that HFNC in status asthmaticus resulted in equal to greater efficacy of bronchodilator therapy, reduced work of

breathing, less tachycardia, and shorter ED times in children with status asthmaticus [101, 102]. Despite low-grade evidence specific to this population supporting this modality, HFNC as a safe and effective method of respiratory support for patients with acute asthma exacerbations is widely accepted and thus not controversial.

Noninvasive Positive-Pressure Ventilation (NIPPV)

For patients with acute asthma exacerbations, NIPPV aims to prevent collapse of airways during exhalation, reduce microatelectasis, and unload respiratory muscle work, thereby preventing respiratory fatigue. NIPPV has been reported to be feasible and clinically effective in improving symptoms in pediatric ICU patients with status asthmaticus when compared to standard therapy [103]. In a randomized crossover trial (N = 20), NIPPV for 2 h decreased work of breathing, respiratory rate, accessory muscle use, and dyspnea as compared with standard therapy [19]. Another randomized pilot study (N = 20) found that adding NIPPV to standard care reduced their clinical asthma scores, oxygen requirement, and respiratory rate compared to standard care alone [104].

Support for the use of NIPPV in acute asthma exacerbations has also been noted in two large registry studies. In a study from the PHIS database containing 13,552 PICU patients, use of NIPPV occurred 3–5% of children with asthma, and sites that used noninvasive ventilation more often appeared to have reduced rates of endotracheal intubation and mechanical ventilation [34]. Similarly, a study from the VPS database noted NIPPV use in 6% asthmatic patients, and PICU length of stay was lower in high-utilization centers [105]. These reports suggest the potential for NIPPV to become an important part of the management of status asthmaticus in pediatric patients. With more study, standardization and optimization of this mode of respiratory support in management pathways for this patient population should be prioritized. Currently, we support the use of NIPPV in children with status asthmaticus as a stop-gap measure to prevent worsening respiratory failure and avoid the potential complications of endotracheal intubation and mechanical ventilation [106, 107].

Tracheal Intubation

Observational studies report that 10–14% of children admitted to the PICU for asthma require invasive mechanical ventilation [34, 108, 109]. There is no standard protocol for when to intubate a child in status asthmaticus. In one study of 51 episodes of status asthmaticus, 41% were intubated for respiratory acidosis, 37% for clinical fatigue, and 22% for cardiopulmonary arrest [98]. While arterial or venous blood gas data can be helpful in deciding when to intubate an asthmatic, Newth and colleagues found that only 48% of patients with fatal or near-fatal status asthmaticus in a multicenter cohort from the CPCCRN (n = 260) collaborative had blood gas data prior to intubation, with an average partial pressure of carbon dioxide (pCO_2) of 52 mmHg [11]. Clinical intuition therefore seems to be the major driving force leading to intubation of children with status asthmaticus and respiratory failure. Specific indicators for intubation include exhaustion and fatigue despite maximal therapy, worsening mental status, refractory hypoxemia, increasing hypercapnia, hemodynamic instability, impending coma or apnea, increasing metabolic acidosis, or upper airway compromise. Importantly, practice varies widely across centers too, particularly between children's hospitals and community centers [97]. Children managed at community hospitals were 3.3 times more likely to be intubated despite similar severity of illness and with many children routinely not receiving standard asthma therapies like corticosteroids [110, 111].

The decision to intubate should not be taken lightly as severe asthmatics are at high risk for severe morbidity and mortality during intubation. Worsening status asthmaticus is characterized by dynamic alveolar hyperinflation with associated diffuse microatelectasis and pulmonary hyper-

tension, relative hypovolemia from dehydration, β-agonist-induced metabolic acidosis, hypercarbia from respiratory muscle fatigue, reduced left ventricular filling from tachycardia, and increased left ventricular afterload from negative inspiratory intrathoracic pressures [21]. Additional concerns include instrumenting the hyper-reactive airway for intubation, which accentuates respiratory obstruction; analgesic sedative drugs used for intubation, which can cause systemic vasodilation and reduce myocardial contractility; transitioning to positive-pressure ventilation, which further reduces venous return; and the risk of barotrauma associated with mechanical ventilation and hyperinflated lungs [112].

Prior to intubation, efforts must be made to maximize management of status asthmaticus using bronchodilators, intravenous corticosteroids, magnesium, aminophylline, judicious correction of hypovolemia with intravenous fluids, and, if possible, a trial of noninvasive ventilation [97, 113–117]. Ketamine is the first choice for pre-intubation sedation because of its potentially advantageous bronchodilator and hemodynamic effects [118–121], but the use of adjunctive short-acting sedatives like midazolam, propofol, or dexmedetomidine can also be helpful. Strategies for achieving sedation and analgesia must take into account their systemic vasodilatory, respiratory depressant, myocardial contractility, and other side effects [122]. Advanced airway skills are essential, and neuromuscular blockade is desirable to minimize the number of attempts required for successful intubation [123].

Following intubation, chest rise and auscultation of breath sounds may be difficult to elicit in the setting of severe airway obstruction. For this reason, in-line end-tidal CO_2 monitoring is essential to the verify correct placement of the endotracheal tube [124–127]. Manual ventilation following intubation must limit the tidal volumes and respiratory rates used, to avoid accentuating barotrauma and allowing complete exhalation between breaths. Attempts to normalize pH by correcting hypercapnia are unnecessary and potentially harmful [128]. Correction of hypoxemia and permissive hypercapnia (i.e., pH 7.2–7.3) are reasonable goals. Close bedside observation of all intubated asthmatic patients is required for the first few hours after initiating mechanical ventilation, since the risk of life-threatening complications and unanticipated hemodynamic effects is highest in that period.

Mechanical Ventilation

Although there are no absolute criteria for mechanical ventilation, clinicians should consider stepwise escalation in support from inhaled therapies to intravenous therapies and noninvasive mechanical support and, ultimately, culminating in invasive mechanical ventilation for refractory or rapidly progressive respiratory failure. Mechanical ventilation, either noninvasive or invasive, is generally designed to overcome the dramatically increased work of breathing inherent to status asthmaticus. Most clinicians agree that a low respiratory rate, long expiratory time ventilator strategy is optimal to permit CO_2 clearance. The amount of positive end-expiratory pressure (PEEP) to set on the ventilator, on the other hand, is controversial [129–133]. After initiation of mechanical ventilation, total $PEEP_{tot}$ should be measured using an expiratory pause maneuver [134]. $PEEP_{tot}$ represents the sum of the PEEP set by the ventilator and the PEEP generated by air trapping, typically referred to as auto-PEEP. While some clinicians support measuring auto-PEEP to regulate the ventilator PEEP in order to actually reduce alveolar hyperinflation and also recruit areas of atelectasis [133], others do not support this concept and recommend using minimal PEEP [112, 124]. The controversy surrounding the practice of higher PEEP settings in status asthmaticus is primarily due to reports of paradoxical responses that lead to undesirable increases in FRC in some patients with status asthmaticus [129–131]. Interpretation of the data generated from these studies however has varied, and a consensus on optimal PEEP strategy for status asthmaticus has yet to be reached [132]. We recommend careful titration of ventilator PEEP close to the $PEEP_{tot}$, which attempts to maintain airway patency during expiration. Patients must be monitored closely, and ventilator

PEEP should be carefully weaned as clinical condition improves.

The optimal mode of ventilation for status asthmaticus is also not clear [6]. Regardless of mode of ventilation, goals while on mechanical ventilation should include minimizing dynamic hyperinflation and air trapping, reduction in atelectasis, and implementation of permissive hypercapnia to avoid ventilator-induced lung injury and air-leak complications [119]. Lung protective strategies from close monitoring of the converse dependent variables can be used with either volume-targeted or pressure-targeted modes. For instance, when using a volume-targeted mode, inspiratory plateau pressures measured via inspiratory pause maneuvers while the patient is neuromuscularly blocked must be measured regularly, as high inspiratory plateau pressures (>30 mH_2O) can cause life-threatening pneumothoraces [135]. For patients on pressure-targeted modes of mechanical ventilation, tidal volumes must be followed closely and set inspiratory pressures reduced as airway resistance improves. We most commonly utilize pressure-regulated volume control ventilation for patients with status asthmaticus, which has the theoretical advantages of offering the high initial inspiratory flow associated with pressure-targeted modes and the ability to set and limit tidal volumes associated with volume-targeted modes of ventilation.

Case Scenario Resolution

After receiving three consecutive albuterol nebulization treatments (2.5 mg each), one nebulization treatment with ipratropium bromide (500mcg), and one dose of intravenous methylprednisolone (1 mg/kg) in the emergency department without improvement, continuous inhaled albuterol therapy is initiated at 20 mg/hr (~0.5 mg/hr), and she is admitted to the pediatric intensive care unit for continuous monitoring, hourly vital signs and hourly clinical respiratory scores (CRS). Upon arrival at the unit, her physical exam continued to be concerning, with a prolonged expiratory phase with wheezing appreciated in all lung fields and suprasternal and subcostal retractions. She had difficulty in taking in full sentences. Vital signs were remarkable for heart rate 155 beats/min, respiratory rate 50 breaths per minute, and blood pressure 90/45 mmHg.

Intravenous magnesium of 25 mg/kg is administered over 30 minutes, and a magnesium infusion is started at 15 mg/kg/hr. Continuous inhaled albuterol, inhaled ipratropium bromide every 8 h, and intravenous methylprednisolone 1 mg/kg every 6 h also continue to be administered after arrival to the PICU. One hour later, after reassessment and no change in CRS, an intravenous theophylline bolus of 5.7 mg/kg/hr is administered, and an infusion is initiated at 0.89 mg/kg/hr. Noninvasive positive airway pressure is also applied.

Over the next 12 h, she slowly improves and is transitioned to high-flow nasal cannula. A recommended stepwise algorithm for the management of status asthmaticus is included in Fig. 4.1.

Take-Home Messages

- All patients with status asthmaticus should be immediately placed on continuous cardiorespiratory monitoring with serial clinical assessments to determine the need for admission to the intensive care unit.
- Inhaled β-agonist therapy and intravenous corticosteroid therapy are the mainstays of treatment for status asthmaticus.
- Intermittent nebulization of ipratropium bromide is also recommended as a first-line therapy for pediatric patients admitted with status asthmaticus.
- Intravenous magnesium sulfate and aminophylline represent relatively low

cost and safe "second-tier" therapies for patients with refractory status asthmaticus.

- Routine use of intravenous terbutaline or heliox gas mixture cannot be recommended, but these therapies may have a role in preventing intubation and mechanical ventilation in select patients.
- Compelling but not conclusive evidence exists to support the use of noninvasive positive pressure for children with status asthmaticus.

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Part II

Cardiovascular Controversies

5 Medical Management of Acute Fulminant Myocarditis

Fabio Savorgnan and Paul A. Checchia

Introduction

Myocarditis is a disease characterized by inflammation in the myocardium that results in cardiac-histologic and anatomical alterations as well as functional derangements secondary to myocardial destruction [1]. In a multi-institutional study conducted in 2005, from a total of 427,615 pediatric patients discharged, myocarditis accounts for 0.05% of pediatric discharges in the United States [2]. In a study from the Pediatric Health Information System (PHIS) database consisting of 514 patients with myocarditis diagnosed between April 2006 and March 2011, 80% required intensive care, 45% received mechanical ventilation, 19% were placed on extracorporeal membrane oxygenation (ECMO), and 4% received ventricular assist device (VAD) support [3]. In one series, fulminant myocarditis, defined as myocarditis with initiation of symptoms in the preceding 2-week period, composed 38% of the cases of myocarditis in children [4].

Acute fulminant myocarditis is diagnosed when patients have symptoms, usually within the preceding 2 weeks, which progress to severe heart failure, hypotension, and cardiogenic shock. Alternatively, in acute, non-fulminant myocarditis, the onset of illness is less distinct, heart failure symptoms are less severe, and hypotension is infrequent [5, 6].

Etiologies

While viruses frequently cause myocarditis, toxins or immunologic disease can also be the cause [1]. The most frequent viruses were once thought to be enteroviruses, including Coxsackie B. Recently, studies show that parvovirus B19, human herpesvirus 6, and less frequently adenovirus are the most common viral etiologies of myocarditis. In some countries within South America, *Trypanosoma cruzi* is a frequent cause of myocarditis [7–10] (Table 5.1).

Pathogenesis

Basic science research proposes that there are three phases in the myocarditis course [11]. The first phase involves massive damage to the myocardium due to viral infection itself and the innate immune system.

Phase 2 is characterized by a cross-reaction between myocardial-specific antigens and viral structure, a pathogenesis called molecular mimicry. The acquired immune system is involved in phase 2. Patients with a self-controlled immune response, which clears the infection and,

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Table 5.1 Common etiology of myocarditis

Infectious	Inflammatory
Enterovirus (Coxsackie B)	Kawasaki disease
Adenovirus	Rheumatologic disease
Parvovirus B19	
HHV6 (human herpesvirus)	
Lyme (*Borrelia*)	Toxins
Cytomegalovirus (CMV)	Cocaine
Epstein-Bar virus (EBV)	Iron (hemochromatosis)
Hepatitis C	Copper (Wilson's)
Chagas (South America, presents with right heart failure)	Arsenic

Ginsberg and Parrillo [1]

thereafter, stops the inflammatory process, would not injure the myocardium in a way that would result in fulminant myocarditis. Patients with an uncontrolled immune response suffer damage to the myocardium due to persistent inflammation and ultimately progress to fulminant myocarditis [5, 12–14].

In phase 3, patients develop to chronic dilated cardiomyopathy. This end result is likely due to (1) massive damage during the initial phase, (2) persistent inflammation, or (3) no eradication of the virus leading to ongoing infection and inflammation [5, 12–14] (Fig. 5.1).

Clinical Presentation

A retrospective study performed at 7 tertiary pediatric hospitals reviewed 171 patients with myocarditis. The median age of the patients was 13.1 years (25%, 75%: 2.1, 15.9) with a bimodal distribution: 24% were less than 2 years and 46% were between 13 and 18 years [15]. Many patients present with heart failure contemporaneous with a recent viral illness. Myocarditis may present with a variety of symptoms from abdominal pain to cardiogenic shock and sudden death [1]. In a nationwide survey to determine the clinico-epidemiological features of myocarditis in Japanese children and adolescents observing initial nonspecific symptoms, fever was observed in 48%, nausea or vomiting was observed 30%, abdominal pain was observed in 9.5%, diarrhea was observed in 7.7%, and cough was observed in 17% of patients studied. Further, the study found that gastrointestinal (GI) tract symptoms – specifically nausea, vomiting, abdominal pain, and diarrhea – were more frequent than cardiopulmonary symptoms at the onset of the disease (45% vs. 25%, P = 0.01) [4]. Regarding cardiovascular manifestations at admission, this study also found congestive heart failure (CHF) was present in 36% of children, arrhythmias were present in 22%, syncope was noted in 10%, and cardiogenic shock occurred in 13% [4].

Myocarditis can be confused with acute myocardial infarction when presenting with chest pain, S-T changes on electrocardiogram (ECG), elevations of troponin, and creatine kinase-MB (CK-MB). Assessment of the coronary arteries performed by echocardiogram, computed tomography (CT) scan, and/or magnetic resonance imaging (MRI) can help distinguish myocarditis

Case Scenario

After returning from summer vacation, a 15-year-old, previously healthy girl presents to the emergency department with a 3-day history of stomach pain and vomiting and a 1-day history of labored breathing and decreased energy. One week ago, she was seen by the primary care doctor complaining of sore throat and fever. She had white spots in her posterior oropharynx. Testing for group A streptococcal infection was negative.

Her vital signs include heart rate 160 beats per minute, blood pressure 70/40 mmHg, respiratory rate 50 breaths per minute, and oxygen saturation as determined by pulse oximetry 90%. Her physical examination was notable for the following: moderate respiratory distress with rales throughout her lung fields, prominent S3 gallop auscultated on cardiac exam, liver was palpable 5 centimeters below the right costal margin, and cool and clammy extremities with diminished pulses. Her face was also notably swollen.

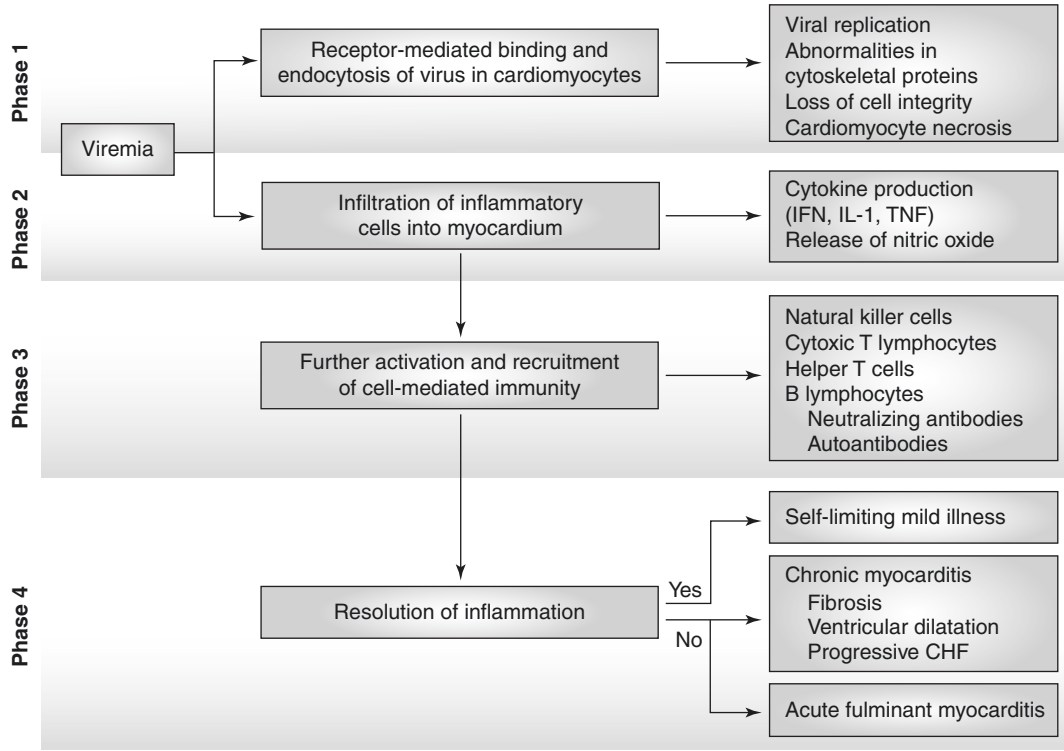


Fig. 5.1 Pathogenesis of myocarditis. Abbreviations: *CHF* congestive heart failure, *IFN* interferon, *IL-1* interleukin, *TNF* tumor necrosis factor. (Gupta et al. [5])

from myocardial infarction [16, 17]. Arrhythmias are also commonly seen as a consequence of myocardial infection and inflammation. Sinus tachycardia, atrioventricular conduction delays, and/or supraventricular and ventricular arrhythmias are the most frequent types of arrhythmias in fulminant myocarditis [17].

Diagnosis

Patients with acute fulminant myocarditis can present with tachycardia, hypotension, S3 gallop resulting from severe heart failure, elevated jugular venous pressure, facial edema, and other signs of severe heart failure including pulmonary rales and wheezing with impending respiratory failure [1]. C-reactive protein, erythrocyte sedimentation rate, troponin, and CK-MB values are frequently elevated. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide are also commonly elevated in patients with severe heart failure [1]. Most patients will have electrocardiogram (ECG) abnormalities, though typically these abnormalities are nonspecific and, in some cases, subtle (Fig. 5.2a, b). Echocardiography is essential to diagnose and quantitate regional and global left and right ventricular function, the presence of pericardial effusion, and valvular regurgitation. Importantly, fulminant myocarditis usually presents with a non-dilated left ventricle with severe systolic dysfunction as well as increased wall thickness reflecting myocardial edema. In contrast, acute but non-fulminant myocarditis presents with dilated left ventricle but normal wall thickness. Right ventricular systolic dysfunction is more common in fulminant myocarditis and can be a sign of poor prognosis [1, 17–19].

In a study to evaluate right ventricular, systolic function in patients with active myocarditis, 23 patients with biopsy-proven myocarditis were studied. The patients were divided into those with normal right ventricular function (normal right ventricular descent: the descent

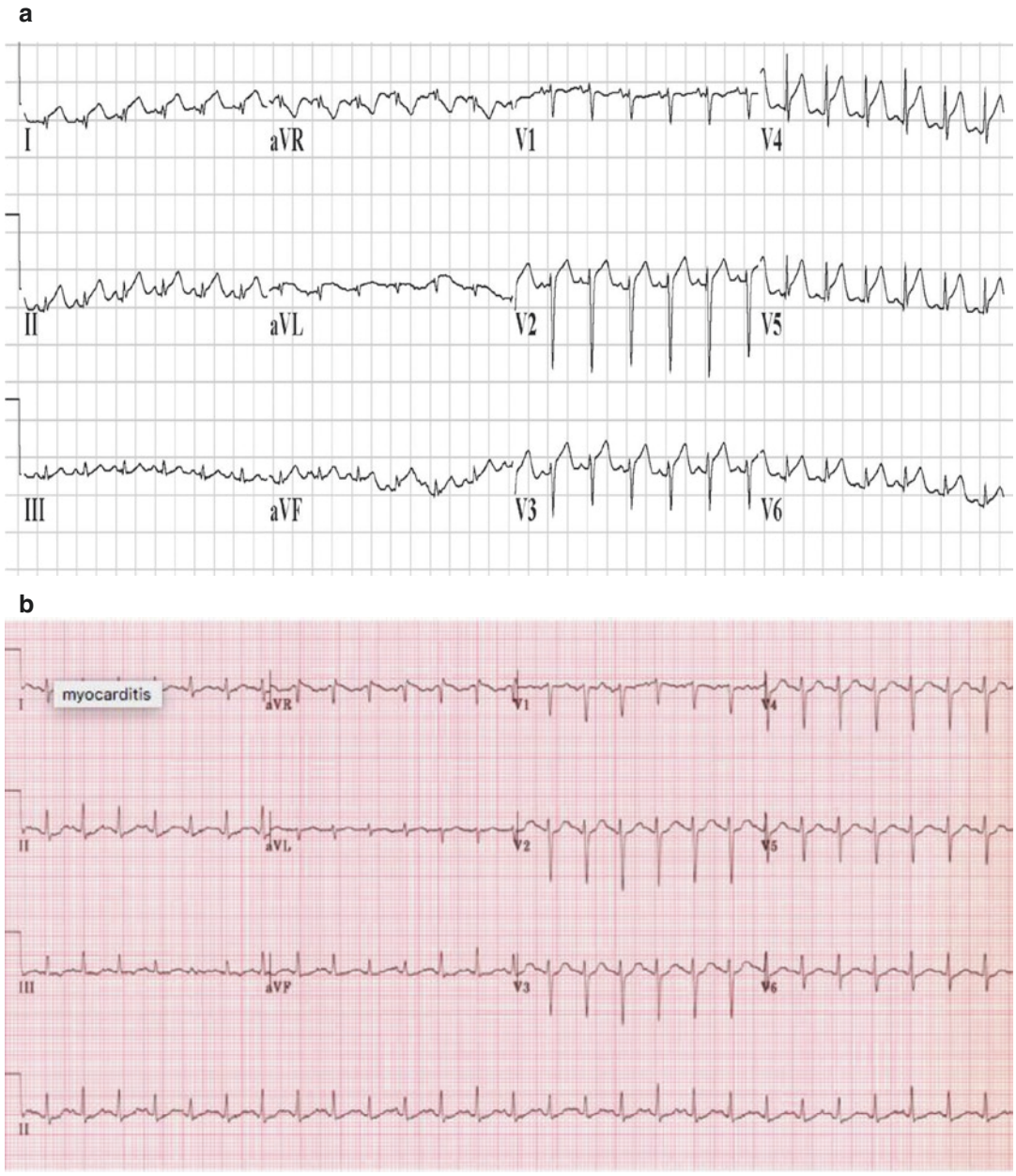


Fig. 5.2 (**a**) ECG of a patient with myocarditis demonstrating a low-voltage rhythm (requiring double standard calibration) along with diffuse, nonspecific S-T elevations, most notable in leads I, aVL, and the left precordial leads (V_4–V_6). (**b**) ECG of patient with myocarditis demonstrating subtle nonspecific S-T changes in leads II, III, and aVF

of the base right ventricle in systole of more than 1.9+/−0.1 cm) and those with abnormal right ventricular function (abnormal right ventricular descent: the descent of the base right ventricle in systole of 0.8 +/− 0.1 cm). The likelihood of an adverse outcome (defined as death or need for cardiac transplantation) was greater in patients with abnormal right ventricular function (right ventricular descent ≤1.7 cm) [19].

Cardiac magnetic resonance imaging (CMR) has been increasingly utilized as part of the diagnostic evaluation for myocarditis. CMR can evaluate anatomy and function of the right and left ventricles. In addition, CMR can evaluate the myocardium for edema, hyperemia, and fibrosis. CMR is more sensitive when performed more than 7 days after the onset of symptoms [20–23]. Because inflammation associated with myocarditis is patchy in nature, the CMR can help to guide the endomyocardial biopsy to minimize the possibility of sampling error [23]. Three CMR criteria for myocarditis include:

1. Enhancement on T2-weighted imaging consistent with edema
2. Early enhancement on T1-weighted imaging consistent with hyperemia
3. Late gadolinium enhancement (LGE) also consistent with myocardial fibrosis

Studies have demonstrated 85% diagnostic accuracy for myocarditis by CMR when any of the two criteria are present [1, 24].

The gold standard for diagnosis of myocarditis is endomyocardial biopsy [25]. The Dallas Criteria were created in order to have a standardized pathologic definition of myocarditis. This criteria requires evidence of cellular inflammatory process in the myocardium and myocardial necrosis [25]. In the last 10 years, progress in immunohistochemistry techniques has enhanced sensitivity in the detection of myocarditis [9, 14, 26]. There are disadvantages associated with endomyocardial biopsy including different interpretations by different pathologists, sampling error due to scattered focal presentation of the disease, and risk for cardiac perforation during the procedure [25]. Currently, endomyocardial biopsy is recommended in patients with fulminant myocarditis, severe ventricular arrhythmias, or advanced heart block according to recommendations in the scientific statement from the American Heart Association/American College of Cardiology/European Society of Cardiology [27]. Endomyocardial biopsy is a class I indication (condition for which there is evidence and/or general agreement that a given procedure is beneficial, useful, and effective) to differentiate lymphocytic myocarditis from giant cell myocarditis and eosinophilic myocarditis because immunosuppressive therapy is indicated in the latter two conditions [27, 28].

Case Scenario: Continued

The patient was admitted to the pediatric intensive care unit and the following studies were obtained:

- ***Chest x-ray:*** *diffuse bilateral haziness throughout the lungs fields.*
- ***Laboratory studies:*** *(normal values).*
  - *C-reactive protein 20 mg/L (<3.0 mg/dl).*
  - *Erythrocyte sedimentation 70 mm/h (0–29 mm/h).*
  - *Troponin I 3.5 ng/ml (<0.01 ng/dl).*
  - *CK-MB 40 IU/L (5-25IU/L).*
  - *Viral PCR and bacterial culture were negative.*
- ***Electrocardiogram:*** *Subtle nonspecific S-T changes in leads II, III, and aVF (Fig. 5.2b).*
- ***Echocardiogram:*** *Dilated left ventricle with severe systolic dysfunction, EF 25%. The left ventricle demonstrated increased wall thickness, as well as moderate mitral regurgitation. A mild pericardial effusion is also seen (Fig. 5.3a and b).*
- ***CMR:*** *Diffuse decrease in left ventricular function is observed. The left ventricle also demonstrated regional edema on T2-weighted imaging. A mild pericardial effusion is present (Fig. 5.4).*
- ***Biopsy:*** *It was not performed in this case. The decision not to perform endomyocardial biopsy was a clinical decision in this particular patient.*

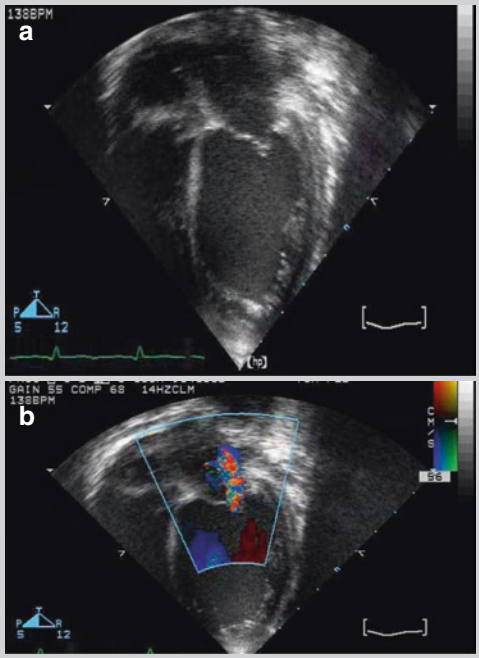


Fig. 5.3 (**a**) Fulminant myocarditis – echocardiographic image, apical four-chamber view. (**b**) Fulminant myocarditis with mitral regurgitation

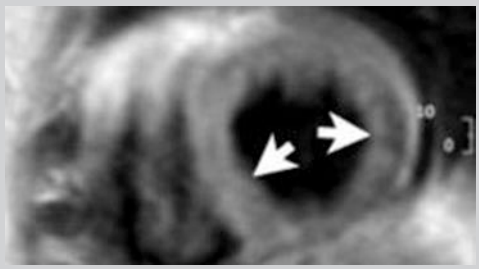


Fig. 5.4 Early contrast-enhanced cardiovascular magnetic resonance (CMR) imaging demonstrating hyperemia/edema of the myocardium in a patient with acute fulminant myocarditis

Treatment Strategies

Extremely poor ventricular function can cause fulminant myocarditis. The poor ventricular function leads to low cardiac output and heart failure. Management is tailored to alleviating the symptoms of heart failure and improving hemodynamic abnormalities. *Management strategies include:*

- *Diuretics*: Diuretics are given to treat congestion in patients with heart failure [29, 30].
- *Vasodilators*: Nitroglycerin and nitroprusside can be used in patients with high or normal blood pressure. At lower doses (range: 0.25–2 mcg/kg/min), intravenous nitroglycerin decreases systemic venous resistance, which reduces left ventricular filling pressures and pulmonary congestion. At higher doses (range: 3–6 mcg/kg/min), reduced systemic arterial resistance occurs, which reduces afterload on the left ventricle and should improve cardiac performance [31]. Nesiritide is a recombinant form of human B-type natriuretic peptide. Nesiritide increases C-GMP and therefore causes vasodilation and increases urine output. In the ASCEND-HF trial (an adult trial), nesiritide use was not associated with a decreased in mortality or rehospitalization [32]. Data in pediatric patients however suggest that nesiritide may be safe and effective when used to treat severe heart failure. It can improve diuresis, decrease filling pressures, and improve functional class [33].
- *Inotropic agents*: Patients with severe heart failure and reduced blood pressure may not benefit from vasodilators. In severe heart failure patients, inotropic agents may be necessary to maintain end-organ perfusion [29, 30]. Dobutamine stimulates β-receptors, which causes increased contractility and decreased peripheral arterial vascular resistance, but data from adult with advanced heart failure have demonstrated that dobutamine may not be helpful. Suggest that unfortunates effects with the uses of dobutamine [34]. In cardiogenic shock, the initiation of epinephrine is recommended. Epinephrine has an inotropic and chronotropic effect, which increased cardiac output and perfusing pressure. Caution must be exercised however as use of epinephrine can also cause rhythm disturbances and worsen heart ischemia due to increased oxygen demand in the myocardium. Finally, milrinone is an inotropic, an afterload-reducing, and a lusinotropic agent for the left ventricle. Milrinone can be used in the treatment of myocarditis with poor left ventricular function

and reasonable blood pressure. Caution need to be exercised in the use of milrinone in the setting of low blood pressure due to its afterload-reducing effect, which can worsen the low blood pressure.

- *Oral heart failure therapies*: Standard oral heart failure therapies such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (carvedilol), and aldosterone antagonists should be considered when hemodynamic stability improves but, in fact, have little role in the acute presentation of fulminant myocarditis.
- *Mechanical ventilation*: Patients who do not improve with medical therapy and present with worsening respiratory distress may benefit from the use of mechanical ventilation. This strategy reduces the afterload on the left ventricle and therefore improves the function of the left ventricle [35].
- *Advanced life support*: Some patients with myocarditis fail medical therapy and progress to refractory, end-stage shock with extremely poor cardiac performance. In those unfortunate patients, the only tool available may be mechanical circulatory support (MCS) to rescue the patients and bridge them to recovery or cardiac transplantation. Early deployment of circulatory support can improve end results in patients with fulminant myocarditis. In patients with fulminant myocarditis, survival rates associated with extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD) vary in different studies. In the studies reviewed, worse survival rates were typically associated with studies that were done a long time ago, that were performed in facilities with less experience, and that concerned patients with concomitant, multi-organ dysfunction [3, 6, 36–47]. In the aforementioned retrospective analysis of 514 patients with myocarditis utilizing the PHIS database, 26% died and 13% underwent heart transplantation. Ninety-five patients (accounting for 18% of the patients studied) required ECMO, and the use of ECMO was independently associated with death or transplant [3]. The Extracorporeal Life Support Organization (ELSO) Registry from 1995 to 2006 showed myocarditis as a reason for ECMO deployment in 1.3% of ECMO runs. The survival to discharge was 61% in this cohort of infants, children, and young adults [39]. In another study utilizing the ELSO database with the purpose of analyzing data outcomes of extracorporeal cardiopulmonary resuscitation (eCPR) in patients with structurally normal heart, the overall survival to hospital discharge was 32%. From this study, 20 patients presented with myocarditis, and 15 patients survived to hospital discharge [48].

Immunomodulatory treatments have also become an important part of the management of myocarditis at many centers. These therapies include:

- **Corticosteroids:** Corticosteroids decrease inflammation and temper increased capillary permeability often seen in acute myocarditis. In a Cochrane Database review of 8 randomized clinical trials (RCTs) which include 719 patients with myocarditis, there was no statistical difference in mortality in patients who received corticosteroids versus placebo. This study includes adult and pediatric patients. Patients who received corticosteroids however did have better ventricular function and lower cardiac enzyme measurements in comparison to placebo. Of note, the studies in this Cochrane Database review were determined to be of poor quality in general [42]. Further, because corticosteroids are commonly used in combination with other therapy that alter the immune system, it is challenging to isolate their benefit in the treatment of myocarditis patients from other treatments given simultaneously [49–51].
- **Immunoglobulin (IVIG)**: In the treatment of pediatric myocarditis, the use of IVIG is highly controversial. To date, much of the evidence is based on retrospective data. No randomized controlled trial (RCT) in the pediatric population has yet to be conducted. In one retrospective chart review of 171 adult patients who presented with myocarditis,

mortality, heart transplantation, and readmission did not differ between patients who received IVIG and corticosteroids in comparison to patients who did not received immunotherapy [15]. On the other hand, some smaller studies have showed significant improvement in heart function and cardiac rhythm disturbances with the use of IVIG in patients with acute fulminant myocarditis [2, 52–54]. Due to the life-threatening nature of acute fulminant myocarditis and absence of evidence of harm with these therapies, we recommend use of corticosteroids and IVIg for patients with severe clinical presentations requiring intensive care therapies such as high level of inotropic support, mechanical ventilation, or mechanical circulatory support.

- **Cyclosporine/azathioprine:** Cyclosporine inhibits interleukin-2 production, and azathioprine is a purine synthesis inhibitor. The Myocarditis Treatment Trial including 111 adult patients with histological diagnosis of myocarditis studied the role of immunosuppression in adults with myocarditis and found no benefit in the use of cyclosporine, azathioprine, and corticosteroids in comparison to conventional therapy [49]. A randomized control study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy conducted in Europe included 85 adults with virus-negative myocarditis and found significant improvement in heart function in patients who received prednisone and azathioprine compared to placebo. However, similar pediatric studies do not exist at the moment [55]. A subset of patients – patients who fail medical therapy given for a reasonable period of time (i.e., 12–24 weeks) with evidence of inflammatory cells in the myocardium and an absence of viral organisms by immunohistochemistry – may benefit from the use of cyclosporine, azathioprine, and/or corticosteroid [56]. In other words, immunomodulatory therapies in these cases should be aimed at patients with persistent inflammation but without active viral infection.

Outcomes

In a large retrospective study performed from May 2011 to November 2016, 187 patients were evaluated; the rate of in-hospital death or heart transplantation was 26% versus 0% in fulminant myocarditis versus non-fulminant myocarditis, respectively ($P < 0.0001$) [57]. The study of 514 patients with acute fulminant myocarditis from PHIS database reported a mortality rate of 7.3% [3]. A study from the Pediatric Cardiomyopathy Registry (PCMR) compared children who were

Case Scenario – Concluded

Shortly after admission to the cardiovascular intensive care unit, the patient deteriorated clinically with severe hypotension and severe respiratory distress. She was endotracheally intubated and mechanical ventilation was initiated. Milrinone and epinephrine infusions were initiated and titrated to improve perfusion. In this case, corticosteroids and immunoglobulin were administered in the first 12 h of admission to the cardiovascular intensive care unit. We administered Solu-Medrol 10 mg/kg/dose every 6 h (6 doses) and immunoglobulin 1 gram/kg/dose every 24 h (3 doses). Over the next 3 days, the patient improved and mechanical support was avoided. She tolerated weaning off mechanical ventilation by her third hospital day and continued to improve clinically, weaning off epinephrine over the next 24 h. She was then transferred to the cardiac step-down unit where milrinone was weaned off over the course of 1 week. The following week, the patient was discharged home on appropriate chronic-heart-failure medications (furosemide, captopril, and carvedilol). The patient was scheduled for follow-up in a week from the discharge date by the assigned cardiologist. Immunotherapy was not continued in this case because the patient was improving clinically on the treatment strategy.

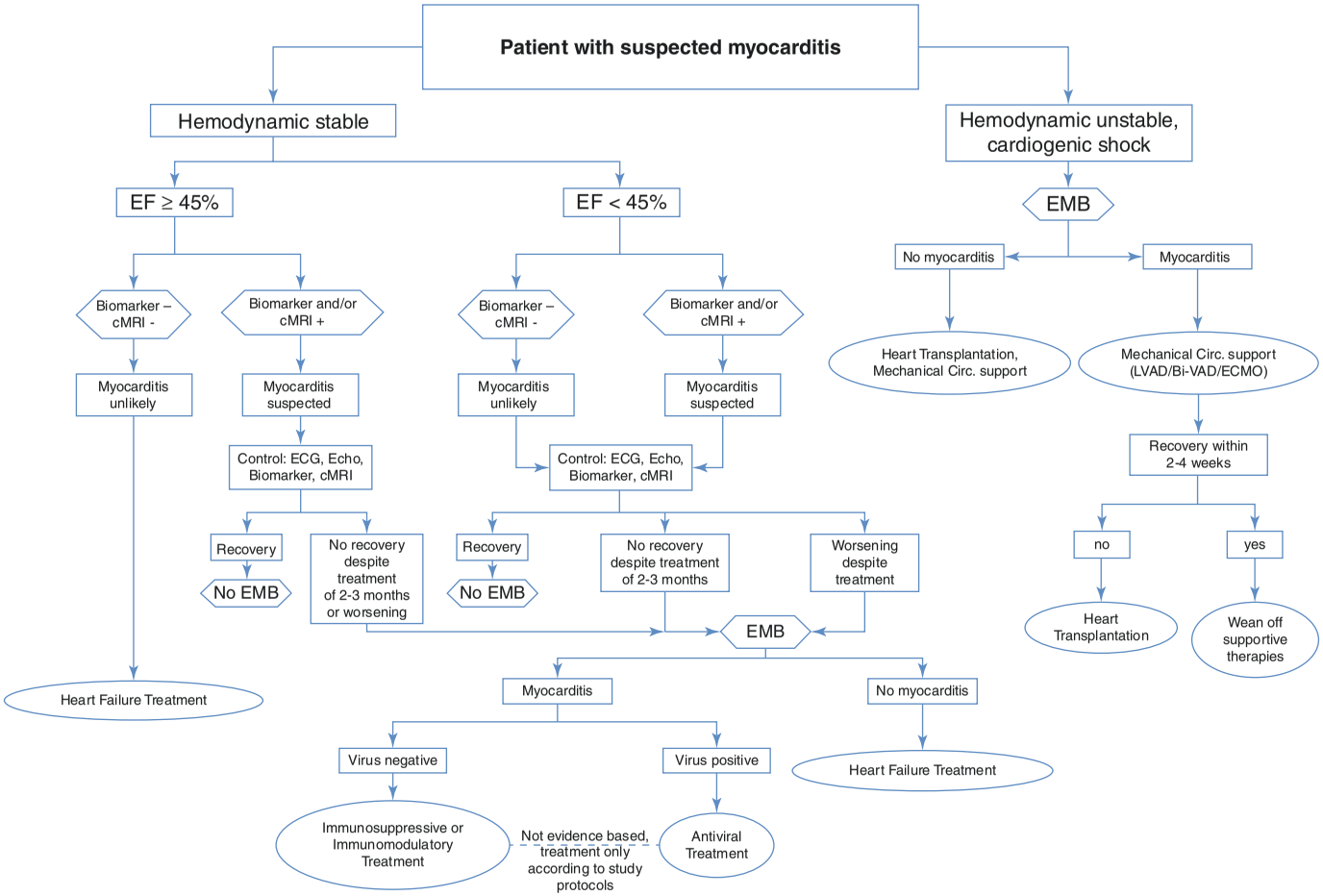
diagnosed with myocarditis clinically with or without biopsy confirmation (n = 372) to children who were diagnosed with idiopathic dilated cardiomyopathy (n = 1123). The study found better outcomes (death, transplantation, and echocardiographic normalization 3 years after presentation) in patients with myocarditis in comparison to patients with idiopathic dilated cardiomyopathy (P = 0.003) [58]. Another report, a recent retrospective chart review from 7 tertiary care pediatric hospitals that included 171 patients with myocarditis, found that patients presenting with worsening left ventricular function at admission (ejection fraction less than 30% or shortening fraction less than 14%) had higher B-type natriuretic peptide but had lower troponins at admission. The study also showed that patients with GI symptoms (42%) and patients with moderate to severe ventricular dysfunction with less than 21% and lower shortening fraction on echocardiogram (40%) were more likely to die or require transplantation. Specifically, patients with GI symptoms and/or lower shortening fraction were at increased risk for death (9.5% vs. 0%) or transplantation (16% vs. 3.3%) [15].

Summary

A reasonable approach to diagnosis and management of myocarditis has been recently published by Kindermann and colleagues, which is provided in Fig. 5.5 [59]. The diagnosis and management are dictated in large part by the clinical presentation. Patients who present with acute fulminant myocarditis requiring intensive care therapies and mechanical support should go under EMB. This step is important, as patients with fulminant cardiovascular collapse without myocarditis are unlikely to recover and, thus, may need to be considered for heart transplantation sooner rather than later. Though not included in the algorithm, we also recommend corticosteroids and IVIg as immunomodulatory therapies as discussed in the clinical case scenario for patients with acute fulminant myocarditis. For patients with less severe acute myocarditis, biomarkers (e.g., B-type natriuretic peptide, troponins), echocardiography, and CMR should be used to make the diagnosis. For these patients, EMB and immunomodulatory therapies should be considered only if clinical improvement does not occur within a reasonable period of time (i.e., 12–2 4 weeks) or the patient's condition worsens. In these cases, however, immunomodulatory therapies should be utilized only if persistent inflammation is noted without active viral infection.

Key Points

- Myocarditis is a disease characterized by inflammation in the myocardium that results in cardiac-histologic and anatomical alterations accompanied by functional derangements secondary to myocardial destruction.
- Parvovirus B19 and human herpesvirus 6 have been identified as the most frequent causes of viral myocarditis.
- Myocarditis may present with a variety of symptoms from abdominal pain to cardiogenic shock and sudden death.
- Echocardiography is essential to diagnose and quantitate regional and global left and right ventricular function, though cardiac magnetic resonance imaging (CMR) is increasingly utilized as part of the diagnostic evaluation for myocarditis.
- The gold standard for diagnosis of myocarditis is endomyocardial biopsy; CMR can inform an endomyocardial biopsy in order to avoid sampling error.
- We recommend use of corticosteroids and IVIg in patients who present with acute fulminant myocarditis, especially those patients who require mechanical support due to failure of medical therapy.
- Patients with less severe myocarditis with minimal improvement with medical therapy over a reasonable period of time warrant EMB, and those found to have evidence of persistent inflammatory cells in their myocardium and an absence of viral organisms by immunohistochemistry may benefit from the use of immunotherapy.



Proposed diagnostic and therapeutic algorithm for patients with suspected acute myocarditis considering biomarkers, cardiac magnetic resonance Imaging (cMRI), and endomyocardial biopsy (EMB). BI-VAD = biventricular assist device; Circ. = circulatory; ECMO = extracorporeal membrane oxygenation; LV = left ventricular; LVAD = left ventricular assist device.

Fig. 5.5 Proposed diagnostic and therapeutic algorithm for suspected myocarditis. Proposed diagnostic and therapeutic algorithm for patients with suspected acute myocarditis considering blomarkers, cardiac magnetic resonance imaging (cMRI), and endomyocardial blopsy (EMB). *BI-VAD* biventricular assist device, *Circ* circulatory, *ECMO* extracorporeal membrane oxygenation, *LV* left ventricular, *LVAD* left ventricular assist device. (Kindermann et al. [59]. Acknowledgment: Jack Price, MD and Kristina Jovanovic, RN)

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6 Pediatric Cardiac Transplantation and Mechanical Assist Devices

Juan M. Lehoux, Kimberly D. Beddows, and Jacqueline M. Lamour

Introduction

The number of heart transplant candidates who are listed and the number performed in children has been steadily increasing in the United States. In 2015, the number of new pediatric candidates added to the waiting list was 644, the highest number to date. There were 460 pediatric transplants performed, 16% of the total number of heart transplants in the United States, compared to 297 in 2004 [1]. Heart transplantation is the best option for children with end-stage heart disease. In the recent era, overall 1-year and 5-year survivals are 90.7% and 81.4%, respectively [2]. Improvement in perioperative management has accounted for the improved survival over the eras (Fig. 6.1). The use of mechanical assist devices has also increased tremendously over the years. Patients with a ventricular assist device (VAD) at the time of transplant have tripled from 8.8% in 2002–2005 to 24.6% in 2012–2015 [1]. There are no large, randomized, controlled trials in the management of end-stage heart disease, use of mechanical assist devices, or heart transplantation management in pediatrics. In many instances, the heterogeneous nature of the pediatric heart failure population and the small numbers relative to adult patient populations make this type of study impractical. As with other areas of pediatric medicine, we often extrapolate from adult clinical trials, large pediatric registry data, and single-center studies. We aim to discuss the current use and challenges with mechanical assist devices in the pediatric population. We will also look at some contemporary issues in pediatric heart transplantation such as immunosuppression, retransplantation, and rejection surveillance.

Overview of Mechanical Assist Devices

In 2006, there were nearly 1,400 heart failure hospitalizations in children [3]. Heart failure-related intensive care mortality in patients with cardiomyopathy has been reported at 11% [4]. When comparing patients with cardiomyopathy, mean length of stay for heart failure admission in children is significantly longer than in adults,

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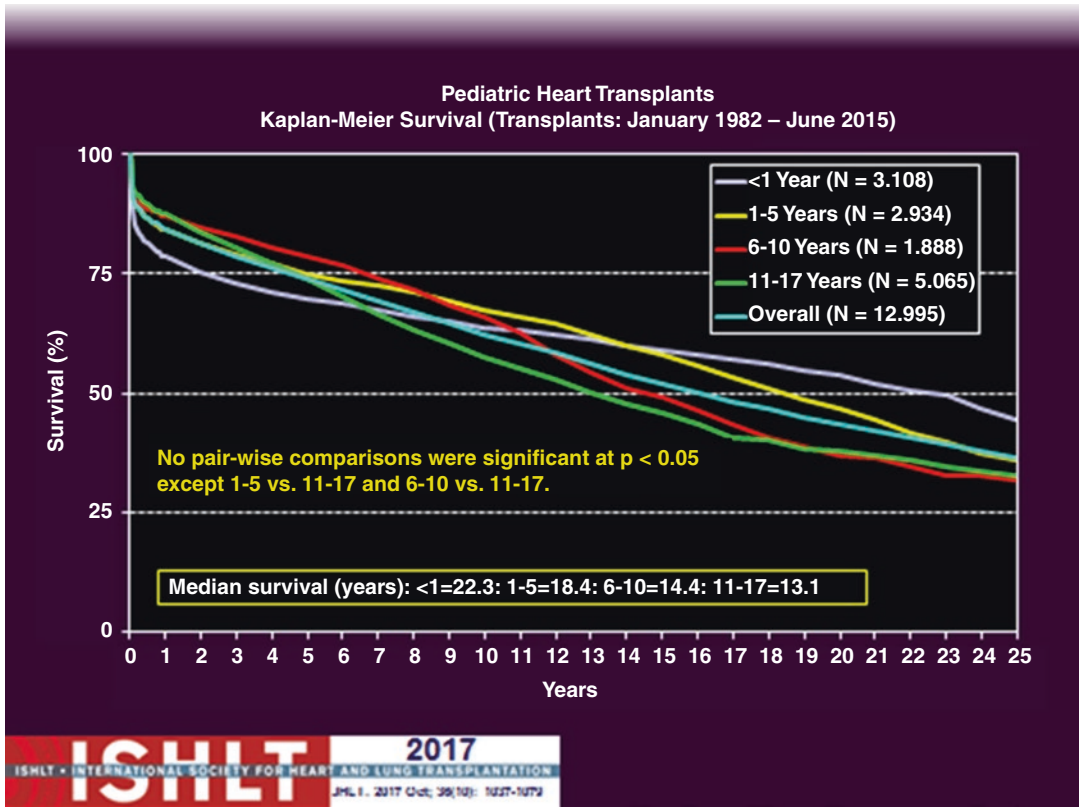


Fig. 6.1 Kaplan-Meier survival of pediatric heart transplants performed between Jan. 1982 and June 2015. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. The median survival is the estimated time point at which 50% of all of the recipients have died

16 days versus 7 days, respectively [5]. The differences in length of stay are likely related, at least in part, to the disparity in out-of-hospital options for young children as compared to adults. For instance, there are limited mechanical assist device options for children that would allow for discharged home. Although mortality rates for both pediatrics and adults with cardiomyopathy have decreased over time, overall mortality is worse in children. Infants have the highest mortality rate of any age group, including patients greater than 70 years of age [5].

The prevalence of children born with congenital heart disease worldwide is approximately 1% [6]. Advances in surgical technique in infants with congenital heart disease have palliated patients that would have otherwise died in earlier eras, but a significant proportion of these patients will develop end-stage heart failure that require heart transplantation [7]. As is the case in all solid organ transplantation, the demand for organs exceeds the supply. So, although transplant remains the best treatment option for children with end-stage heart failure, waitlist mortality remains an issue. Mechanical circulatory support provides a temporary solution to the shortage of donor hearts [8]. In the adult population, there has been significant investment by industry in the research and development of ventricular assist devices. These devices have revolutionized the treatment of advanced heart failure in adults [9]. The field of mechanical circulatory support in children has lagged behind but in the recent era has made great strides.

Pediatric Ventricular Assist Devices

ECMO

Extracorporeal membrane oxygenation (ECMO) is a method of support in which the device completely supports circulation and gas exchange. The device is commonly employed for patients with heart or respiratory failure. Depending on the indication for its use, it can be veno-venous for purely respiratory support or venoarterial for cardiorespiratory support. The contemporary ECMO circuit is composed of a centrifugal pump, a membrane oxygenator, and a heater/cooler device. Cannulas connecting the device to the patient are usually implanted into peripheral blood vessels either via surgical cutdown or percutaneously. In neonates and infants, the usual route of cannulation is via the right cervical vessels. A cutdown is made over the right lateral aspect of the neck and the carotid artery and jugular vein are then used as insertion sites for cannulas that allow inflow and outflow from the device. ECMO can also be implanted from the femoral vessels if size allows or via central cannulation for patients in postcardiotomy shock. One advantage of ECMO is that it is rapidly deployable at the bedside, allowing for salvage of critically ill patients, sometimes after cardiac arrest with cardiopulmonary resuscitation (CPR) in progress. Since ECMO cannulas can be introduced peripherally, sternotomy is avoided in these patients, simplifying subsequent operations.

ECMO support carries significant risk of morbidity and mortality that worsens as support time increases. In the Berlin Heart EXCOR Investigation Device Exemption (IDE) trial, the Extracorporeal Life Support Organization (ELSO) registry was used for historical controls. Patients were divided into two cohorts based on body surface area (BSA). No patient with a BSA < 0.7 m^2 survived longer than 21 days on ECMO, and in patients with a BSA 0.7–1.5 m^2, survival approached zero at 28 days [10]. This study highlights the unsuitability of ECMO as a long-term support strategy. ECMO should therefore be restricted to short-term (<30 days) support as a bridge to recovery, transplantation, or implant of a more durable ventricular assist device.

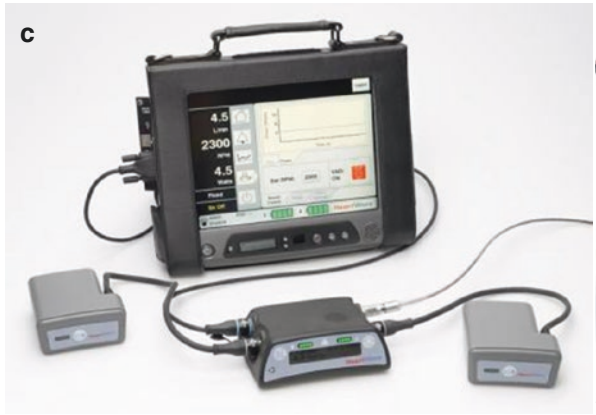
Berlin Heart

The Berlin Heart EXCOR is the only dedicated pediatric VAD that is approved for use as bridge to transplantation (Fig. 6.2a). The Berlin Heart EXCOR is paracorporeal and a pneumatically driven pulsatile ventricular assist device that can be used to support the left, right, or both ventricles. The VAD is made in a variety of sizes for use in infants, children, and adolescents. Typically the 10, 15, and 25 ml devices are used in infants and small children given that larger children are candidates for continuous-flow devices designed for use in adults with a much better side effect profile [11]. The Berlin Heart EXCOR has proven to be to be superior to ECMO support for end-stage heart failure in children. The device however is associated with significant morbidity that includes bleeding, infection, and stroke. The use of the Berlin Heart EXCOR carries an almost 30% risk of stroke with varying degrees of neurologic dysfunction [10]. Patients often require multiple pump exchanges due to thrombus formation inside the device, incurring significant cost.

Paracorporeal Centrifugal Pumps (CentriMag, PediMag)

The CentriMag and PediMag are extracorporeal blood pumps that can provide complete hemodynamic support in adults and children (Fig. 6.2b). The pumps have fully magnetically levitated rotors that minimize blood-related complications such as hemolysis. The CentriMag is designed for use in patients that are greater than 20 kg. The PediMag pump is of similar design but optimized to provide support for children that are less than 20 kg. These devices are cleared by the FDA for use in acute support situations for either ventricle (6 h) or as a right ventricular assist device (RVAD) for up to 30 days. Despite the current FDA-approved indications, these pumps are routinely

Fig. 6.2 Mechanical assist devices. (**a**) Berlin Heart EXCOR biventricular support and console with varying sizes of pumps. (**b**) PediMag device and console. (**c**) HeartWare HVAD console and pump. (**d**) Thoratec HeartMate II LVAD. (**e**) HeartMate 3 LVAD



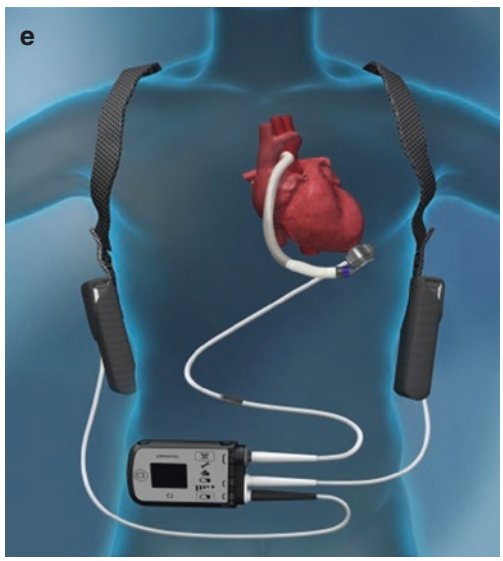


Fig. 6.2 (continued)

used off label for much longer periods as part of the ECMO circuit or as paracorporeal ventricular assist devices. Some centers, in an effort to reduce the cost associated with frequent pump exchanges often required with the Berlin Heart EXCOR, use these continuous-flow devices as an alternative. Use of the CentriMag and PediMag devices connected via Berlin heart cannulas has been described in small case series [12–14].

HeartWare HVAD

The HeartWare HVAD is a fully implantable, continuous centrifugal flow device (Fig. 6.2c). The pump's only moving part is a magnetically stabilized rotor. A single drive line exits the body and connects to an external controller device and batteries. There are no mechanical bearings making it highly durable. The device has been extensively used as bridge to transplant in adults and has recently been approved for destination therapy [15]. Given the better side effect profile associated with continuous-flow devices versus older pulsatile flow pumps, the HVAD is preferred to the Berlin Heart EXCOR in larger children. Though designed to be used in adult patients, the use of the HeartWare HVAD is possible in children with BSA greater than 0.6 m^2 with modifications to the implant technique (i.e., preperitoneal pocket vs. intra-pericardial) [16]. Patients and their guardians can be trained in the day-to-day management of the HVAD. Children supported with this device have been able to go to school and lead a relatively normal life while waiting for heart transplantation.

Thoratec HeartMate II

The Thoratec HeartMate II LVAD is a fully implantable left ventricular assist device approved for use as both bridge to transplant and destination therapy (Fig. 6.2d). The device features an axial rotor supported by ruby bearings and can provide up to 10 liters of blood flow per minute. The HeartMate II has been approved for use in adults since 2008 and has been implanted in over 20,000 patients. In the adult population, the HeartMate II has been shown to improve both survival and quality of life with an improved side effect profile, when compared to older pulsatile designs [7]. The device is implanted via a median sternotomy and placed in a surgically created preperitoneal pocket. A single drive line exits the abdomen and connects the device controller and batteries. Due to its size, this device can only be used in adult-sized patients (BSA greater than 1). Despite the decreased incidence of adverse events compared to older, pulsatile devices, there are still significant issues with morbidity associated with this device including stroke, gastrointestinal bleeding, intractable drive line infections and pump thrombosis [17].

Thoratec HeartMate 3

The HeartMate 3 LVAS (left ventricular assist system) is the most recent ventricular assist device approved for use as bridge to transplant (Fig. 6.2e). The device, which features a completely magnetically levitated rotor that provides wide spaces for blood flow, is designed for improved hemocompatibility and reduced pump-related morbidity. The HeartMate 3 has proven to be highly resistant to pump thrombosis. Its design and reduced size makes it easier to implant [18, 19]. Given its proven benefits and recent approval as bridge to transplant, the HeartMate 3 is our device of choice in the adolescent population. The HeartMate 3 is larger than the HeartWare HVAD, which may make implant in smaller children more challenging.

Decision-Making in Pediatric Mechanical Support

Adequate decision-making plays a significant role in mechanical circulatory support. Despite recent advances in technology, the use of invasive devices is associated with significant morbidity and mortality and must be weighed against continued medical management with potential further deterioration and end organ damage [9]. In

the adult population, given the availability of newer-generation devices with a more favorable side effect profile, the decision to proceed with VAD implant is simplified. In the current era, continued medical management in the setting of worsening functional status and end organ dysfunction is no longer indicated and, furthermore, is associated with worse outcomes even if implant of a VAD is eventually undertaken. Dependence on intravenous inotropic support is the usual indication that prompts VAD implantation. There are, of course, some exceptions to this rule, such as favorable blood type with short transplant wait times in the bridge-to-transplant patient.

In pediatrics, the decision to proceed with VAD implantation is complicated by several factors including patient size, device availability, blood type, expected transplant wait time, etiology of heart failure, and overall condition of the patient. There is significant variability in practice across the world that considers the abovementioned factors with no approach being supported by evidence. Decisions on the use of mechanical support in the pediatric patient with heart failure must therefore be based on physician experience and sound physiologic rationale.

Patient Size

Small Children (BSA < 0.6 m^2)

There are limited mechanical support options for small children in heart failure [20]. ECMO is commonly used in conjunction with CPR (ECPR) or when short duration of support is anticipated. Long-term mechanical support options currently available are the Berlin Heart EXCOR and the PediMag LVAD connected to Berlin Heart cannulas. Due to the limited options and high morbidity associated with mechanical support in small children, we seek to minimize the child's exposure to a device as long as it is reasonable to do so. In children who are less than 5 kg, every attempt is made to delay VAD implantation. Pulmonary artery banding has been reported as a temporizing measure for patients with dilated cardiomyopathy with preserved right ventricular function [21]. Banding the pulmonary artery will increase the right ventricular pressure and shift the interventricular septum leftward. This reconfiguration of the septum can reduce mitral regurgitation by reducing mitral valve annulus diameter and reportedly improve cardiac output. Pulmonary artery banding in very small children with dilated cardiomyopathy may be an acceptable alternative to VAD allowing the child to grow to sufficient size for a safer VAD implantation or to be transplanted [21].

A comprehensive evaluation to rule out reversible causes of heart failure accompanied by multidisciplinary management discussions should take place for every child admitted in heart failure. If deterioration progresses despite inotropic support, mechanical ventilation is the next step in escalation of care. Intubation should be done in a controlled setting with surgical consultation immediately available should ECPR need to be deployed. It is not uncommon for a child whose status is deteriorating to arrest while attempting intubation. In this scenario, ECPR with prompt restoration of cardiac output can be lifesaving [22]. Mechanical ventilatory support decreases cardiac preload and afterload in the failing heart and also reduces the effort made by a child with limited cardiopulmonary reserve [23]. Ventilator dependence should trigger VAD implantation, with the goal of liberation from mechanical ventilation. Long-term mechanical ventilation and its required sedation cause progressive deconditioning, which can affect posttransplant outcomes. Being on mechanical ventilation is a known risk factor for poor outcome after heart transplantation [24, 25]. Successfully implanting a durable VAD that restores adequate cardiac output and allows the patient to be mobilized, rehabilitate, and gain weight is worthwhile despite the risks of surgery.

Right heart catheterization can be helpful in assessing the right heart function prior to implantation but should be weighed against the risk. Echocardiographic evaluation of the right heart can often lead to concerns of post-VAD implant right heart failure. Because of high left-sided filling pressures and high pulmonary artery pressures, the right heart can appear to be severely

dysfunctional. Once the LVAD is implanted and the filling pressures of the left ventricle improve, often what appeared to be a failing right ventricle can provide adequate cardiac output to fill the left-sided device. There is evidence that the use of biventricular VADs (BiVADs) is associated with worse outcomes [26]. Avoidance of biventricular support at all costs however is also ill advised. A child struggling in low cardiac output due to RV failure after VAD implantation can develop worsening end organ dysfunction. With the Berlin EXCOR, evidence of LVAD under filling, low cardiac output, and high right-sided filling pressures should prompt RVAD implant as soon as possible. Under filling of the left-sided device also causes wrinkles to form on the pump diaphragm, providing a nidus for clot formation even if anticoagulation is adequate. Clot formation increases the risk of embolus and its associated neurologic and vascular complications.

When right heart function is marginal, under filling of the Berlin Heart EXCOR can occur, increasing the risk of pump thrombosis and its associated morbidities including stroke. For this reason, some centers will implant the Berlin Heart EXCOR cannulas in the usual fashion and connect a PediMag continuous-flow pump instead of the pulsatile Berlin Heart EXCOR when RV dysfunction is present. This approach allows the patient to recover from the initial postoperative right ventricular dysfunction without the associated risk of an under-filled Berlin Heart EXCOR device. Once the child is extubated, the marginal right ventricular function usually improves, allowing for the patient to be transitioned to a Berlin Heart EXCOR device for long-term support. It is important to note that this approach requires close monitoring for progressive right ventricular dysfunction. Marginal LVAD flows with evidence of end organ dysfunction in the setting of right ventricular dysfunction should prompt RVAD implant before further clinical deterioration ensues.

Key points in small children (BSA < 0.6 m²):

- *VAD team evaluation once inotropic support is started.*
- *VAD implant if ventilator dependent.*
- *Avoid BiVAD implant if possible.*
- *Do not delay in RVAD implant if evidence of right heart dysfunction develops post LVAD implant.*

Larger Children (BSA > 0.6 m²)

Children whose body surface area is >0.6 m² become candidates for the HeartWare HVAD. This device, as described above, is designed for use in adults and approved for long-term support. In adults, the HVAD has a significantly better side effect profile than older paracorporeal pulsatile devices that are designed similar to the Berlin Heart EXCOR [11]. In pediatrics, there has been great interest in using continuous-flow devices in the hope of replicating the results seen in adults. There is currently little evidence to support using implantable continuous-flow devices rather than the Berlin Heart EXCOR, but given the reduced incidence of adverse events reported in the adult literature, many centers favor VAD implant earlier in the disease course [27]. It is our practice to consider implant of the HeartWare HVAD in larger children as soon as the child becomes dependent on one or more positive inotropic drugs (e.g., milrinone, dobutamine, etc.). Regional wait times, blood type, and overall condition of the patient will factor into the decision to implant the device or to continue to wait for transplant on inotropic infusions. Restoration of adequate cardiac output before the onset of end organ dysfunction has been shown to improve VAD outcomes in adults. The HeartWare HVAD is connected via a single drive line to a small controller and batteries. This design makes it possible for patients to resume many normal activities that improve the physical and psychological condition of the child. Implant of the HVAD is not free of the complications that affect all newer-generation continuous-flow devices such as drive line infections, gastrointestinal bleeding, and stroke. Despite these possible complications, it is thought that the benefits of earlier VAD support outweigh these concerns. It is not inconceivable that as VAD technology improves and adverse effects decrease, VAD

implant will become an option for patients who are in significant heart failure but not yet inotrope dependent.

Adult-sized adolescents can be implanted with any VAD currently on the market. The HeartMate 3 device was recently approved as a bridge-to-transplant device. The HeartMate 3 device has been designed for improved hemocompatibility in an effort to reduce adverse events. The device has been widely used in Europe and has been implanted may times in the United States as part of the Momentum 3 trial [18]. In both the European and US experience with this device, there has been a dramatic reduction in pump thrombosis and need for pump exchange. Pump thrombus has been a significant source of morbidity and mortality in patients supported on VADs. The resistance to thrombosis demonstrated by the HeartMate 3 LVAD opens up exciting possibilities for future changes in the anticoagulation management that will hopefully decrease the rate of bleeding complications. FDA approval of the HeartMate 3 makes it our device of choice in adult-sized adolescents over the older HeartMate II.

Key points in larger children (BSA > 0.6 m^2):

- *Implant when patient is dependent on inotropic infusions.*
- *Use centrifugal continuous-flow devices.*
- *HeartMate 3 preferred device when the child's BSA is greater than 1 (i.e., adult size) due to its relative resistance to pump thrombosis.*
- *May discharge home on VAD support with adequate patient and caregiver education.*

Anticipated Duration of Support

Bridge to Recovery

Heart failure due to a potentially reversible etiology, like viral myocarditis or arrhythmia-induced cardiomyopathy, is often treated with mechanical support once medical management becomes untenable. ECMO support provides adequate short-term support and avoids more invasive options. In patients with surgically correctable conditions, central ECMO cannulation for post-cardiotomy shock avoids cannulating the ventricle as is frequently necessary for VAD implant. If a reasonable period of time (1–2 weeks) has passed with little evidence of recovery, then alternate, longer-term support options should be discussed. Conversion to a long-term VAD while awaiting transplant will depend on the anticipated wait time on the heart transplant list. Centers must take regional and patient-specific factors into account when deciding when to abandon the short-term support strategy in favor of a longer-term device.

Bridge to Transplant

In patients whose heart failure etiology is unlikely to recover, VAD implantation is done as a bridge to transplantation. The benefits of VAD support while awaiting transplant are significant in both the adult and pediatric population [28]. A common scenario is a child with heart failure who acutely deteriorates and requires emergent ECMO cannulation or ECPR. Once the child is hemodynamically stable on ECMO and recovery of end organ dysfunction has been proven, the decision between waiting for heart transplantation on ECMO and transitioning the patient to a more durable VAD must be made. The decision will depend on several factors. Blood type can significantly affect wait times. If the child is a candidate for ABO-incompatible heart transplant or if the blood type is AB, which are associated with the shorter wait times in some regions, it may be reasonable to avoid the insult of VAD implant. Wait times also vary widely by geography, and because listing across blood groups in infants is an accepted practice, listing across blood groups does not necessarily shorten waitlist times. It is important to be familiar with the local organ procurement organization (OPO) to assist with decision-making and estimate wait times. If the anticipated wait time is greater than several weeks, it is reasonable to transition the patient to a durable VAD.

Once the VAD is implanted, the physiological impact of the procedure must be evaluated to

decide when to activate the patient on the transplant list. Some centers will inactivate recently implanted patients for several weeks to wait for recovery. We believe that the decision to make a recently implanted patient active on the transplant list must be made on a case-by-case basis. In a small child recently implanted with a Berlin Heart, who is doing well several days post implant with no evidence of end organ dysfunction, significant inflammation, or fluid retention, it is reasonable to proceed with transplant if an adequate heart becomes available. The risk of continued exposure to the VAD should be weighed against the risk of performing a heart transplant on a debilitated patient who has just undergone a major operation. In older patients who have been implanted with a continuous-flow device, it is reasonable to wait a longer period before reactivation on the transplant list. The lower risk of adverse events with newer continuous-flow devices shifts the risk/benefit analysis toward waiting for the patient to recover and transition from a catabolic to an anabolic state.

Destination Therapy

In patients who are not candidates for transplantation but are suffering from heart failure, there are several devices that are FDA approved for long-term support. In the pediatric population, destination therapy is not a common indication for implant. There are several reports of implants in patients with progressive degenerative conditions that disqualify them for heart transplant [29, 30]. These cases have so far been the exception rather than the rule. We expect that as device technology improves, destination therapy may become a viable alternative to heart transplantation in pediatric patients.

Special Circumstances

Ventricular Assist Device Therapy in Functional Single Ventricles

There has been limited enthusiasm for VAD therapy as bridge to transplant in single-ventricle patients in various stages of palliation. Studies have shown dismal outcomes when single-ventricle patients with shunt physiology undergo VAD therapy, with slightly better results in patients that have undergone second and third stage of the single-ventricle palliation [31]. Given the available evidence, we would not offer VAD therapy to a single ventricle before the last stage of palliation. In these cases, we would support the patient with ECMO as bridge to transplant. In patients with failure of the Fontan circulation, if VAD therapy is being considered, it is critical to determine the mechanism of failure. Cardiac catheterization should be performed to document the ventricular filling pressure and confirm anatomy. If the patient has failed Fontan physiology with normal ventricular filling pressure, a VAD implant is unlikely to improve outcomes and the patient should be transplanted. If there is high ventricular filling pressure, then a VAD may improve the patient's symptoms [32].

There are other risk factors and comorbidities that have to be considered when considering VAD placement in a Fontan patient as a bridge to transplant. Multiple sternotomies cause significant scar formation that can make the operation technically challenging. Patients with failing Fontan physiology are also commonly debilitated by protein-losing enteropathy and have limited immunologic and hepatic reserve to tolerate the insult of a major operation. Due to these potentially complicating factors, VAD therapy has not become commonplace as a bridge to transplant in this population, even if there is objective evidence of possible benefit. Multidisciplinary evaluation that includes cardiology, cardiac surgery, hepatology, and anesthesia should be completed before any surgical procedure is undertaken.

Anticoagulation After VAD Implant

Management of anticoagulation while on mechanical support is a critical component to achieve good outcomes and avoid complications [33]. In older children implanted with continuous-flow devices, the anticoagulation strategy is similar to the adult patient. A heparin infusion is started 24–48 hours post implant after

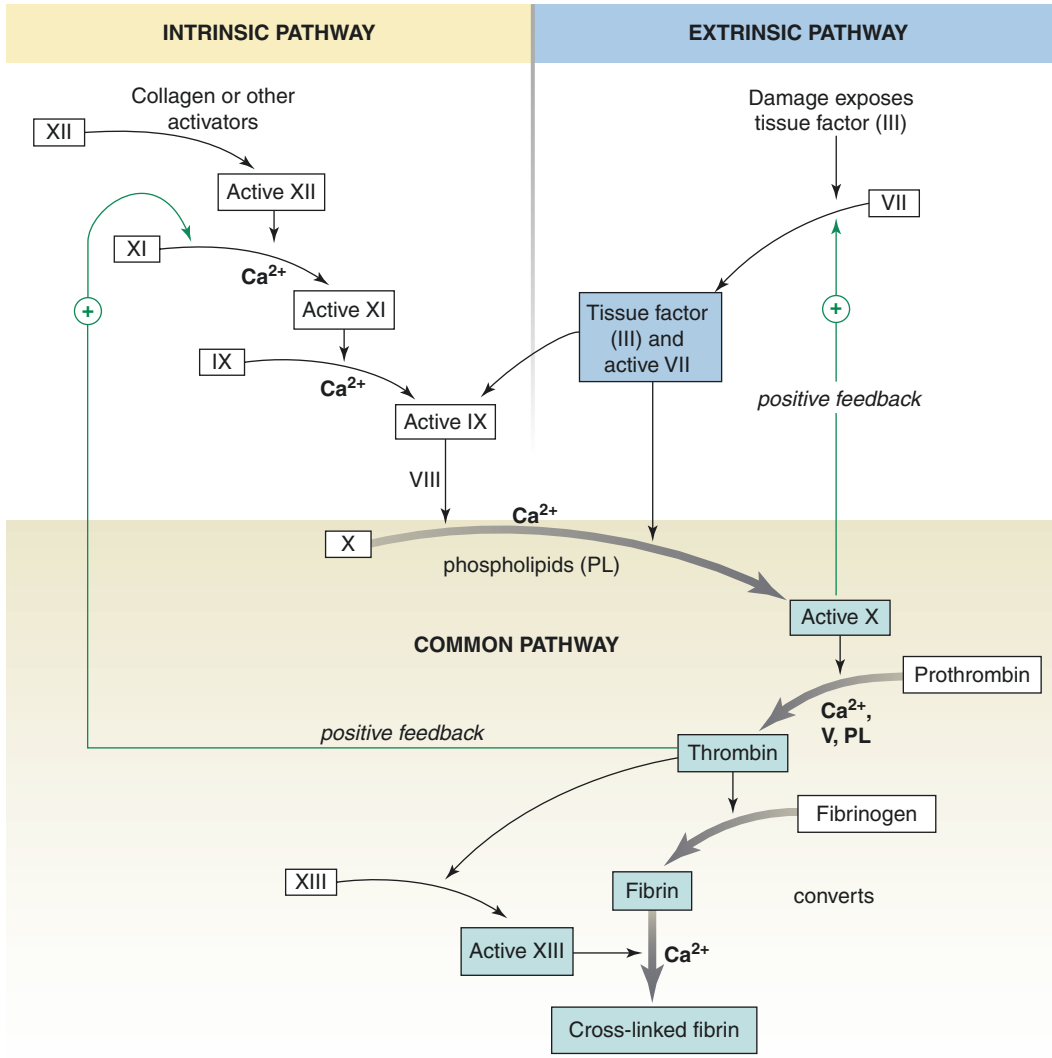


Fig. 6.3 Clotting cascade

postoperative bleeding resolves. Heparin binds to the enzyme inhibitor antithrombin III which then inactivates thrombin and factor Xa. Aspirin is started 48–72 hours after the patient returns from the operating room. Aspirin irreversibly blocks the formation of thromboxane A2 in platelets preventing platelet aggregation for the life of the affected platelet. Warfarin is then started in preparation for discharge once the patient is tolerating a regular diet. The international normalized ratio (INR) goal is 2–3. Warfarin inhibits the synthesis of clotting factors II, VII, IX, and X in addition to regulatory factors, proteins C and S (Fig. 6.3).

Smaller children supported with the EXCOR device are especially prone to embolic complications primarily because the pumps must be run at lower rates. Lower flow through the device makes thrombus formation more likely. In this high-risk population, management of anticoagulation postoperatively is especially important. In young patients, anticoagulation is challenging for a variety of reasons. Hemostasis is a complex process involving many proteins, and the level of proteins

involved in hemostasis changes significantly with age. An example of this variation is the enzyme inhibitor antithrombin III (AT3). In children, normal AT3 levels are less than 50% of adult levels. This relative AT3 deficiency can pose a challenge, given that AT3 is the pharmacologic target of heparin, the most commonly used anticoagulant for VAD patients both intra- and postoperatively. Because of these developmental variations in hemostasis, clotting and bleeding can be unpredictable.

Once anticoagulation is started, monitoring practices vary widely. Many tests are often ordered with sometimes contradictory results. Adding to the difficulty, it is unclear what value of a given test indicates adequate anticoagulation therapy in the pediatric population [34]. Early in the Berlin Heart IDE EXCOR trial, a protocol was put in place to standardize the management of the anticoagulation across all patients in the trial (Tables 6.1 and 6.2). Referred to as the Edmonton protocol, it is still the standard for the management of anticoagulation for patients on the EXCOR VAD [33]. Despite the use of a standardized anticoagulation protocol, the Berlin Heart IDE trial had very high rates of stroke, pump thrombosis, and bleeding. These complications are related to multiple patient and device factors including size and design of the pump. Surgeons depend on heparin anticoagulation for cardiopulmonary bypass and are therefore familiar with the drug and comfortable with its use in children. Unfractionated heparin has important downsides when used in the pediatric patient. The reason heparin is called unfractionated is because it has molecules of varying sizes in a single vial. Because of the variable molecular size, there is variable activity of the molecule against thrombin and factor Xa. The amount of the 18-saccharide unit that is active and binds to AT3 is variable. Heparin also has a propensity to adhere to positively charged plasma proteins that can alter the bioavailability of the drug. All these factors make for a nonlinear response to heparin dosing. Chronic exposure to heparin also causes osteopenia in already debilitated children and, although less common than in adults, can cause heparin-induced thrombocytopenia (HIT) [35, 36].

The challenges that arise when using heparin as the principal drug in an anticoagulation regimen have prompted some in the field of pediatric heart failure and mechanical support to try alternate strategies with more predictable drugs. VanderPluym et al. have championed the use of direct thrombin inhibitors in mechanically supported children [36]. The ideal alternate to heparin would be a drug that is reliable, with highly predictable dosing, fast onset, and a short half-life. Ideally, the drug would not require other factors or plasma proteins to get the job done and would not be impacted by renal or hepatic dysfunction. Direct thrombin inhibitors meet most if not all of these requirements. The most commonly used direct thrombin inhibitor in mechanically

Table 6.1 Edmonton antiplatelet protocol for Berlin Heart EXCOR

	Initiation parameters	Goal antiplatelet
>48 hrs	Plt > 40,000 ADP inhibition <70% MAckh>56 mm	Start dipyridamole (4 mg/kg/day divided in 4 doses) titrate to TEG ADP inhibition
4–7 days	All drains removed AA inhibition <70% MAckh >72 mm	Start ASA (1 mg/kg/day divided in 2 doses) titrate to TEG AA inhibition

Plt platelets, *ADP* thromboelastography adenosine diphosphate pathway, *AA* thromboelastography arachidonic acid pathway, *MAckh* maximum amplitude, citrated blood sample activated with kaolin and heparinase, *ASA* acetylsalicylic acid; aspirin

Table 6.2 Edmonton anticoagulation protocol for Berlin Heart EXCOR

	Initiation parameters	Goal anticoagulation
24–48 hrs	Plt > 20,000, TEG MA > 46	Start UFH, goal anti-Xa 0.35–0.5
2–4 days	No bleeding, normal renal function	Transition Lo LMWH eventual anti-Xa 0.6–1
>1 week	>12 months old, no bleeding, tolerating enteral feeding	Warfarin with goal INR 2.7–3.5 bridge with LMWH if INR < 2.7

Plt platelets, *MA* maximum amplitude, *TEG* thromboelastography, *UFH* unfractionated heparin, *LMHW* low molecular weight heparin, *INR* international normalized ratio

supported children has been bivalirudin. Bivalirudin directly inhibits thrombin, which in turn is responsible for cleaving fibrinogen into fibrin and activating factor XIII, which stabilizes a thrombus by fibrin cross-linking. Bivalirudin has linear pharmacokinetics, with a dose- and concentration-dependent activity in prolonging the activated clotting time (ACT), activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time. It has quick onset with almost immediate effect and does not bind to plasma proteins. Bivalirudin does not depend on AT3. The drug is also metabolized by proteolysis and less than 20% of it is excreted by the kidney. The half-life of the drug is 25 min, which mitigates some of the concern about the lack of antidote. In the case of significant bleeding or prior to a procedure, turning off the infusion is usually sufficient for reversal of anticoagulation. Like all drugs however, bivalirudin has several associated risks. Renal dysfunction will increase its half-life. When on bivalirudin, blood stasis must be avoided; proteolysis will degrade the drug in static blood and allow clotting. If a procedure in which stasis is expected such as a pump weaning trial, transition to heparin anticoagulation should be strongly considered. For unclear reasons, chronic use of bivalirudin requires increasing the dose over time. Although there is no antidote for the drug, fresh frozen plasma (FFP) and activated factor VIIa may be used if life-threatening bleeding were to occur. The need to reverse bivalirudin acutely is rarely necessary due to its short half-life, though half-life will be prolonged in patients with severe renal dysfunction. Importantly, bivalirudin is dialyzable.

There is experience in using bivalirudin in mechanically supported children. Bivalirudin has been used successfully in children on ECMO when there is concern for HIT and when anticoagulation with heparin becomes difficult, which can be indicated by increasing doses to maintain adequate anticoagulation or the need for multiple doses of AT3. In some published series, the use of bivalirudin on ECMO has shown no difference in rates of thromboembolism or bleeding compared to heparin [37]. The drug has also been used successfully during cardiopulmonary bypass for adults and children with HIT [38–40]. Experience with the use of bivalirudin with the EXCOR is limited but so far encouraging. Rutledge et al. reported six patients supported with the Berlin Heart EXCOR. These patients were switched to bivalirudin due to heparin-associated complications including HIT and pump thrombosis. In this small series, one patient had a stroke with complete recovery. The rest of the patients had no complications while on the drug and five were successfully transplanted [41]. Studies are actively underway to definitively confirm the superiority of direct thrombin inhibitors over the Edmonton protocol. There is currently no set pediatric dosing for bivalirudin in these clinical scenarios. The Boston group recommends a bolus (0.1–0.2 mg/kg) if urgent increase in anticoagulation is needed followed by ACT measurement [36]. If the ACT is greater than 225 seconds following the bolus, an infusion is started at 0.15–0.5 mg/kg/hr, always starting at lower doses in patients with renal dysfunction. Once bivalirudin is initiated, therapy is titrated based on aPTT measurements, with target levels of 1.5–3 times that of baseline measurements, depending of the patient's individual risk of bleeding (e.g., within the early postoperative period, abnormal platelet function) versus clotting risk (e.g., fibrin visible in the pump, systemic infection with increased inflammation). All bleeding must stop in the early postoperative period before starting bivalirudin. Once the infusion is started, an aPTT is measured. The aPTT is also measured every 4 h after dose change. Checking daily aPTT and INR is recommended, in addition to weekly thromboelastography (TEG) with platelet mapping, lactate dehydrogenase, C-reactive protein, and full coagulation studies (Table 6.3) [36].

Heart Transplantation

Early posttransplant survival has improved over the eras. Infant and adolescent median survivals are 22.3 and 13.1 years, respectively (Fig. 6.1). Patients who survive the first year after transplant have a median survival of 15 years in all age groups [2]. As survival improves, the focus in

Table 6.3 VanderPluym et al.'s recommendations for starting and titrating bivalirudin

Bivalirudin dosing	Starting bolus	Starting infusion dose
	0.1–0.2 mg/kg	0.15–0.5 mg/kg/hr
Bivalirudin monitoring and titration		
aPTT results	**Adjustment**	
1–15 seconds out of target range	+/−0.2 mg/kg/hr. from initial infusion rate	
16–30 seconds outside of target range	+/− 0.5 mg/kg/hr. from initial infusion rate	

VanderPluym [36]

pediatric transplant medicine can change to find ways to enhance long-term survival and improve quality of life by decreasing the morbidity that is inherent with this therapeutic modality.

Immunosuppression

Immunosuppression is the mainstay of transplantation management, but each of the drugs used can have adverse effects (Table 6.4). Combinations of drugs that have evolved over the years have decreased the incidence of rejection while minimizing toxicity by avoiding the need to use high doses of any single drug. However, it is difficult to say which regimen is ideal due to lack of pediatric randomized, controlled trials. Without such trials, we cannot adequately account for selection bias and the numerous covariates that affect transplant outcomes. Clinical practice has changed over the years as newer drugs that are more immunosuppressive with less cosmetic side effects or that target different inhibitory pathways of T- and B-cell replication have become available. The 2017 International Society for Heart and Lung Transplantation (ISHLT) registry report shows that over the eras, cyclosporine and azathioprine use has decreased, while tacrolimus and mycophenolate mofetil (MMF) use has increased. Similarly, as more pediatric studies suggest that induction therapy may decrease risk of early rejection while not increasing the risk for infection and malignancy, its use in clinical practice has changed [42, 43]. In the recent era, 70% of pediatric heart transplant recipients received some form of induction therapy with the majority of patients receiving anti-thymocyte globulin. Despite the changes in clinical practice, no survival benefit has been shown with any of these changes [2].

Table 6.4 Adverse effects of immunosuppression

Drug	Adverse effects
Tacrolimus	Hyperkalemia, hypomagnesemia, hyperglycemia, metabolic acidosis, elevated transaminases, nephrotoxicity, tremors, hypertension, headaches, leg cramps, hair loss
Mycophenolate	Myelosuppression, gastrointestinal side effects, headaches, viral reactivation infections (CMV, EBV), lymphoma, pregnancy loss, and fetal malformations
Cyclosporine	Hyperkalemia, hypomagnesemia, hyperglycemia, metabolic acidosis, hyperlipidemia, hypertension, nephrotoxicity, tremors, seizures, gingival hyperplasia, hypertrichosis
Sirolimus	Gastrointestinal side effects (nausea, diarrhea, stomach cramps), hyperlipidemia, proteinuria, impaired wound healing, mouth ulcers, myelosuppression, elevated transaminases, pneumonitis, headaches, acne, leg cramps, hypertension
Azathioprine	Myelosuppression, gastrointestinal side effects, elevated transaminases, rash
Prednisone	Hypertension, hyperglycemia, gastrointestinal side effects, weight gain hirsutism, edema, irritability, insomnia, acne, osteoporosis, growth suppression, poor wound healing, adrenal suppression

Given the side effects of corticosteroid use, not using them for chronic therapy would be preferable. Since the 1980s, single-center series have reported low rejection rates and comparable survival outcomes to registry data using steroid avoidance maintenance regimens [44–46]. Each of these reports, however, had different immunosuppression protocols – some varied over time within the same center and used echocardiography as the primary surveillance tool for detection of rejection. Moderate cellular rejection by endomyocardial biopsy is not necessarily associated with echocardiographic changes and therefore may underestimate cellular rejection [47].

More recently, Singh et al. reported on 55 consecutive patients from 2 centers who received the same immunosuppression protocol consisting of induction with thymoglobulin and a maintenance regimen of tacrolimus and MMF. Rejection surveillance used endomyocardial biopsy at frequent intervals during the first year posttransplant. An 87% freedom from rejection at 1 year was reported, which at the time was lower than that reported in the International Society for Heart and Lung Transplantation (ISHLT) registry. There were 15 patients considered not eligible for the protocol at the time of transplant due to high risk of antibody-mediated rejection. Excluding these patients may have lowered the incidence of early rejection in this cohort. This report was the first dual center study in pediatric heart transplantation to have a standardize immunosuppression protocol and rejection surveillance. Auerbach et al. (2014), using the Organ Procurement and Transplantation Network (OPTN) database and the Pediatric Heart Transplant Society (PHTS) database, used propensity matching to mimic randomization and were able to show no difference in graft survival between steroid-free patients and those on maintenance steroids at 1 year [48]. As is frequently the case with large registry databases, the comorbidities of steroid use, such as hypertension and diabetes, were not analyzed due to incomplete data sets. Additionally, baseline immunosuppression was not able to be analyzed in either study.

Sirolimus and everolimus are classes of drug that inhibit the mechanistic target of rapamycin (mTOR). mTOR regulates cellular metabolism, growth, and proliferation. Their use in pediatrics remains very low, with less than 2% of patients on one of these drugs at the time of transplant discharge [2]. There is evidence in the pediatric heart literature that conversion from a calcineurin inhibitor to an mTOR inhibitor as primary immunosuppression or its use with a lower dose of calcineurin inhibitor can improve renal function [49–52]. However, the adverse effects may make its use challenging. Chinnock et al. reported hyperlipidemia in 50% of patients, anemia and neutropenia in 40%, and aphthous ulcers in 15%. Asante-Korang et al. reported a significant increase in cholesterol and triglycerides with mTOR use, and leucopenia and aphthous ulcers in 32% of patients. It is thought that mTOR inhibitors may reduce the development of graft vasculopathy due to its anti-proliferating effects, though this has yet to be clearly demonstrated in pediatric heart transplant. A double-blind study of 634 de novo adult heart transplant recipients randomized to either high everolimus, low-dose everolimus, or azathioprine showed a lower incidence of graft vasculopathy at 6 months by intracoronary ultrasound and a lower rate of CMV infection in both everolimus groups compared to azathioprine [53]. A similar randomized, open-label trial using sirolimus in de novo adult heart transplant patients showed a reduction in acute rejection episodes and graft vasculopathy at 2 years [54]. In contrast, in a recent study using the Pediatric Heart Transplant Society database, no difference was found in time to rejection, hospitalization for infection, renal insufficiency, graft vasculopathy, or survival between patients on sirolimus at 1 year posttransplant and propensity-matched controls [2]. A similar study looking at early initiation of mTOR inhibitors did not show a reduction in graft vasculopathy or survival benefit, but patients treated with mTOR inhibitors had a higher rate of rejection in the first year [42].

The multiple single-center protocols for induction and maintenance immunosuppression make it difficult to make comparisons and recommendations about the ideal immunosuppressive regimen. Expansion of the evidence base relating to the efficacy and safety of these drugs in pediatric heart transplant recipients is necessary and imminent. The TEAMMATE Trial (Tacrolimus/Everolimus against Tacrolimus/MMF) recently funded by the Department of Defense is the first randomized, multicenter trial in pediatric heart transplant to compare the efficacy and safety of two drug regimens in preventing major adverse events from 6 to 36 months after transplant (clinicaltrials.gov NCT03386539). Additionally, the prospective, observational, multicenter Clinical Trials in Organ Transplantation in Children, alloantibodies in children, funded by the National Institute of Allergy and Infectious Diseases (NIAID) will give the pediatric heart transplant community a unique opportunity to look at a

cohort of pediatric heart transplant recipients treated with the same immunosuppression protocol [55]. Enrolled patients were started on a steroid-sparing protocol including 5-day thymoglobulin induction followed by maintenance therapy with tacrolimus and MMF. Target levels of tacrolimus based on time from transplant were suggested in addition to suggested guidelines for treating sensitized patients perioperatively [55].

Retransplantation

Pediatric retransplantation accounts for 5% of total pediatric transplants [56]. The lack of uniformity in patient selection, comorbidities, and length of follow-up, along with small numbers in single-center series, make it difficult to distinguish appropriate candidates from those that would do poorly after a second transplant. There have been several studies looking at large registries to assess outcome after retransplantation and to identify risk factors for poor outcome, the most recent of which uses data from the ISHLT registry [57–59]. One-year survival after retransplantation was similar to primary transplant, but long-term survival was worse. Survival after primary transplant was 84%, 72%, and 60% at 1, 5, and 10 years and in the retransplant group 81%, 63%, and 46%, respectively. The median survival in primary transplant recipients was 15 years compared to 8.7 years for retransplanted children [57].

Graft vasculopathy is the most common indication for retransplantation, accounting for more than 50% of cases [57]. It has better survival than those retransplanted for other reasons (Fig. 6.4). Survival after retransplant nears that of primary transplants but only if retransplanted longer than

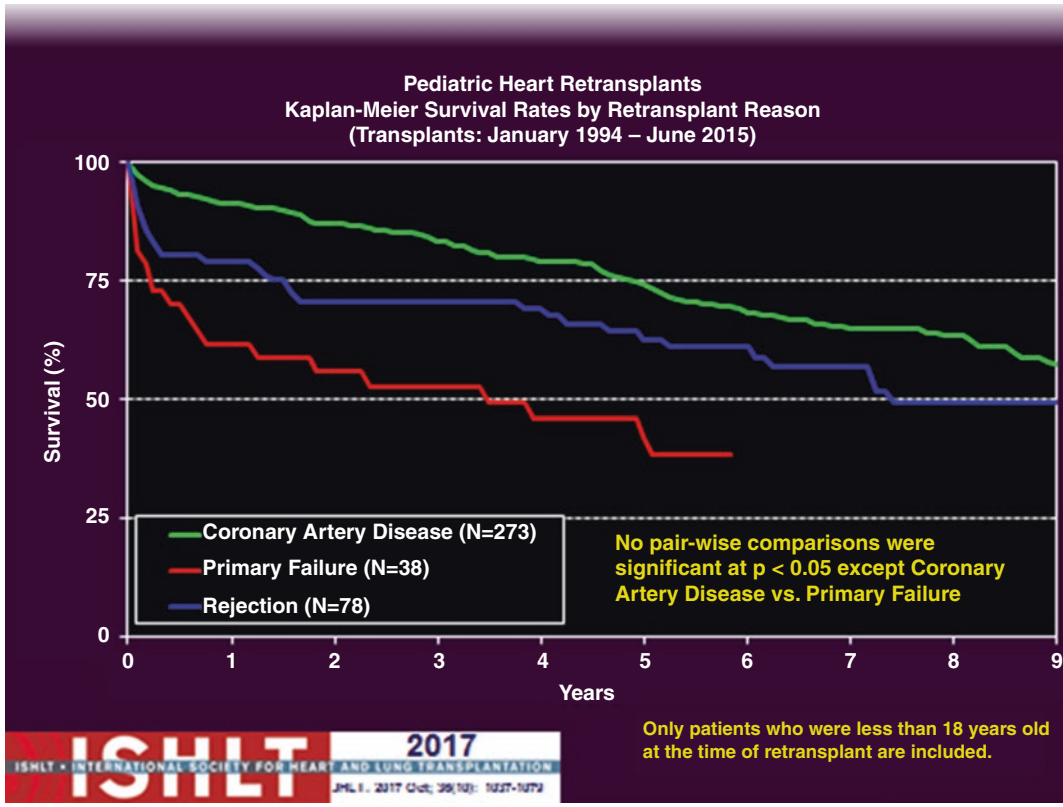


Fig. 6.4 Kaplan-Meier survival rates in pediatric heart retransplant by reason. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients

5 years after the original transplant. Patients retransplanted less than 1 year after the initial transplant, presumably for graft failure, have the worst survival (Fig. 6.5). Multiple risk factors for poor outcome reflecting disease acuity while waiting for retransplant have been reported. They include being in the ICU, need for intubation, dialysis or cardiac operation prior to retransplant, or developing an infection prior to retransplant [57–59].

In addition to inferior survival in children who receive second transplants, there is also more morbidity associated with retransplantation. An increased rate of late rejection, graft vasculopathy, and renal failure has been reported [57]. Given these findings and the known shortage of organs and waitlist mortality in patients awaiting primary transplant, controversy will remain regarding the role of retransplantation. Transplant programs have a responsibility to their patients and need to be responsible stewards of donor organs. A careful assessment of why the first transplant failed, particularly if early after transplant, is necessary to maximize the potential for a successful second transplant and appropriate use of donor organs. Being able to risk stratify candidates who would derive the most benefit from retransplantation is imperative.

Rejection Surveillance

Rejection is a major cause of morbidity and mortality after heart transplant. Fortunately, there has been a decrease in the percentage of patients being treated for rejection early after transplant

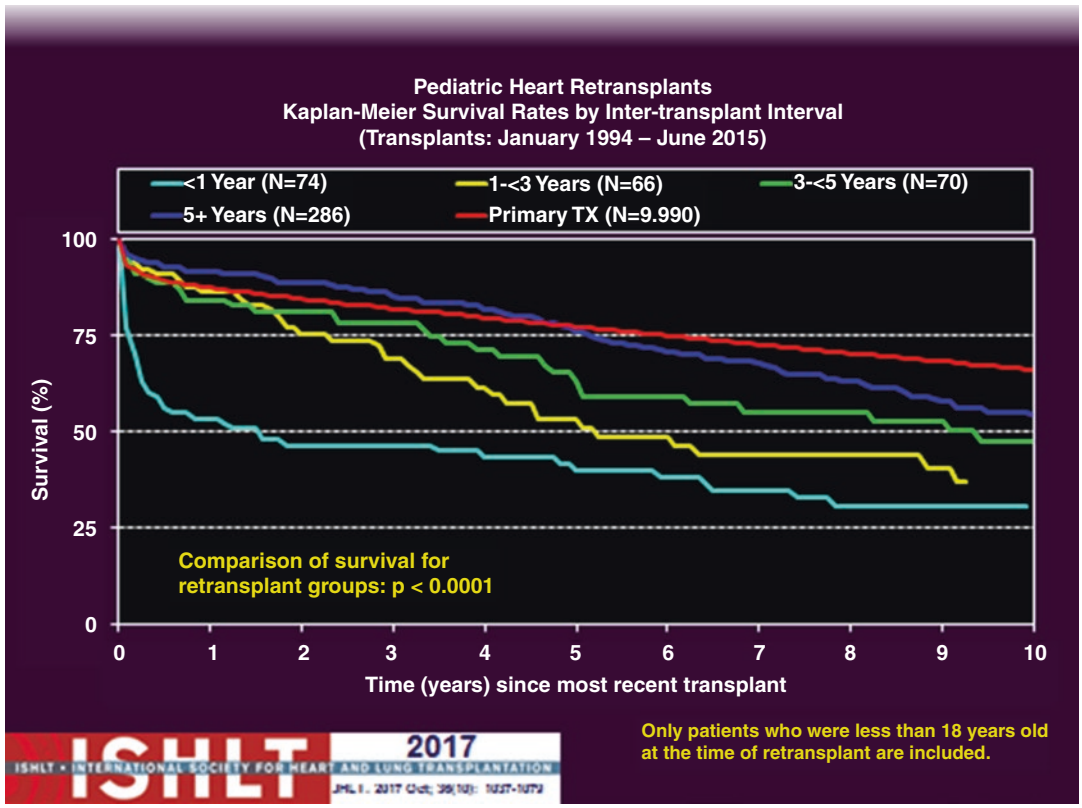


Fig. 6.5 Kaplan-Meier survival rates by inter-transplant intervals. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. A significant p-value means that at least one of the groups is different than the others, but it doesn't identify which group it is

in all age groups and genders [2]. Endomyocardial biopsy (EMB) is widely utilized as a surveillance method to detect asymptomatic rejection. There has been debate over the decades on the risk and benefit of endomyocardial biopsy compared to noninvasive imaging modalities to detect rejection. Endomyocardial biopsy is an invasive procedure with a complication rate in children reported from 1.1% to 4.7% [60, 61]. Infants less than 6 months and 8 kgs make up the highest-risk group for complications [61]. Centers vary in the frequency of surveillance EMB during the first year. Centers that historically have transplanted many infants have relied on noninvasive imaging, in particular echocardiography. Whether there is a difference in patient outcomes based on rejection surveillance technique and the optimal frequency of EMB is still unknown. As discussed in earlier sections, practice variation is great in pediatric heart transplant, making it challenging to answer these questions [62–64]. The Pediatric Heart Transplant Society, a consortium of 55 centers that have transplanted 6491 patients listed less than 18 years of age, has started the process of trying to answer some of these questions (http://www.uab.edu/medicine/phts/). The first step is identifying what are the practice variations in the various centers. Building consensus and drafting protocols will then lead to multicenter trials that can study rejection surveillance and the impact on outcomes in a uniform, scientific manner. The pediatric heart transplant community already has momentum in designing trials as in the CTOTC and TEAMMATE Trial discussed in previous sections; the PHTS is another example. These multicenter collaborative efforts will allow the pediatric heart transplant community to answer questions that have caused contemporary controversy.

Key Points

- Heart transplantation in children is the procedure of choice for children with end-stage heart disease.
- The indication and timing of VAD implantation depends on several factors including patient size, device availability, blood type, expected transplant wait time, etiology of heart failure, and overall condition of the patient.
- Anticoagulation remains a challenge in children on mechanical assist devices, particularly in infants and young children.
- Heart transplant survival has improved over the eras as a result of improved patient selection, ICU care, and choice of immunosuppressive drugs.

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7 Surgical Management of Hypoplastic Left Heart Syndrome

Peter Sassalos and Richard G. Ohye

Introduction

Congenital heart disease is the most common birth defect [1]. The incidence is about 40,000 United States (US) births per year and 1,000,000 worldwide births per year [2, 3]. It accounts for approximately 4.2% of all neonatal deaths [4]. The most common severe form of congenital heart disease is hypoplastic left heart syndrome (HLHS), affecting almost 1000 US births per year [5].

Hypoplastic left heart syndrome is defined by underdevelopment of the left side of the heart with associated systemic outflow obstruction. This consists of mitral stenosis or atresia, a non-apex-forming hypoplastic left ventricle, aortic stenosis or atresia, a hypoplastic ascending and arch aorta, coarctation of the aorta, and a patent ductus arteriosus. Although not strictly classified as a single ventricle or functionally univentricular heart by the Congenital Heart Surgery Nomenclature and Database Project [6], it shares common pathophysiology and treatment with these lesions. In contrast to normal hearts with a series circulation, there are intracardiac shunt(s) present with mixing of blood in a parallel circulation (Fig. 7.1). This produces abnormal systemic oxygen delivery and volume loading of the functional single ventricle. The clinical presentation depends on the degrees of systemic and pulmonary outflow obstruction determining the systemic (SBF) and pulmonary blood flow (PBF). Patients with a balanced circulation may initially be asymptomatic. Those with inadequate PBF will present with cyanosis, and those with excessive PBF will present with heart failure. Those with systemic outflow obstruction significant enough to require ductal patency for systemic output, such as HLHS, may present in shock. These factors contribute to the poor prognosis if left untreated.

Early HLHS patients had no or few surgical options. This diagnosis was universally fatal. However, the field of congenital heart surgery has made great advancements over the past 40 years. This progress can be particularly seen in these patients. Early treatment included interest in primary heart transplantation [7, 8] and the development of the Norwood procedure [9]. Current traditional surgical management of HLHS consists of staged palliation to a Fontan circulation (Fig. 7.2). This is composed of the Norwood procedure at birth, second-stage superior cavopulmonary connection at typically 4–6 months of age, and a completion Fontan procedure at 18–48 months of age.

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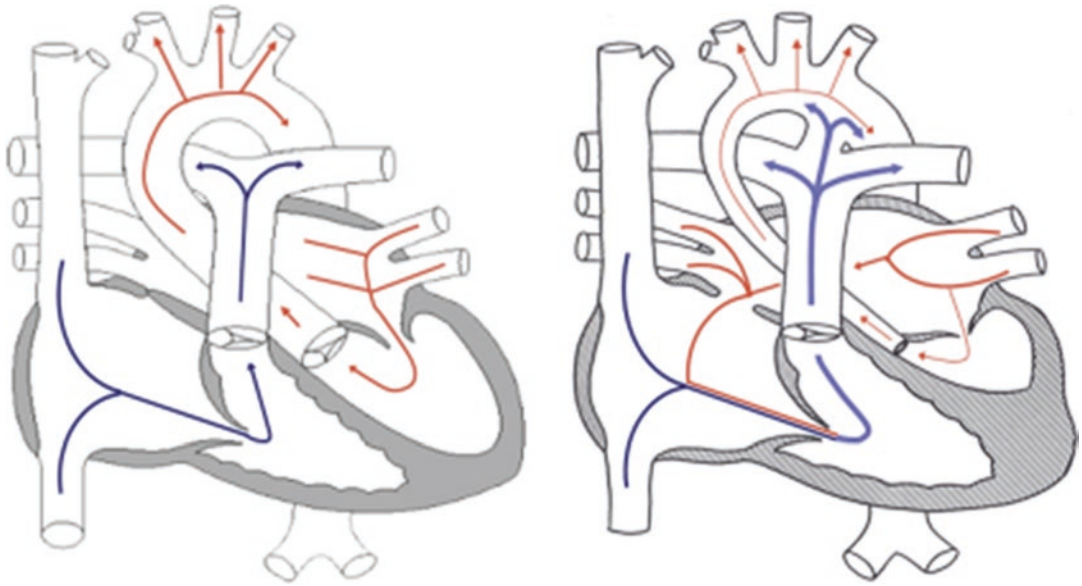

Fig. 7.1 A comparison of a normal series circulation to a HLHS parallel circulation

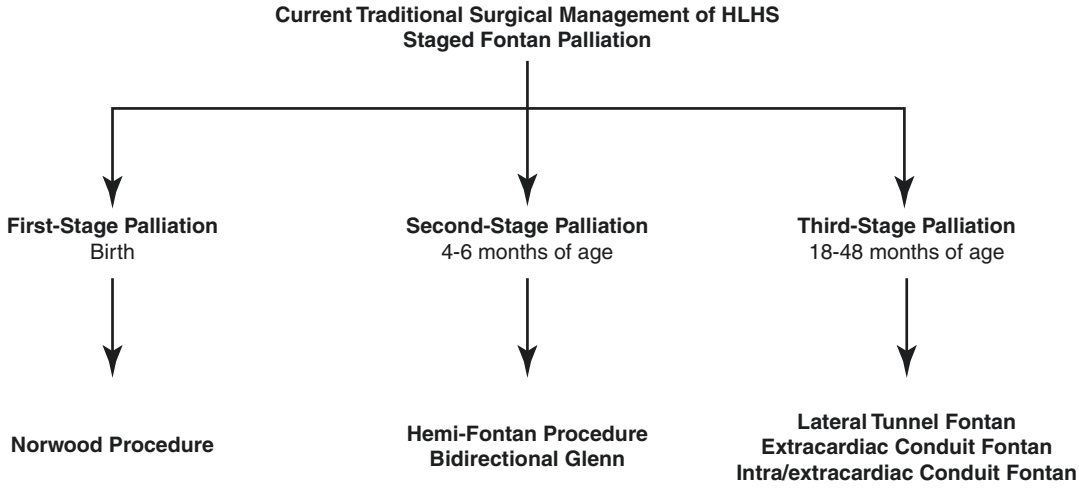

Fig. 7.2 Current traditional surgical management of HLHS consists of staged palliation to a Fontan circulation

Based on this standard management, outcomes have dramatically improved. The aggregate outcomes of staged palliation of all participants of the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS CHSD) were reported in 2016. The aggregate operative mortality for the Norwood procedure was 15.6%, the hemi-Fontan or bidirectional Glenn procedure was 2.1%, and the Fontan procedure was 1.4%. The aggregate average postoperative length of stay for the Norwood procedure was 42.2 days, the hemi-Fontan or bidirectional Glenn procedure was 13.8 days, and the Fontan procedure was 13.4 days [10]. In

experienced centers, hospital survival following the Norwood procedure has been reported greater than 90% [11].

Despite these advances, there is still significant morbidity and mortality associated with HLHS. This has led to investigation into new and alternative therapies. As a result, there is substantial practice pattern variation among institutions and between individual surgeons, cardiologists, and intensivists.

Wernovsky et al. conducted an online survey in 2007 evaluating management of HLHS in 52 centers worldwide thought to manage 1000 neonates with HLHS annually. The results demonstrated considerable variability in most parameters. Some results favored a consensus opinion, whereas others favored equivocal or even controversial conclusions. Of note, the type of intensive care unit in which patients were managed, both before and after surgery, varied widely among centers [12]. Pasquali et al. then conducted a study in 2012 to evaluate practice pattern variation in perioperative care of neonates undergoing the Norwood procedure using the Single Ventricle Reconstruction (SVR) trial dataset. This also demonstrated significant variability in preoperative, intraoperative, and postoperative variables (Table 7.1) [13]. However, of particular interest, significant differences also existed for in-hospital mortality and transplantation between centers. One may then theorize that practice pattern variation and current controversies in the management of these patients may be partially responsible for these differences. Therefore, if best practices can be identified, hopefully outcomes for HLHS patients may improve. This has already been demonstrated in adult cardiac surgery with the Michigan Society of Thoracic and Cardiovascular Surgery (MSTCVS) [14] and Northern New England Cardiovascular Disease Study Group [15]. Through adoption of practices used by high-performing centers, variation in care was reduced, outcomes were improved, and hospital costs lowered. Similar efforts are now being made through the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) [16].

Table 7.1 Practice pattern variation in perioperative care of neonates undergoing the Norwood procedure using the Single Ventricle Reconstruction (SVR) trial dataset. The range is the differences in practice between each center. This demonstrates significant variability in preoperative, intraoperative, and postoperative variables. (Adapted from Pasquali et al. [13]) (*DHCA* deep hypothermic circulatory arrest, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *HCT* hematocrit, *RCP* retrograde cerebral perfusion)

Practice pattern variation	
Preoperative variables	
Fetal diagnosis	55–85%
Intubation	29–91%
Intraoperative variables	
Total bypass support time	74–189 min
Aortic cross-clamp time	33–73 min
DHCA only	3–100%
RCP only	3–93%
Lowest HCT	22–41%
Classic arch reconstruction	41–100%
Postoperative variables	
ICU stay	9–44 days
Hospital stay	19–44 days
Ventilator time	4–16 days
Open sternum	35–100%
ECMO	7–35%
Enteral tube	2–100%
Home monitoring	1–100%
Death or transplant during Norwood hospitalization	7–39%

Another controversial topic is regionalization of care to centers of excellence. Using the 2003 Kids' Inpatient Database, hospital mortality for the Norwood procedure and arterial switch operations were studied as a function of institutional volume. A total of 624 Norwood procedures performed at 60 hospitals, with a case range of 1–31 operations a year at each site, were evaluated. An inverse relationship was demonstrated between institutional volume and mortality with 35%, 26%, and 17% mortality in hospitals performing 2 per year, 10 per year, and 20 per year, respectively [17]. Using the STS CHSD, 2555 patients undergoing the Norwood procedure at 53 centers by a total of 111 surgeons were also evaluated. This demonstrated that lower center and surgeon volume were associated with higher mortality [18]. To better understand these differences, a large analysis of the 2006–2009 STS CHSD was

Table 7.2 The current controversies in the surgical management of HLHS which will be the focus of this chapter

Current controversies
Fetal cardiac intervention
First-stage palliation
Norwood procedure
Shunt type
Deep hypothermic circulatory arrest versus regional cerebral perfusion
Delayed sternal closure
Hybrid Norwood
Postoperative management
Second-stage palliation
Third-stage palliation
Role of a fenestration
Mechanical circulatory support
Transplantation

performed including 40,930 patients at 72 centers. Interestingly, there was no difference in complication rates between high, middle, and low mortality hospitals. However, low mortality hospitals had the lowest failure to rescue rate (the probability of death after a complication) [19]. This has now become a well-known phenomenon that has been demonstrated across many other surgical specialties [20].

As is clearly evident, multiple current controversies exist regarding surgical management of HLHS (Table 7.2). They will therefore be discussed in the remainder of this chapter.

Patient Scenario

A 2.5 kg male born at 35 weeks gestational age with a postnatal diagnosis of HLHS presents from an outside hospital in shock. The patient is intubated and begun on prostaglandin infusion and vasoactive support. A transthoracic echocardiogram demonstrates a nonrestrictive atrial septum, HLHS consisting of mitral stenosis and aortic stenosis, a 3 mm ascending aorta, and no evidence of coronary sinusoids. The resident physician caring for this baby asks what surgical options are available as well as if something could have prevented or mitigated the severity of this condition.

Fetal Cardiac Intervention

Prenatal diagnosis of HLHS has increased. Since 2012, 82% of Norwood procedures performed at the University of Michigan had a prenatal diagnosis. This allows surveillance of high-risk lesions, the opportunity for counseling, optimal timing and location of delivery, and better transition to postnatal care. Although it has not clearly demonstrated improved survival [21], there is evidence of decreased morbidity [22]. In addition, it offers the consideration for fetal cardiac intervention (FCI) performed in select quaternary referral centers.

Fetal cardiac interventions are reserved at this time for HLHS patients with either aortic valve stenosis or a restrictive/intact atrial septum. It has been proposed that aortic valve stenosis in a fetus with an initially normal-sized left ventricle can progress to HLHS. Therefore, the hope is that fetal balloon valvuloplasty can prevent this progression. It is currently selectively utilized in patients who are not yet thought to have HLHS or in patients who may have potential for biventricular repair [23–33].

A restrictive or intact atrial septum is a known risk factor for HLHS [34]. It leads to pulmonary venous obstruction and irreversible pulmonary vascular changes that are unfavorable to a patient destined for staged Fontan palliation. Therefore, the hope is that fetal balloon atrial septostomy or atrial septal stent placement can prevent these changes [35, 36]. Although these therapies have shown some promising results, additional work is needed as they carry high risk with an estimated procedural fetal loss at approximately 10–15% [21].

First-Stage Palliation

Norwood Procedure

First-stage palliation for HLHS has traditionally been the Norwood procedure [9]. This procedure is performed within the first 7–14 days of life via a median sternotomy using cardiopulmonary bypass. The three goals of the procedure are to

provide unobstructed pulmonary venous return, unobstructed systemic outflow, and adequate, but restricted, pulmonary blood flow (Table 7.3). Unobstructed pulmonary venous return is achieved by an atrial septectomy which creates a nonrestrictive atrial septal defect to allow pulmonary venous return to the dominant right ventricle. Unobstructed systemic outflow is accomplished by connecting the dominant right ventricle to the systemic circulation. Initially, the ascending aorta and aortic arch are reconstructed to alleviate systemic arterial outflow obstruction. The main pulmonary artery is then divided, and the pulmonary root is connected to the augmented ascending aorta. Therefore, the right ventricle becomes the systemic ventricle as cardiac output will flow through the pulmonary (neo-aortic) valve into the ascending aorta. Our preference is allograft patch augmentation under hypothermic circulatory arrest without regional cerebral perfusion. Lastly, adequate and restricted pulmonary blood flow is necessary. This is achieved by creation of a systemic-to-pulmonary artery shunt, which replaces pulmonary blood flow from the native main pulmonary artery and patent ductus arteriosus. Options include a classic Blalock-Taussig shunt, modified Blalock-Taussig shunt (MBTS), central aortopulmonary shunt, or right ventricle-to-pulmonary artery shunt (RVPAS).

Table 7.3 The goals of first-stage palliation and how they are achieved in the traditional versus hybrid Norwood procedures (PA, pulmonary artery; PDA, patent ductus arteriosus; PGE, prostaglandin)

Goals of first-stage palliation		
Goal	Traditional Norwood	Hybrid Norwood
Unobstructed pulmonary venous return	Atrial septectomy	Atrial septostomy or atrial septal stent
Unobstructed systemic outflow	Connect dominant right ventricle to aorta Aortic arch reconstruction	PDA stent (transthoracic or percutaneous) or PGE infusion
Adequate and restricted pulmonary blood flow	Systemic-to-pulmonary artery shunt	Bilateral PA bands

Shunt Type

Shunt type has been an actively investigated topic. The two main types used today are the MBTS and RVPAS, at the discretion of the operating surgeon. The MBTS provides PBF from the innominate artery to the right pulmonary artery using a polytetrafluoroethylene (PTFE) graft, typically 3.0–4.0 mm in size. Our preference is a 3.5 mm non-ringed and non-stretch PTFE graft. The RVPAS provides PBF from the right ventricle to the central pulmonary arteries using a graft. Our preference is a ringed PTFE graft, typically 5.0 or 6.0 mm in size, depending on the size of the patient. The proximal anastomosis can be sutured to the right ventriculotomy or placed within the ventricular cavity using a transmyocardial technique [37]. The distal anastomosis can similarly be performed either ways [38].

The MBTS had been the traditional shunt type despite an early description of the RVPAS by Norwood [39]. However, the RVPAS was popularized in the early 2000s by Kishimoto and Sano [40–43]. As a result, it is often referred to as the Sano shunt or modification. The theoretical advantages of the RVPAS are noncontinuous shunt flow only in systole without diastolic runoff; improved diastolic systemic perfusion leading to improved coronary blood flow, hemodynamic stability, and end-organ perfusion; and improved survival. The theoretical disadvantages are less PBF leading to more cyanosis, less pulmonary artery (PA) growth with more interventions, and a right ventriculotomy with decreased systemic ventricular function and increased arrhythmogenicity (Table 7.4).

A landmark study, the SVR trial, was therefore performed to attempt to answer the impact of shunt type. The Pediatric Heart Network (PHN), funded by the National Heart, Lung, and Blood Institute (NHLBI), sponsored this trial. The SVR trial was a multicenter, randomized clinical trial of 549 neonates with HLHS or other single right ventricle anomalies who underwent either a

Table 7.4 The theoretical advantages and disadvantages of the right ventricle-to-pulmonary artery shunt at the Norwood procedure. (PA, pulmonary artery; PBF, pulmonary blood flow)

Theoretical advantages and disadvantages of the right ventricle-to-pulmonary artery shunt	
Advantages	Disadvantages
Noncontinuous shunt flow in systole	Less PBF
No diastolic runoff	More cyanosis
Improved diastolic systemic perfusion	Less PA growth
Improved coronary blood flow	More PA interventions
Improved end-organ perfusion	Right ventriculotomy
Hemodynamic stability	Decreased systemic ventricular function
Improved survival	Increased arrhythmogenicity

MBTS or RVPAS at the time of a Norwood procedure. Of note, the SVR trial was the first randomized control trial comparing two operations in congenital heart surgery. The primary outcome was transplant-free survival at 12 months, which was statistically better at 74% for the RVPAS as compared to 64% for the MBTS. Secondary outcomes were perioperative morbidity after the Norwood procedure, unintended cardiovascular interventional procedures, right ventricular function by echocardiography, pulmonary arterial size by angiography, and neurodevelopment at 14 months [44].

The longer-term results at both 3 and 6 years have now also been reported. At 3 years, transplant-free survival was not statistically different at 67% for RVPAS as compared to 61% for the MBTS. The RVPAS group had more catheter interventions and worse RV ejection fraction [45]. At 6 years, transplant-free survival was not statistically different at 64% for RVPAS as compared to 59% for the MBTS. The RVPAS group had more catheter interventions pre-Fontan, and there was no difference in either RV ejection fraction or complications between the two groups. However, there was overall significant morbidity in both groups [46]. In addition to these results, the SVR database has led to a plethora of other important PHN studies as well [47].

Despite this landmark trial, the controversy regarding shunt type still exists. The initial survival benefit of the RVPAS has statistically been lost in longer-term studies; however, the trend still is present. Overall survival for patients with HLHS needs to improve, and continued investigation into ideal shunt type at the Norwood procedure remains an important clinical question.

Deep Hypothermic Circulatory Arrest Versus Regional Cerebral Perfusion

Cardiopulmonary bypass technique during the Norwood procedure differs between surgeons and institutions, particularly pertaining to aortic arch reconstruction. Options performed include standard cardiopulmonary bypass with variable degrees of systemic cooling, deep hypothermic circulatory arrest (DHCA), regional cerebral perfusion (RCP), or maintenance of total body perfusion. In general, there is a 50% metabolic reduction for every 10° Fahrenheit (7 °C) decrease in temperature, known as the metabolic reduction Q10 rule. Cooling the patient allows decreased cardiopulmonary bypass flow and systemic oxygen delivery with end-organ preservation. For DHCA, the head is placed in ice, and the patient is cooled to 18 °C for at least 20 min to ensure even cooling. The pump is then turned off and the patient exsanguinated into the venous reservoir for the period of aortic arch reconstruction. This is our preference. In contrast, RCP can be performed by retrograde flow through the superior vena cava (SVC) or antegrade into the head vessels, typically the innominate artery, either by direct cannulation or through a graft. This can be performed during DHCA to maintain continuous cerebral perfusion. A few groups have also described perfusing the brain using the above RCP techniques, as well as the lower body by cannulating the descending aorta.

The Boston Circulatory Arrest Study was a single-center randomized control trial that evaluated perioperative neurologic effects associated with DHCA versus low-flow cardiopulmonary bypass during the arterial switch operation for transposition of the great arteries. This demon-

strated higher risk of clinical seizures, higher risk of ictal activity on EEG monitoring, and greater release of creatine kinase brain isoenzyme associated with DHCA [48]. Long-term neurodevelopmental outcomes at 4 and 8 years of age were then evaluated. At 4 years of age, there was no difference in IQ or overall neurologic status; however, DHCA patients had worse motor coordination and planning [49]. At 8 years of age, both groups were associated with increased risk of neurodevelopmental abnormalities; however, the DHCA patients generally had greater functional deficits [50].

The University of Michigan then conducted a single-center randomized control trial that evaluated neurodevelopment outcomes associated with DHCA versus RCP in patients undergoing the Norwood procedure. Neurodevelopment was measured prior to second-stage palliation and at 1 year of age. This study did not suggest improved outcomes with RCP [51]. At this time, both strategies will continue to be used until further multicenter studies show clear consensus on which technique is related to superior outcomes.

Delayed Sternal Closure

Delayed sternal closure refers to temporary patch closure of the skin with the sternum left open at the time of the Norwood procedure and other complex congenital heart surgeries. The sternum is then closed as a separate operation typically several days later either in the intensive care unit or operating room. The proposed advantage is to provide more space in the setting of decreased function, myocardial edema, and coagulopathy. This can minimize the effects of diastolic dysfunction and elevated filling pressures, potential compression of anterior structures such as the RVPAS, increased vasoactive requirements with hemodynamic instability, tamponade physiology, and cardiac arrest. The proposed disadvantages are infectious and wound healing risks, need for an additional operation and anesthesia, and prolonged mechanical ventilation. A study using the STS CHSD evaluated 1283 infants undergoing the Norwood procedure from 45 centers. It demonstrated practice pattern variation with regard to delayed sternal closure and that centers with greater use had higher postoperative infection and length of stay [52]. Some institutions and surgeons choose to electively leave all patients open, whereas others selectively decide based on individual patient factors (Table 7.2). Our preference is the latter based on an intraoperative decision by the surgeon.

Patient Scenario

A hybrid Norwood procedure was recommended given the size, age, and presentation of the patient. Once the patient was stabilized with end-organ recovery, he was taken to the operating room for this procedure performed jointly by a congenital heart surgeon and interventional cardiologist. A median sternotomy was performed. Bilateral PA bands were constructed from 3.0 millimeter Gore-Tex graft and applied. Catheter-based distal PA pressures of approximately 15 mmHg were achieved. An angiogram was then performed to assess ductal and arch anatomy. A PDA stent was placed with a completion angiogram performed. The chest was closed and the patient transferred to a dedicated pediatric cardiothoracic intensive care unit.

Hybrid Norwood

Given the significant morbidity and mortality associated with the Norwood procedure, collaboration between surgeons and interventional cardiologists led to a less invasive alternative strategy first described by Gibbs et al. in 1993 [53]. It has since been advanced by teams in Giessen, Germany, and Columbus, Ohio. This hybrid Norwood procedure, also known as hybrid stage I palliation, has become an evolving therapy in the armamentarium for repair of HLHS.

The hybrid Norwood procedure achieves the same goals of the traditional Norwood procedure

without cardiopulmonary bypass (Table 7.3). Unobstructed pulmonary venous return is achieved by balloon atrial septostomy or atrial septal stent placement. Unobstructed systemic outflow is accomplished by placement of a patent ductus arteriosus (PDA) stent, either percutaneous or transthoracic via the main pulmonary artery, or by continuous prostaglandin infusion. Adequate, but restricted, pulmonary blood flow is achieved by placement of bilateral PA bands. Despite the same goals, multiple strategies have been employed to achieve this result (Fig. 7.3). The Giessen technique is a median sternotomy for placement of bilateral PA bands followed by percutaneous PDA stent placement and atrial septal intervention [54]. The Columbus technique is a median sternotomy for placement of bilateral PA bands and transthoracic PDA stent placement followed by delayed percutaneous atrial septal intervention, except in cases of restrictive or intact atrial septum [55]. An additional technique described is placement of a reversed MBTS to ensure coronary perfusion in HLHS patients with aortic atresia [56].

The surgical indications for the hybrid Norwood procedure are also quite variable. Some centers have adopted this for all HLHS patients, and others have selectively used it only for high-risk subgroups. Our preference to date has been the latter. High-risk patients are defined as less than 2.5 kg [57], less than 34 weeks gestation, intact or highly restrictive atrial septum, severe tricuspid regurgitation, severe right ventricular dysfunction, severe noncardiac medical or genetic conditions, renal dysfunction, intracranial hemorrhage or neurologic injury, contraindication to cardiopulmonary bypass, severe ascending aortic hypoplasia (<2 millimeters), coronary sinusoids (mitral stenosis, aortic atresia), and postnatal cardiac arrest or shock. Of note, the hybrid Norwood has also been used for potential biventricular patients with Shone's complex and high-risk features, interrupted aortic arch with high-risk features, and critical aortic

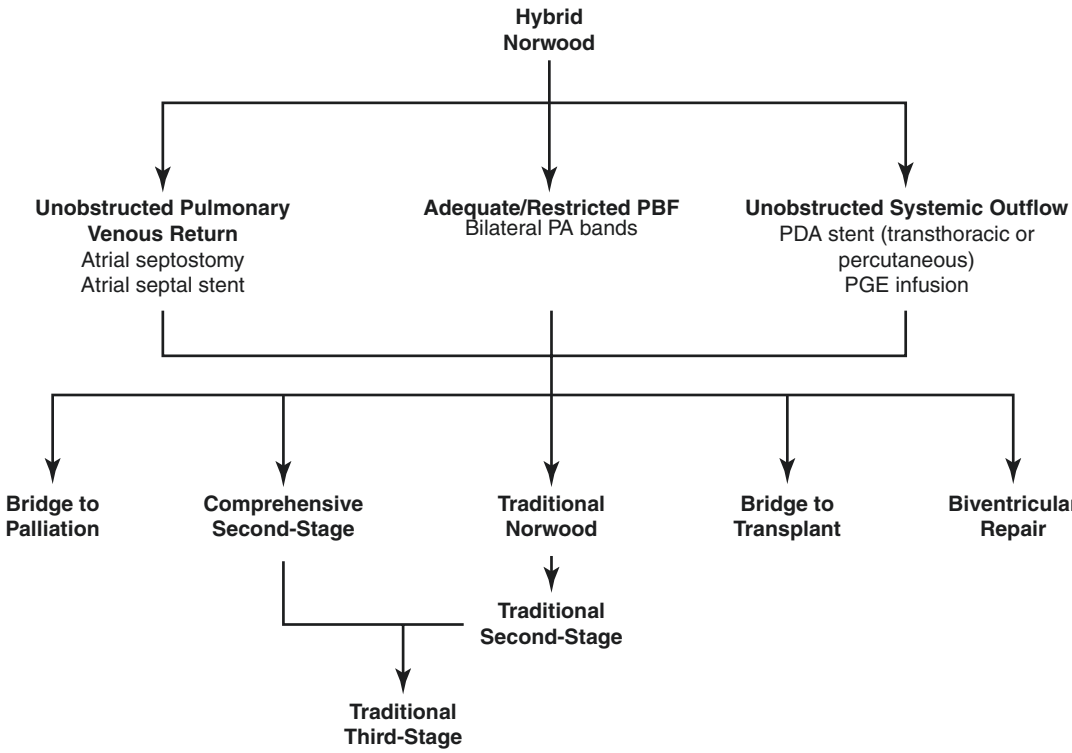

Fig. 7.3 Hybrid Norwood treatment algorithms and subsequent pathway options

stenosis with poor left ventricular function. The main contraindication to a hybrid Norwood procedure is unfavorable aortic arch and ductal anatomy for PDA stent placement with concern for reverse coarctation, especially in the setting of aortic atresia.

Once the hybrid Norwood procedure has been performed, the subsequent treatment pathway is also controversial (Fig. 7.3). Options include bridge to palliation, comprehensive second-stage traditional Norwood, bridge to transplant, or biventricular repair for non-HLHS patients. Our preference for suitable candidates has been to proceed with a traditional Norwood procedure at approximately 8–12 weeks of age followed by routine staged Fontan palliation. Comprehensive second-stage palliation consists of removal of bilateral PA bands with possible PA augmentation, removal of the PDA stent, the traditional Norwood procedure without the systemic-to-pulmonary artery shunt, and a superior cavopulmonary connection. Both the Giessen and Columbus groups have instead favored this approach. The Giessen single-center 15-year experience of 154 patients with HLHS or variants has been reported. The hybrid Norwood procedure was used for 107 patients, 33 with biventricular repair, 7 with heart transplantation, and 7 with comfort care. Eighty-nine patients went on to comprehensive second-stage palliation. Mortality for first stage was 1.2%, interstage 6.7%, and comprehensive second stage 9%. Overall unadjusted 1- and 15-year survival for all patients was 84% and 77%, respectively [54].

Using the STS CHSD, the outcomes following comprehensive second-stage palliation were reviewed. It consisted of 209 patients, 68% with HLHS, from 49 centers between 2010 and 2016. Overall operative mortality was 12.4%, postoperative major complications occurred in 26.8%, and postoperative ECMO was utilized in 8.1%. Of note, 81 procedures were performed at one institution with most centers only performing 1–2 procedures [58]. Although the results are discouraging, no definitive conclusions can be made. Unfortunately, given the infancy of this treatment and variable practice patterns, the scarcity of published results have yet to define a best practice.

Patient Scenario

Postoperative management consisted of balancing the circulation. The patient initially had high oxygen saturations with increasing lactic acidosis. The FiO_2 was therefore decreased to 21% and milrinone infusion initiated. Heparin infusion was begun for the PDA stent. The patient was extubated 2 days later and eventually transferred to the floor. He was discharged after approximately 1 month with nasoenteral feeds, aspirin, furosemide, and digoxin. Extensive counseling was performed with the family prior to discharge, and the patient was entered into the interstage program.

He then underwent a traditional Norwood procedure at approximately 8 weeks of age. The operation consisted of an atrial septectomy, connecting the dominant right ventricle to the systemic circulation, removal of the PDA stent, aortic arch reconstruction using pulmonary allograft patch under DHCA without RCP, an RVPAS using a 6-millimeter-ringed Gore-Tex tube graft, and removal of bilateral PA bands without PA augmentation. The sternum was left open and the skin sutured to a temporary patch.

The patient had hemodynamic instability and volume overload which improved after several days. Delayed sternal closure was then performed followed by extubation 2 days later. The remainder of the course was unremarkable and followed that of the hybrid Norwood hospitalization described above.

Postoperative Management

The postoperative management following either a traditional or hybrid Norwood procedure mandates a thorough understanding of the pathophysiology regardless of the strategy followed at each institution. The goals are to maintain acceptable total cardiac output and balance PBF and SBF to

maintain adequate systemic oxygen delivery. This is assessed by clinical exam, routine vital signs, intracardiac pressure monitoring, continuous mixed venous oximetry, near-infrared spectroscopy (NIRS), continuous pulse oximetry, arterial and venous blood gas sampling, and markers of end-organ function. Typically, the goal is a mean arterial blood pressure approximately 40–45 mmHg, an oxygen saturation 70–75%, an arteriovenous difference of 20%, normal pH, a PCO_2 40 mmHg, a PO_2 30–40 mmHg, normal lactic acid levels without significant base deficit, and a hematocrit greater than 40%. To achieve this physiologic balance, the systemic (SVR) and pulmonary vascular resistance (PVR) can be manipulated to control respective blood flows. The SVR can be increased by systemic vasoconstrictors such as vasopressin, norepinephrine, epinephrine, or high-dose dopamine infusions. The SVR can be decreased by systemic vasodilators such as milrinone, direct arterial vasodilators, or alpha-antagonists. The PVR can be increased by increasing PCO_2, either through decreased minute ventilation or addition of inhaled CO_2, or decreasing PO_2, either by lowering the FiO_2 and PEEP or administration of sub-ambient O_2. The PVR can be decreased by decreasing PCO_2, increasing PO_2, or adding pulmonary vasodilators such as inhaled nitric oxide or oral sildenafil. In addition, optimization of medical therapy is important with temperature control, appropriate pain and sedation control, possible neuromuscular blockade, inotropic support, acid-base management, and adequate oxygen carrying capacity with blood transfusion as needed. In general, the goal for the balance between SBF and PBF is generally a ratio of 1:1, which maintains both adequate peripheral oxygen saturation (~75%) and systemic cardiac output.

Second-Stage Palliation

This stage is typically performed between 4 and 6 months of age. Once deemed an appropriate candidate, the options include the hemi-Fontan or bidirectional Glenn procedure (Fig. 7.2). Both create a superior cavopulmonary connection as the source of pulmonary blood flow while volume unloading the ventricle. The previous systemic-to-pulmonary artery shunt is removed.

The bidirectional Glenn procedure creates this connection by an end-to-side anastomosis between the divided SVC and a longitudinal ipsilateral branch pulmonary arteriotomy. In contrast, both the original and modified hemi-Fontan procedures create this connection by suturing a right atriotomy to the central pulmonary arteries which are augmented with an allograft patch. The right atrium, which is now a common atrium due to the previous atrial septectomy, is partitioned by patch. Therefore, the SVC return enters the partitioned superior portion of the common atrium to flow into the pulmonary arteries. The inferior vena cava (IVC) return enters the partitioned inferior portion of the common atrium to enter the right ventricle [59, 60].

There remains controversy as to the appropriate second-stage palliation. Excellent results have been demonstrated with both procedures. The choice becomes institution and surgeon dependent largely based on experience. The bidirectional Glenn procedure is currently the more commonly performed second-stage palliation at most centers. Advocates favor this approach for the technical ease and ability to perform without cardiac arrest or even without cardiopulmonary bypass [61, 62]. However, the hemi-Fontan is our procedure of choice at the University of Michigan unless anatomically not feasible, such as some cases of anomalous pulmonary venous connections, select cases of abnormal relationship and position of the atria to the ventricles, and some forms of heterotaxy with anomalous systemic venous connections. If bilateral SVC is present, we elect to perform a right modified hemi-Fontan with a left bidirectional Glenn procedure. Although technically more challenging, it is favored because it is felt for many reasons to make patients more suitable Fontan candidates [59]. Optimal PA anatomy is ensured through

routine augmentation of the branch pulmonary arteries. This more complex operation simplifies the lateral tunnel Fontan when the postoperative hemodynamics are more demanding. The entire cardiac output, with the exception of a fenestration, passes through the lungs at the Fontan stage. Therefore, longer anesthetic and cardiopulmonary bypass times can negatively impact the lungs which more seriously affect a Fontan patient. Lastly, mathematical modeling has demonstrated that the hemi-Fontan with lateral tunnel Fontan circulation has more favorable flow patterns with less energy loss and more equal distribution of IVC blood flow, as compared to the bidirectional Glenn with extracardiac conduit Fontan circulation [63].

Third-Stage Palliation

This stage is typically performed between 18 and 48 months of age depending on the type of Fontan performed. Once deemed an appropriate candidate, the options include the intra-atrial lateral tunnel Fontan, otherwise known as the lateral tunnel Fontan, the extracardiac conduit Fontan, or the intra-/extracardiac conduit Fontan (Fig. 7.2). Each completes the Fontan circulation by directing the IVC blood directly to the lungs. Following this stage, the entire deoxygenated systemic venous return will drain directly into the pulmonary arteries, driven only by central venous pressure. The oxygenated pulmonary venous return drains into the common atrium to be delivered to the systemic circulation via the systemic right ventricle.

The extracardiac conduit Fontan is performed by placement of an interposition graft, typically an 18–20 mm stretch PTFE graft, between the divided IVC and either the SVC or an arteriotomy on the inferior aspect of the PA involved in the bidirectional Glenn anastomosis. There is controversy though as to the ideal size of the conduit [64] and location of the latter anastomosis [65]. The intra-/extracardiac conduit Fontan is a modification of this where an anastomosis is performed between the end of the conduit and the atrium surrounding the orifice of the IVC and any additional hepatic veins. The conduit is then brought through the atriotomy which is closed around the conduit. The completion of the conduit is then performed in a similar fashion to the extracardiac conduit described above [66, 67].

In contrast, the lateral tunnel is performed through a right atriotomy from the inferior cavoatrial junction to just inferior to the previously placed hemi-Fontan patch (which is later removed). A lateral tunnel the width of the IVC is created with a PTFE patch. The patch is sutured around the internal orifice of the IVC, anterior to the right pulmonary veins, around the orifice of the SVC, and the anterior edge of the patch is then incorporated into the atriotomy closure. This creates a lateral tunnel pathway within the common atrium where SVC and IVC return is directed into the pulmonary arteries [59, 60, 68, 69].

There also remains controversy as to the appropriate third-stage palliation. Excellent results have been demonstrated with both procedures [70–82]. Once again, the choice becomes institution and surgeon dependent largely based on experience. The extracardiac conduit Fontan is currently the more commonly performed third-stage palliation. Advocates favor this approach for technical ease, ability to perform without cardiac arrest or even cardiopulmonary bypass [71, 83, 84], decreased arrhythmogenicity due to less atrial suture lines and the atrium excluded from higher venous pressures [67, 85], and less PA reconstruction if transplantation required in the future [86].

However, the lateral tunnel Fontan is our procedure of choice at the University of Michigan when anatomically possible for several reasons. The procedure is performed with technical ease following the hemi-Fontan procedure. There are more favorable flow patterns as described above [63]. Less prosthetic material is used which preserves growth potential and possibly decreases thrombogenicity [69]. Fenestration is easily performed, and more ready percutaneous catheter access to the common atrium is maintained. In

addition, a large study from the STS CHSD of 2,747 subjects undergoing the Fontan operation from 2000 to 2009 (lateral tunnel 47%, extracardiac 63%) demonstrated superior early outcomes for the lateral tunnel Fontan. After adjustments for patient factors, a multivariable analysis demonstrated that several factors, including the use of an extracardiac conduit Fontan, were associated with a significantly higher incidence of takedown/revision, Fontan failure, and longer length of stay [80].

Lastly, advocates of the intra-/extracardiac conduit Fontan favor this approach because it offers the advantages of both of the other techniques [67]. However, it is the least commonly performed technique at this time.

Role of a Fenestration

With each of these options, one must decide on a fenestration. This is a communication between the Fontan pathway and the common atrium which can be created using a variety of techniques [86–90]. It can be thought of similar to an atrial septal defect in a normal heart. Without a fenestration, an increased transpulmonary gradient could lead to decreased cardiac output, cardiogenic shock, and a failed Fontan circulation. The advantage is to lower Fontan pressures and increase overall systemic oxygen delivery by maintaining cardiac output through right-to-left shunting, particularly in the initial postoperative period. The disadvantages are right-to-left shunting with decreased oxygen saturations, risk of paradoxical emboli, and potential need for fenestration closure [87]. Early on, it was routinely used by many centers. However, as the extracardiac conduit Fontan has become more common, fenestrations with this technique are more challenging to create and less durable. This has prompted these centers to selectively fenestrate only high-risk candidates with successful results [87, 91]. Our preference continues to be routine fenestration of all Fontan patients, albeit with a very small fenestration (2.8–3.0 mm), which generally closes spontaneously after the postoperative period.

Patient Scenario

The patient then underwent a hemi-Fontan procedure at 6 months of age followed by a lateral tunnel Fontan procedure with a 3 mm fenestration at 2 years of age. The patient has done well and is being evaluated in a neurodevelopmental clinic and followed by his referring cardiologist at an outside hospital. He has no evidence of a failing Fontan circulation at this time.

Mechanical Circulatory Support

Mechanical circulatory support, both short and long-term, is challenging in patients with HLHS at various stages of palliation. The anatomy and surgical reconstructions are complex. In addition, many of these patients have limited vascular access given their extensive hospitalizations and repeat catheterizations.

Extracorporeal membrane oxygenation (ECMO) is the mainstay of short-term support. It is tailored to patient factors and the stage of palliation. As a general rule, femoral cannulation is not considered in patients less than 15 kg at our institution. Pre-first-stage HLHS patients are very difficult to support through peripheral cannulation. As a result, some centers will not offer ECMO at this stage. First-stage patients have multiple options, either transthoracic or peripheral cannulation, depending on the time from surgery and surgeon preference. Second-stage patients are also difficult to support. Cannulation of both the superior cavopulmonary pathway and the common atrium is recommended. Failure to decompress the SVC can lead to decreased cerebral perfusion and higher risk of neurologic injury. Third-stage patients also have multiple options, either transthoracic or peripheral, again dependent on multiple factors. For transthoracic cannulation, the surgeon can cannulate either the lateral tunnel or extracardiac conduit instead of the common atrium.

In general, ECMO portends a poor prognosis in HLHS and other single ventricle patients. A

retrospective review of 20 patients with a cavopulmonary connection requiring ECMO reported 55% of patients having known vessel occlusion complicating cannulation options, a 25% incidence of severe neurologic injury, and 30% survival at 35-month follow up [92]. A retrospective review from the Extracorporeal Life Support Organization (ELSO) of 230 Fontan patients requiring ECMO demonstrated only a 35% survival to hospital discharge [93]. A retrospective review of HLHS patients requiring ECMO after the Norwood procedure between 2001 and 2010 at the University of Michigan demonstrated 43.8% survival to hospital discharge, 35.9% survival to second-stage palliation, and only 25.4% survival to third-stage palliation [94].

Long-term support unfortunately lacks an ideal device at this time. There is active investigation into cavopulmonary assist, such as a viscous impeller pump [95] or systemic ventricular assist device [96]. Case reports have been published using the Berlin Heart [97, 98], and other devices are also being considered. As this area evolves, hopefully more established treatments will develop. Regarding patients with failing Fontan physiology, there is a serious need for transplantable hearts with limited donor availability.

Transplantation

Heart transplantation was considered early on as primary treatment for HLHS [7, 8]. However, due to limited donor availability and advancements made in staged palliation, it is less commonly utilized. For example, children in need of heart transplantation have the highest solid organ waitlist mortality [99]. Despite this, it does play a role at each stage. The current indications in HLHS are primary transplantation if poor RV function, candidates unable to proceed to the next stage of palliation or with poor right ventricular function and/or tricuspid regurgitation, and those with sequelae of a failed Fontan circulation [21], of who will likely comprise the largest need in the future.

Conclusion

The most common severe form of congenital heart disease is HLHS. Current traditional surgical management of HLHS consists of staged palliation to a Fontan circulation. Based on this standard management, outcomes have dramatically improved. However, despite these advances, there is still significant morbidity and mortality associated with HLHS. This has led to investigation into new and alternative therapies. As a result, multiple controversies exist for the surgical management of HLHS. Advancements in understanding and continued collaboration will be paramount to establish best practices and resolve these current controversies. The hope is this will translate to continued improvement in outcomes for this challenging group of patients.

Take-Home Points

- Current traditional surgical management of HLHS consists of the Norwood procedure at birth, second-stage superior cavopulmonary connection at typically 4–6 months of age, and a completion Fontan procedure at 18–48 months of age.
- Current controversies include regionalization of care to centers of excellence, the role of fetal cardiac intervention, appropriate management at each stage of palliation, and the role of mechanical circulatory support and transplantation.
- Controversies in first-stage palliation with the Norwood procedure include the appropriate shunt type, use of deep hypothermic circulatory arrest or regional cerebral perfusion, need for delayed sternal closure, differences in postoperative management, and the evolving role of the hybrid Norwood procedure.

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Part III

Gastrointestinal Controversies

Nutritional Support in the Pediatric ICU

8

Kimberly I. Mills and Nilesh M. Mehta

Case Scenario

A 12-month-old female with no significant past medical history is admitted to the medical-surgical ICU following a dog bite resulting in extensive injuries to the maxillofacial area and neck. The infant weighs 8 kg (5th %; weight-for-age z-score − 1) and is 70 cm long (10th %; height-for-age z-score − 0.8). Given the severity and location of injuries, an emergent surgical airway was secured, and she was taken to the operating room for wound debridement and tracheostomy. She returned to the intensive care unit for postoperative management. The surgical team was unable to place a nasogastric tube in the operating room given the location of her injuries. The extent of her injury had left a significant portion of open and denuded mucosa involving her mandible and lateral neck similar to a burn injury. Finally, the surgical team requested deep sedation and, if necessary, paralysis to ensure adequate tract formation given her new tracheostomy for at least 5 days.

This vignette illustrates several questions regarding the assessment of nutritional needs and provision of optimal nutrients during critical illness. Specific questions related to this vignette include:

- What was the baseline nutritional status of the patient?
- Was she at risk for further nutritional deterioration during her hospitalization?
- What type of metabolic stress response should we expect during the acute and convalescent phase of this injury?
- How should we determine the optimal energy and protein requirements during the acute and subacute phases of recovery?
- What is the best route for nutrient delivery, enteral versus parenteral?
- Is there a role for supplementation with micronutrients to aid in wound healing?

In this chapter, we will review the current evidence and concepts related to these questions and

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provide recommendations to guide bedside practice.

Introduction

Providing optimal nutrition to infants and children during critical illness is a vital aspect of their care. On admission, the prevalence of malnutrition in critically ill children is staggering – ranging between 20% and 47% in recent studies [1–6]. Additionally, nutritional status may further deteriorate during critical illness as a result of increased metabolic demands, failure to accurately estimate energy needs and inadequate nutrient delivery [7]. Malnutrition remains underrecognized in critically ill infants and children and has been associated with deleterious outcomes such as a higher rate of infectious complications, prolonged duration of mechanical ventilation, longer lengths of stay, increased resource utilization, and higher mortality [3–6, 8–14]. Individualizing nutritional support for critically ill children is challenging yet essential, as they represent a heterogeneous population in relation to age, disease process, comorbidities, presenting nutritional status, and metabolic response to stress. The provision of optimal nutrition during critical illness requires screening and identification of those at risk for nutritional deterioration, a detailed comprehension of the metabolic stress response, accurate estimates or measurement of energy expenditure to guide energy prescriptions, determination of the optimal route and timing of nutrient delivery, monitoring for intolerance to nutrient delivery, and the development of meaningful outcome measures to assess the impact of nutritional interventions. Updated guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) in 2017 highlight the current literature related to several aspects of bedside practice and identify key areas for further investigation [15]. As higher-quality studies including randomized controlled trials and other pragmatic study designs become available, these unanswered questions should coalesce into uniform evidence-based guidelines.

Defining Malnutrition

The definition of malnutrition in pediatrics is inconsistent across publications. To address this concern, ASPEN recently published guidelines unifying the diagnosis of pediatric malnutrition to facilitate early identification of those at risk, compare prevalence among centers, develop screening tools, implement uniform thresholds for intervention, and formulate evidence-based recommendations (Fig. 8.1) [16]. The new guidelines include recommendations for use of anthropometric variables, growth, chronicity of malnutrition, etiology, pathogenesis, and impact on functional outcomes to define pediatric malnutrition. The recent consensus statement concluded with the following definition of pediatric malnutrition [16]:

> An imbalance between nutrient requirements and intake, resulting in cumulative deficits of energy, protein or micronutrients, that may negatively affect growth, development and other relevant outcomes.

Following the development of a uniform definition, a standardized set of diagnostic indicators was generated to document malnutrition in routine clinical practice [17]. The recommended indicators include (1) weight-for-length *z*-score or body mass index (BMI), (2) length-for-age *z*-score, (3) mid-upper arm circumference (MUAC), or (4) velocity of weight gain or loss over time. Simple anthropometry on admission to the intensive care unit can predict clinical outcomes and must be prioritized [4, 5, 11, 12]. Ultimately, the acceptance of a uniform definition and validated diagnostic indicators of pediatric malnutrition should facilitate evidence-based clinical practice and advance research in the area of critical care nutrition.

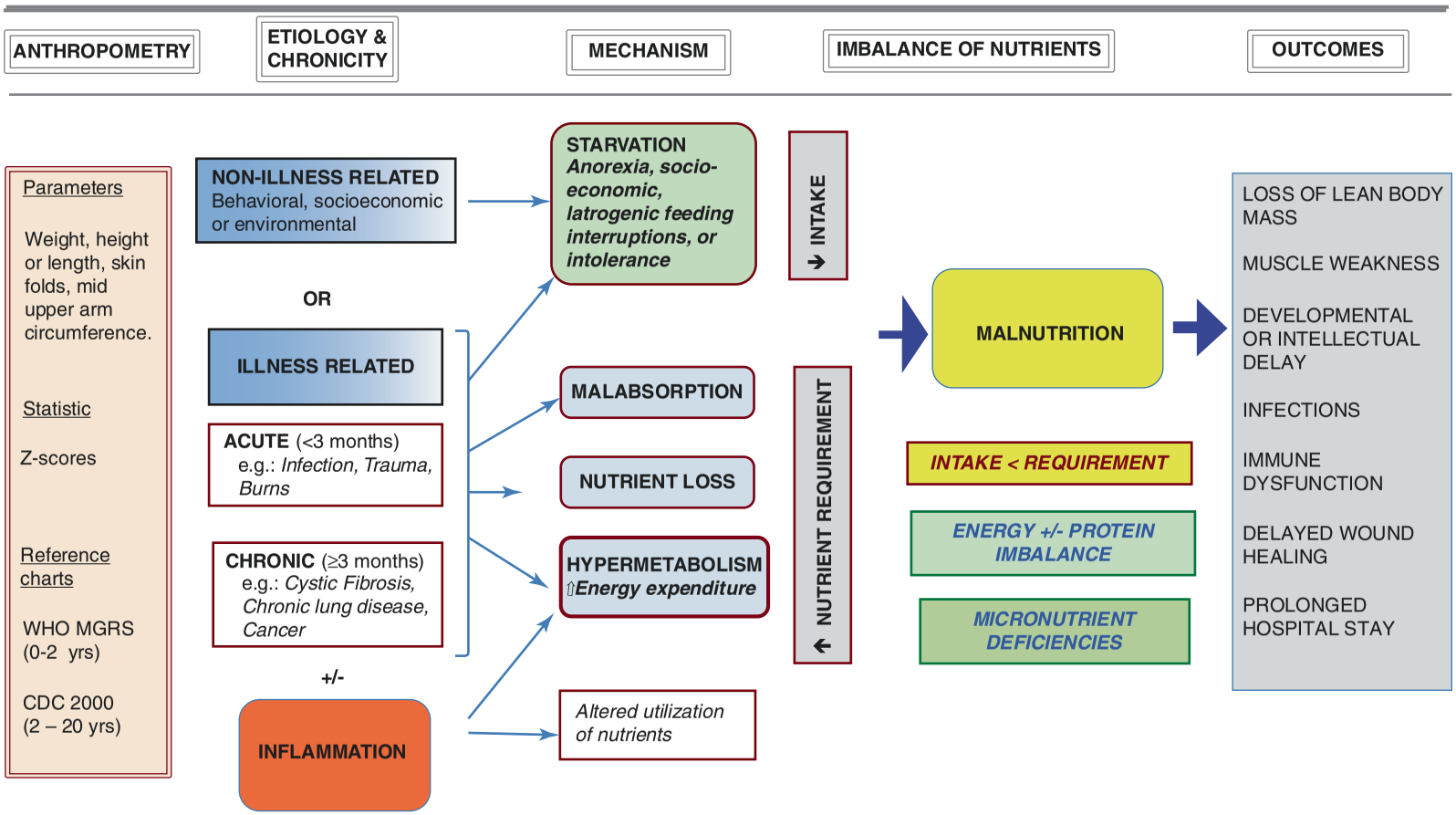

Fig. 8.1 ASPEN's new definition for pediatric malnutrition in hospitalized children. (Reprinted with permission [16]. Abbreviations: *WHO* World Health Organization, *MGRS* Multicenter Growth Reference Study, *CDC* Centers for Disease Control and Prevention)

Screening for Malnutrition

Given the concerns for preexisting malnutrition and further nutritional deterioration while critically ill, a detailed nutritional assessment should be performed on patients at risk for malnutrition or nutritional deterioration early during their hospitalization. The nutritional assessment should include a detailed dietary history, recent changes in anthropometry, alterations to their functional status (i.e., ability to perform normal daily activities), and a nutrition-focused physical examination. Due to limited resources, a detailed nutritional assessment on every patient may not be feasible. Thus, developing a validated screening tool to identify those at risk for malnutrition at admission and facilitate allocation of limited resources to those who would benefit the most from early nutritional intervention is necessary. The current ASPEN/SCCM guidelines suggest that within 48 h of admission a weight and height/length be measured in order to facilitate calculation of *z*-scores for body mass index (BMI) or weight-for-length measurements [15].

There are several screening tools currently available (Table 8.1), but none have been validated to identify those at risk for malnutrition in the pediatric ICU population. The Pediatric Yorkhill Malnutrition Score (PYMS), the Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP), and the Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGkids) were recently evaluated in 2,567 children across

Table 8.1 Available screening tools to evaluate the presence and severity of malnutrition in pediatric patients upon admission. Abbreviations: *mo* months old, *hrs* hours, *yo* years old

Screening tool	Variables	Population	Outcome
Pediatric Subjective Global Nutritional Assessment (SGNA) [18]	Food intake Ability to eat Difficulty retaining food Pain Disease severity	Pediatric patients >1 mo admitted to medical or surgical ward for ≥48 hrs	Weight loss >2% during admission
Pediatric Nutritional Risk Score (NRS) [19]	Weight and height Ideal body weight BMI-for-age MUAC Triceps skinfold thickness Mid-arm muscle area Handgrip strength Albumin Transferrin Hemoglobin Total lymphocyte count	Pediatric patients >1 mo and < 18 yo requiring major elective surgery	Major/minor infectious complications Major/minor noninfectious complications Postoperative LOS Non-prophylactic antibiotic use Unplanned reoperation Readmission
Pediatric Yorkhill Malnutrition Score (PYMS) [20]	BMI History of recent weight loss Changes in nutritional intake Current medical condition's effect on nutritional status	Pediatric patients 1 to 16 yo admitted to medical or surgical ward	Compare PYMS score to full dietitian's assessment of malnutrition risk
Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGkids) [21]	Subjective clinical assessment High-risk disease Nutritional intake Weight loss	Pediatric patients 1 mo to 18 yo admitted to medical or surgical ward	Weight-for-length/height z-score Prevalence of acute malnutrition Hospital LOS
Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP) [22]	Diagnosis' impact on nutrition Dietary intake Weight and height	Pediatric patients 2–17 yo admitted to medical or surgical ward for >24 hrs	Compare STAMP score to full dietitian's assessment of malnutrition risk

Europe [23]. The study demonstrated that the identification and classification of malnutrition risk varied across the screening tools and were unable to detect a considerable portion of undernourished children. Based on these findings, the authors recommended that none of the screening tools could be utilized in clinical practice. In the absence of a validated formal screening tool, most centers rely on admission weight-for-age or BMI-for-age *z*-scores to identify those at risk for nutritional deterioration in the ICU. This approach is reasonable and necessary, as clinical outcomes (i.e., rate of infectious complications, length of stay, duration of mechanical ventilation, and mortality rate) in the ICU have been associated with poor nutritional status at admission using various anthropometric measurements [4, 5, 11, 12]. Specifically, one multicenter, retrospective cohort study demonstrated admission BMI *z*-score-predicted mortality for children receiving mechanical ventilation [13]. Although there are challenges with obtaining accurate anthropometrics upon admission to the ICU, the association of malnutrition with poor clinical outcomes should prioritize procurement of these measurements.

The development of a validated pediatric nutrition screen specific for critically ill children is therefore paramount for the assessment of nutritional risk in a timely and accurate manner. Until an appropriate screening tool is established, the development and implementation of a nutrition support team (i.e., interdisciplinary team comprised of physicians, dietitians, nurses, and pharmacists with specialty training in nutrition) in the ICU should be considered, as they have been shown to improve surveillance for those at risk for malnutrition and aid in individualized nutritional prescriptions [24].

Metabolic Stress Response

A basic understanding of the metabolic stress response can assist in the accurate assessment of energy expenditure and help tailor individualized nutritional prescriptions in the critically ill. Increased counter-regulatory hormones, such as glucagon, cortisol, and epinephrine, induce insulin and growth hormone resistance in response to stress after injury, infection, surgery, or trauma [25]. This neuroendocrine response drives the catabolism of endogenous protein, carbohydrate, and fat (Fig. 8.2) [27]. Protein catabolism is the sine qua non of the metabolic stress response. The continuous degradation and decreased synthesis of muscle protein, resulting in a net negative nitrogen balance, result in a large pool of free amino acids. The free amino acids are redistributed, from visceral proteins (i.e., albumin), which comprise erythrocytes, granulocytes, lymphocytes, and other solid tissue organs, to inflammatory response proteins (i.e., C-reactive protein, fibrinogen, haptoglobin) that aid in wound healing and tissue repair. The remaining free amino acids are shuttled to the liver to partake in gluconeogenesis. In addition, carbohydrate breakdown leads to an increase in glucose oxidation and thus gluconeogenesis [28]. Gluconeogenesis is essential in critical illness as it ensures adequate energy reserves for glucose-dependent organs such as the brain, red blood cells, and renal medulla. Finally, the metabolic stress response increases fatty acid oxidation as well, providing ketones as a secondary fuel source for the brain [29].

The provision of protein, carbohydrate, and fat does not suppress the metabolic stress response during critical illness as it does during starvation [30, 31]. As a result, protein, carbohydrate, and lipid catabolism continue despite nutrient intake. Protein breakdown often exceeds protein synthesis and if unmatched by adequate concomitant intake can result in loss of lean body mass and nutritional deterioration [31]. The loss of muscle mass is not isolated to skeletal muscle alone, but may affect cardiac and diaphragmatic muscles resulting in cardiorespiratory insufficiency. Likewise, the provision of carbohydrate does not stop gluconeogenesis but instead results in "stress hyperglycemia" [32]. Finally, increased lipid demand in the setting of limited fat stores and inadequate provision can lead to essential fatty acid deficiency, especially in preterm infants [33, 34].

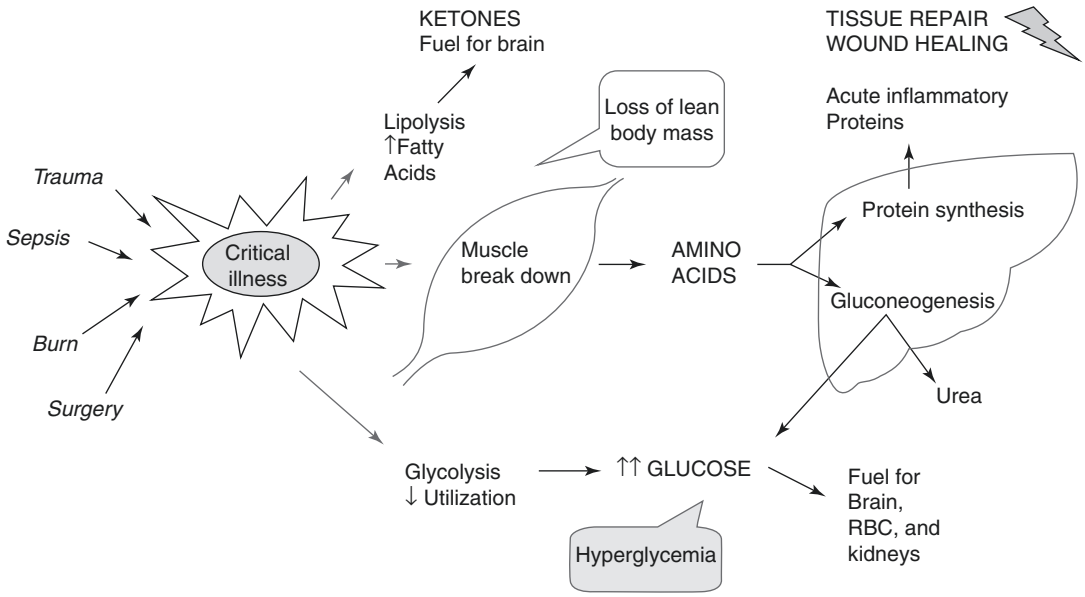

Fig. 8.2 Pathways of the metabolic stress response during critical illness. (Reprinted with permission [26])

Determining Energy Requirements

The metabolic state during critical illness is dynamic and unpredictable, ranging from hypometabolism (<90% of predicted measured resting energy expenditure) as a result of sedation, mechanical ventilation, and targeted temperature management to hypermetabolism (>110% of predicted measured resting energy expenditure) as seen in severe burn injuries [35–39]. Inaccurate energy estimates can result in underfeeding or overfeeding with potential negative clinical consequences [26, 40–43]. Underfeeding can lead to poor wound healing, impaired oxygen utilization, increased infection risk, poor neurodevelopmental outcomes, and increased mortality, while overfeeding can result in hypertriglyceridemia, hyperglycemia, hepatic steatosis and cholestasis, increased carbon dioxide production, and uremia [44–46].

Indirect calorimetry (IC) remains the gold standard and current ASPEN/SCCM guideline recommendation to measure resting energy expenditure in critically ill children [43, 47, 48]. IC, which is typically performed using a metabolic cart, measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to calculate the respiratory quotient (RQ), which is calculated as $RQ = VCO_2/VO_2$. RQ values range from 0.6 to 1.4 based on the type of substrate utilized by the patient. Carbohydrate oxidation results in higher carbon dioxide production and therefore higher RQ, whereas lipolysis is associated with comparatively lower VCO_2 measurements and hence a lower RQ. Mixed fuel utilization results in typical RQ ranging from 0.8 to 1.2. Although carbohydrate excess may increase the RQ value, the use of RQ as a measure of overfeeding is not recommended [49]. IC has several limitations as it is not reliable in children that weigh less than 5 kg, those supported with an inspired O_2 concentration greater than 60%, or in patients with a sizeable air leak (i.e., around endotracheal tube, chest tube).

Though IC is deemed the gold standard for measuring energy expenditure in critically ill children, the majority of ICUs lack the resources and expertise to operationalize IC in their daily clinical management [50–53]. When IC is not available and despite substantial evidence against their accuracy, clinicians utilize predictive equations based on patient demographics to estimate resting energy expenditure (Table 8.2) [39, 43, 52–57]. If predictive equations are utilized, the

Table 8.2 Available predictive equations to calculate resting energy expenditure. Abbreviations: *yo* years old, VCO_2 volumetric carbon dioxide production (mL/min), RQ_{macro} respiratory quotient based on the ratio of carbohydrate to fat in the diet

Schofield	**<3 yo** Male: REE = 60.9 * weight (kg) – 54 Female: REE = 61 * weight (kg) – 51 **3–10 yo** Male: REE = 22.7 * weight (kg) + 495 Female: REE = 22.5 * weight (kg) + 499 **10–18 yo** Male: REE = 17.5 * weight (kg) + 651 Female: REE = 12.2 * weight (kg) + 746
World Health Organization (WHO)	**<3 yo** Male: REE = (60 * weight (kg)) – 54 Female: REE = (6.1 * weight (kg)) – 51 **3–10 yo** Male: REE = (22.7 * weight (kg)) + 495 Female: REE = (22.5 * weight (kg)) + 499 **10–18 yo** Male: REE = (17.5 * weight (kg)) + 651 Female: REE = (12.2 * weight (kg)) + 746
Harris-Benedict	**Male** REE = 66.5 + (13.75 * weight (kg)) + (5.003 * height (cm)) = (6.775 * age) **Female** REE = 655 + (9.563 * weight (kg)) + (1.85 * height (cm)) – (4.676 * age)
Recommended Daily Allowance (RDA)	<6mo REE = 108 kcal/kg/day 6mo-1yo REE = 98 kcal/kg/day 1-3yo REE = 102 kcal/kg/day 4-6yo REE = 90 kcal/kg/day 7-10yo REE = 70 kcal/kg/day 11-14yo Male: REE = 55 kcal/kg/day Female: REE = 47 kcal/kg/day 15-18yo Male: REE = 45 kcal/kg/day Female: REE = 40 kcal/kg/day
VCO_2-derived	REE = [3.941 (VCO_2/RQ_{macro}) + 1.106 (VCO_2)] * 1440

ASPEN/SCCM guideline currently recommends using either the Schofield or World Health Organization (WHO) equation without the addition of "stress" or "activity" correction factors [52]. Moreover the guidelines recommend against using the Harris-Benedict equation and Recommended Daily Allowances (RDA) to determine resting energy expenditure, as they have been shown to overestimate resting energy expenditure in critically ill patients and lead to overfeeding [58].

As IC is not universally available and predictive equations are inaccurate, there is an impetus to develop consistent, accurate, accessible, and innovative ways to measure resting energy expenditure in the critically ill. Volumetric carbon dioxide measurement (VCO_2) represents one promising means to accomplish this goal. By synthesizing physiologic data into a simplified equation, VCO_2 measurement was recently modeled into an equation to predict resting energy expenditure in mechanically ventilated children and was found to be more accurate than currently available predictive equations [59, 60]. As continuous VCO_2 measurements in mechanically ventilated patients are increasing in availability in most ICUs, this equation may replace previous predictive equations in the future.

Determining Nutrition Prescription

Total Energy Goals

Several observational studies have demonstrated improved clinical outcomes when adequate energy intake is achieved in the PICU [3, 48, 61]. In spite of this finding, children admitted to the ICU have been shown to not achieve adequate energy requirements during their first week of admission [50, 62, 63]. Based on cohort studies and presumed hypometabolism in a variety of pediatric disease states, the current ASPEN/SCCM guidelines recommend achieving at least two thirds of prescribed energy requirements by the end of the first week of critical illness [3, 37, 42, 61, 64, 65].

Total Protein Goals

Based on several randomized controlled and prospective, multicenter cohort trials a minimum of 1.5 g/kg/day of protein delivery should be achieved to encourage a positive nitrogen balance according to the ASPEN/SCCM guidelines [48, 66–70]. Specifically, to avoid cumulative protein deficits, ASPEN's recent guidelines recommend higher protein intake goals than those recommended by the Dietary Reference Intake (DRI), which were historically based on healthy children (Table 8.3) [71]. The rationale for increased protein goals is related to increased protein breakdown and turnover during critical illness. In support of higher protein intake goals, a large, multicenter prospective study demonstrated higher enteral protein intake to be associated with lower mortality in mechanically ventilated children (Fig. 8.3) [6]. The optimal protein intake for critically ill infants, however, is likely higher and may be around 2.5–3 g/kg/day based on previous cohort studies [67, 70, 72]. Increasing protein goals beyond 3 g/kg/day and especially in infants less than 1 month of age has not been adequately studied and may lead to a rising blood urea nitrogen level. Finally, as pediatric formulas were not designed for critically ill children, prescribed standard formulas have a limited protein/energy ratio that may restrict the amount of protein delivered [73]. To overcome this dilemma, the field is currently examining the feasibility and efficacy of adding modular protein supplements (i.e., Beneprotein®) to standard formulas in children, a practice embraced by adult ICUs for the last decade [73, 74].

On the other hand, a secondary analysis of the Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial demonstrated that supplying greater than 1 gm/kg/day of protein was associated with worse clinical outcomes (i.e., increased infectious complications and longer duration of mechanical ventilation), as opposed to carbohydrate and fat

Table 8.3 Recommended daily protein intake (g/kg/day) for pediatric patients. Abbreviations: *DRI* Dietary Reference Intake, *ASPEN* American Society for Parenteral and Enteral Nutrition [71]

	Age range	Recommended protein intake (g/kg/day)
DRI 2005	0–6 months	1.52
	7–12 months	1.2
	1–3 years	1.05
	4–13 years	0.95
	14–18 years	0.85
ASPEN 2009	0–2 years	2–3
	2–3 years	1.5–2
	3–18 years	1.5

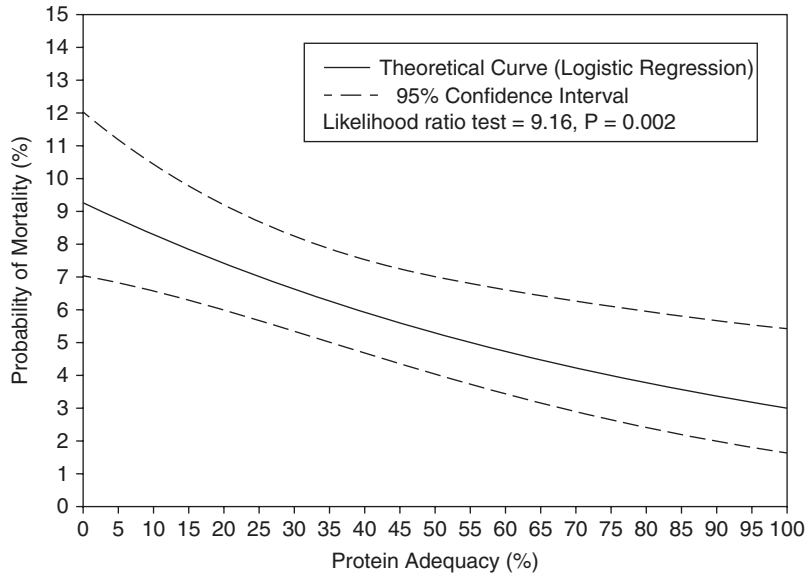

Fig. 8.3 Relation between enteral protein intake adequacy and 60-day mortality in mechanically ventilated children (n = 1245). (Reproduced with permission [6])

[75]. These findings were similar to those represented in a secondary analysis from a similar adult randomized controlled trial [76]. Critical review of the study cautions against a change in daily clinical practice however, as the study was observational in nature and not developed as a dosing study, unique clinical outcomes were developed as primary outcome measures, reference macronutrient doses used in the study were higher than recommended by the ASPEN/SCCM guidelines, and there was no examination of the interaction between different macronutrient levels. Hence, until further studies are available to clarify the conflicting data, use of the ASPEN/SCCM guidelines for protein delivery in critically ill patients is appropriate.

Determining the Delivery Route of Nutrition

Enteral Nutrition

Enteral nutrition (EN) is the preferred mode of nutrient delivery in critically ill children. Regardless of most diagnoses, sedative, and vasoactive use, EN has been shown to be safe and beneficial [77, 78]. As timing of EN initiation has been associated with nutritional adequacy, initiation of EN within 24–48 h of ICU admission, known as "early EN," is preferred according to the ASPEN/SCCM guidelines [6, 79–81]. Furthermore, achieving two thirds of the prescribed energy and protein goals via EN within the first week of critical illness may be associated with improved clinical outcomes [3, 6]. Early EN has demonstrated a lower risk of infection, reduced LOS, improved anthropometrics, and improved survival when compared to EN initiated later [61, 79, 82–84].

When initiating EN, the question remains whether to begin with gastric or postpyloric feeds. Currently, initiating feeds via the gastric route is preferred and physiologic; however there is no evidence to support this recommendation from the ASPEN/SCCM guidelines. Considering postpyloric feeds requires available technical expertise in placing the feeding tube and may result in a delay in initiation of EN [85–87]. However, postpyloric feeds may be beneficial in patients who suffer from feeding intolerance and are at risk for aspiration [88, 89]. One randomized controlled trial demonstrated reduced gastric residual volumes (GRVs) in patients who were fed postpyloric compared to gastric, although two randomized controlled trials have not demonstrated a reduction in the rate of aspiration [85, 86].

Another consideration when initiating EN is to whether to begin with continuous versus intermittent feeds. Existing data is currently conflicting and insufficient for the ASPEN/SCCM guidelines to recommend one practice as opposed to the other. The only evidence currently available consists of two randomized controlled trials that demonstrated no difference in EN tolerance between continuous and intermittent feeds [90, 91]. Based on these data, the delivery method for enteral nutrition can be determined by provider preference.

Once EN is initiated, maintenance of EN remains challenging, as interruptions are common [92, 93]. Barriers to optimal EN include delayed initiation, mechanical feeding tube issues, perceived feeding intolerance, noninvasive positive-pressure ventilation use, and prolonged fasting around procedures including intubation and extubation (Fig. 8.4) [81, 92, 94]. A prospective cohort study found that over half of the interruptions to EN in the PICU were avoidable [92]. These avoidable interruptions were associated with a threefold increase in parenteral nutrition (PN) use and a significant delay in achieving the prescription goal; thus an effort to minimize interruptions is of paramount importance. Methods to minimize avoidable interruptions include careful consideration regarding timing of procedures, guideline development and adherence around duration of fasting, and a dedicated team of nurses and support from interventional radiology to assist in the successful and expedient placement of feeding tubes.

Once EN is initiated, there is no uniform method to advancing EN. A stepwise algorithmic approach to advancing EN in the ICU has been shown to improve time to goal prescription,

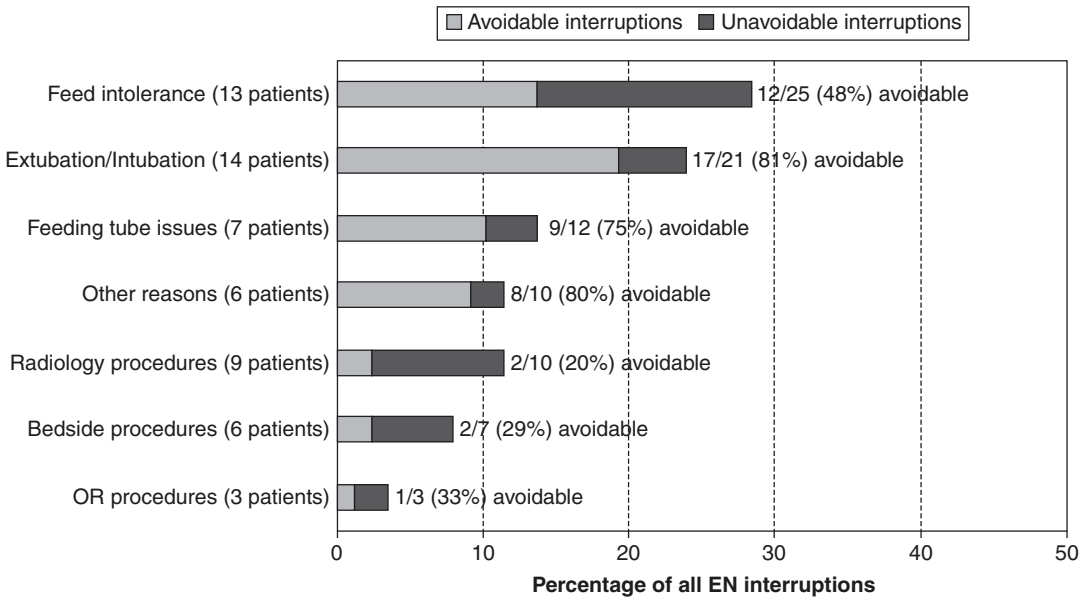

Fig. 8.4 Reasons for interruptions to enteral nutrition, both avoidable and unavoidable [92]. (Reproduced with permission)

increase the percent of patients who achieve their prescription goal, reduce interruptions to nutrition, decrease PN use, and improve nutritional and clinical outcomes (Fig. 8.5) [80, 95–98]. Devising an algorithm for use in the ICU should provide guidance on detecting and managing intolerance to ensure appropriate and expedient EN advancement [50].

Perceived feeding intolerance is one of the primary reasons for interrupting EN. Currently, feeding intolerance lacks a uniform description and could possibly refer to gastroesophageal reflux, vomiting, constipation, diarrhea, or malabsorption. Traditionally, gastric residual volume (GRV) was used to define feeding intolerance; however its accuracy has been questioned, and it is no longer recommended in adult ICUs [73, 99–101]. As there are no comparable pediatric studies to support this move, the use of GRVs is cautiously recommended in the most recent ASPEN/SCCM guidelines [15]. Despite a lack of definitive data in pediatrics, many centers use prokinetic agents (i.e., erythromycin, metoclopramide), antiemetics, acid suppression, antidiarrheals, and laxatives as adjuncts to EN.

The benefits of EN have been demonstrated in both human and animal studies. Gastrointestinal mucosal integrity and motility may improve when EN is prescribed [102]. These beneficial effects of EN are likely related to engaged gut-associated lymphoid tissue (GALT), mucosal immunity, and improved gastrointestinal blood flow [103–106]. Additional studies are required to further understand the benefits of providing early EN. Universally advanced and clearer stepwise algorithms need to be developed and should be supported by evidence considering gastric versus postpyloric, continuous versus intermittent, and methods to obviate interruptions to EN.

Parenteral Nutrition

When enteral nutrition fails, parenteral nutrition (PN) is advised [15, 107]. In addition, when EN is not feasible or contraindicated, such as following major abdominal surgery, when there are concerns for intestinal ischemia or in a low cardiac output state, PN should be considered. Furthermore, if a patient is severely malnour-

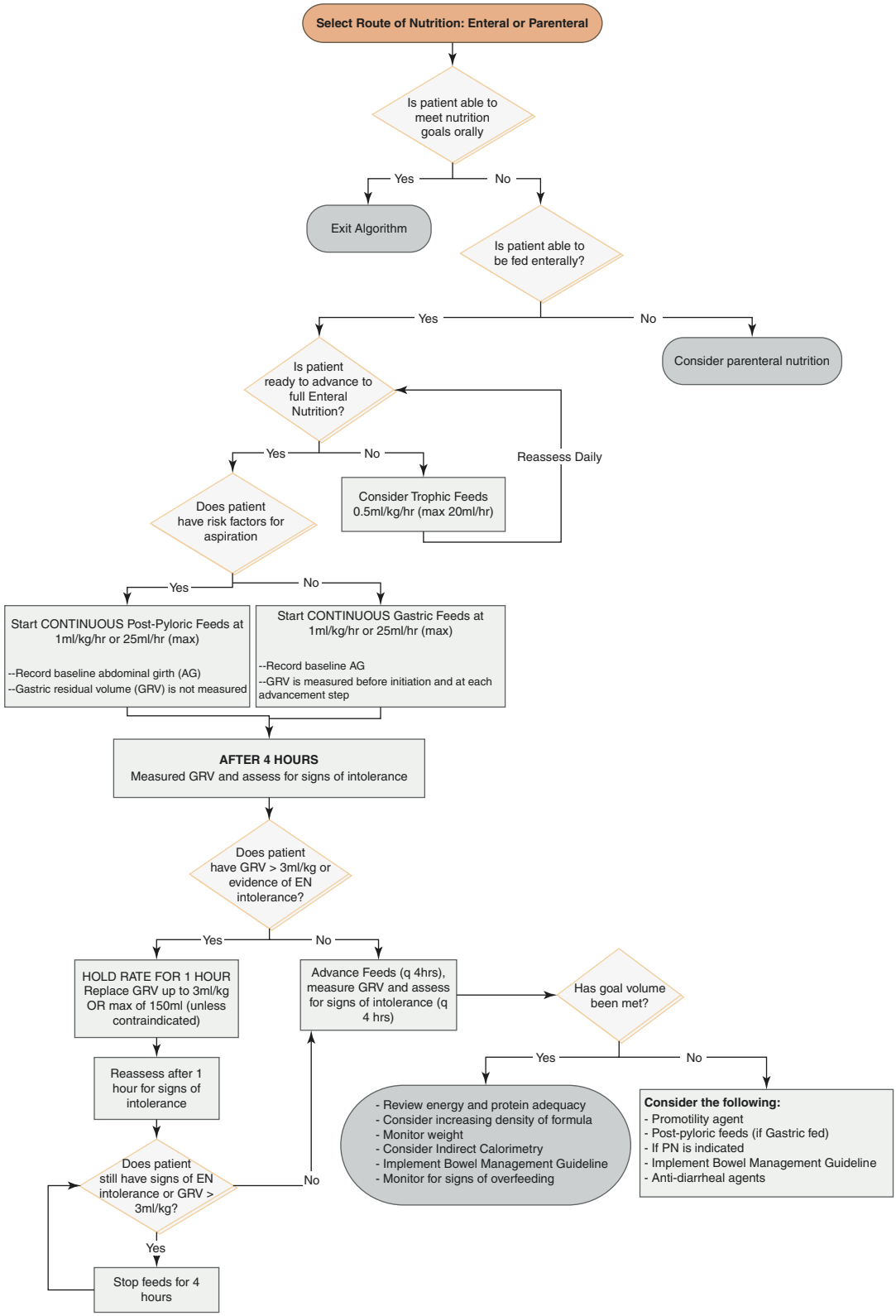

Fig. 8.5 Example of a stepwise algorithm for initiating and advancing enteral nutrition [95]. (Reproduced with permission)

ished, at high risk for nutritional deterioration during their hospitalization (i.e., severe burn injury), or a neonate (<30 days old) and not able to achieve energy and protein goals via EN, PN should be initiated.

The optimal timing for initiation of PN remains controversial. Adult studies have reported a potential benefit when PN is initiated after day 3 if nutritional goals are not met by EN but inferior clinical outcomes if PN is initiated earlier [108–111]. Prior to the publication of the PEPaNIC trial, there was a dearth of randomized, controlled trials addressing the effects of PN on clinical outcomes in children [112, 113]. The PEPaNIC trial was a three-center trial in critically ill children who were randomized to receive either an early (<24 h) or late (>7 days) PN strategy. The study demonstrated improved outcomes in the children who received the late PN strategy, specifically by lowering the rate of new infections, decreasing ICU length of stay, shortening the duration of mechanical ventilation, and decreasing renal replacement therapy utilization. Several issues regarding the study methods need to be reviewed: the portion of the calories that were provided via PN was small; energy goals were calculated by predictive equations, putting the subjects at risk for overfeeding; and subjects at risk for malnutrition were treated similarly to those well-nourished and identified using the STRONGkids screening tool, which has not been previously validated in the ICU population [114]. Hence, the current ASPEN/SCCM guidelines recommend exercising caution when applying these results broadly in clinical practice, particularly in vulnerable newborns and severely malnourished children [15]. Furthermore, the recent publication of NUTRIREA-2, a study examining the safety of early enteral versus parenteral nutrition in mechanically ventilated adults with shock, demonstrated no difference in hospital-acquired infections among the two groups and not surprisingly demonstrated an increased rate of feeding intolerance in the enteral group [115]. In summary, the ASPEN/SCCM guidelines advise against initiating PN within the first 24 h of admission and to consider a delayed PN approach in children who are not severely malnourished. Following that recommendation, the timing of supplemental PN needs to be made on an individualized basis and should take in consideration the nutritional and clinical status of the patient.

The macronutrient composition of PN and particularly the alternative lipid emulsions are being extensively studied. Recommendations for protein intake mirror the current enteral recommendations, although further research into the route of protein supplementation and its effects on clinical outcomes is needed [15]. With the recent Food and Drug Administration's (FDA) approval of alternative lipid formulations, emerging literature has indicated benefits in utilizing olive oil- and fish oil-based lipids. Non-soy-based lipid formulations have demonstrated a trend toward improved survival, shorter duration of mechanical ventilation, and ICU length of stay [116, 117]. These clinical improvements are thought to be secondary to higher antioxidant content, immune modulating, and less inflammatory properties [118]. As an additional benefit, these lipid formulations have been shown to reduce the incidence and possibly reverse PN-associated liver disease in patients with short gut syndrome and PN dependence [119].

Additional studies are required to determine the optimal timing for PN initiation and the role of supplemental PN for critically ill children in general. Ongoing research regarding the potential benefits of alternative lipid formulations may lead to a uniform recommendation in the future.

Role of Micronutrients as Immunonutrition

The role of micronutrients as immunomodulators in critically ill patients surfaced as an area of research over a decade ago. Micronutrients and antioxidants were hypothesized to diminish inflammation or replete nutrients depleted by stress. Glutamine, arginine, selenium, copper, and zinc are a few of the studied micronutrients to date. Several randomized controlled trials comparing various forms of immunonutrition have been undertaken and have yet to demonstrate any clinical benefit [120–123]. Furthermore,

a majority of these studies combine the micronutrients making it difficult to interpret the impact of a single micronutrient. Two such examples are glutamine and arginine supplementation. Clinical outcomes in critically ill children prescribed glutamine did not differ when compared to control; however in several adult studies, glutamine has been associated with an increased mortality rate [124, 125]. Likewise, arginine, hypothesized to improve immune function and wound healing, was associated with increased mortality in septic patients in an adult trial [126]. Thus, the potential for harm, paucity of pediatric data, and poor quality of designed studies have led the recent ASPEN/SCCM guidelines to not recommend immunonutrition [15].

Case Scenario Conclusion

To highlight the issues raised in this chapter, we conclude with our recommended management of the patient in the opening vignette.

Anthropometric measurements were obtained upon admission, and the patient was described as "well-nourished" based on her normal weight-for-age and height-for-age z-scores. However, given her diagnosis and expected trajectory, she was deemed high risk for experiencing nutritional deterioration while hospitalized. As enteral access was not secured in the operating room and the likelihood of obtaining enteral access within the first 5 days of her admission was low, she was prescribed parenteral nutrition. While sedated, paralyzed, and mechanically ventilated, her total energy and protein goals were calculated to be two-thirds her resting energy expenditure, as estimated by the Schofield equation and ASPEN guidelines. We did not add additional micronutrients to her parenteral nutrition. After her first tracheostomy change and on day 6 of admission, indirect calorimetry was performed and found her to be slightly hypermetabolic – 110% predicted resting expenditure – at which time we adjusted our total energy and protein goals. Given the anticipated prolonged duration of critical illness, she returned to the operating room on day 7 of admission, and a gastrostomy tube was placed. Nutrition was transitioned from exclusively parenteral to enteral nutrition over the next 48 h. To aid our nutrition support care team in tailoring their nutrition prescription, indirect calorimetry was performed weekly while she was in the ICU and continued to show her to be mildly hypermetabolic. She maintained weight during her first 2 weeks of critical illness and then began to gain weight during week 3. She was weaned from mechanical ventilation over her first month of illness and transferred to the surgical ward with a tracheostomy collar in place.

Key Points

1. Malnutrition is prevalent in critically ill children. Simple anthropometric assessment on admission must be prioritized to allow early detection of severely malnourished children who are likely to have worse clinical outcomes.
2. The new definition of pediatric malnutrition includes anthropometry, growth, chronicity of malnutrition, etiology and pathogenesis, and impact on functional outcomes. Screening tools that reliably identify malnourished or at-risk patients in the PICU need to be developed.
3. The metabolic stress response is unpredictable. The catabolism of protein is the characteristic feature and may result in loss of lean mass, which has been associated with poor clinical outcomes. Higher protein delivery is necessary to achieve a positive protein balance. However, the optimal protein dose asso-

ciated with improved clinical outcomes during critical illness is being investigated.
4. Indirect calorimetry remains the gold standard to estimate energy expenditure. Predictive equations to estimate energy expenditure may be inaccurate.
5. Adequacy of nutritional delivery, defined by optimal energy and protein intake, is associated with improved clinical outcomes. Hence, a timely and safe nutrient delivery strategy is an essential part of critical care.
6. Early enteral nutrition is safe and associated with improved clinical outcomes.
7. Supplemental parenteral nutrition should be considered if energy and protein goals have not been achieved via enteral nutrition within the first week of illness.
8. Immunonutrition is currently not recommended.

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9 Medical Management of Acute Liver Failure

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Introduction and Definition

Acute liver failure (ALF) is among the very few dramatically devastating illnesses in medicine. It is a rare disorder characterized by rapid-onset severe hepatocellular injury and dysfunction which can quickly progress to multisystem organ failure and death. It is characterized by signs of severe liver function abnormalities including jaundice, coagulopathy, and/or hepatic encephalopathy within a few weeks of onset of the disease. In adults, ALF is defined as onset of hepatic encephalopathy within 8 weeks of signs of hepatic dysfunction, i.e., jaundice and coagulopathy [1]. This definition of ALF in adults cannot be applied directly to children because it is difficult to accurately assess age-appropriate mental status and exact duration of illness in children. Also, hepatic encephalopathy may not be clinically apparent until terminal stages of liver failure in children [2]. This makes diagnosis of acute liver failure especially challenging in children [3, 4].

The Pediatric Acute Liver Failure (PALF) study group is a multisite, multinational consortium established in 1999 to prospectively study ALF in children [3, 5]. This study group defines PALF as biochemical/laboratory evidence of liver injury in a child with no known evidence of chronic liver disease and:

(a) Prothrombin time (PT) ≥15 s or international normalized ratio (INR) ≥1.5 not corrected by vitamin K administration in presence of hepatic encephalopathy (HE)
(b) PT ≥20 s or INR ≥1.5 not corrected by vitamin K administration irrespective of the presence or absence of hepatic encephalopathy [3]

The exact incidence of PALF is unknown; however, PALF accounts for about 10–15% of pediatric liver transplants performed in the USA annually [6]. A specific diagnosis is not available for almost half of these patients [3]. The data for outcome of this devastating illness is limited. The recent data regarding patient outcome from the PALF study group demonstrated that age less than 3 years, indeterminate or non-acetaminophen-induced liver failure, higher grades of encephalopathy, bilirubin ≥5 mg/dL, and INR ≥2.55 on admission are all associated with worse outcomes [3].

Etiology

The etiology of ALF in children varies between infants versus older children [7]. The most common overall cause of PALF is indeterminate.

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Up to 40–50% patients with PALF lack a specific etiological diagnosis partly due to lack of thorough diagnostic evaluation [8]. In infants, infections and metabolic diseases are the most common known etiologies for PALF [7, 8]. Herpes simplex virus is the most commonly identified infectious etiology in these children. Galactosemia, tyrosinemia, and fatty acid oxidation defect are the commonly identified metabolic disorders in this age group, while neonatal hemochromatosis was the most common cause of liver failure in the neonatal period [7]. In children older than 7 months of age with ALF, drug toxicity, especially with acetaminophen overdose, and autoimmune hepatitis are the most commonly identified etiologies [7, 8]. In developing countries, infectious etiologies remain the most common identified cause of acute liver failure through all age groups. Hepatitis A viral infection is the most common infectious agent in these countries [8].

Diagnostic Evaluation

All children with ALF should undergo thorough systematic evaluation for the underlying etiology of acute liver failure along with the assessment for liver injury, dysfunction, and multisystem complications. This diagnostic evaluation should be individualized and directed toward the age-specific causes of acute liver failure. A detailed medical history including onset of symptoms and neurological changes; history of exposure to infections or medications; family medical history including history of liver disease, consanguinity, genetic, metabolic, or autoimmune diseases; and/or sibling death should be obtained in all patients with acute liver failure. A thorough physical examination with special attention to mentation and neurological status is imperative.

Radiological and laboratory tests in PALF should be obtained to evaluate underlying etiology, to assess the extent of liver injury and failure, or to monitor for potential complications of liver failure. A comprehensive metabolic panel including electrolytes, blood urea nitrogen (BUN), creatinine (Cr), and albumin, liver enzymes, total and fractionated bilirubin, gamma-glutamyl transferase (GGT), coagulation profile along with prothrombin time (PT) with international normalized ratio (INR), a complete blood count with differential and platelets, and a reliable serum ammonia level should be obtained in all the patients at diagnosis and thereafter monitored closely. Additional tests to assess for etiology of liver failure should be tailored to the age and presentation of the illness. These should be targeted to evaluate for infectious, metabolic, and autoimmune liver diseases in addition to drug or other toxin exposures (Table 9.1) [9]. A complete abdominal ultrasound with Doppler should be obtained in all patients with PALF, but additional imaging studies like CT, MRI, and/or MRCP should be considered based on the individual case. Liver biopsy should be considered early in the course of PALF to assess for the cause of liver failure and the extent and pattern of hepatocyte injury. Transjugular approach is preferred in the setting of severe coagulopathy with liver failure. The level of necrosis might be underestimated on liver biopsy [10]. Submassive or massive liver necrosis is associated with poor prognosis [11].

Management

Management of acute liver failure is very challenging due to multiple reasons. The multisystem organ involvement with potential for rapid deterioration and death in absence of timely liver transplant makes this disease one of the most difficult diseases to manage. At the same time, there is a tremendous potential for self-recovery without transplant and unnecessary morbidity can be avoided by preventing transplants in these cases. There is a lack of adequate data on management of PALF due to its rarity and currently, the majority of our clinical practice guidance is derived from adult studies. Hence, many principles of management of this disease are currently unclear and controversial.

Table 9.1 Diagnostic evaluation [85]

Age-based causes	Diagnostic evaluation
Idiopathic or indeterminate (all ages)	Liver function tests: AST, ALT, GGT, alkaline phosphatase, fractionated bilirubin, albumin, total protein Coagulation: PT-INR, aPTT, fibrinogen, factors V, VII, VIII Ammonia level, blood gas, CBC with PLT, and differential Complete metabolic panel: electrolytes, BUN, creatinine, blood glucose, Ca, Mg, P Imaging studies: ultrasound liver with Doppler study Tissue diagnosis: liver biopsy; muscle biopsy as indicated
Infectious:	
1. Infancy: HSV 1 and 2 – most common, enterovirus, adenovirus, hepatitis B, hepatitis C, EBV, CMV, HHV 6, parvovirus 2. Preadolescence: hepatitis A, B, C, D, E, non-A and non-B viral hepatitis, EBV, CMV, enterovirus, adenovirus, HHV-6, parvovirus 3. Adolescents: hepatitis A, B, C, D, E, non-A and non-B viral hepatitis, EBV, CMV	Viral PCR for EBV, CMV, enterovirus, adenovirus, HHV-6, HSV 1 and 2, parvovirus Viral hepatitis serology including anti-HAV Ig M, HBsAg, anti-HBe Ig M and Ig G, anti-HCV, and anti-HEV
Metabolic:	
1. Infancy: fatty acid defects, mitochondrial defects, galactosemia, tyrosinemia, etc. 2. Preadolescence: Wilson's disease, fatty acid oxidation defects, mitochondrial defects, etc. 3. Adolescents: Wilson's disease, etc.	Serum lactate, pyruvate, amino acid profile, carnitine profile, acyl-carnitine profile Urine amino acid/organic acid profile, urine succinylacetone, serum ceruloplasmin, and 24-h urine copper
Immune dysregulation:	
1. Infancy: neonatal hemochromatosis 2. Preadolescence/adolescence: autoimmune hepatitis, HLH	Ferritin, iron, TIBC Antinuclear antibody, anti-smooth muscle antibody, anti-liver-kidney-microsome antibody, Ig G level, anti-soluble liver antigen/anti-liver pancreas antibody, anti-liver cytosol type I antigen
Drug toxicity or accidental ingestion:	
1. Infancy: acetaminophen, acetylsalicylic acid, valproic acid, etc. 2. Adolescence: acetaminophen, tetracycline, ecstasy, toxic mushroom *Amanita phalloides* poisoning, etc.	Serum acetaminophen level, urine toxicology screen

HSV herpes simplex virus, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus, *HHV-6* human herpesvirus 6, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *PT-INR* prothrombin time and international normalized ratio, *aPTT* activated partial thromboplastin time, *PCR* polymerase chain reaction, *HAV* hepatitis A virus, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C Virus, *HEV* hepatitis E virus, *TIBC* total iron-binding capacity, *HLH* hemophagocytic lymphohistiocytosis

General Principles of Management

Pediatric patients with acute liver failure are best managed in intensive care units (ICU) by a multidisciplinary medical team. Intensive care units play a pivotal role by close monitoring and supporting of failing organs as well as providing clinical stability for multiple lifesaving interventions. Advances in critical care have contributed significantly toward decreasing mortality in adult ALF patients [12]. We can safely assume that similar advances in pediatric critical care will definitely improve outcomes in PALF.

Patients with PALF demonstrating signs of altered mental status and/or worsening coagulopathy should be closely monitored in the ICU with frequent neurological and cardiorespiratory assessments. After initial

characterization of presentation and stabilization of the patient, further management should be focused on monitoring and supporting the patient and organ systems, identifying and treating complications (Table 9.2), employing targeted diagnostic evaluation, and optimizing outcomes [5].

Close collaboration between pediatric intensivist, pediatric hepatologist, transplant surgeons, neurologist, nephrologist, and metabolic/genetic disease specialist is crucial to provide the best outcome for the patient. Early transfer to a transplant center should be of utmost importance to facilitate the multidisciplinary approach and

Table 9.2 Management of complications in PALF [85]

Organ system	Complications	Management of complications
Central nervous system	Hepatic encephalopathy Cerebral edema Intracranial hypertension	Supportive care in ICU, minimal stimulation Endotracheal intubation for grade 3 or 4 encephalopathy Consider CT/MRI head for any acute mental status changes Prophylactic HTS (3–30%) or mannitol 0.25–1.0 gm/kg IV bolus, repeated once or twice
Cardiovascular	Systemic hypotension due to intravascular volume depletion Hyperdynamic circulatory failure	Adequate fluid resuscitation with IV crystalloids Norepinephrine for volume-refractory hypotension Consider vasopressin and its analogs
Adrenal	Relative adrenal insufficiency (RAI) Hepatoadrenal syndrome	Consider a trial of systemic steroids in patients with persistent vasopressor, fluid refractory shock
Respiratory	Acute respiratory failure Pulmonary edema Pulmonary hemorrhage Acute respiratory distress syndrome (ARDS)	Endotracheal intubation for respiratory failure or airway protection in advanced stages of hepatic encephalopathy Ventilator strategies: low tidal volumes (5–8 ml/kg of predicted weight) and moderately elevated PEEP levels; avoid sustained hyperventilation
Renal	Acute kidney injury (AKI) Hepatorenal syndrome	Preventive measures: maintain fluid balance, minimize nephrotoxic medications or IV contrast CRRT is preferred
Fluid, electrolytes, and nutrition	Hypoglycemia Hyperammonemia Intravascular volume depletion Alkalosis and acidosis Electrolyte abnormalities Catabolic state with negative nitrogen balance and increased energy expenditure	Continuous glucose infusion to maintain euglycemia Consider CRRT Frequent monitoring and correction of electrolytes and acid-base balance Avoid hyponatremia to prevent cerebral edema Enteral nutrition with high caloric density formula to avoid excess free water Parenteral nutrition: a safe second-line choice in patients who cannot be fed enterally
Hematological	Coagulopathy not corrected by vitamin K administration Disseminated intravascular coagulopathy	Plasma or platelet transfusions only recommended prior to invasive procedure or during active bleeding Vitamin K administration is recommended
Gastrointestinal	Gastrointestinal bleeding Ascites	H2 blocker or proton pump inhibitors for prophylaxis of gastrointestinal bleed Spironolactone for diuresis in patients with ascites who have respiratory compromise or discomfort
Infectious	Systemic inflammatory response syndrome Bacterial infections such as staphylococci, streptococci, and enteric gram-negative bacteria	Aggressive surveillance with cultures and empiric antibiotics in the presence of SIRS, worsening encephalopathy, refractory hypotension No role for prophylactic antimicrobials

HTS hypertonic saline, *CRRT* continuous renal replacement therapy, *SIRS* systemic inflammatory response syndrome

timely decision-making for critical aspects of patient care and interventions including transplantation and its evaluation.

Central Nervous System

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with liver failure in the absence of a preexisting brain disease. It is characterized by progressive but reversible deterioration of behavior, cognition, and mentation in patients with PALF. The clinical features of hepatic encephalopathy can range from overt coma to irritability to minor changes in behavior and motor or cognitive skills. In children, features of HE can be subtle and difficult to assess and range from mild irritability to inactivity to coma. Table 9.3 describes the clinical stages of encephalopathy originally developed to assess patients with cirrhosis but is used in ALF for the lack of a better clinical tool. In the Pediatric Acute Liver Failure study group database, the majority of the patients (75%) had grade 1–2 hepatic encephalopathy, and grade 3 and 4 encephalopathy were seen in 17% and 7% patients, respectively. Out of 348 patients included in this study group, more than half developed hepatic encephalopathy [3].

The exact pathogenesis of hepatic encephalopathy is complex, is not completely understood, and involves a number of interrelated factors [4, 13]. Ammonia is a by-product of nitrogen metabolism that is generated from the breakdown of glutamine by glutaminase, an enzyme within the enterocytes of the small intestine and colon, and by urease-producing bacteria that inhabit the gut. This gut-derived ammonia enters the urea cycle to be detoxified into urea and excreted in the urine. Ammonia that bypasses this detoxification is converted to glutamine in hepatocytes, skeletal myocytes, and astrocytes in brain. Astrocytes are the most abundant type of cells in the brain. They are very sensitive to a rapid increase in ammonia, which subsequently leads to cellular edema due to increased influx of water secondary to osmotic gradient created by increased intracellular glutamine. Although hyperammonemia has been implicated to play a pivotal role in development of hepatic encephalopathy, a consistent correlation between the plasma concentration of ammonia and clinical manifestation of HE has not been established [14]. In addition to hyperammonemia, increased proinflammatory circulatory cytokines like IL-1β, IL-6, and TNF-α can modulate cerebral blood flow and cellular permeability to have direct or permissive effects on development and progression of HE into cerebral edema [15].

Management of Hepatic Encephalopathy

Given the potential for rapid neurological deterioration in patients with PALF and HE, early recognition and prompt management of HE are

Table 9.3 Stage of encephalopathy [4, 5]

Grade	Symptoms	Signs	Reflexes	EEG
Grade 0	Normal	None	Normal	Normal
Grade 1	Inconsolable crying, confused, not acting like self	Difficult to examine	Difficult to examine; normal or hyperreflexic if able to examine	Difficult to obtain
Grade 2	Inconsolable crying, drowsiness, not acting like self	Difficult to examine	Normal or hyperreflexic	Difficult to obtain
Grade 3	Combativeness, increasing somnolence, stupor	Rigidity	Hyperreflexic, positive Babinski sign	Generalized slowing
Grade 4	Comatose, may or may not arouse with painful stimuli	Decerebrate or decorticate posturing	Absent	Abnormal, very slow, delta activity

necessary to decrease morbidity and mortality in these patients. As mentioned above, these patients should be closely monitored in a critical care setting with frequent neurological assessments. There should be minimal stimulation, and unnecessary interventions should be avoided. Endotracheal intubation for airway protection or controlled ventilation in advanced stages of encephalopathy should be considered. Head of the bed should be elevated to 20–30°, and the patient's head should be maintained in the midline to provide optimal CSF drainage and jugular venous outflow. Aggressive efforts to maintain normothermia are crucial as fever and shivering may exacerbate intracranial pressure (ICP). Ventilation, oxygenation, and mean arterial pressures should be meticulously monitored and maintained.

Lactulose and nonabsorbable oral antibiotics like neomycin and rifaximin have been used for prophylaxis and management of HE in patients with chronic liver disease and cirrhosis. Lactulose is a synthetic nonabsorbable disaccharide which can be used to decrease intraluminal pH in the colon and prevent uptake of ammonia from the gastrointestinal lumen. Given the central role of increased arterial ammonia levels in the pathogenesis of hepatic encephalopathy, one could assume that ammonia-lowering strategies might be effective in halting the progression of neurological deterioration. While the abovementioned agents have a role in preventing progression of HE associated with cirrhosis in patients with chronic liver disease, there are no controlled trials to support the use of these medications to treat hepatic encephalopathy in ALF [16–18]. In one nonrandomized retrospective series, there was no improvement in outcome with lactulose therapy [19]. Lactulose use should be avoided in PALF as it has the potential to cause intravascular volume depletion, hypernatremia, and bowel distension or megacolon, which can be dangerous during transplant [16, 17]. Neomycin is also not recommended due to increased risk of nephrotoxicity [16]. L-Ornithine L-aspartate (LOLA) and L-ornithine phenyl acetate (LOPA) have shown promising results in adult trials [20]. These work by increasing renal excretion of ammonia. Currently, there is no data to support their use in PALF. The benefit of continuous renal replacement therapy (CRRT) in reducing serum ammonia and improving 21-day transplant-free survival has been demonstrated in a recent cohort study from US ALF study group registry [21].

Management of Intracranial Hypertension and Cerebral Edema

The goal in the management of cerebral edema and intracranial hypertension is maintaining adequate cerebral perfusion pressure (CPP) while lowering and maintaining intracranial pressure (ICP) to less than 20 mm Hg to assure adequate perfusion of the brain [4, 22]. Close clinical monitoring is strongly recommended but highly challenging in pediatric patients, especially if they have progressed to grade 3–4 HE. Cushing's triad of irregular breathing, systemic hypertension, and bradycardia is not uniformly present. Intracranial pressure monitoring can be used to assess CPP to avoid hypoxic brain injury. Multiple studies have been done to evaluate the safety and efficacy of invasive intracranial pressure monitoring in management of ALF, but there has been no demonstrated improvement in survival [23–25]. The use of invasive intracranial monitoring in PALF is controversial owing to the lack of sufficient evidence for its routine use and safety. Maintaining systemic blood pressure by adequate volume resuscitation and use of vasoactive medications as well as aggressively treating fluid overload with CRRT are crucial to maintain adequate CPP.

The principal therapy to reduce cerebral edema and increased intracranial pressure is administration of osmotic agents like hypertonic saline and mannitol [26]. Mannitol is a hyperosmolar agent, which works by promoting movement of water from astrocytes into the serum by increasing osmolality of serum. Mannitol also decreases viscosity of blood causing vasoconstriction, which leads to less cerebral blood volume and decreased ICP. It is used as a first-line agent in management of increased ICP in adults with ALF [16, 17]. The recommended dose for

use is 0.25–1.0 gm/kg IV bolus that can be repeated once or twice [16, 17]. The majority of information on mannitol in PALF is extrapolated from adult literature. The effect of mannitol is transient, and it is difficult to achieve sustained reduction of ICP to acceptable levels with mannitol alone. The use of mannitol is not recommended in presence of renal failure, hypovolemia, or serum osmolality >320 mOsm/L [16, 17].

Hypertonic saline (3–30%) decreases ICP by mechanisms similar to mannitol. In addition, it also stabilizes cerebral endothelial cell volume and improves cerebral circulation. In a randomized controlled trial from King's College, patients who received hypertonic saline had decreased ICP from baseline in the first 24 h, and the incidence of ICP >25 mm Hg or greater was significantly lower than control group; however, it did not show improved survival in patients treated with HTS [27]. The use of hypertonic saline in treatment of elevated ICP in PALF has not been studied. In patients with PALF who have elevated ICP, it is reasonable to maintain serum sodium level around 145–150 mmol/L, especially now that hypertonic saline has been established as a standard of care in management of pediatric patients with traumatic brain injury [28]. There are no randomized clinical trials regarding the use of hypertonic saline or mannitol in children. Hypertonic saline provides all benefits of hyperosmolar agent without the hemodynamic side effects associated with mannitol. According to 2012 guidelines for the medical management of severe traumatic brain injury in children, use of hypertonic saline is favored over the use of mannitol for management of ICH [29].

Patients with ALF hyperventilate due to the metabolic milieu associated with ALF, and this, in turn, helps restore cerebral autoregulation, vasoconstriction, and reduction of ICP. Effects of hyperventilation are temporary and continuous hyperventilation offers no survival benefit in patients with ALF [30]. Moreover, it has the potential to worsen cerebral edema due to cerebral hypoperfusion. According to American Association for the Study of Liver Disease (AASLD) position paper for management of ALF, hyperventilation may be used to manage acute life-threatening mannitol-refractory worsening of intracranial pressure to delay impending cerebral herniation, but sustained hyperventilation should be avoided in patients with ALF.

Hypothermia prevents cerebral edema by decreasing cerebral metabolism, neuronal inflammation, and oxidative stress. It also decreases ammonia level and improves cerebral hemodynamics. Therapeutic hypothermia to 32–35° has been used in adults with ALF to reduce ICP for successfully bridging these patients to liver transplantation. There have been a few reports of beneficial effects of therapeutic hypothermia in adult patients with ALF [31, 32]. However, there have been complications reported with therapeutic hypothermia too. These include cardiac dysrhythmias, increased risk of infection, coagulopathy, electrolyte disturbances, hyperglycemia, and theoretical decreased hepatic regeneration [31, 32]. A multicenter retrospective cohort analysis of 97 patients enrolled in the US ALF study group did not find a difference in 21-day mortality as well as transplant-free survival with or without the use of therapeutic hypothermia [33]. There is no data to support the use of therapeutic hypothermia for neuroprotection. However, hyperthermia should be aggressively managed to avoid worsening of ICP. Currently, active normothermia (36–37°) remains the standard of care as it offers the best risk-benefit ratio [4].

Early identification of neurological decline and timely therapeutic interventions to minimize neurological morbidity are crucial in ALF because neurological morbidity is a major determinant of outcome in ALF [4]. However, clinical assessment of neurological status in pediatric patients can be difficult. Head imaging with computerized tomography (CT) scan is used to exclude intracranial hemorrhage as a cause of sudden decline in neurological status. However, in a recent single-center retrospective pediatric study assessing the role EEG in management of PALF by Hussain et al. [34], CT and magnetic resonance imaging (MRI), even though abnormal in 13% of patients, failed to demonstrate consistent abnormalities to suggest the presence of cerebral edema. There was no association between EEG and CT/MRI findings in this study.

However, there was increased mortality in patients with certain EEG abnormalities. These included moderate to severe slowing, epileptiform discharge, and electrographic seizure. EEG seems to be a very sensitive tool to screen not only for subclinical seizures but also declining neurological status in patients progressing to grade 3 or 4 encephalopathy or with unexplained clinical deterioration [34, 35]. Transcranial Doppler ultrasonography has been shown to be helpful in measuring dynamic changes in ICP in a small retrospective study in adults with ALF [36]. There are no studies for this diagnostic modality in PALF.

Seizure activity worsens cerebral edema by increasing the oxygen requirement of the astrocytes [35]. The true frequency of seizures in patients with ALF may be underestimated without continuous EEG. In the study by Hussain et al. 11% of patients had clinical seizures; however, almost 5% of patients had subclinical nonconvulsive seizures [34]. Continuous EEG should be used in patients with grade 3 or 4 HE or with acute decline in neurological status to rule out subclinical seizures [4, 35]. Aggressive antiepileptic therapy should be implemented to control seizures to prevent further neurological morbidity. Phenytoin can be used for prompt control of epileptiform activity, and short-acting benzodiazepines can be used in phenytoin-refractory cases [17]. Valproic acid should be avoided if mitochondrial disease is suspected as the underlying etiology for ALF. Prophylactic phenytoin has been tried to suppress subclinical epileptiform activity in adults with ALF; however, a subsequent trial demonstrated no benefit of its use in preventing seizures, brain edema, or improving survival [35, 37]. There are no pediatric trials to support the use of prophylactic phenytoin in management of PALF. Prophylactic phenytoin, therefore, cannot be recommended in PALF at this time. Although there are rare reports of drug-induced liver injury with levetiracetam, it can be safely used in management of seizures in PALF.

Pain can arise from multiple diagnostic and therapeutic interventions and procedures in patients with PALF. Psychomotor agitation is known to increase ICP, and this may be especially deleterious in advanced stages of hepatic encephalopathy. Pain management and sedation are important components of critical care management of children with ALF. Sedating nonintubated patients may be necessary, and anxiolytics should be used after carefully weighing the benefit of reducing agitation versus blunting the signs of neurological deterioration and exacerbating encephalopathy [4]. Also, numerous drugs used for sedation and analgesia have hepatic or renal clearance. There is a lack of sufficient data for the use of standard sedative or analgesic agents in PALF. Short-acting agents, with appropriate dose adjustments for liver dysfunction, should be used. Benzodiazepines can have prolonged sedative effect when used in patients with hepatic impairment and should be avoided. Furthermore, benzodiazepines and propofol have the potential to worsen HE by increasing gamma-aminobutyric acid (GABA) neurotransmission [38]. Propofol in limited doses and for short period of time may be used in older children without mitochondrial disease, due to shorter recovery time and neuroprotective effect through decreased cerebral blood flow and decrease in ICP [4, 39]. Opioid agents with short half-life such as fentanyl and remifentanil can be used concurrently to improve cardiovascular stability [16]. Dose adjustments are recommended while using dexmedetomidine for its sedative and analgesic effect in PALF as it is metabolized primarily in the liver [40]. Atracurium and cisatracurium are the preferred agents for neuromuscular blockade in PALF. These undergo ester hydrolysis and Hoffman elimination, and their duration of action in liver failure is similar to the same in normal liver function [41]. Vecuronium and rocuronium should be avoided in ALF as they undergo hepatic metabolism.

Cardiovascular

Hyperdynamic circulatory failure with low mean arterial pressure occurs in ALF due to peripheral vasodilation caused by elevated circulatory cytokines. This significantly decreases peripheral tissue oxygenation exacerbating multi-organ

failure. Depleted intravascular volume due to decreased intake as well as increased transudation into extravascular space adds to this hemodynamic instability.

As with any patient with hypotension, intravascular volume status should be assessed and replenished with adequate volume replacement [17]. If the patient remains hypotensive after fluid resuscitation, vasopressors should be initiated to maintain mean arterial pressures within the age-appropriate normal range. This is crucial to assure adequate cerebral perfusion pressure. Norepinephrine has been the preferred agent in adults, mainly, because it provides a more consistent and predictable increase in cerebral perfusion while minimizing tachycardia and preserving splanchnic circulation [16]. Despite the lack of adequate pediatric data on choice of vasopressors, norepinephrine does seem to be a reasonable choice to optimize organ perfusion in PALF [4]. Vasopressin and its analogues can be used in volume- and norepinephrine-refractory cases to potentiate its effects; however, these should be used cautiously due to the potential direct cerebral vasodilatory effect that may worsen intracranial hypertension [16, 17]. Echocardiography can be used to assess for systolic and diastolic dysfunction in patients not responding to volume and vasoactive support.

Adrenal

Although there is a discrepancy in the definition, relative adrenal insufficiency/hepatoadrenal syndrome has been well described in septic shock as well as ALF [42]. A third of adults with ALF may develop relative adrenal insufficiency, and its incidence seems to be directly proportional to the severity of liver failure [43]. Low HDL levels with increased circulatory endotoxins and proinflammatory markers like TNF-α lead to impaired cortisol secretion and impaired adrenal function that can depress sensitivity to catecholamines [43, 44]. No data is available to define this condition in PALF or to guide diagnosis and management of relative adrenal insufficiency in PALF. However, children with PALF and vasopressor/fluid refractory hypotension may benefit from a trial of systemic corticosteroid administration [16, 45, 46].

Respiratory

In adults, about 20–30% patients with ALF are diagnosed with acute respiratory distress syndrome (ARDS) [47]. Exact incidence of ARDS in PALF is unknown. According to the PALF study group data, almost 40% children with PALF required ventilator support [3]. Endotracheal intubation may be required in PALF either for airway protection in patients with hepatic encephalopathy or for management of respiratory failure secondary to sepsis, fluid overload-associated pulmonary edema, pulmonary hemorrhage, or ARDS.

There are no pediatric trials directing mechanical ventilation in children with PALF. Mechanical ventilation strategies in PALF should aim at decreasing ventilator associated lung injury while providing maximum neuroprotection in the setting of elevated intracranial pressure. Conservative tidal volume ventilation (5–8 ml/kg of predicted body weight) with moderately elevated positive end expiratory pressures should be titrated to maintain normocapnia and avoid hypoxemia [48]. As mentioned above, sustained hyperventilation should be avoided as the effects of hyperventilation on intracranial pressure are temporary, and there is a potential risk of worsening cerebral edema by causing cerebral hypoxia [17]; however, it may be used briefly in sudden life-threatening worsening of intracranial pressure that is refractory to osmotic agents to delay impending cerebral herniation.

Renal

Acute kidney injury (AKI), and subsequent renal failure, is a relatively common complication of ALF. In large retrospective review using patients in the US Acute Liver Failure study group (ALFSG), AKI was seen in almost 47% patients with ALF [49]. In this study, there was decreased

overall survival in patients with AKI versus patients without AKI. Also, there was decreased transplant-free survival in patients needing renal replacement therapy (RRT) or with advanced AKI versus those without AKI [49]. Although exact incidence of AKI in PALF is unknown, the prospective PALF study reported the need for hemofiltration in nearly 10% of patients [3]. AKI has been reported in 15–20% of children with ALF where it was associated with decreased survival [50].

AKI in ALF can be multifactorial, and causes include hypovolemia, sepsis, acute tubular necrosis, nephrotoxic medications, acetaminophen-induced renal injury, and functional renal failure [51, 52]. Functional renal failure can arise from a mechanism similar to hepatorenal syndrome in chronic liver disease. Intrarenal vasoconstriction leads to decreased renal perfusion and subsequent kidney injury [51–53].

Assessment of renal dysfunction in children with ALF may be augmented by using multiple criteria such as the combination of serum creatinine (sCr), urinary output, and fluid balance aid in diagnosing AKI. SCr by itself may overestimate renal function, and change of SCr over baseline is more relevant over a single value to assess progression of renal injury [54, 55]. Urinary biomarkers like neutrophil gelatinase-associated lipocalin, IL-18, kidney injury molecule-1, and liver-type fatty acid-binding protein are emerging for evaluation of pediatric AKI; however, these have not been studied in PALF [56].

Management of AKI in PALF should be focused on interventions to reduce kidney injury and prevent progression to renal failure. Adequate hydration, avoiding excessive diuresis, maintaining adequate renal perfusion pressure, and minimizing the use or adjusting the dose of intravenous contrast and nephrotoxic medications are some measures to prevent AKI in ALF [16, 17, 52]. Intravenous fluid challenge should be considered in patients with suspected prerenal azotemia, but volume overload should be avoided in patients with PALF [4].

The criteria for initiation or discontinuation of RRT in PALF are ill-defined due to lack of sufficient data. RRT (hemofiltration or dialysis) can help correct electrolyte imbalances, worsening acidosis, fluid overload, and hyperammonemia. The degree of kidney injury, electrolyte disturbance, and fluid imbalance should be integrated into the decision to start RRT in patients with PALF [4]. Continuous renal replacement therapy is preferred over intermittent hemodialysis due to lower risk of hemodynamic instability and worsening ICP [17, 55]. In a recent study on a large cohort of patients enrolled in ALFSG, serum ammonia modulation with CRRT improved 21-day transplant-free survival [21]. Although there is inadequate data in PALF regarding use of CRRT in management of HE, early use of CRRT should be considered in patients at a greater risk of progression of HE (e.g., high-grade encephalopathy, advanced AKI, vasopressors, etc.).

AKI in PALF resolves after restoration of liver function in majority of cases. However, in certain circumstances, simultaneous liver and kidney transplantation must be considered. In adults, indications for concurrent liver/kidney transplantations are based on degree and duration of renal injury and are strongly considered if patient has needed dialysis for 8–12 weeks [57]. However, there is minimal data, mainly based on single-center experience, available for guidance regarding liver/kidney transplant in children [58].

Fluid, Electrolytes, and Nutrition

Acid-base imbalances, electrolyte abnormalities, and metabolic derangements are common in PALF and need to be identified and corrected fastidiously due to their life-threatening potential. Serum electrolytes should be monitored frequently and corrected meticulously to prevent mortality and decrease morbidity in these critically ill patients. Alkalosis and acidosis both may occur in ALF and should be managed by correcting the cause of acid-base imbalance [17]. Hyponatremia and hypokalemia can be secondary to ascites, dilution from aggressive volume resuscitation, and urinary losses from diuretic use. Hyponatremia should be strictly avoided as it can exacerbate cerebral edema.

Hypophosphatemia, hypocalcemia, and hypomagnesemia are commonly observed, can be profound, and should be corrected.

ALF is a catabolic state with negative nitrogen balance due to decreased oral intake and increased energy expenditure. Caloric requirements in these patients increase by about 20% [59]. There is some data to guide nutrition in children with chronic liver disease and cirrhosis which can be extrapolated to PALF in the absence of studies to guide nutritional support in PALF [59]. Nutrition in PALF should be aimed at providing adequate calories to meet the metabolic needs, enough glucose to maintain euglycemia, and appropriate amounts of protein to overcome negative nitrogen balance without worsening hyperammonemia [60]. In general, enteral feeds should be used when possible. Formula with high caloric density should be preferred to avoid excess free water administration [16]. Parenteral nutrition is safe in PALF and can be used as a second-line option to provide adequate nutrition in patients who cannot tolerate enteral feedings [60]. When using parenteral nutrition, intravenous lipids can be used as a source of nutrition; however, they should be avoided in patients with some disorders such as mitochondrial diseases due to the concern for abnormal fat metabolism [61]. Glucose infusion rates as high as 10–15 mg/kg/min may be required to maintain euglycemia in patients with ALF [4]. Children with ALF have dysregulated homeostatic responses to hypoglycemia, and signs of hypoglycemia may be obscured in the patients with HE. Even though tight glycemic control is promoted for critically ill patients in certain ICUs across the nation, a significant risk can be created with such aggressive interventions in children with PALF and should be avoided [4, 16, 17].

Hematology-Coagulopathy

In a recent study on 1770 adults with ALF enrolled in ALFSG, spontaneous or post-procedural bleeding was deemed as a proximate cause of death in less than 5% of patients, half of whom had bled after the placement of an ICP monitor [62]. Overall incidence of bleeding was about 10% with spontaneous upper gastrointestinal bleed being the most common location in ALF. Although elevated INR with or without encephalopathy is a universal requirement for diagnosing a patient with ALF, INR is not a good predictor of risk of bleeding. Elevation in INR is due to decrease in both pro- and anticoagulant factors, and it reflects the synthetic dysfunction of the liver more precisely than the risk of bleeding in ALF. In the abovementioned study, a low platelet count, severity of systemic complications, and SIRS were found to be more important risk factors for bleeding than INR [62]. Platelet count as well as some less commonly used coagulation tests like thromboelastography may be better in assessing the severity of bleeding diathesis [63, 64] as well as guiding potential interventions.

Administration of vitamin K is recommended as vitamin K deficiency has been reported in adults with ALF [65]. Prophylactic administration of plasma to correct INR may be deleterious not only due to associated adverse effects of volume overload, transfusion-related lung injury, and immune dysregulation but also due to its potential to exacerbate a preexisting hypercoagulable state leading to microvascular thrombosis worsening the primary hepatic injury [62]. However, plasma transfusion can be used prior to invasive procedures or in the setting of active bleeding [17]. In patients with ALF at risk of volume overload due to renal injury, recombinant factor VIIa (rFVIIa) can be used to facilitate invasive procedures; however, these must be used with caution as systemic venous thrombosis has been reported with its use [66, 67]. Platelet transfusions are advised if platelets <10,000 or <50,000 with evidence of overt bleeding or need for invasive procedure. However, platelet transfusion is not recommended for platelet count >50,000 [16, 17].

Gastrointestinal

Clinically significant bleeding is rare despite the degree of elevation of INR [68]. Gastrointestinal

bleeding in patients with ALF is mainly stress induced or acid related. The AASLD guidelines on management of ALF recommend H2 blockers or proton pump inhibitors (PPI) for prophylactic prevention of this type of GI bleeding [17]. Variceal bleeding is rare in patients with ALF. Ascites may develop in a minority of patients with ALF, and spironolactone is the drug of choice to manage ascites of hepatic origin. Diuresis is indicated only if there is respiratory compromise or significant discomfort due to abdominal distension. Aggressive diuresis should be avoided to prevent precipitation of hepatorenal syndrome [5].

Infection: SIRS

The liver is involved in multiple immune-related functions which are disturbed in ALF making these patients more susceptible to infection. Additionally, these patients have defects in many other host defense mechanism pathways which decrease their ability to fight against infections. As a result, infection and systemic inflammatory response syndrome contribute to significant morbidity and mortality in these patients. Bacterial infections account for 10–37% of mortality in adults with ALF [69, 70]. In a retrospective review, the incidence of bacterial infection in children with PALF was about 25%, and bacterial infections were associated with increased morbidity in these patients [71]. Systemic inflammatory response syndrome (SIRS) has been reported in 50–60% of adults with ALF [69]. Increased SIRS components are directly correlated to increasing mortality and are strongly associated with worsening encephalopathy. Encephalopathy has been shown to progress in majority of patients with infection and in 50% of patients with greater than two SIRS components versus 25% of patients without SIRS [72]. There are no retrospective or prospective studies to assess the association or incidence of infection or SIRS with outcomes in PALF.

In spite of several studies examining the use of prophylactic antibiotics in management of ALF, the results remain inconclusive. There are no clear guidelines for the use of prophylactic antibiotics or antifungals for liver failure in adults or children, and these should be avoided [16, 17]. Pulmonary, urinary, and blood stream infections are the most common sites for bacterial infection, and gram-positive cocci like staphylococci and streptococci and enteric gram-negative bacilli are the most commonly isolated organisms [66]. Obtaining appropriate evaluations in patients with ALF and signs/symptoms of infection should not be delayed. This may include chest x-ray and urine and blood cultures with any suspicion of infection, SIRS, refractory hypotension, or worsening encephalopathy [16, 17]. Empiric antibiotics should be initiated in patients exhibiting SIRS and should have adequate coverage for the abovementioned bacterial infections.

Liver Support Systems

In acute liver failure, CRRT is highly effective in the removal of smaller molecules of water-soluble toxins, i.e., urea, ammonia, etc. However, the larger or albumin-bound non-water-soluble molecules like cytokines, bile acids, bilirubin, and metabolites of aromatic amino acids and medium chain fatty acids are not successfully removed during hemodialysis. These large albumin-bound non-soluble molecules accumulate and contribute to progression of liver failure [73, 74]. High-volume hemofiltration has been used to remove circulatory cytokines and was associated with improved hemodynamics and encephalopathy [75]. In a randomized control trial in adults with ALF, high-volume nonselective plasmapheresis demonstrated improved transplant-free survival when compared to a control group along with decreased SIRS score and SOFA score [76]. High-volume plasmapheresis dampened innate immune response, and early use of plasmapheresis might provide a window of homeostasis for the liver to regenerate [76]. However, a small retrospective pediatric study failed to show survival benefit with the use of plasma exchange [77].

Artificial Support Systems

Artificial and bioartificial systems have been devised to help detoxify the plasma or blood and support the patient either until the native liver recovers or as a bridge to transplant. The artificial support systems use series of filters to provide detoxification support. These sorbent-based systems use adherent particles in an extracorporeal circuit to help detoxify the blood from various cytokines which indirectly help improve the biochemical and clinical parameters in patients. Molecular adsorbent recirculating system (MARS) and Prometheus are the two commercially available liver support systems. These have been successfully used in adults with ALF to improve biochemical parameters like ammonia as well as HE [78]. However, a recent RCT failed to demonstrate any survival benefit with the use of MARS in patients with liver failure [79]. A recent pediatric case series on use of MARS in 20 patients with PALF reported significant improvement in serum ammonia, bilirubin, bile acids, and creatinine levels but without any survival benefit [80].

Bioartificial Support Systems

The bioartificial or biologic systems use cellular material which, in theory, not only provide detoxification but have the potential to mimic synthetic functions of the hepatocytes. These types of support systems use hepatocytes, human or nonhuman in origin, with or without concurrent use of other sorbents. Five such systems are currently being clinically tested. These include HepatAssist™, extracorporeal liver support device (ELAD™), modular extracorporeal liver support system (MELS™), bioartificial liver support system (BLSS™), and Amsterdam Medical Center bioartificial liver (AMC-BAL™). A randomized control trial assessing the role of bioartificial liver support system did not demonstrate any benefit in survival between treatment and control group [81].

The limited studies evaluating the role of artificial and bioartificial liver support systems have demonstrated improvements in biochemical profile but have limited clinical and survival benefits. Plasma exchange may improve survival; however, further studies are needed to justify its use in PALF. Based on lack of convincing survival benefit in adult studies and paucity of data in PALF, liver support systems are not currently advocated in children with liver failure [82].

Liver Transplantation

Liver transplantation is a lifesaving intervention in patients who fail to show signs of spontaneous recovery with supportive care and have otherwise guarded prognosis. Timely transplantation is critical to minimize posttransplant morbidity and improve survival in these patients. About 10% of pediatric liver transplants in the USA are performed on children with PALF [6]. Uncontrolled sepsis, certain mitochondrial disorders, and cerebral edema with uncal herniation are contraindications for liver transplant, and the AASLD guidelines for evaluation of a pediatric patient for liver transplantation recommend identifying underlying etiology for PALF to recognize treatable etiologies (Table 9.4) as well as contraindications for liver transplant [83].

Liver transplantation for ALF has been associated with inferior outcomes than liver transplantation for chronic liver diseases [84]. In the SPLIT database, factors predicting worse outcomes were age <1 year, advanced/grade 4 HE, and need for dialysis prior to transplantation [84]. In a recent single-center outcome report on 122 PALF patients who underwent liver transplantation, 1-year, 5-year, and 10-year survival rates were 81%, 77%, and 73%, respectively [85]. In the same study, low creatinine clearance and less than 7 days between onset or jaundice and encephalopathy were associated with poor patient survival. Age less than 2 years, low creatinine clearance, and PELD/MELD score greater than 25 were associated with increased graft loss [85].

Table 9.4 Etiology specific treatment [4, 5]

Etiology	Diagnosis	Treatment
Infections		
Hepatitis B	Hepatitis B PCR, hepatitis B surface or e antigen	Lamivudine, tenofovir, entecavir
HSV 1,2	Viral PCR, viral culture from vesicles, oropharynx, conjunctiva, blood, and CSF	IV acyclovir
Enterovirus	Viral PCR	Pleconaril – possibly helpful
Parvovirus	Viral PCR	IV immunoglobulin – possibly helpful
Metabolic		
Galactosemia	Elevated urine non-glucose-reducing substances, galactose-1 phosphatase uridyl transferase enzyme assay	Switch to lactose-free formula
Tyrosinemia type 1	Markedly elevated AFP, elevated urine succinylacetone, enzyme assay or genetic testing for fumarylacetoacetate hydrolase	PO NTBC
Wilson's disease	Low serum ceruloplasmin, high 24-h urine copper, high liver copper, presence of Kayser-Fleischer rings (in approximately 50% patients)	Copper chelation with agents like D-penicillamine, trientene, zinc, etc.; sometimes plasmapheresis may be needed
Immune dysregulation		
Autoimmune hepatitis	Autoimmune hepatitis serology (see Table 9.1); elevated Ig G levels	IV methylprednisolone while concomitant evaluation for LT
Gestational alloimmune liver disease (GALD)/ neonatal hemochromatosis	High serum ferritin; lip/salivary gland biopsy; characteristic features on MRI brain/liver/ pancreas	High-dose IV immunoglobulin; can also be given prophylactic during pregnancy May need exchange transfusion
Hemophagocytic lymphohistiocytosis (HLH)	Cytopenias, high serum triglyceride and ferritin, low fibrinogen; high soluble IL-2 receptor, low or absent NK cell activity; genetic testing and/or bone marrow biopsy proved to be diagnostic	High-dose corticosteroids, chemotherapy and/or bone marrow transplantation
Drugs/exposures		
Acetaminophen	History suggestive or suspicious of ingestion; elevated acetaminophen level 4 h after ingestion	NAC should be started as soon as possible in all patients where acetaminophen overdose is suspected.
Amanita toxicity	History of *Amanita phalloides* and *Amanita virosa* ingestion	PO or IV silibinin
Others		
Budd-Chiari syndrome	Finding of hepatic vein thrombosis on imaging studies	TIPS – if possible; LT might still be necessary

AFP alpha-fetoprotein, *LT* liver transplantation, *NTBC* 2-(2-nitro-4-trifluoro-methyl-benzoyl)-1,3-cyclohexadion, *IL* interleukin, *NK cell* natural killer cell

Prognosis

There are several prognostic scoring systems available; however, none of these have been able to well-define the indications for liver transplantation. The King's College Hospital Criteria (KCHC), the Model for End-Stage Liver Disease (MELD) score, and the Sequential Organ Failure Assessment (SOFA) score are among the few most frequently used prognostic scoring systems in adults. However, none of these adequately predict outcome or candidacy for transplantation, and the AASLD guidelines for management of acute liver failure recommend against using these

for organ allocation [17]. Prognostic scoring systems for PALF are poorly defined and not adequately validated. The KCHC has been extensively used in adult ALF; however, when the PALF study group tried to validate the criteria for use in non-acetaminophen-induced PALF patients, it did not reliably predict chance of survival in PALF, and its sensitivity and positive predictive value were significantly lower than the original study [86]. Serum albumin level, serum bilirubin level, PT-INR, age, and weight have been used in the Pediatric End-Stage Liver Disease (PELD) score to predict mortality in children with chronic liver disease [87]. This scoring system has not been validated for use in PALF. The pediatric liver injury unit (LIU) score is an upcoming dynamic scoring system, which incorporates the use of peak values of total bilirubin and PT-INR during hospitalization to stratify patients into low, medium, or high risk of mortality. It may prove to be a beneficial tool for prediction of outcomes in PALF and thus the need for liver transplantation [88, 89]. Currently, we do not have a single universal scoring system to help reliably predict mortality and need for transplantation, thus streamlining the process of listing and organ allocation in PALF.

Outcomes

Before liver transplantation was adopted as a life-saving modality for management of acute liver failure, the overall survival rate for children with PALF was less than 50% and was even worse (less than 10%) for patients with advances stages of encephalopathy. However, more recent data has been promising. In a recent analysis of 348 patients with PALF, 94% of children with acetaminophen-induced liver failure survived [3]. Patients with PALF who did not have an underlying etiology identified had the worst outcome with more than 50% mortality [3]. Patients who never had HE were more likely to recover spontaneously. Total bilirubin $\geq$ 5 mg/dl, INR $\geq$ 2.55, and presence of HE, were identified as risk factors to predict death or need for liver transplantation.

Conclusion

Despite the improvement in supportive care and outcomes in PALF in last few decades, critical care management remains poorly defined and guided mainly by adult data and guidelines. This makes PALF one of the most challenging conditions to manage. Intense supportive care, thorough diagnostic evaluation, and early detection with prompt treatment of complications help improve outcomes. Improved availability of organs for transplant, better prognostic system, and effective liver support systems are highly needed to improve survival and decrease the uncertainty associated with this devastating disease.

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Part IV

Renal Controversies

10 Diagnosis and Management of Acute Kidney Injury in Critical Illness

Tennille N. Webb, Rajit Basu, and David Askenazi

AKI in Critical Illness: A Pediatric Epidemic

Case Scenario

A 10-year-old, 40 kg, Hispanic female presented to the ED with a history of cough, fever, and decompensated shock. She was found to have pneumonia and bacteremia. At presentation, she had mixed respiratory and metabolic acidosis, serum creatinine was 0.9 mg/dL, and BUN was 14 mg/dL. She received 40 mL/kg of normal saline and was intubated, started on a dopamine infusion, and admitted to the PICU. Over the next 12 h, she received an additional 2 L of fluid including 1 L of blood products and was started on a norepinephrine drip.

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The importance of early recognition and proper management of AKI is now at the forefront of critical care medicine. In those who are critically or acutely ill, AKI is exceptionally common and is associated with negative outcomes independent of severity of illness [1–3]. In an effort to better define the global incidence of AKI, a worldwide meta-analysis of over 300 adult and pediatric retrospective and prospective cohort studies was performed [4]. The incidence of AKI was approximately 34% in children based upon KDIGO-defined AKI criteria. Higher rates of AKI were found in those who were critically ill, including those in the ICU and post-cardiac surgery. The occurrence and outcomes of KDIGO-defined AKI in a worldwide ICU population was investigated in the adult population in the Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) [5]. This was the first multinational, cross-sectional study on the epidemiology of AKI in a worldwide ICU population. AKI occurred in over half of the ICU patients with an independent association between AKI severity and mortality. On various continents, the rate and mortality of those with AKI were very similar.

In children, a recent cross-sectional analysis of over two million pediatric hospital admissions in the United States identified risk factors for AKI [6]. The incidence of AKI was found to be higher in African Americans, in teenagers aged 15–18 years of age, and in neonates admitted to

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the pediatric ICU. Neonates, and those requiring renal replacement therapy, had the highest mortality rates. In addition to this cross-sectional study, our understanding of AKI in the pediatric ICU has greatly expanded with the recent multinational, multicenter prospective study entitled AWARE (Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Critically Ill Children) [7].

The AWARE study examined pediatric and young adult patients admitted to the pediatric ICU and children admitted to the pediatric cardiac ICU (but not after surgery for congenital heart disease). This study provides the most comprehensive analysis of the epidemiology of AKI with recruitment from over 30 pediatric ICUs from four continents. Findings revealed that during the first 7 days of ICU admission, AKI occurred in approximately one-fourth of the patients and severe AKI occurred in approximately 12%. Even after controlling for multiple potential confounders and severity of illness scores, severe AKI and receipt of renal replacement therapy (RRT) were significant predictors of death by 28 days of admission. Severe AKI was also associated with increased use of mechanical ventilation, RRT, and longer ICU length of stay. These findings correlate with aforementioned adult data, specifically with AKI-EPI.

Defining AKI in the neonatal population is challenging due to confounders including the presence of maternal serum creatinine (sCr) and immaturity of the proximal tubules. For these reasons, investigations are ongoing to identify biomarkers to assist with AKI diagnosis in neonates. A 24 center, multinational study was recently performed: the AWAKEN (Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates) study [8]. Of the over 2000 infants studied, 30% (605) of the patients were found to have AKI with the majority of those being less than 29 weeks gestation followed by those greater than 36 weeks gestation. AKI was defined by the neonatal modified KDIGO criteria [9]. Like the AKI-EPI and the AWARE studies, even after adjusting for multiple potential confounders, those with AKI had longer length of hospital stay and higher mortality.

Children who undergo surgery to correct congenital heart lesions commonly develop cardiac surgery-associated AKI (CS-AKI), with an incidence of up to 50% postoperatively and with an even higher incidence in neonates [10, 11]. Emerging data now reveals that factors such as prolonged cardiopulmonary bypass (CPB) time, young age, and higher RACHS-1 (Risk Adjusted classification for Congenital Heart Surgery) category are less likely to be independently associated with CS-AKI. The increase in CS-AKI is likely attributed to the increased complexity of heart surgeries that are performed along with increased survival of patients with congenital heart lesions. CS-AKI is also associated with increased length of ICU hospital stay and mortality [11, 12].

Outcomes Ascribed to AKI

AKI is common in adults, children, and neonates admitted to intensive care units [1, 7, 13]. Even after controlling for numerous potential confounders, those with AKI have higher mortality, prolonged mechanical ventilation, and increased ICU length of stay. In addition, growing evidence suggests that AKI is not only associated with short-term but also long-term consequences such as chronic kidney disease (CKD) and end-stage renal disease (ESRD) [14, 15]. Even if an AKI episode seems to resolve and the sCr returns to baseline, there is evidence that these patients may have "subclinical CKD" and are at higher risk to progress to CKD [16]. In a prospective study, the association between children with AKI in the pediatric and cardiac ICU and the incidence of CKD at 1–3 years after AKI was evaluated, and it was found that 10% developed CKD (eGFR <60 mL/min/1.73m^2) and an additional 50% were at risk for development of CKD (measured GFR 60–90 mL/min/1.73 m^2, hypertension, or hyperfiltration) [15]. In the kidney transplant population, those who develop AKI within 3 years of kidney transplantation are at an increased risk for development of CKD and graft failure [17]. Unfortunately, although guidelines for care suggest that all patients should have kidney

follow-up within 3 months of hospital discharge, very few programs have a systematic method to follow these patients, and in some reports, only 40% of those who develop AKI may actually follow up with a nephrologist [18].

Recognition: Does It Matter?

Current AKI criteria include both sCr and urine output for diagnosis; however, until recently, many studies on AKI in the pediatric ICU did not include oliguria. The importance of inclusion of both for diagnosis remains in question. There are quite a few studies that suggest omitting oliguria fails to identify a significant number of individuals with AKI.

Serum Creatinine as a Metric for AKI

Serum creatinine currently remains the gold standard for AKI diagnosis as it is often readily available and inexpensive. Importantly, sCr changes act as a biomarker of kidney function, not injury. Serum creatinine changes are often seen days after the initial injury, thus delaying diagnosis and early management. Serum creatinine is not the ideal biomarker in the detection of AKI as it is affected by many other nonrenal factors such as gender, muscle mass, and fluid balance. It is extremely important to be mindful of those patients who are fluid overloaded and its effects on the measurement of sCr, likely masking the severity of AKI. Prior studies have demonstrated that failure to correct sCr for fluid balance underestimates the prevalence of AKI, therefore suggesting that in some cases, oliguria may be a better indicator of AKI [19, 20].

Urine Output as a Metric for AKI

There is limited independent data on inclusion of urine output as criteria for AKI diagnosis, and its use is somewhat controversial. Using oliguria in the definition for AKI must be done in the context of additional clinical criteria including hydration status, use of diuretics, and urinary tract obstructions. The AWARE study demonstrated that not including oliguria as a criterion for AKI failed to identify a significant number of patients with AKI and oliguria in of itself was associated with an increased risk of mortality [7]. Unfortunately, obtaining both urine and sCr can be difficult in children in the critical care setting. If an indwelling bladder catheter is not in place, the clinician then must depend on reports of number of voids or weighing of diapers and not having a true hourly urine flow rate. Of course, risks and benefits must be considered in the decision of maintaining an indwelling bladder catheter with concerns of increased risk of infection.

More individuals are diagnosed with AKI by incorporating urine output criteria than by using sCr alone [21–24]. In a prospective observational study of over 300 critically ill patients, the authors demonstrated that the diagnosis of AKI occurred earlier in patients with oliguria in comparison to those without [24]. In another prospective observational study in critically ill adults, the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria with sCr alone was compared to sCr plus urine output. Using the RIFLE criteria with sCr alone failed to recognize as many patients with AKI, failed to identify the maximum AKI severity, and led to delays in AKI diagnosis. Incorporation of urine output into the definition was associated with higher mortality [23]. The added value of urine output was also recently explored in a retrospective analysis of over 30,000 hospital admissions over 8 years. In this cohort, approximately 75% of the patients developed AKI. Individuals who met both sCr and urine output criteria for AKI had worse outcomes than those who met only one criterion [25]. Collectively, these studies strongly support the need for both sCr and urine output in defining AKI in the ICU population.

Definitions

There are several definitions of AKI in the published literature which were initially based upon absolute changes in sCr. In 2005, a consensus categorical definition was proposed entitled the

Table 10.1 RIFLE classification of AKI

RIFLE classification criteria		
Class	Serum creatinine or GFR	Urine output
Risk	Increase in serum creatinine × 1.5 or GFR decrease >25%	Less than 0.5 mL/kg/h for more than 6 h
Injury	Increase in serum creatinine × 2 or GFR decrease >50%	Less than 0.5 mL/kg/h for more than 12 h
Failure	Increase in serum creatinine × 3 or serum creatinine >4 mg/dL with an acute rise >0.5 mg/dL or GFR decrease >75%	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h
Loss	Persistent acute renal failure (complete loss of kidney function >4 weeks)	
End-stage kidney disease	End-stage renal disease >3 months	

Table 10.2 AKIN classification of AKI

AKIN classification criteria		
Stage	Serum creatinine	Urine output
1.	Increase in serum creatinine of ≥0.3 mg/dL or increase ≥150–200% (1.5–2-fold) from baseline	Less than 0.5 mL/kg/h for more than 6 h
2.	Increase in serum creatinine >200–300% (>2–3-fold) from baseline	Less than 0.5 mL/kg/h for more than 12 h
3.	Increase in serum creatinine >300% (>3-fold) from baseline or ≥ to 4 mg/dL with an acute increase of at least 0.5 mg/dL or on renal replacement therapy	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

Table 10.3 KDIGO classification of AKI

KDIGO classification criteria		
Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or ≥ 0.3 mg/dL increase	Less than 0.5 mL/kg/h for 6–12 h
2	2–2.9 × baseline	Less than 0.5 mL/kg/h for ≥12 h
3	3 × baseline or increase in serum creatinine ≥4 mg/dL or initiation of renal replacement therapy or, in patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	Less than 0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

RIFLE criteria (Table 10.1). A modified version of the RIFLE criteria, pRIFLE, was developed for the pediatric population in 2007 [26]. In 2008, modifications to RIFLE culminated in the Acute Kidney Injury Network (AKIN) classification (Table 10.2). Subsequently, additional modifications defining AKI were made by Kidney Disease: Improving Global Outcomes (KDIGO) (Table 10.3). The KDIGO AKI definition includes a combination of the RIFLE, pRIFLE, and AKIN definitions and encompasses both adult and pediatric criteria [27].

A recent study in pediatrics compared the incidence of AKI in both the ICU and non-ICU settings between pRIFLE, AKIN, and KDIGO according to creatinine changes [28]. This retrospective study revealed that both AKI incidence and staging varied among all three definitions. By detecting the most stage 1 cases, pRIFLE generated the largest AKI cohort. In reference to AKI diagnosis, AKIN and KDIGO were the two that corresponded most accurately. These findings demonstrate that while these definitions are similar, there are differences significant enough to cause variation in AKI staging. There should be a constant pursuit to find methods to improve the ability to predict meaningful outcomes. It is possible that incorporation of fluid overload and biomarkers may improve our ability to properly detect AKI. For now, KDIGO-defined AKI should be the standardized criteria used for AKI diagnosis.

Biomarkers

Novel biomarkers are continually being examined to obtain an earlier, accurate diagnosis of AKI. The nature of current biomarkers such as sCr and oliguria leads to delayed AKI diagnosis. If novel biomarkers are validated as early markers of AKI, they can be incorporated with other markers of kidney injury or combined with risk

factors to better guide appropriate management. Based upon their specific physiological characteristics, biomarkers can be divided into categories of markers of tubular injury, glomerular filtration rate (GFR), inflammation, and cell cycle arrest [29]. Some of the common biomarkers investigated include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC), kidney injury molecule-1 (KIM-1), IL-18, liver-type fatty acid-binding protein (L-FABP), tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7). While these biomarkers are promising for AKI diagnosis, reference ranges for pediatrics and widespread availability continue to be a challenge and require more investigation.

NGAL is a marker of tubular injury and is one of the most extensively studied AKI biomarkers with over 200 studies in the medical literature. Both serum and urine NGAL (uNGAL) are upregulated following nephrotoxic and ischemic injury such as ischemia-reperfusion injury, drug toxicity, hypoxia, and bacterial infections [30–32]. In both the neonatal and pediatric population requiring CPB, NGAL measured within 2 h after initiating CPB was found to be an excellent early predictor of AKI [33]. In a single-center, case-control study of pediatric patients, the utility of multiple urinary biomarkers of AKI after CPB was evaluated. Urine NGAL was the only biomarker elevated at 2 h post initiation of CPB with an area under the operating curve (AUC) of >0.9 for AKI predictive ability. It was not until 12 h that the combination of NGAL with other biomarkers improved the AUC for the prediction of AKI [34]. While NGAL has been extensively studied and its utilization continues to increase, there are still some ongoing concerns such as confounders in which NGAL is affected including sepsis [35] and urinary tract infections [36]. Furthermore, determining the cutoff values for uNGAL in varying age groups such as adult vs pediatric vs neonatal population remains an ongoing issue. The impact of uNGAL over a variety of hospitalized patients with ages ranging from 4 months to 25 years, with various diagnoses including nephrotic syndrome, cancer, and hypoplastic left heart syndrome, was evaluated in a single-center study. Specified cutoff values for interpretation of AKI risk were used based upon cutoff values generated by their clinical laboratory. The trend of serial uNGAL values provided both predictive and prognostic value and served as a means of support for clinical decision-making in their population [37].

Cystatin C is a marker of GFR. It is an endogenous cysteine protease inhibitor that is produced in all nucleated cells and is not affected by gender or muscle mass [38]. CysC has a relatively short half-life of 2 h and responds rapidly to changes in GFR. A recent meta-analysis of 13 studies evaluated the ability of CysC to predict AKI. Of the 13 studies, most were adult studies and involved individuals post-cardiac surgery. Serum CysC had an AUC of 0.96 for predicting AKI. However, subgroup analysis revealed that only when measured within 24 hour of renal injury or ICU admission was serum CysC of diagnostic value [39]. A multicenter prospective study of almost 300 children undergoing cardiac surgery evaluated whether measuring pre- and postoperative serum CysC improved the prediction of AKI in comparison to sCr. Postoperative serum CysC measured within 6 h of CPB strongly predicted the development of AKI with an AUC of 0.89 (AKI was defined by sCr AKI). Postoperative serum CysC also predicted longer ICU length of stay and longer duration of ventilation [40]. There is apprehension about utilizing CysC alone in detecting AKI because it is affected by multiple factors including corticosteroids, thyroid function, and CRP levels. These elements make its value questionable in accurately detecting AKI. Serum CysC in combination with urine NGAL was investigated in a retrospective analysis of 345 pediatric patients who underwent CPB. Combining both serum CysC and urine NGAL at 2 h post-CPB was superior to sCr alone in predicting both AKI severity and duration [41].

KIM-1 is also a marker of tubular injury [42]. KIM-1 was evaluated in 40 pediatric patients after CPB and was found to be elevated at 12 h post-CPB with an AUC of 0.83 in the individu-

als who developed AKI [42]. Another study set out to characterize the patterns of KIM-1 and uNGAL in the pediatric ICU and assess their properties in identifying those at risk for the development of AKI. KIM-1 was not found to be as reliable in identifying those at risk for AKI development and peaked between 12 and 24 h post-ICU admission with an AUC of 0.74. The patients with sepsis had higher levels of both uNGAL and KIM-1, irrespective of development of AKI [43]. As demonstrated, these studies yield conflicting results for the accuracy of KIM-1 in predicting AKI.

IL-18 is a pro-inflammatory cytokine that is a mediator of ischemic renal injury [44]. By systemic review and meta-analysis, the utility of biomarkers in predicting the need for RRT in critically ill patients was evaluated. IL-18 had an AUC of 0.66 in predicting the need for RRT [45]. In a prospective, multicenter cohort study of children with congenital cardiac lesions, it was found that IL-18 peaked at 6 h post-cardiac surgery. IL-18 along with uNGAL improved risk prediction for severe AKI including the need for dialysis, mechanical ventilation, and length of hospitalization; however, it was only moderately accurate in diagnosing severe AKI with an AUC of 0.72 [46]. Another analysis demonstrated that in non-septic critically ill children, IL-18 increased before sCr and predicted the severity of AKI as well as mortality [47].

L-FABP is induced in the proximal tubule early after AKI. In a single-center study of pediatric patients post-CPB, L-FABP was found to increase 6 h post-CPB with an AUC of 0.77 in predicting AKI [48]. In contrast, a prospective multicenter study consisting of children and adults undergoing CPB found that L-FABP was not associated with AKI development [49].

IGFBP7 and TIMP-2 are markers of cell cycle arrest [29]. There are limited pediatric studies on the use of [TIMP-2]*[IGFBP7] for the prediction of AKI. In a case-control study evaluating 50 patients at high risk for AKI development post-CPB, it was found that [TIMP-2]*[IGFBP7] was significantly increased at 4 h post-CPB with an AUC of 0.81 [50].

While there continues to be ongoing investigation of biomarkers for early AKI detection, incorporating their use into routine clinical practice remains a challenge. Expecting a single biomarker to replace sCr and urine output for investigating renal function is not realistic. The combination of novel biomarker(s) with current standards of assessing renal function will likely prove more effective. For example, combining sCr, CysC, and uNGAL can help delineate glomerular from structural tubular damage. Aside from CysC, uNGAL is the most studied and readily available biomarker but does not yet have widespread availability. Its use is advantageous in comparison to other biomarkers as uNGAL has been shown to be elevated within 2 h of injury and is not removed by dialysis, so it can also be used as a measure of renal recovery even in those patients receiving dialysis and appears to be closer to validation in the pediatric population.

Furosemide Stress Test

While not labeled as a biomarker, furosemide has been examined as a means to determine renal tubular function. Furosemide is a highly protein-bound loop diuretic that is not filtered at the glomerulus and is actively transported to the tubular lumen. Its use results in natriuresis by inhibiting active chloride transport in the thick ascending limb of the loop of Henle. Therefore, the urinary response to furosemide provides a functional assessment of renal tubular function. There are an increasing number of adult studies that have examined the kidney's response to furosemide as a marker of renal functional reserve in AKI in what is known as the furosemide stress test (FST). What makes this test ideal is that often in the setting of oliguric AKI, many are "challenged" with a dose of furosemide in order to determine if the patient will have a urinary response. In many cases, multiple doses are

given to no avail thus delaying the initiation of RRT. Standardization of the FST in the pediatric ICU population will assist in predicting those who will likely have progression of AKI thus allowing earlier intervention such as timely initiation of RRT.

In an adult study, it was hypothesized that the FST could predict which patients would have progression of AKI. This was done by measuring urine volume and flow after the administration of 1–1.5 mg/kg of furosemide. The sum of the urine volume at the first 2 h after receiving furosemide had the best predictive ability for progression to AKIN stage 3 within 14 days of performing the FST. Urine volume of less than 200 mL at 2 h offered the best sensitivity and specificity for predicting AKI progression [51]. The FST was combined with other AKI biomarkers in the previous study cohort. The combination of the FST with uNGAL increased the prediction of progression to AKIN stage 3, receipt of RRT during admission, and inpatient death [52]. These findings suggest that in combination with uNGAL, the FST may improve risk stratification in early AKI.

The FST was evaluated in neonates at risk for CS-AKI. Neonates and infants less than 90 days of age who received furosemide within 24 h of CPB were included in a single-center, retrospective study [53]. Hourly and cumulative urine output for 6 h after the initial postoperative furosemide dose was evaluated. The maximum urine output occurred in the first hour with almost half of the cumulative urine output in the first 2 h with an average urine output of 1.6 mL/kg/h. Cumulative urine output was lower in patients with CS-AKI. Furosemide response had significant areas under the curve predictive of CS-AKI, prolonged peritoneal dialysis, prolonged mechanical ventilation, and peak fluid overload greater than 15%. Unlike the adult data, a specified cutoff point for cumulative urine output after furosemide was unable to be determined for CS-AKI prediction. While prospective studies will be needed for validation of furosemide stress testing in this population, current data suggests combining the FST with novel AKI biomarkers may aid early assessment of renal function and serve as a guide for clinical decision-making.

Risk Stratification

The concept of renal angina was devised to apply objectivity in the assessment of AKI risk analogous to the components for angina pectoris [54]. While there are no specific symptoms of AKI such as chest pain for angina pectoris, clinical signs such as oliguria and fluid overload were utilized. Renal angina therefore identifies those at higher risk of AKI and guides the use of additional diagnostic evaluation for those who will benefit from additional biomarker assays. From this idea, the renal angina index (RAI) was derived, which is a product of AKI risk and signs of injury, with a value of >/=8 as fulfillment of renal angina (Fig. 10.1). This model was found to be useful in the pediatric critical care population of detecting likelihood of severe AKI development 3 days post-ICU admission [55]. Additionally, urinary biomarkers combined with RAI improved AKI prediction [56]. The authors illustrate that these findings provide a potential model for AKI risk stratification upon early ICU admission (Fig. 10.2).

Management Options

Understanding the etiology of AKI allows for the elimination of offending agents and reversible etiologic factors which include low oncotic pressure, low hydrostatic pressure, abdominal compartment syndrome, bladder obstruction, and nephrotoxic medications. To date, there are no medications or therapies that prevent or treat AKI, and management is largely based upon early detection, removal or mitigation of the offending agent and supportive therapy. Modifications that can improve outcomes in those with AKI include prevention of worsening kidney injury, nutrition optimization, minimization of fluid overload, and optimization of acid/base and electrolyte balance.

AKI Risk Tranche

Risk Factor	Risk Tranche	Risk Score
ICU Admission	Medium	1
History of Transplantation (Solid Organ or Bone Marrow)	High	3
Vasoactive Support & Mechanical Ventilation	Very High	5

X **= Renal Angina Index (Range 1-40)**

AKI Injury Tranche

Change in Creatinine	Fluid Overload %	Injury Score
<0	<0 – 5%	1
1.0 – 1.49x	5 – 9.99%	2
1.5 – 1.99x	10 – 14.99%	4
>2x	≥15%	8

Fig. 10.1 Renal angina index (RAI). (Copyright permission obtained and adapted from Basu et al. [55])
Renal angina index (RAI) – Based on existing pediatric AKI literature, tiered AKI risk strata were assigned point values for "risk" and "signs" of injury. The worse parameter between change in estimated creatinine clearance from baseline and % fluid overload was used to yield an injury score. The RAI index score can range from 1 to 40. A cutoff value of >/= 8 is used to determine fulfillment of renal angina (from Basu et al. [55] with permission)

Fluid Overload

Case Scenario Continued

After 24 h, her total intake since admission was 4.2 L and she had voided 200 mL. Her BUN was 30 mg/dL, and her sCr was 1.7 mg/dL. After 48 h, she had a total volume intake of 5.4 L with 400 mL of urine output. She was on 70% Fi02 with a progressive increase in ventilator settings. She had not received any nephrotoxic medications. A renal ultrasound revealed normal-sized hyperechoic kidneys with a decompressed bladder with an indwelling bladder catheter in place. Her calculated fluid overload was 12.5%. Urine NGAL was 247 ng/mL and serum albumin was 1.9 mg/dL. She was given 1 g/kg of 25% albumin over 4 h followed by a 1 mg/kg dose of furosemide intravenously. If medical therapy did not achieve the goal of net negative fluid balance over the next 12 h, RRT would be initiated.

Fluid overload, as a consequence or perhaps a biomarker of AKI, is significant because it is the most common indication for continuous renal replacement therapy (CRRT) in critically ill children [57]. It has been demonstrated in the critically ill pediatric population that those who were initiated on CRRT at greater than 20% fluid overload had significantly higher mortality rates than those who were initiated at 10–20% fluid overload even after controlling for severity of illness and numerous potential confounders [57].

A three-phase fluid management model has been proposed in an effort to assist with proper resuscitation and attempt to prevent fluid overload [58]. Based upon clinical status, management approaches of critically ill individuals with AKI or those individuals at risk for AKI development are divided into the following three phases: (1) fluid resuscitation, (2) maintenance of fluid balance, and (3) fluid recovery/removal (Fig. 10.3). While aggressive fluid resuscitation may be essential in the resuscitation phase, overly aggressive resuscitation that

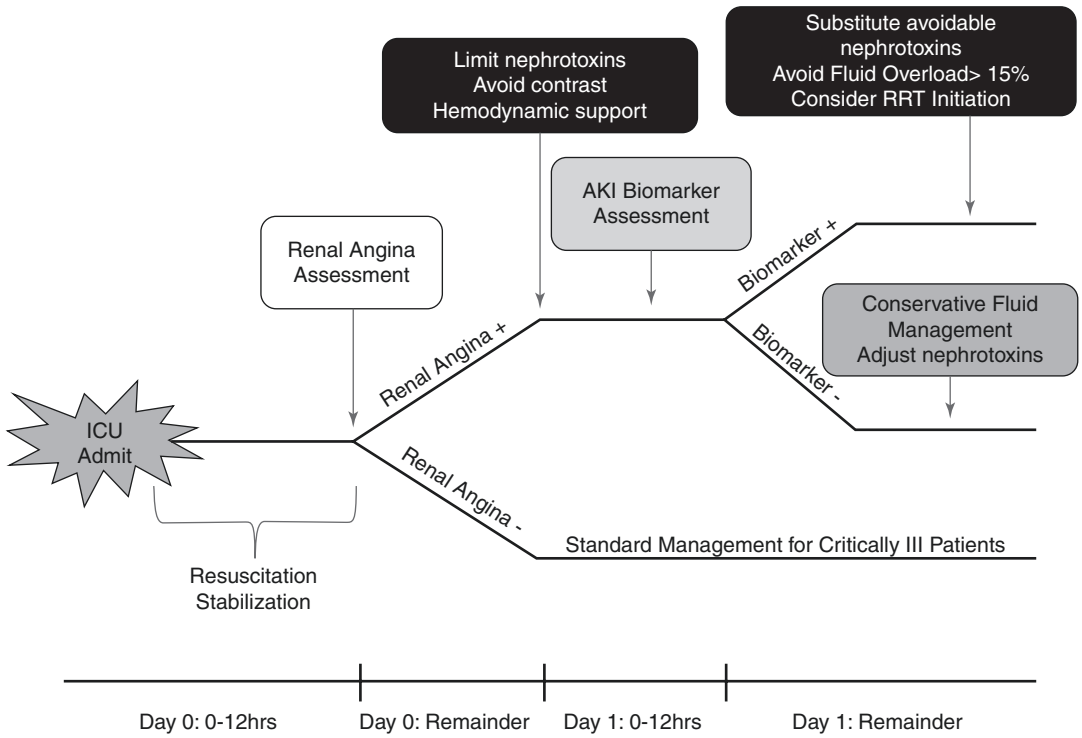

Fig. 10.2 Schema of use of RAI for AKI stratification after ICU admission. (Copyright permission obtained and adapted from Menon et al. [56])
Represented is a potential trial of prospective evaluation on outcome based on the use of the RAI for AKI risk stratification after ICU admission (from Menon et al. [56] with permission)

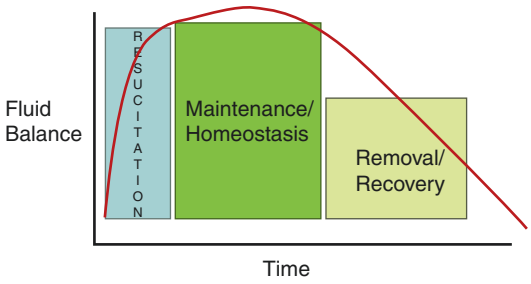

Fig. 10.3 The AKI fluid paradigm. (Copyright permission obtained and adapted from Goldstein [58])
AKI fluid epidemiology paradigm and proposed fluid accumulation three-phase conceptual model for the patient with AKI (from Goldstein [58] with permission)

continues into the maintenance phase is what usually leads to the need for fluid removal via CRRT or aggressive diuresis with resultant electrolyte imbalances in the recovery phase. During fluid resuscitation, the goal is to restore end-organ perfusion; however, in the setting of AKI, attention must be paid to the physiological response to fluids to avoid propagation of fluid overload. During the maintenance phase, fluid needs are assessed, including nutrition, ongoing hydration, and potential blood products and are balanced against output. It is during this phase that the physician must determine if the individual is able to maintain a safe balance between required intake and output. To assist with this decision, the percent cumulative fluid overload should be calculated (**% fluid overload = ((fluid input (L) – fluid output (L)) / (patient ICU admission weight (kg)) × 100**) and tracked to avoid worsening fluid overload and kidney function as well as identify an increased risk of mortality. Options during this time are to either limit volume intake, initiate diuretics, or initiate renal replacement therapy. Limiting volume risks inadequate nutrition in

an individual that may already be in a catabolic state. While diuretics are potentially another option for volume control, close attention must be paid to the kidney's response without delaying what may be ultimately required, which is RRT. In theory, the fluid removal phase should not be aggressive or urgent if the first two phases were appropriately managed [58].

Preventive Therapies

Employing preventive therapies requires knowledge of the timing of renal injury. While the exact timing of injury can be difficult to identify, in certain settings such as patients following CPB, it is known. The pathophysiology of the injury is very complex, but this is one area in which utilization of biomarkers has been progressing to provide earlier diagnosis.

Various medications have also been examined in the setting of CS-AKI prevention including fenoldopam and theophylline/aminophylline in efforts of AKI prevention. However, multiple studies have not demonstrated their effectiveness in decreasing the incidence of AKI. A randomized trial of children receiving prophylactic aminophylline post-CPB did not demonstrate AKI prevention [59]. A single-center trial examined the effects of implementing a "KDIGO bundle" that used a multifactorial approach in prevention of CS-AKI in high-risk populations. This bundle consisted of multiple components including nephrotoxin avoidance, hyperglycemia prevention, and optimization of fluid status [60]. While the occurrence and severity of AKI were reduced, there was no impact on secondary outcomes of need for RRT during hospitalization or length of stay. Utilization of a type of "KDIGO bundle" for CS-AKI can be beneficial in the neonatal and pediatric population as well. Once early diagnosis of CS-AKI is obtained, we should be "proactive" by attempting to mitigate worsening outcomes associated with AKI progression as opposed to "reactive" later as AKI progresses.

Renal Replacement Therapy

Case Scenario Continued

The urine output did not significantly improve over the next 12 h, uNGAL increased to 310 ng/mL, and calculated fluid overload increased to 14%, and she was placed on CRRT. Three days after CRRT initiation, urine output improved, uNGAL trended down to 100 ng/mL, and CRRT was discontinued. The patient's kidney function steadily improved over the next 2 weeks, uNGAL trended down to less than 50 ng/mL, and she was transferred to the floor in stable condition. She was scheduled for a follow-up visit with pediatric nephrology to evaluate for long-term renal sequelae after AKI.

There continues to be an ongoing debate regarding the best time for RRT initiation. As addressed above, those with significant fluid overload at the time of RRT initiation, particularly in those with greater than 20% fluid overload, have been shown to have worse outcomes. The timing of RRT has been evaluated in two adult randomized trials: a single-center study known as the ELAIN (the Early Versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury) trial and a multicenter trial known as the AKIKI (Artificial Kidney Initiation in Kidney Injury) trial. ELAIN was a single-center study that randomized critically ill patients with KDIGO stage 2 AKI and elevated uNGAL [61] to early vs delayed RRT. Early intervention was RRT initiation within 8 h of AKI diagnosis and delayed defined as RRT initiation within 12 h of KDIGO stage 3 AKI or no initiation of RRT. Patients randomized to early initiation of RRT had a reduced 90-day mortality, earlier recovery of renal function by day 90, decreased duration of RRT, and decreased length of stay in comparison to late initiation.

In contrast, the AKIKI trial had very different findings. Patients with severe AKI, defined as KDIGO stage 3, were randomized to either the early strategy or delayed strategy. Those in the early strategy initiated RRT immediately after randomization and those in the delayed strategy initiated RRT if very specific clinical criteria such as hyperkalemia and pulmonary edema were met [62]. There was no difference in mortality between the two groups. While these discrepant findings are concerning and somewhat discouraging, care must be taken when evaluating the differences in these two trials including the inclusion criteria and sample size.

Early intervention of RRT was evaluated in the CS-AKI population in an effort to determine if peritoneal dialysis (PD) catheter placement in infants undergoing CPB at high risk for AKI improved outcomes [63]. Early initiation of PD resulted in better fluid balance and improved clinical outcomes including shorter time to negative fluid balance, decrease in ventilator time, and fewer electrolyte abnormalities. This was further confirmed in a single-center randomized trial in PD versus furosemide for fluid overload prevention in infants after cardiac surgery [64]. There was no difference in negative fluid balance between the two groups on postoperative day 1; however, those randomized to receive furosemide were more likely to develop 10% fluid overload and have longer duration of mechanical ventilation, longer requirement for inotropes, and more electrolyte abnormalities.

Fluid overload is one clinical situation in which RRT is often delayed. While there is no definitive data on specific criteria for initiating RRT, there is strong evidence that suggests that an individual who is at least 20% fluid overloaded has worse outcomes. Having a framework for early, multidisciplinary decision-making regarding identification and management of fluid overload allows the medical team to be "proactive" as opposed to "reactive." This can prevent worsening fluid overload or identify the possible need for RRT prior to reaching 20% fluid overload.

Case Scenario Conclusion

The clinical scenario presented throughout the chapter provides the opportunity to not only understand the importance of initiation of RRT prior to significant fluid overload but also demonstrates the usefulness of the RAI for AKI risk stratification upon ICU admission (Fig. 10.2). *The initiation of this predictive model should be within 12 h of ICU admission. Upon presentation to the ICU, the patient required ongoing fluid resuscitation and vasoactive support for stabilization. Based on her AKI risk tranche value of 5 for mechanical ventilation and vasoactive support and her AKI injury tranche value of 4 based upon her change in serum creatinine as well as fluid status, her RAI would be calculated as 20 which fulfils criteria for renal angina, and the decision for standard ICU management should not be pursued. Proactive decisions would be made to limit nephrotoxin exposure and to closely follow drug levels of required nephrotoxins. Biomarker assessment in this patient revealed an elevated uNGAL, which continued to rise and is suggestive of moderate to high AKI risk. She also had worsening fluid overload at which time the decision was made to initiate CRRT. It was beneficial to have nephrology involved in a multidisciplinary approach when the patient was approximately 10% fluid overloaded to begin the discussion on additional therapeutic options and the possible need for RRT. Trending uNGAL was also particularly helpful in predicting renal recovery and assisted with the daily decision on whether or not CRRT should be continued.*

What Lies Ahead

Advances in RRT

The ability to provide adequate RRT safely to neonates remains a challenge due to difficulties in vascular access as well as the relatively large extracorporeal volume (ECV) required by current machines. Currently, the smallest CRRT circuit available in the United States has an ECV of approximately 90 mL, which equals over half of the circulating blood volume of a 2 kg neonate. In an effort to provide safe RRT therapy in this population, the Aquadex™ machine has been adapted to provide continuous veno-venous hemofiltration (CVVH) via incorporation of prefilter replacement fluid [65]. Aquadex™ is FDA approved for use in adults with heart failure who require fluid removal. The circuit has an ECV of 33 mL therefore requiring blood priming for infants less than 4 kg. Because of the smaller circuit, the machine can operate at a slower blood flow that can be accommodated by smaller vascular catheters, widening the scope of infants who can benefit from this modality. A case series was performed in critically ill children documenting the use of Aquadex™ for fluid removal, with the smallest patient weighing 2.7 kg and the youngest age of 4 days old. RRT was safely performed, and there were no deaths associated with the use of CVVH. Ongoing utilization of Aquadex™ by a small subset of nephrologists continues to show promising results in the neonatal population. There are also new machines being used in Europe that have been designed explicitly for the neonatal and infant population; however, these are not yet available in the United States. One such machine is the CARPEDIEM™ (Cardio-Renal Pediatric Dialysis Emergency Machine) which has circuits available with ECV less than 30 mL [66], and the NIDUS (Newcastle Infant Device) which has an ECV of 10 mL and can be used with a single lumen 4 F catheter. There is optimism that the CARPEDIEM™ and NIDUS will soon be FDA approved for use in the United States potentially expanding the group of children who can safely benefit from RRT.

Electronic Medical Records

Advanced technology such as electronic medical records (EMR) and data warehouses should be leveraged to improve AKI identification and enhance management and healthcare quality. The idea of incorporating data technology to improve AKI management and research has been recently explored with the idea of increasing AKI quality improvement [67]. As suggested, AKI can potentially be diagnosed via EMR based upon KDIGO-defined AKI criteria. However, some significant challenges include lacking a baseline sCr for proper staging as well as tracking hourly urine output in patients without indwelling bladder catheters. EMR can be used to alert providers when their patient has developed or has had worsening AKI. There are trials that have published data on e-alerts for AKI with some documenting failure to show any improvement in clinical outcomes, while others have demonstrated their effectiveness [68–70]. As previously mentioned, long-term follow-up of individuals with AKI is suboptimal, and there is evidence of long-term sequelae including CKD and ESRD. Opportunities exist for EMR to make improvements in this area by tracking individuals and prompting appropriate follow-up for not only the patient but also alerting their primary physician.

Summary AKI remains extremely common and impacts outcomes for critically ill pediatric patients. AKI is no longer thought to be a transient event, but there is evidence of long-term sequelae including hypertension, proteinuria, CKD, and ESRD that should be monitored via long-term care. The standardization of an AKI definition via KDIGO has improved the ability to better evaluate AKI in the pediatric population including better understanding of the epidemiology. Urine output should be a part of AKI surveillance programs. The ongoing investigation of novel biomarkers and their proper incorporation into clinical decision making has made promising strides in AKI research with anticipation of providing earlier diagnosis, thus leading to timely therapy and better long-term outcomes. Fluid overload is common in AKI and is associated with poor outcomes, therefore ongoing evaluation and management of fluid balance is very important. Care must be taken to not become overly aggressive with fluid resuscitation in order to prevent the need for emer-

gent fluid removal later on. New technology has made significant advancements and promises to improve the safety of RRT in neonates or small infants who would have otherwise not been eligible for these therapies.

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Management of Fluid Overload in the Pediatric ICU

11

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Introduction

The clinical implications of fluid overload and its management currently remain controversial within the pediatric critical care literature. Resuscitation with intravenous fluids is often necessary in critical care for maintenance of perfusion during shock or hypovolemic states. In recent years, a shift toward early recognition of sepsis has encouraged rapid and early initiation of fluid at illness presentation with the hopes of improving outcomes. As a consequence, aggressive early fluid resuscitation can contribute to fluid overload states in the setting of critical illness. Recent literature in both adult and pediatric patients suggests that fluid overload in critical illness can have harmful effects and contribute to morbidity and mortality [1]. However, the definition and management of fluid overload remain unclear, likely reflecting the complex relationship between volume resuscitation, fluid distribution, and critical illness.

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Pathophysiology

Some of the difficulties surrounding fluid management in critically ill patients arise from our incomplete understanding of the movement and distribution of fluid within the body, particularly in the setting of systemic disease states and therapeutic agents that impact endothelial permeability and vascular autoregulation.

Total body water accounts for approximately 60% of body weight and is distributed between the intracellular space (ICS) and the extracellular space (ECS). The percentage of water per body weight fluctuates with age, such that premature infants and term newborns have higher total body water relative to adults, which rapidly decreases to adult values during the first year of life [2]. The intracellular space accounts for 55% of total body water, while the remaining 45% exists within the ECS. The ECS is further divided into three compartments: intravascular space or plasma (IVS), interstitial space (ISS), and transcellular space (TCS), which account for 15%, 45%, and 40%, respectively, of total extracellular fluid. The transcellular space refers to digestive, cerebrospinal, intraocular, pleural, peritoneal, and synovial fluids [3]. The movement of water between the three compartments of the extracellular space occurs through a semipermeable membrane [4].

The homeostatic state of fluid movement within the body is determined by a balance between the physical properties between the

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fluids that exist within each individual compartment and the properties of the semipermeable membranes that separate them, as detailed in Table 11.1 [4]. Fluid movement is further tightly regulated by feedback loops involving the central nervous, endocrine, and renal systems [2].

Movement of fluids across the capillary bed had previously been largely described through the Starling principle, which relies upon assumptions that the capillary and postcapillary venules behave as semipermeable membranes absorbing fluid from the interstitial space. This relationship is illustrated through the use of Eq. 11.1. In this assumption, transvascular exchange depends largely upon a gradient between oncotic and hydrostatic pressure. At the arterial end, the dominant pressure gradient present is that of a hydrostatic pressure differential, and therefore, the driving force for fluid movement is away from the higher capillary hydrostatic pressure and toward the lower interstitial fluid hydrostatic pressure. Fluid movement in this direction is termed filtration (Fig. 11.1) [4].

Table 11.1 Summary of properties of body fluids by compartment

Properties	Plasma or IVS	Interstitial fluid	Intracellular fluid
Colloid osmotic pressure (mmHg)	25	4	0
Osmolality (mOsm/kg)	280	280	280
pH	7.4	7.4	7.2
Na + (mmol/L)	142	143	10
K+ (mmol/L)	4	4	155
Cl- (mmol/L)	103	115	8
Ca++ (mmol/L)	2.5	1.3	<0.001

Table created by Grace Ker

Starling's Equation for Fluid Movement

$$Jv = Kf\left[\left(P_c - P_{is}\right) - \sigma\left(\pi_c - \pi_{is}\right)\right] \quad (11.1)$$

Kf = Filtration constant
Jv = Fluid movement
Pc= Capillary pressure
Pis= Interstitial fluid pressure
$\pi_{c=}$ Capillary colloid osmotic pressure
$\pi_{is=}$ Interstitial colloid osmotic pressure

As fluid moves throughout the length of the capillary bed toward the venule end, filtration will eventually lead to a comparatively increased concentration of proteins within the intravascular space and thus an increased intravascular oncotic pressure in comparison to the interstitial fluid. This differential in oncotic pressure at the venule end of the capillary is greater than the hydrostatic differential, and so there is reversal of flow based on an overall pressure gradient that leads to absorption of fluid back into the intravascular space [4]. This process is summarized in Fig. 11.2. The Starling concept of filtration and absorption for fluid movement is demonstrated in Fig. 11.3.

Despite Starling's principles of fluid movement being generally considered the standard, in 2004, Adamson and colleagues revised the Starling equation, theorizing that non-fenestrated capillaries filter fluid throughout their entire length into the interstitial space and that absorption through the venules does not occur despite a rise in capillary oncotic pressure, which is unable

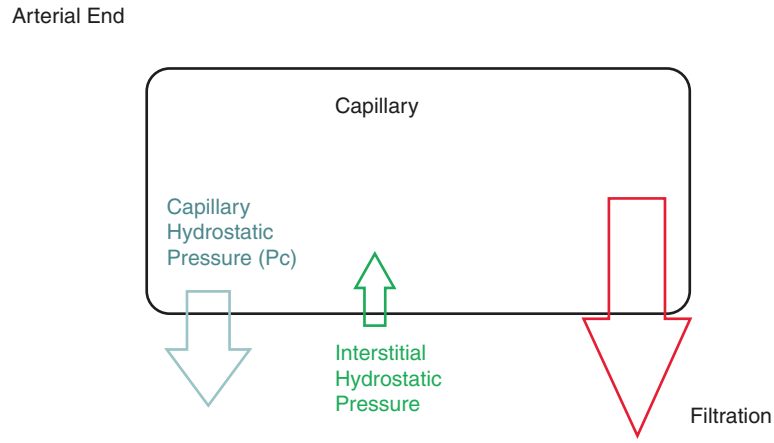

Fig. 11.1 Diagram demonstrating relationship between hydrostatic pressures within the capillary bed at the arterial end. (Image created by Grace Ker)

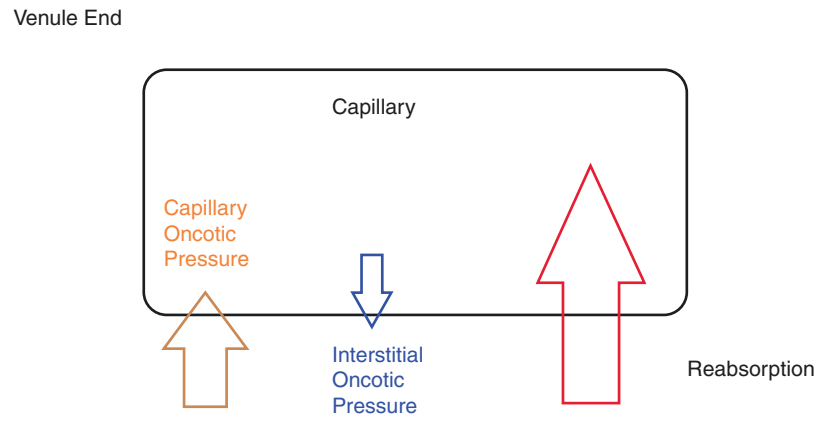

Fig. 11.2 Diagram demonstrating relationship between oncotic pressures within the capillary bed at the venule end. (Image created by Grace Ker)

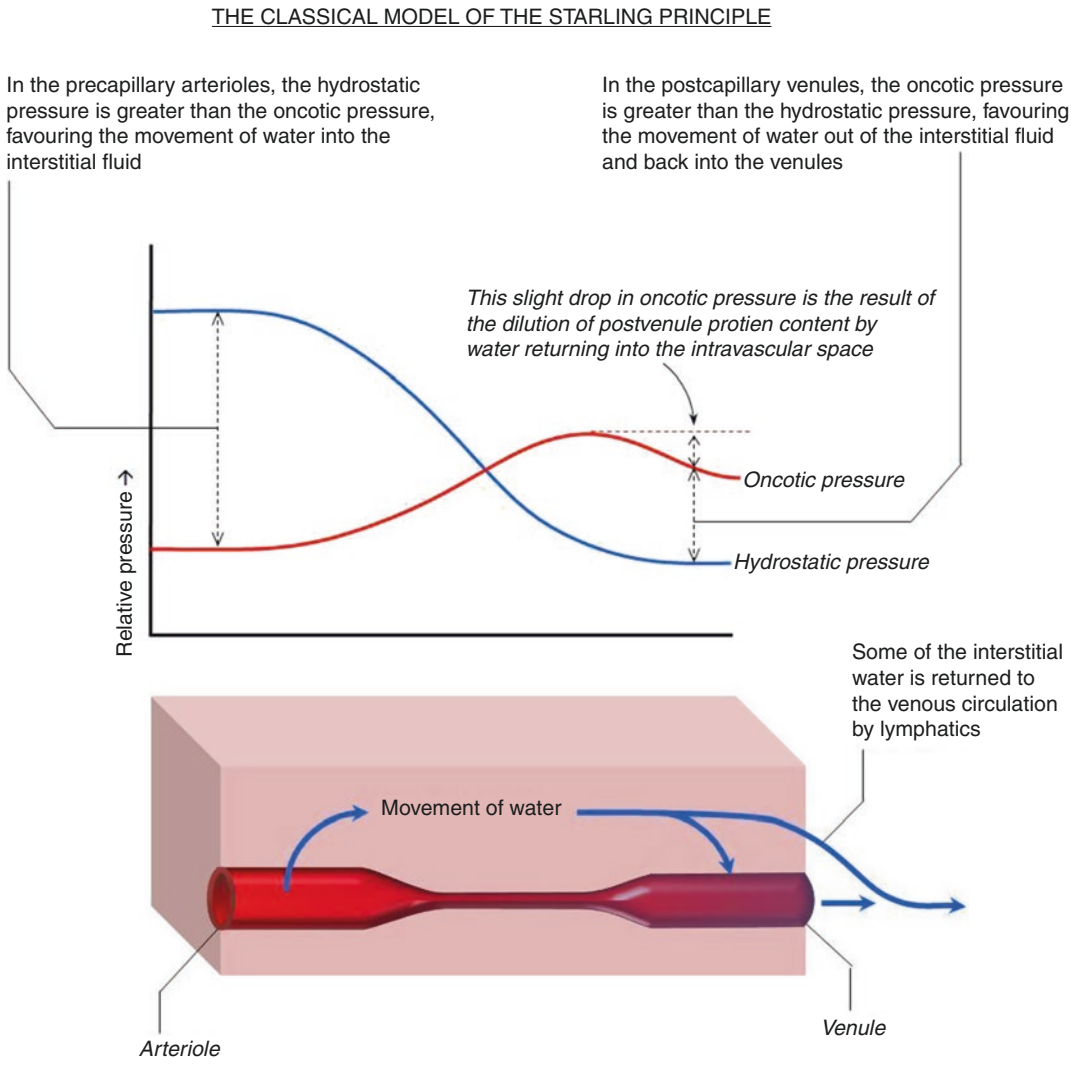

Fig. 11.3 Image demonstrating the Starling principle for fluid movement. At the arterial end, hydrostatic pressure exceeds oncotic pressure with relative movement of water into the interstitial fluid via filtration. At the venule end, oncotic pressure is greater than hydrostatic pressure which then favors the movement of fluid into the vasculature via absorption. ("Image courtesy of Alex Yartsev, www.derangedphysiology.com")

to overcome hydrostatic forces. Therefore, there is no true reversal of filtration. Instead, filtered fluid circulates throughout the interstitial space and largely returns to the circulation as lymph [5]. This principle for fluid movement is influenced by substances that exist in the multiple layers between the interstitial space and intravascular space [5]. These layers include a subglycocalyx space which is largely protein-free and an endothelial glycocalyx space which consists of a matrix of glycoproteins and proteoglycans. The endothelial glycocalyx layer serves as a semipermeable membrane separating plasma from interstitial space. Rather than gradients between the interstitial oncotic pressure and intravascular oncotic pressure that serve as a driving force for fluid movement, it is the subglycocalyx capillary oncotic pressure (πs) that serves as the major determinant in transcapillary flow (Jv) [5]. This model and the function of the endothelial glycocalyx in fluid movement are illustrated in Fig. 11.4. Further research into the translation of

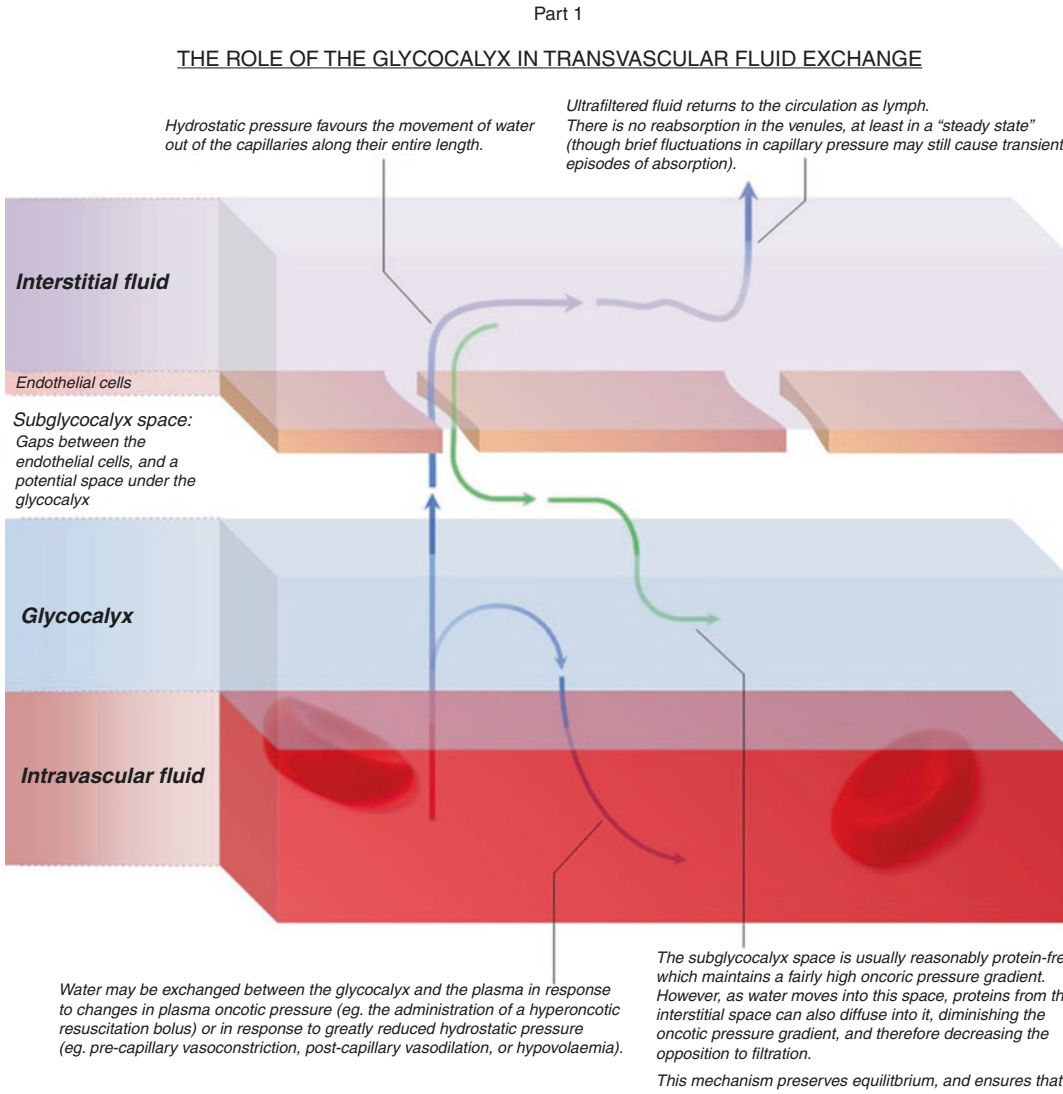

Fig. 11.4 Image demonstrating the role of the endothelial glycocalyx in fluid exchange (part 1) and revised model of the Starling principle (part 2) involving the subglycocalyx illustrating the increase in oncotic pressure throughout the vessel does not exceed hydrostatic pressure with no true reversal of filtration occurring. ("Image courtesy of Alex Yartsev, www.derangedphysiology.com")

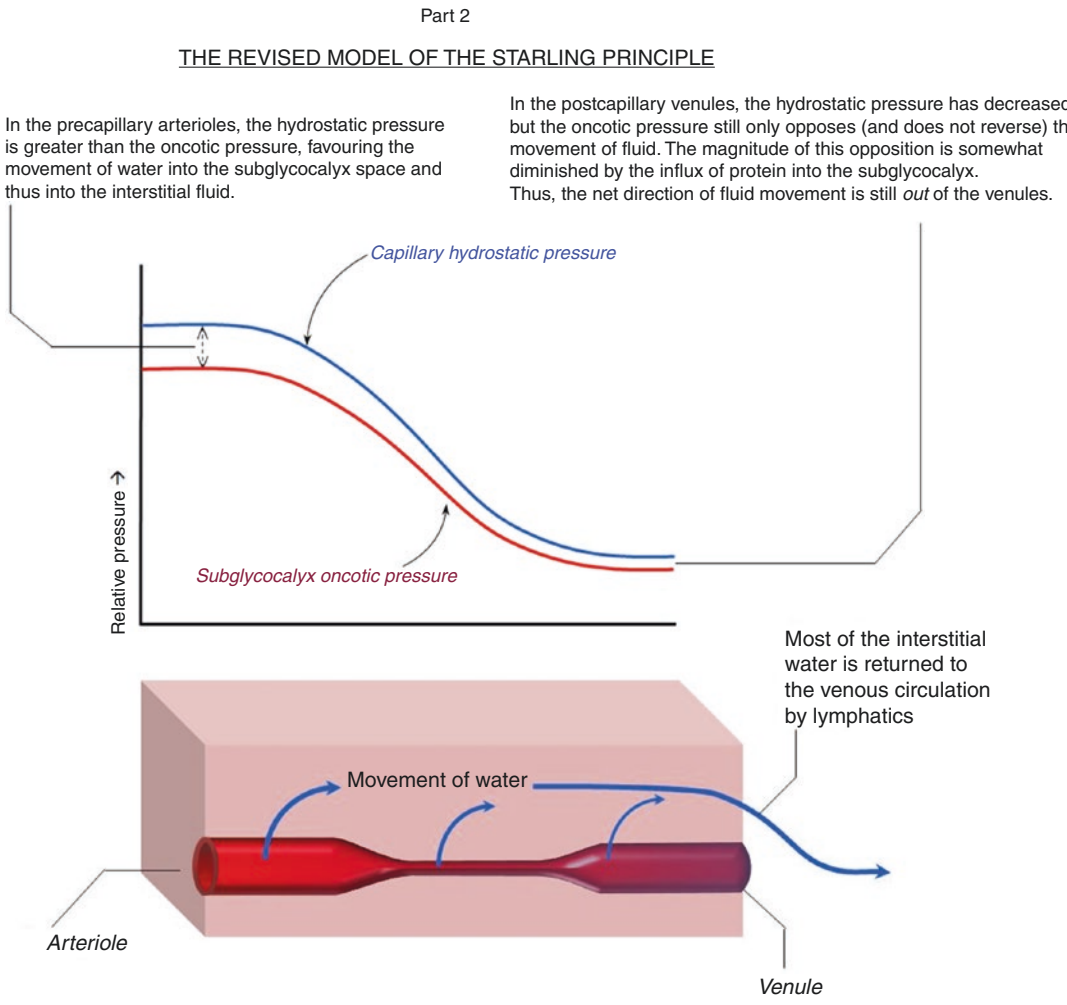

Fig. 11.4 (continued)

this model into clinical practice could lead to improvements in the management of fluid status in critically ill patients.

Fluid management strategies, particularly in states of shock, are often complicated by the need to balance maintenance of oxygen delivery to match metabolic demand and maintain cardiac output without avoiding fluid overload. Shock states and critical illness often have underlying systemic inflammation resulting in anasarca and capillary leak, altering normal fluid movement between compartments [6]. Dysregulation of fluid distribution within intracellular and extracellular compartments, along with aggressive fluid resuscitation and impaired renal clearance, ultimately leads to hypervolemia and fluid overload.

Fluid overload states can impact organ function influencing morbidity and mortality. Excessive fluid can alter the efficiency of the heart by moving ventricular compliance far to the right on the Frank-Starling curve, potentially resulting in impaired cardiac function. Hypervolemia can cause pulmonary alveolar and interstitial pulmonary edema, precipitating respiratory failure [7]. Specifically, worsening pulmonary edema will negatively affect lung compliance, potentiate V/Q mismatch, and, consequently, worsen both ventilation and oxygenation. Finally, particularly during stress states,

renal perfusion may be impaired causing the development of acute kidney injury (AKI), which further complicates the ability of kidneys to maintain euvolemia.

An understanding of fluid distribution and movement in the body therefore becomes critical during periods of fluid resuscitation and overload. Management strategies targeting such pathophysiologic mechanisms are designed to help reduce morbidity and mortality associated with fluid overload and multiorgan dysfunction.

Measurement of Fluid Overload

Case

A 12-year-old female presents to the emergency room with septic shock in the setting of acute influenza infection requiring intubation and aggressive fluid resuscitation. Four days after presentation, her hemodynamics have improved, and she is able to be weaned off inotropic support without difficulty. Her chest X-ray is significant for pulmonary edema. A central venous catheter within the internal jugular vein measures a central venous pressure of 5 cmH_2O. Her weight is 2 kg above her baseline, but her intake/output flowsheet shows that she is overall in a negative fluid balance of 1 L for the duration of her hospitalization. Among the physician team caring for her, there is disagreement about her hydration status. Some physicians feel that she is euvolemic, while others feel that she is grossly fluid overloaded. Possible management pathways are discussed at length. A nurse asks if there is one clear best method to evaluate for fluid overload in a critically ill pediatric patient.

Despite an acknowledgement that fluid overload can be associated with poor outcomes in critical care populations, the optimal clinical definition of fluid overload remains unclear [8]. In 2001, Goldstein et al. developed definitions for fluid overload that relied upon measuring fluid input and output from PICU admission [9]. This method for calculation of fluid overload is demonstrated below:

$$\%\text{FO} = \frac{\text{Sum of daily fluid } (\text{fluid in} - \text{fluid out})}{\text{ICU admission weight}} \times 100.$$

The majority of pediatric studies since then have largely utilized this definition for the purposes of research and clinical identification. However, this method is potentially error prone as it relies upon precise accounting of daily fluid balance and accurate calculations. As an alternative method, fluctuations in weight have been used in some studies. For example, in a study of patients receiving continuous renal replacement therapy (CRRT), measurements of weight at hospital or ICU admission and initiation of CRRT were utilized to determine fluid overload percentage with formulas as demonstrated below [8]:

$$\%\text{FO} = \frac{\text{CRRT initiation weight} - \text{ICU admission weight}}{\text{ICU admission weight}} \times 100$$

OR

$$\%\text{FO} = \frac{\text{CRRT initiation weight} - \text{Hospital admission weight}}{\text{Hospital admission weight}} \times 100.$$

These calculations were compared with the standard method of intake and output assessment and were found to have a high degree of correlation with similar predictive ability for mortality [8]. Therefore, it is possible the two methods could be utilized interchangeably in the clinical setting, though the method of utilizing daily weights rather than summation of daily fluid intake is likely the less labor-intensive means of determining fluid overload.

Despite the fact that both calculations have been validated and are relatively easy to perform, discrepancies between weight measurements and intake/output calculations often occur, thereby complicating management decisions. These discrepancies likely result from the limitations of

these two methods. For instance, fluid-based calculations are unable to fully account for insensible losses, and weight-based calculations are vulnerable to errors that can occur through the use of different scales or weighing techniques. One relatively novel method devised to address such issues involves the use of bioimpedance as a measurement tool to determine fluid overload status.

Bioimpedance utilizes electrical properties of biological tissues in evaluating their response to electrical current with either active (in which electrostimulation triggers ionic activities inherent within tissue cells) or passive response (i.e., response only occurs with external stimulation) [10]. The ability of tissues to impede frequency signals is then extrapolated mathematically to calculate the composition of the tissue. While it has a variety of medical applications, bioimpedance has been proposed as a method to evaluate for fluid status due to its ability to estimate total body fluid and extracellular fluid. However, although multifrequency bioimpedance has been reported as a reliable measure of estimating body water compartments in adults [10], the pediatric literature to support its use remains sparse. Milani et al. recently attempted to evaluate the use of multifrequency bioimpedance measurements in pediatric patients requiring maintenance dialysis and found that measurements of body water compartments were imprecise when compared with gold standard measurements of bromide or deuterated water dilution, two methods which, while accurate, remain impractical for daily clinical use [10]. Although bioimpedance may serve as a potential noninvasive alternative to assess for fluid status in the future, its reliability in critically ill pediatric populations has yet to be realized.

The determination of fluid overload in the critical care setting depends upon the accurate assessment of intake and output from admission and relating this information to each patient's baseline weight. Our recommendation is to use the Goldstein method of daily intake and output in comparison from admission weight to evaluate for percentage of fluid overload [9]. When fluid intake or output measurements are unavailable or incomplete, daily weight measurements can be substituted as a reliable method to measure fluid overload. Regardless of the method of fluid overload measurement, interpretation of fluid status still requires clinician expertise, particularly in settings where physical exam and calculated values are discrepant. The child in the scenario above experienced a significant inflammatory response and capillary leak secondary to her infectious process which predisposed her to pulmonary edema and fluid overload. It is not uncommon for critically ill patients to have intravascular volume depletion concurrent with total body fluid overload. Therefore, despite signs of fluid overload on clinical examination, if the patient were to remain hypotensive or unable to tolerate diuresis, it would be suggestive of ongoing low intravascular volume despite overall fluid overload which would alter clinical decision-making regarding the timing of diuresis or fluid removal therapies.

Managing Fluid Overload with Renal Replacement Versus Diuretic Therapy

Case

A 16-year-old female presents with septic shock in the setting of Staphylococcus aureus infection requiring aggressive fluid resuscitation and vasoactive support in the first 24 h. The next day, her hemodynamics have improved, and she is able to be weaned off inotropic support, though anasarca is noted on physical exam and pulmonary edema is seen on chest radiography. An attending physician who is rounding suggests initiation of diuresis with furosemide, but another attending is concerned that aggressive medical diuresis may worsen the patient's hemodynamic status and instead recommends initiation of renal replacement therapy, specifically continuous veno-venous hemodiafiltration. A resident asks if any method of fluid removal has been proven to result better outcomes in critically ill children.

Currently, options for managing fluid overload are limited to fluid restriction, medical management with diuretics, and/or renal replacement therapy (RRT). The decision regarding which to initiate in the setting of fluid overload is often influenced by multiple extrinsic factors including physician preference, ease of access, size of the patient, hemodynamic stability, and bleeding risk.

Diuretic Therapy

In fluid overload, diuretics are used to maximize renal salt and water excretion in the setting of volume overload. Diuretics are also used in acute renal failure with the intention of converting oliguric to non-oliguric acute renal failure. Non-oliguric renal failure has lower associated morbidity and may prevent the need for future dialysis [11]. However, the use of diuretics is associated with certain risks including electrolyte derangements, ototoxicity among the neonatal population, and AKI especially when used in conjunction with radiocontrast agents.

In patients with AKI, the effect of loop diuretics may be blunted secondary to reduced tubular secretion [12]. Therefore, it has been hypothesized that a lack of diuretic responsiveness may correlate with the degree of acute kidney injury. Kakajiwala et al. retrospectively evaluated infants after congenital heart surgery and found that responsiveness to furosemide was lower among patients with AKI. Their study defined lack of furosemide responsiveness as urine output of less than 1.7 mL/kg/h at 2 h or 1.9 mL/kg/h at 6 h after diuretic administration. After correcting for fluid balance, it was found that lack of furosemide responsiveness was predictive of AKI. While diuretic use may be beneficial in the management of fluid overload, a lack of responsiveness to diuretic therapy may be reflective of concurrent renal injury which can complicate clinical course and management.

At the moment, diuretics remain a mainstay of therapy given that worsening fluid overload contributes to increased mortality and morbidity, but the ideal method of administration remains unclear. In 1992, Singh et al. evaluated in a prospective randomized controlled trial continuous versus intermittent furosemide in postoperative pediatric cardiac patients. Patients were randomized to either IV intermittent (1 mg/kg furosemide every 4 h to be increased by 0.25 mg/kg every 4 h to a maximum of 1.5 mg/kg) or continuous IV infusion (0.1 mg/kg/h of furosemide doubled every 2 h to a maximum of 0.4 mg/kg/h) to maintain urine output >1.0 mL/kg/h. Data showed that those who received the continuous infusion had less variability in urine output and required a lower cumulative daily dose of furosemide, suggesting that continuous infusions may be more advantageous in this patient population [13]. Klinge et al. attempted to replicate this evaluation with 57 postoperative cardiac patients in a prospective, randomized study. Patients were given either intermittent IV furosemide or a continuous infusion of furosemide when urine output fell to less than 1 mL/kg/h and CVP was more than 5 cmH_2O. Patients in the intermittent IV furosemide group required less furosemide over the 3-day study period (1.2 mg/kg/day vs 1.8 mg/kg/day) to achieve the same, targeted urine volume of >1 mL/kg/h [14]. Continuous infusions of furosemide result in more consistent hourly urine output and may be preferred to intermittent dosing in hemodynamically unstable patients.

Alternative diuretic choices to furosemide are another area of ongoing study among the pediatric population. Ethacrynic acid, which can be used as an alternative to other loop diuretics in the setting of sulfa drug allergies, has been studied dating as early as the 1960s. The mechanism of action is identical to furosemide and other loop diuretics – direct reversible blockade of Na/K/2Cl binding sites in the thick ascending loop of Henle. Ethacrynic acid has been reported to be 30% less potent than furosemide [15]. Ethacrynic acid was studied in 22 children aged 2–17 years of age with congestive heart failure. They reported 3.6% average weight loss in patients administered with ten intermittent doses of ethacrynic acid, with an increase in urinary volume by a factor of 2.5 over a 24-h period and with minimal electrolyte abnormalities [16]. In 2015, Ricci et al. performed a prospective randomized double-blinded study on 74 pediatric patients undergoing elective cardiac

surgery comparing furosemide versus ethacrynic acid. Patients were included in the study if they had clinical signs of fluid overload and randomized to either receive furosemide or ethacrynic acid, with primary outcome measuring mean urine output on postoperative day 0. Urine output was noted to be higher among patients who received ethacrynic acid (6.9 mL/kg/h) compared with furosemide (4.6 ml/kg/h, p = 0.002) despite a lower cumulative dose of ethacrynic acid (0.22 mg/kg/h vs 0.33 mg/kg/h, $p < 0.0001$), suggesting that less ethacrynic acid may be required to achieve the same urine output as furosemide in this patient population. The occurrence of AKI was not statistically significant between groups, and no complications linked to electrolyte disorders were observed in either group. Based on these data, it can be concluded that ethacrynic acid is at least as efficacious as furosemide in children recovering from cardiac surgery and may have a role in other critically ill patient populations such as those with sulfa allergies. It is important to note however that ethacrynic acid is currently markedly more expensive than furosemide which, in the current health-care climate, will be a barrier to its use.

Additional diuretic options include bumetanide (a loop diuretic) and thiazide diuretics such as chlorothiazide and metolazone, which act to inhibit Na/Cl co-transporter channels in the proximal part of the distal convoluted tubule. This latter class of diuretics, when used in conjunction with a loop diuretic, may provide a synergistic effect, given that the mechanisms of action of the two classes of drugs are different. Serum electrolytes, especially sodium, potassium, and chloride, should be monitored frequently, as the risk of electrolyte abnormalities increases when these two classes of drugs are used concurrently [17].

Aminophylline has been described as adjunctive therapy for diuresis. Aminophylline is a methylxanthine that functions as a diuretic by acting as an adenosine receptor antagonist, which serves to increase renal blood flow and inhibit solute reabsorption. In cases of oliguria refractory to traditional loop diuretics, there is some thought that aminophylline may help increase efficacy of loop diuretics by promoting dilation of afferent glomerular arterioles and increasing glomerular filtration rate (GFR) [18]. Pediatric and neonatal studies confirm benefits of adjunctive therapy of aminophylline when used in combination with furosemide therapy. Pretzlaff et al. administered a bolus of 6 mg/kg of aminophylline to pediatric patients aged 2–46 months of age with fluid overload who were concurrently treated with furosemide infusions of ≥6 mg/kg/day. Theophylline levels were measured as peak levels 30 min after administration. The mean peak level was 8.3 mcg/mL, and urine output was positively correlated with theophylline level. After administration, patients were noted to have a significant increase in urine output (>80%) during the first 2 h [19]. A neonatal case study described five infants, 26–38 weeks of age, receiving furosemide infusions at 0.2–0.6 mg/kg/h with ongoing oliguria who were loaded with 4 mg/kg of aminophylline and treated with increasing doses until diuresis was achieved. All infants demonstrated weight loss, reduction of mean airway pressure, and FiO2 requirements, along with the resolution of pleural effusions. Aminophylline may therefore be helpful for patients with ongoing fluid overload despite loop diuretic therapy. For patients who receive multiple doses of aminophylline in this setting, monitoring of serum concentrations based on traditional protocols to prevent toxicity would be prudent.

Renal Replacement Therapy

The utility and timing of RRT for fluid overload remain controversial. The majority of studies that have evaluated the use of RRT as a therapeutic modality in critically ill children have done so in the setting of an underlying diagnosis of acute kidney injury and other concurrent comorbidities. Fluid overload frequently occurs in conjunction with renal disease associated with multiorgan dysfunction and is intimately intertwined physiologically with acute kidney injury. RRT for fluid overload within the critical care environment is initiated in the setting of AKI or ARF in approximately 4–8% of all intensive care patients [20–22].

Although there are multiple modalities of RRT available (e.g., peritoneal dialysis, intermittent hemodialysis, or continuous hemofiltration), use of continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodiafiltration (CVVHDF) has become increasingly preferred by pediatric critical care providers [1]. Implementation of RRT for critically ill children who become anuric or develop accepted criteria for dialysis (i.e., life-threatening hyperkalemia or uremia) secondary to AKI is the standard of care and, accordingly, not controversial. Use of RRT, however, in the setting of fluid overload in patients without anuria or other definite criteria for dialysis is more debatable. Studies in pediatric patients have shown that the percentage of fluid overload prior to initiation of therapy is independently associated with survival in all patients receiving CVVH or CVVHDF [1, 20, 23]. For example, in one retrospective study of critically ill children with multiorgan dysfunction, fluid overload was independently associated with mortality; fluid overload was 15.5% in non-survivors versus 9.2% in survivors ($p < 0.01$) [1]. Adult studies have shown similar findings. In one prospective study of adult patients, 90-day mortality was doubled among those who had fluid overload at the time of RRT initiation (identified as greater than 10% fluid overload) [20]. Another adult study demonstrated that increased positive mean daily fluid balance after RRT initiation was also associated with increased mortality [23]. Despite these studies and others on the use of RRT with AKI and fluid overload, the ideal timing for initiation of RRT therapies remains unclear. Perhaps more importantly, it has not been clearly demonstrated that RRT utilization for fluid overload leads to improvement in survival outcomes. A meta-analysis in 2008 evaluating all randomized controlled trials available in adult literature regarding the utilization of RRT demonstrated a mortality risk reduction that was inadequately powered to demonstrate statistical significance [24]. A similar systematic review of adult data performed in 2011 looked to compare early versus late initiation of RRT and showed an association with reduced mortality, but results were complicated by significant statistical heterogeneity [25].

In summary, fluid overload greater than 10% has been associated with increased mortality and poor outcomes in pediatric and adult patients with critical illness. Diuretic medications, with furosemide generally accepted as the first-line agent, can be beneficial in improving urine output. Method of administration (continuous vs intermittent IV) can be based on provider preference and patient factors (e.g., hemodynamic stability, available intravenous access sites, etc.). Adjunctive treatment with aminophylline may be considered in refractory oliguria in patients already receiving traditional diuretic therapies. While current literature does not support RRT implementation based solely on the percentage of fluid overload, it should be considered as therapeutic option for fluid removal in patients with persistent or worsening fluid overload greater than 10% of pre-illness weight despite maximal medical therapy. As the use of CVVH and CVVHDF becomes more commonplace, improved research will hopefully allow for better developed algorithms to dictate fluid removal therapies in the critical care setting.

Fluid Overload and Mechanical Ventilation

Case

A 4-month-old child presents to the hospital with respiratory distress in the setting of enterovirus-induced pneumonitis. At the time of initial presentation, he is noted to be tachycardic with poor urine output for which he receives aggressive fluid resuscitation. His respiratory status continues to worsen, and by day 4 of illness, he is endotracheally intubated and placed on mechanical ventilation. His chest X-ray shows increased interstitial markings consistent with pulmonary edema. The resident asks if the fluid resuscitation contributed to his decompensation and asks if this will significantly impact his recovery.

Fluid overload and respiratory compromise are often connected, particularly in conditions such as sepsis in which systemic inflammation and endothelial injury lead to significant capillary leak and extravasation of fluid into the interstitial space. In recent years, an emphasis on increased early fluid resuscitation for septic shock and the emergence of sepsis protocols with early goal-directed therapy have created the potential for patients to experience more clinically significant long-term fluid overload.

Stabilizing hemodynamics with aggressive fluid resuscitation may come at a cost. Emerging literature shows that prolonged positive fluid balance after hemodynamic stability has been achieved can have a negative impact on organ function and respiratory recovery. These findings are present even when correcting for the underlying severity of illness at the time of presentation. For example, fluid overload ≥15% has been independently associated with prolonged ventilation and increased hospital length of stay [26].

Fluid overload has been associated with increased mortality and duration of mechanical ventilation in children identified with acute lung injury (ALI), [27] a finding which was also observed in the pediatric arm of the Calfactant in Acute Respiratory Distress Syndrome trial [28]. This trial was a multicenter prospective evaluation of intratracheally administered surfactant use in adult and pediatric patients diagnosed with ARDS/ALI. The pediatric arm consisted of 24 children's hospitals across 6 countries and evaluated all-cause mortality at 90 days after study entry, with secondary outcomes of oxygenation changes after intervention, ventilator-free days at 28 days, and total duration of ICU stay [29]. Greater accumulated positive fluid balance from day 1 to day 7 of illness was associated with in-hospital mortality ($p < 0.001$), with non-survivors averaging 8.7 ± 9.5 L/m^2 compared with 1.2 ± 2.4 L/m^2 in survivors. Increased cumulative fluid overload was also associated significantly with less ventilator-free days and longer durations of PICU and hospital stay [28].

In one of the few studies that has examined fluid overload in the pediatric setting in the absence of RRT, Arikan and colleagues found that fluid overload was independently associated with compromised respiratory function. Specifically, peak fluid overload correlated significantly with peak oxygenation index (OI) and Pediatric Logistic Organ Dysfunction (PELOD) score [26]. In a single-center retrospective review of 636 mechanically ventilated children, percent fluid overload correlated with number of invasive ventilation days and OI at 48 h of mechanical ventilation [30]. There are a small number of studies that did not identify a relationship between fluid overload and respiratory morbidity. One such example is a post hoc analysis of a study conducted by the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) that did not show an association between cumulative fluid balance and other respiratory measures such as duration of ventilator weaning and extubation outcomes, though this analysis included all mechanically ventilated patients rather than the subset with ALI or ARDS [31].

While there may be some conflicting data on the relationship between fluid overload and respiratory morbidity, the overwhelming majority of published studies examining this relationship has identified negative consequences of this relationship. For this reason, some authors have hypothesized that active avoidance of early fluid overload may be an appropriate therapeutic goal for patients with underlying critical respiratory illness to reduce time on mechanical ventilation [32]. In a prospective randomized adult trial comparing conservative (i.e., maintenance of central venous pressure ≤ 4 mmHg) versus liberal (i.e., maintenance of central venous pressure 10–14 mmHg) fluid strategies in patients with acute lung injury, oxygenation index and lung injury score were lower, and the number of ventilator free days was higher in patients who received the conservative fluid strategy. There was no statistical difference in the primary endpoint of 60-day mortality: 25.5% versus 28.4% in the conservative and liberal arms of the study, respectively [33]. To our knowledge, similar pediatric studies have not yet been conducted.

Outcomes for patients requiring mechanical ventilation are dependent on multiple factors,

and there are enough published data to conclude that fluid overload likely contributes to worse outcomes in these patients. Moreover, there are no studies that have demonstrated any benefit of fluid overload on respiratory function or outcomes. Recent reviews of ALI and ARDS management in pediatric patients have yet to make recommendations regarding concurrent fluid management strategies [34]. Despite the current lack of guidelines, it is reasonable to conclude that careful attention to fluid management and avoidance of fluid overload whenever possible in patients with respiratory disease are warranted.

Fluid Overload and Cardiac Surgery

Case

A 4-month-old female undergoes surgical repair of tetralogy of Fallot. She returns from the operating room endotracheally intubated on mechanical ventilation. Her first night of hospitalization is complicated by significant hemodynamic instability necessitating frequent fluid boluses. Over the next day, she becomes progressively more fluid overloaded with diffuse anasarca and worsening pulmonary edema. The resident asks if there are specific risks of fluid overload in the postoperative cardiac patient when compared with other patients.

Pediatric patients undergoing cardiac surgery represent a unique population in which their pathophysiology predisposes them to fluid accumulation in the postoperative period. This predisposition can vary based on many factors including the age of the patient and the underlying comorbidities that may be present. Neonates are at particular risk to develop fluid overload due to their increased total body water distribution and renal immaturity. Indeed, fluid overload can occur early in the postoperative period, tending to develop more readily in patients that are younger with cyanotic heart lesions and/or worse kidney function at baseline [35]. Many of the children with these risk factors also have complex lesions requiring longer CPB durations. Prolonged exposure to CPB and the stress of surgery augments the postoperative inflammatory response and consequent capillary leak, likelihood of low cardiac output, and AKI, making fluid overload almost unavoidable in some cases. In a recent retrospective review of 193 children who underwent cardiac surgery, the amount of fluid administered in the first 6 h of ICU admission after surgery was the strongest independent risk factor for fluid overload by postoperative day 2 [36]. In one of the largest prospective studies to date focused on this issue, which examined characteristics and outcomes of 1525 children who underwent cardiac surgery over a 4-year period at a single institution, Lex et al. noted that patients who were more likely to develop fluid overload greater than 5% were significantly younger (median 151 days versus 448 days) and smaller (4.3 kg versus 8.4 kg) and had longer duration of CPB (131 min versus 78 min) and aortic cross clamp (69 min versus 39 min) and lower urine output on postoperative day 1 (1.7 mL/kg/h versus 2.6 mL/kg/h) [37]. A summary of all potential risk factors for fluid overload is listed in Table 11.2.

Multiple studies have found associations of fluid overload with worse outcomes after pediatric cardiac surgery [38]. For instance, a retro-

Table 11.2 Risk factors for fluid overload in cardiac surgery

Preoperative
• Fluid overload secondary to heart failure
• Diminished baseline renal function
• Younger age
• Lower body weight
• Cyanotic congenital heart disease
Intraoperative
• Excessive exogenous fluid and blood products for during surgery
• Longer duration of cardiopulmonary bypass and aortic cross clamp
Postoperative
• Acute kidney injury
• Hemodynamic instability requiring aggressive fluid resuscitation

spective cohort study evaluating 435 neonates undergoing cardiac surgery also recognized this relationship, with fluid overload ≥16% in the postoperative period that was independently associated with worse outcomes including longer hospital stay. These patients were also more likely to experience cardiac arrest requiring CPR, develop thrombosis, or require chest re-exploration. Hazle et al. prospectively identified fluid overload within the first 3 postoperative days following cardiac surgery to be independently associated with poor outcomes in 49 infants <6 months of age who underwent surgery with CPB [38]. Specifically, they found that odds of poor outcome (defined by a composite score that included the need for RRT, time to first extubation, intensive care length of stay, or death within 30 days of surgery) increased by 7% with each 1% increase in fluid overload as calculated by maximum daily weight method, adjusted for peak serum creatinine [38].

Fluid overload is therefore deemed to be hazardous to the postoperative pediatric cardiac patient by current pediatric cardiac intensive care providers. As a result, many centers implement management strategies that are designed to prevent fluid overload. These measures include some or all of the following: intraoperative and postoperative corticosteroids to reduce immunogenic-mediated capillary leak, conservative fluid management, early diuretic administration to mitigate perioperative fluid/blood product administration, and dialysis. Emerging evidence suggests that early dialysis, particularly with peritoneal dialysis (PD), may have benefits to postoperative cardiac patients [39]. A single-center retrospective study of 146 neonates published in 2012 reported that children with AKI after cardiac surgery in which PD was started early (within the first day) had lower 30- and 90-day mortality rates [40]. Of note, 52 complications related to PD were recorded in 44 patients in this study including dysfunction of the catheter (leakage at the insertion site, displacement, or insufficient drainage), hydrothorax, hemoperitoneum related to insertion or withdrawal of the catheter, bowel perforation, and peritonitis. More recently, in an unblinded trial by Kwiatkowski et al., 73 infants with postoperative oliguria (defined as 4 total h of urine output <1 mL/kg/h during the first postoperative 24 h) were randomized to receive either PD or furosemide therapy. Patients who were restricted to furosemide treatment were more likely to develop 10% fluid overload, prolonged mechanical ventilation, and prolonged CICU stay. Also, patients who received PD had fewer electrolyte abnormalities, though two PD-related adverse outcomes were observed – peritoneal bleeding requiring a blood transfusion and hydrocele formation [39].

In summary, postoperative cardiac patients are predisposed to fluid overload due to a variety of factors. Significant fluid overload in postoperative cardiac patients is common and associated with worse outcomes. While fluid overload may be unavoidable in some patients, efforts to minimize the degree of fluid overload are appropriate. For institutions that have the resources and experience to readily implement PD in the early postoperative period, careful risk factor assessment could drive the creation of PD protocols for this patient population. As experience with this modality increases and more data become available, many of the risks associated with PD may decrease, and centers may be more inclined to offer this modality more frequently. In the meantime, conservative fluid management, early initiation of diuretic therapy, and careful attention to daily fluid balance and weight measurements are necessary to temper the risks of fluid overload in children recovering from cardiac surgery.

Fluid Overload and ECMO

Case

A *6-month-old infant with a history of prematurity and chronic lung disease presents to the hospital in respiratory distress from respiratory syncytial virus infection. She is endotracheally intubated and provided mechanical ventilation for respiratory failure with hypoxemia. Despite multiple ventilator maneuvers, her arterial blood gases*

show worsening, severe hypercarbia. She becomes increasingly acidotic and develops hemodynamic instability necessitating aggressive fluid resuscitation. Shortly thereafter, she has a cardiac arrest and is cannulated emergently for venoarterial extracorporeal membrane oxygenation (ECMO). After cannulation, she is noted to be increasingly edematous, which is distressing for the family. They ask if her edema has any implications on her clinical outcome.

In recent years, extracorporeal membrane oxygenation (ECMO) has become a more readily accessible resource for the management of critically ill children, with the number of ECMO centers increasing on a yearly basis [41]. AKI is a common comorbidity for children undergoing ECMO support and has been associated with increased mortality [42]. The burden of illness suffered by children requiring ECMO support makes them prone to more aggressive fluid resuscitation and, accordingly, more fluid accumulation. Despite concerns that fluid overload may be harmful in a variety of clinical situations including mechanical ventilation and postoperative care, there are few studies evaluating its effect, independent of AKI, on patients receiving ECMO.

Of the limited published data, fluid overload on ECMO has been associated with adverse outcomes in neonatal, pediatric, and adult patients. Neonatal studies of children with pulmonary hypertension on ECMO have suggested that edema and fluid mobilization play a role in persistently poor respiratory function and duration of ECMO [43, 44]. Selewski and colleagues retrospectively evaluated fluid overload in 756 pediatric ECMO courses at 6 centers within the United States and Canada. In this study, patients who died while on ECMO had significantly greater peak fluid overload while on ECMO, greater change in fluid overload during their ECMO course, and greater fluid overload at time of ECMO discontinuation. More importantly, in a multivariable analysis, peak fluid overload while on ECMO independently predicted mortality (adjusted odds ratio, 1.09; 95% CI, 1.04–1.15); and both fluid overload at ECMO initiation (adjusted odds ratio, 1.13; 95% CI, 1.05–1.22) and peak fluid overload (adjusted odds ratio, 1.18; 95% CI, 1.12–1.24) predicted hospital mortality, independent of AKI [45]. Though the study population was largely neonates and the diagnosis of AKI was made using serum creatinine values, these multicenter data highlight a potential effect of fluid overload on morbidity and mortality.

Based on current literature, it is unclear whether conservative fluid management, diuretic therapy, or RRT, either alone or in some combination, is a superior management strategy for patients on ECMO. Current CRRT devices can easily be utilized in conjunction with the ECMO circuit, eliminating access as a barrier to its use in this patient population. As a result, many centers have a low threshold for initiating CRRT for ECMO patients. Studies have shown that neonatal ECMO survivors receiving CRRT had an overall better fluid balance and received less diuretic therapy compared with non-CRRT survivors [46]. A systematic review performed of all published literature regarding CRRT and ECMO showed that ECMO survivors receiving CRRT therapy had an overall fluid balance that was less positive compared with those not on CRRT but also noted studies showing longer ECMO duration when CRRT was applied [47]. Additionally, other studies have shown an increased association between mortality and concomitant CRRT on ECMO [48, 49]. Unfortunately, it is unlikely that a prospective RCT will be conducted on the use of CRRT in ECMO patients, as there is no consensus on accepted indications for initiation and practice varies considerably across centers. The risk/benefit ratio must be evaluated for each patient accounting for resource availability, nutritional needs, and the potential for worsening intravascular volume depletion, which can further exacerbate AKI and negatively affect the function of the ECMO circuit.

Conclusion

Fluid overload remains an area of ongoing evolution regarding its definition and management within the clinical setting of the critically ill child. Despite a large body of evidence to indicate that it is associated with increased morbidity and mortality in specific disease states, management strategies are largely dictated by physician experience and preference. Importantly, it can be stated with high confidence that there are no studies to date that suggest that fluid overload is beneficial to patients or has any positive effect on recovery or survival. Definitions of fluid overload have largely relied upon calculated measurements, but these may underrepresent fluid distribution during critical illness and fail to completely capture the intricacies of fluid extravasation that put certain organs at higher risk of complications than others. Clinicians should focus on judicious use of fluids including blood products along with careful assessment of fluid status, thereby allowing for early interventions aimed at prevention of fluid overload states and the associated cellular edema, organ dysfunction, morbidity, and mortality.

Key Points

- The dynamics of fluid movement are complex, and our understanding regarding such is still evolving.
- Current methods of the assessment of fluid overload are potentially error prone and can produce conflicting results. Daily assessment of fluid status however is crucial, and discrepancies between weight and intake/output calculations should be reconciled by clinical exam and available physiologic bedside data.
- Fluid overload is associated with adverse outcomes in multiple disease states, and, to our knowledge, there are no studies that demonstrate that fluid overload is beneficial to patients or their outcomes.
- Options for management of fluid overload include conservative fluid management, diuretic therapy, and RRT including CVVH/CVVHDF and PD. Furosemide therapy is generally accepted as the first-line diuretic agent, but persistent or worsening fluid overload despite conservative fluid management and furosemide therapy should prompt adjunctive treatments or RRT.
- Further research of the effects of fluid overload and its management in specific patient populations and disease states is required to improve our practice and decrease variations in care across centers.

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Part V

Hematologic Controversies

Management of Cardiopulmonary Bypass-Associated Coagulopathy

12

Rania K. Abbasi, Anne E. Cossu, and Scott G. Walker

Coagulopathy in pediatric patients after cardiopulmonary bypass (CPB) is highly complex and multifactorial**.** Numerous controversies and practice variations surround the management of hemostasis after CPB, from the preoperative to the postoperative phases of the surgical process. Though no true consensus exists for many of these practices, there are data available in the literature to provide a better of understanding of hemostasis in congenital heart disease and to guide practice after CPB.

The Coagulation Cascade

To understand the etiology of acquired coagulopathy associated with cardiopulmonary bypass (CPB), it is imperative to have a thorough comprehension of in vivo hemostasis.

The Cascade Model of Hemostasis

The cascade or "waterfall" model of hemostasis was originally proposed in the 1960s [1, 2]. This model described the hemostatic process as a sequence of enzymatic reactions wherein a protease cleaves and activates a subsequent protease in the sequence, resulting in the production of thrombin followed by the formation of a fibrin clot [3]. The most common and prevailing illustration of the cascade model is a Y-shaped paradigm with separate intrinsic and extrinsic pathways that converge upon a common pathway (Fig. 12.1) [4, 5]. The intrinsic and extrinsic pathways are each initiated by factor XII (FXII) and tissue factor (TF)/activated factor VII (FVIIa), respectively. In this model, both pathways lead to the formation of activated factor X (FXa) and activated factor V (FVa). In the common pathway, FXa with FVa activates prothrombin (FII) to thrombin (FIIa), which then cleaves fibrinogen to soluble fibrin. The extrinsic pathway functions to initiate and amplify hemostasis, whereas the intrinsic pathway functions to trigger a thrombin burst, leading to the generation and stabilization of fibrin clot [4].

The cascade model has been greatly useful in the elucidation of in vitro coagulation but was not meant to be a model of in vivo hemostasis. Factor deficiencies in the extrinsic or common pathways can be reflected in the laboratory when determining the prothrombin time (PT). Similarly, factor deficiencies in the intrinsic or common pathways may be reflected in the activated partial thromboplastin time (aPTT). Deficiencies of specific factors in each pathway however do not equally increase the risk of clinical bleeding or hemorrhage [3, 4].

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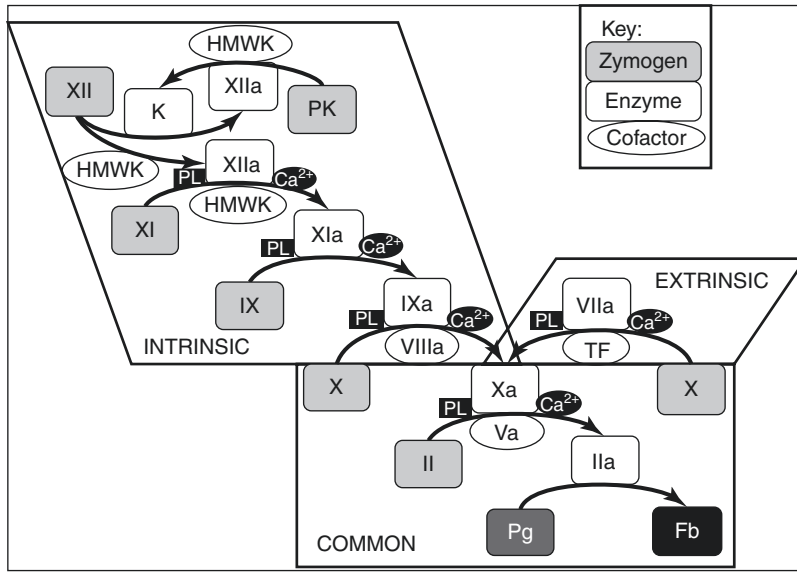


Fig. 12.1 The cascade model of coagulation
This model divides the cascade into separate intrinsic and extrinsic pathways, both of which result in the formation of FXa. The common pathway results in the formation of fibrin from fibrinogen through the action of Xa and Va. Many of the coagulation factors require calcium (Ca^{2+}) and a phospholipid surface (PL). (Adapted from Smith [5] with permission.)

HMWK, high molecular weight kininogen; PK, prekallikrein; K, kallikrein; XII, factor XII; XIIa, activated factor XII; XI, factor XI; XIa, activated factor XI; IX, factor IX; IXa, activated factor IX; VIIIa, activated factor VIII; X, factor X; Xa, activated factor X; VIIa, activated factor VII; TF, tissue factor; Va, activated factor V; II, prothrombin; IIa, thrombin; Fg, fibrinogen; Fb, fibrin

The Cell-Based Model of Hemostasis

Inclusion of cells in the description of the hemostatic process allows for a better understanding of in vivo coagulation and has given rise to the cell-based model of hemostasis. In particular, two types of cells are required for coagulation: platelets and tissue factor (TF)-bearing cells [4]. Existing literature and cell-based experiments propose a model of in vivo hemostasis that occurs in a stepwise and overlapping process [3]. The process involves three distinct phases: initiation, amplification, and propagation. Figure 12.2 depicts the cell-based model of hemostasis [5]. Evidence to date suggests that the clotting cascade is initiated when FVII/FVIIa in plasma binds to TF-bearing cells in the disrupted blood vessel endothelium. Minute amounts of FXa and FIXa are produced and dissociate away from the cell. FXa can slowly and directly activate FV to FVa. Therefore, FXa and FVa can bind together to form the prothrombinase complex, which then cleaves prothrombin to small amounts of thrombin (FIIa). In the amplification phase, thrombin generated on the TF-bearing cells then activates platelets and releases von Willebrand factor (vWF) from vWF/FVIII complex. Released FVIII is subsequently activated by thrombin to FVIIIa. In addition, thrombin activates FV to FVa and FXI to FXIa. Lastly, in the propagation phase, many coagulation proteins become localized to the surface of activated platelets. The release of granule contents from a few activated platelets results in the recruitment of additional platelets to the site of vascular injury. Propagation occurs on the surface of these platelets. FIXa (produced during the initiation phase) binds to FVIIIa (produced in the amplification phase) to form the tenase complex. The tenase complex rapidly generates FXa on the platelet surface. FXa immediately binds to FVa on the platelet surface to form the prothrombinase complex and mediate a burst in thrombin formation [5]. Large amounts of thrombin are available to convert fibrinogen to soluble fibrin monomers by the removal of N-terminal fibrinopeptides A and

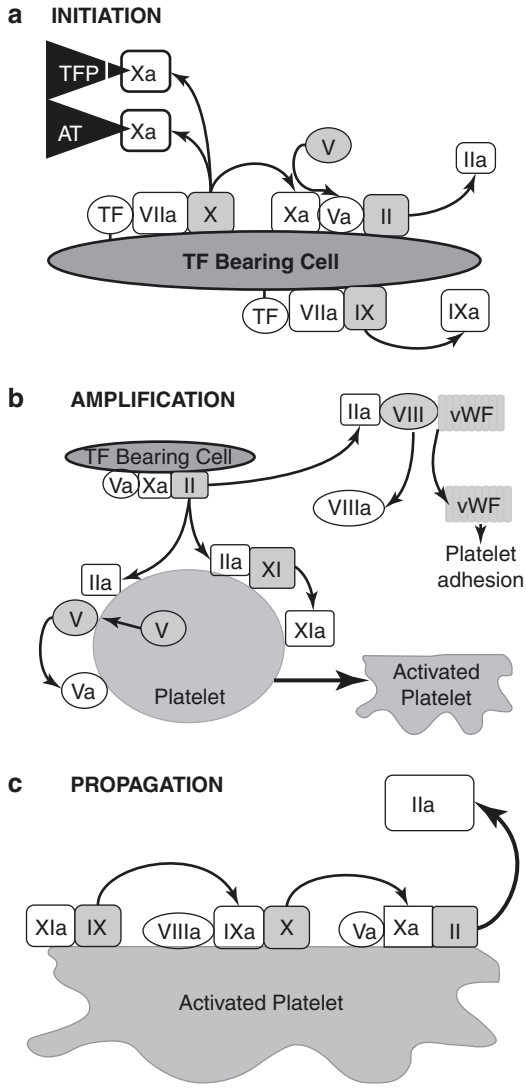


Figure 12.2 The cell-based model of hemostasis
The cell-based model incorporates TF-bearing cells and platelets into hemostasis. (**a**) Initiation phase: initiation occurs on the surface of TF-bearing cells. Small amounts of thrombin and FIXa are produced and dissociate away from the cell. (**b**) Amplification phase: thrombin generated on TF-bearing cells activates platelets and releases vWF from vWF/FVIII complex. Thrombin also activates FV, FVIII, and FXI. (**c**) Propagation phase: many coagulation proteins become localized to the surface of activated platelets. FIXa/FVIIIa (tenase complex) activates FXa, leading to the formation of FXa/FVa (prothrombinase complex) and a burst of thrombin production. (Adapted from Smith [5] with permission.)

B. With the formation of a critical mass of soluble fibrin, there is spontaneous polymerization to fibrin strands, resulting in an insoluble fibrin mesh. Furthermore, thrombin activates FXIII to FXIIIIa, which acts to cross-link insoluble fibrin strands. Fibrin cross-linking dramatically increases fibrin clot stability and strength [5]. A more detailed description of this complex cascade, which is beyond the scope of this text, can be found in several excellent references [3–5].

Fibrinolysis

Fibrinolysis commences as soon as the hemostatic process begins and is necessary to prevent unnecessary accumulation of intravascular fibrin and mediate removal of thrombi. Plasmin is the major fibrinolytic protease (6). Plasminogen is cleaved to form active plasmin by two serine proteases, urokinase-type plasminogen activator (uPA) and tissue plasminogen activator (tPA). Plasmin then cleaves fibrin at specific lysine and arginine amino acid residues, thereby dissolving fibrin clot and generating soluble fibrin degradation products (Fig. 12.3).

Inhibitors are important to prevent excess fibrinolysis. Serine protease inhibitors, or serpins, inhibit plasmin and plasminogen activators through covalent binding and subsequent plasma clearance [6]. Both tPA anduPA are inhibited by plasminogen activator inhibitor-1 and activator inhibitor-2 (Fig. 12.3). Plasmin is inhibited primarily by α_2-antiplasmin and to a lesser extent by α_2-macroglobulin [7]. Thrombin-activatable fibrinolysis inhibitor (TAFI) is a non-serpin inhibitor that removes C-terminal lysine and arginine residues on fibrin, which are the binding sites for plasminogen and tPA, thereby reducing plasminogen activation and plasmin production (Fig. 12.3) [6, 7].

Coagulation in CPB

Postoperative bleeding, which occurs as a result of widespread activation of the hemostatic system, is very common and often problematic in pediatric patients recovering from cardiac surgery with CPB. This hemostatic activation occurs through several mechanisms including the contact system, inflammation, platelet activation, and fibrinolysis [8, 9]. Upon commencement of CPB, there is a 5-fold increase in the production

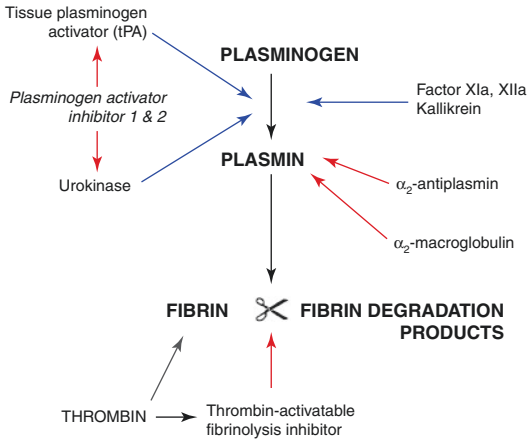


Fig. 12.3 Overview of the fibrinolytic system
Plasminogen is converted to the active protease, plasmin, through the action of tPA and uPA. Plasmin, once produced, can then degrade fibrin into soluble degradation products. Both tPA and uPA can be inhibited by plasminogen activator inhibitors 1 and 2. Plasmin is inhibited by α_2-antiplasmin and α_2-macroglobulin. Thrombin-activatable fibrinolysis inhibitor (TAFI) is a potent inhibitor of fibrinolysis via indirect inhibition of plasmin formation. TAFI binds to arginine and lysine residues on fibrin, which are also binding sites for plasminogen and tPA, thereby preventing conversion of plasminogen to plasmin by tPA [7]. Blue arrows indicate enzymatic activation and red arrows indicate inhibition

of tPA and 20-fold increase in the production of thrombin and soluble fibrin [9, 10]. Soluble and circuit-bound fibrin creates an enormous surface area for plasminogen activation [11–13]. Consequently, after CPB begins, there is a 10- to 100-fold increase in plasmin production [14]. This hyper-fibrinolytic state consumes fibrinogen, leaving little available for hemostasis after CPB. Furthermore, excessive production of plasmin can result in the damage of platelets through plasmin-mediated cleavage of the glycoprotein Ib receptor [15, 16] and partial activation, which makes them less responsive to natural agonists such as adenosine diphosphate and arachidonic acid [17–19].

While hyper-fibrinolytic states are common after CPB, some patients can paradoxically develop a hypo-fibrinolytic state after CPB. Plasminogen activator inhibitor-1 (PAI-1), which prevents plasmin formation, is an acute phase reactant, and serum concentrations are often increased by 15-fold for several hours after CPB termination. The fibrinolytic response to CPB can therefore vary from patient to patient, and, thus far, the prediction of which patients are at risk for bleeding versus thrombosis after CPB has been elusive [9].

Case
A 5-day-old 3-kg neonate is undergoing repair of truncus arteriosus type I. Preoperative laboratory studies include hematocrit 46%, platelets 214,000, and fibrinogen 178 mg/dL. Coagulation studies are otherwise normal. During the operation, the patient is cooled to 28 °C. Duration of CPB is 122 min. Various hemostatic strategies are employed throughout the operation.

Antifibrinolytic Therapy

Prophylactic use of pharmacologic antifibrinolytics to reduce intraoperative and postoperative blood loss after cardiac surgery is a strategy utilized by many institutions. These agents act by inhibiting fibrinolysis and protecting platelets. They are typically administered before the start of CPB and thus prior to stimulation of fibrinolysis by the cardiopulmonary bypass circuit.

There are three antifibrinolytic agents that are used in cardiac surgery to minimize bleeding and reduce the need for blood product transfusion: aprotinin, ∑-aminocaproic acid (EACA), and tranexamic acid (TXA). Aprotinin is the most extensively studied antifibrinolytic agent. It is a serine protease inhibitor isolated from bovine lung tissue. Aprotinin forms reversible complexes which inhibit various types of proteases such as plasmin and kallikrein, thereby preventing fibrin clot degradation [8]. While aprotinin has been shown to reduce the activation of platelets in vitro [17, 20], various studies in adults have demonstrated the efficacy of aprotinin in decreasing hemostatic activation and in preserving platelet function [21–24]. Its efficacy in reducing bleeding and transfusion requirements

after cardiac surgery in adults is also well-established in many randomized controlled trials and meta-analyses [25–29]. Aprotinin has also been studied extensively in pediatric patients, but many of these studies contain conflicting efficacy and safety data. Several prospective, randomized, placebo-controlled, double-blind pediatric studies have found that aprotinin is associated with reduced amounts of bleeding and transfusions of blood products after cardiac surgery, although the differences were not always statistically significant [30–34]. A meta-analysis of 12 randomized controlled studies measured the effect of aprotinin on the proportion of children transfused, the volume of blood transfused, and the volume of chest tube drainage [35]. The combination of the data from these randomized controlled trials clearly demonstrated reduction in the percentage of patients requiring blood product transfusion. Conversely, several randomized, placebo-controlled, double-blind studies have concluded that aprotinin is not efficacious in reducing blood loss or transfusion requirements when compared to placebo in pediatric patients after cardiac surgery [36–39].

Regardless of these conflicting data, there have been safety concerns with the use of aprotinin due to reports of an increased incidence of cardiovascular and cerebrovascular events, renal failure, and mortality when compared to the lysine analogues EACA and TXA [40–43]. The Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study compared the efficacy and safety of aprotinin, TXA, and EACA in adult cardiac surgery patients at high risk for mortality. The trial was stopped at 80% enrollment due to a 53% relative increase in all-cause mortality and doubled risk of death from cardiac causes in the patients who received aprotinin compared to patients who received TXA or EACA [44]. A meta-analysis of randomized controlled trials that analyzed the use of aprotinin, EACA, and TXA in adult patients during non-urgent cardiac surgery found that all three drugs reduced the frequency of transfusion compared with placebo but that aprotinin increased the relative risk of death when compared to TXA and EACA [45]. Bayer Healthcare, under the guidance of the Food and Drug Administration (FDA) and other authorities, removed aprotinin from the worldwide market in November of 2007. Since its suspension from the markets in 2007, the data from three observational studies [41–43] have been reevaluated by the FDA and found not to provide sufficient evidence to show a negative risk/benefit ratio for aprotinin when used for its licensed indication. Similarly, the regulatory authority in Canada (Health Canada) and the European regulatory authority have reanalyzed data from the BART study. In 2011, Health Canada subsequently allowed license of aprotinin to be regranted for adults undergoing myocardial revascularization only. The European regulatory authority also revisited the aprotinin safety data and in 2012 recommended the restoration of the license for use in Europe as well. Aprotinin remains available in Canada, the United Kingdom, Sweden, and the Netherlands.

In contrast, studies examining the safety of aprotinin in pediatric patients have described different results. For example, the safety of aprotinin was evaluated in a large multi-institutional cohort of pediatric patients undergoing cardiac surgery at 35 US children's hospitals from 2003 to 2007 using the Pediatric Health Information Systems Database [46]. In a multivariable analysis from this study, there was no difference in mortality, dialysis, or hospital length of stay in patients who received aprotinin versus those who did not. Despite these data, aprotinin remains unavailable in the United States for use in pediatric patients undergoing cardiac surgery.

EACA and TXA are analogues of the amino acid lysine. EACA and TXA competitively bind to lysine residues on plasminogen, thereby preventing the binding of plasminogen to fibrin [47]. Recall that plasminogen, tPA, and fibrin bind together to activate plasmin, which then degrades fibrin into fibrin degradation products (Fig. 12.3). Plasminogen cleavage to plasmin is thereby inhibited, which results in downstream inhibition of fibrinolysis. TXA may also improve hemostasis by preventing plasmin-induced platelet activation [48].

The role of EACA in reducing postoperative bleeding has been studied extensively in adult

and pediatric patients after cardiac surgery with CPB. Published studies indicate that treatment with EACA reduces bleeding after cardiac surgery with CPB when compared to placebo [49–51]. A meta-analysis of five randomized clinical trials investigated the efficacy of EACA in reducing bleeding and blood product transfusion and maintenance of coagulation tests after pediatric cardiac surgery. The primary conclusions were that, when compared to placebo, prophylactic EACA reduced postoperative blood transfusion, reduced rates of surgical re-exploration, and helped preserve coagulation parameters after pediatric cardiac surgery [52].

TXA, the other lysine analogue, is also commonly used in patients undergoing cardiac surgery with CPB. Several prospective, randomized, double-blind, placebo-controlled studies have demonstrated TXA to be effective in reducing postoperative blood loss in pediatric cardiac surgical patients [53, 54]. One serious complication associated with TXA is the incidence of seizures. A number of studies have reported that TXA is associated with increased incidence of postoperative seizures in adult patients after cardiac surgery [55–59]. A recent meta-analysis of randomized controlled trials was performed with the aim of assessing the risk of seizures with TXA use in adult patients after cardiac surgery. A pooled analysis of 16 studies enrolling 45,235 adult patients demonstrated that TXA therapy was associated with a statistically significant increased (fourfold) occurrence rate of postoperative seizures. This same fourfold increase in the rate of seizures in patients receiving TXA versus EACA was also demonstrated in a study of pediatric cardiac surgery patients, but the difference did not reach statistical significance [63]. The occurrence of seizures with TXA may be dose-related (i.e., increased risk with increased dosage) [58, 60]. A prospective study comparing TXA and EACA with regard to efficacy in reducing postoperative bleeding and safety after pediatric cardiac surgery found that there was no difference in postoperative bleeding in the first 24 h after surgery and that there was no difference in the occurrence of seizures, renal injury, and renal failure [61]. Although pediatric data are not conclusive, the published data from the adult population supports caution when prescribing TXA to patients who may be at increased risk for seizures, regardless of age.

In a meta-analysis of all randomized controlled trials comparing aprotinin, TXA, and EACA in pediatric patients undergoing cardiac surgery, both TXA and aprotinin were significantly associated with reduced packed red blood cell (PRBC) transfusion compared to placebo, while the effect of EACA on red blood cell transfusion could not be determined. Additionally, there was no evidence that EACA and TXA were less effective than aprotinin in reducing perioperative blood loss. In a large multicenter study linking the Society of Thoracic Surgeons Congenital Heart Surgery Database (2004–2008) with medication data from the Pediatric Health Information Systems Database, aprotinin was compared to EACA and TXA in 22,258 patients from 25 centers [62]. When comparing aprotinin to EACA, there was no observed difference in efficacy and safety outcomes when all patients were considered, but EACA was associated with significantly greater in-hospital mortality in the subgroup of patients who underwent redo sternotomy and greater bleeding requiring reoperation in neonates. In contrast, TXA was associated with reduced in-hospital mortality, bleeding requiring surgical intervention, intensive care unit length of stay, and dialysis when compared to aprotinin in an analysis of all patients and in subgroup analysis of neonates. EACA and TXA were not directly compared in this study. Studies that directly compare TXA versus EACA in pediatric cardiac surgery found both agents to be superior to placebo in reducing postoperative bleeding and transfusion requirements, but there were no differences observed in these outcomes between TXA and EACA [63–65].

In summary, based on current data, antifibrinolytic therapy should be part of the management of coagulopathy and bleeding after CPB. Despite an impressive body of literature examining these agents, it remains unclear which of the three available agents are optimal in this clinical setting. For practitioners within the United States, aprotinin is not approved by the FDA and not

available for use, which dictates the use of either TXA or EACA. Recent literature provides evidence that EACA and TXA have, at the very least, similar efficacy in reducing perioperative bleeding and blood transfusion requirements when compared to aprotinin. Until additional data are available, centers should be utilizing antifibrinolytic therapy following CPB, the choice of which can be guided by physician experience and preference.

Case

Tranexamic acid (TXA) is utilized throughout the case. After induction of anesthesia and prior to initiation of CPB, a loading dose of 4 mg/kg is administered over 10 min and followed by an infusion of 3 mg/kg/h throughout the case.

Cardiopulmonary Bypass Strategies and Impact on Coagulopathy

Several practice variations and controversies surrounding CPB management strategies affect coagulation [66]. The degree of allowable hemodilution is one such controversy. Pediatric patients, particularly neonates and infants, are subject to hemodilution due to their small blood volume in comparison to the volume of priming solution within the CPB circuit. Hemoglobin, platelets, and coagulation factors are all diluted, which can adversely affect tissue perfusion, neurocognitive function, and coagulation. Smaller pediatric circuits are used at some centers, as small as ~200 mL, to help minimize the degree of hemodilution [67–72], though even this volume is large relative to small infants (i.e., blood volume of a 3-kg neonate is ~240 mL).

Dilution of blood components frequently leads to increased transfusion requirements [73]. Transfusion targets for children requiring CPB are also controversial. Two key randomized controlled trials from Boston Children's Hospital suggested a minimum hematocrit of 25% while on CPB. In the first study, infants less than 9 months old undergoing biventricular repair were randomized to either hematocrit of 20% or 30% while on CPB. Patients in the 20% hematocrit group had significantly reduced cardiac index, higher serum lactate levels, and worse 1-year psychomotor tests relative to the 30% hematocrit group [74]. The second study randomized infants undergoing biventricular repair to either hematocrit of 25% or 35% while on CPB, assessing the same clinical variables as the earlier study. No significant differences in clinical outcomes were found between groups. The results of these two studies suggest that a hematocrit of 25% may be adequate for neurodevelopmental outcomes [75, 76]. More recently, lower goal hematocrits have been reported in the Jehovah's Witness population, where "bloodless" surgery is requested. While some report hematocrits as low as 21% while on CPB without adverse events, the results of the aforementioned Boston study and absence of long-term neurodevelopmental follow-up in these patients make this practice controversial [77–80].

Techniques for ultrafiltration and hemoconcentration are also variable between institutions. Ultrafiltration was introduced as a component of CPB management to remove excess plasma water and improve hemodilution [81, 82]. It has also been shown to reduce the inflammatory mediator burden induced by CPB. Three modes of ultrafiltration are currently in use: conventional (CUF), modified (MUF), and zero-balance (Z-BUF). Conventional ultrafiltration includes both MUF and Z-BUF. CUF is the original form of ultrafiltration, occurring anytime during the CPB duration [82]. In the early 1990s, MUF was developed as a more efficient mode of ultrafiltration, utilizing different timing (immediately after CPB conclusion) and technique [81]. Z-BUF takes place during the rewarming period, when inflammatory mediator release is greatest. Blood volume is maintained at a constant during the procedure utilizing a balanced electrolyte solution [83]. Multiple studies have demonstrated numerous benefits of both MUF and Z-BUF including reduced transfusion requirements, improved cardiac function, and reduced duration of mechanical ventilation [82, 84–87].

Complications include possible hemodynamic instability or technical difficulties during the ultrafiltration process. While there is no standard ultrafiltration practice between institutions, with many using a combination of the various techniques, the data suggests that ultrafiltration should be implemented in pediatric CPB as a means of tempering the negative effects of hemodilution and, by association, post-CPB coagulopathy.

The composition of the CPB priming solution is an additional source of debate between practitioners. The need for blood in the prime is dependent on several factors, including weight, preoperative hematocrit, and circuit size [72]. Additionally, the target hematocrit of the prime is variable between institutions. Some centers utilize whole blood, others use PRBCs and FFP, and others utilize solely PRBCs—there is no standard practice. The chosen therapy may in part be determined by the institution's blood bank logistics [66, 88]. Several studies have compared fresh whole blood versus stored component therapy in the CPB prime with conflicting results. Studies supporting its use have demonstrated reduced donor exposures and reduced bleeding, presumably due to preserved platelet and coagulation factor function in the whole blood [89–92]. In contrast, a prospective, randomized, double-blind study of 200 infants undergoing cardiac surgery by Mou et al. demonstrated increased ICU length of stay and increased perioperative fluid overload in patients receiving fresh whole-blood prime versus reconstituted blood [88].

The need for FFP in addition to PRBCs in the prime is controversial. Advocates suggest that dilutional coagulopathy can be avoided by utilizing a 1:1 ratio of PRBCs to FFP, based on literature on massive transfusion in trauma patients [93]. Data in congenital cardiac patients are less robust but not without merit. A prospective, randomized study of 20 infants less than 8 kg undergoing CPB compared PRBCs alone versus PRBCs with FFP in the pump prime. There was no difference in 24-h chest tube drainage or postoperative hematocrit, but patients receiving FFP had significantly higher post-CPB fibrinogen levels, fewer cryoprecipitate transfusions, and fewer overall donor exposures [94]. A prospective, randomized study of 121 infants and children undergoing CPB comparing PRBCs with FFP to PRBCs and 20% albumin solutions in the prime demonstrated no clear clinical benefit, with no difference in total transfusions between groups. Patients receiving FFP did, however, have significantly higher fibrinogen levels and clot firmness on hemostatic assay parameters immediately post-CPB [95]. Miao et al. found similar results in 80 pediatric patients comparing PRBCs plus FFP to a PRBCs plus 4% succinylated gelatin prime [96]. Though not conclusive, the literature suggests potential benefits of adding FFP to the CPB prime in the neonatal population; however, it may not be useful in older children [97].

A particularly controversial addition to the pump prime of neonates in recent years is autologous umbilical cord blood. Improvement in prenatal diagnosis of congenital heart disease has allowed for adequate planning, harvesting of cord blood, and surgical correction in the first days of life [98–101]. Umbilical cord blood can be harvested from the neonate and used for up to 3 weeks if preserved with citrate-phosphate-dextrose-adenine (CPDA) solution, the primary anticoagulant utilized in the preservation of whole blood or PRBCs. Typically, 80–90 mL of cord blood can be harvested [99]. While autologous cord blood had been previously used in other neonatal surgery, Fedevych and colleagues first described its use in cardiac surgery in 2012 [98, 99]. Of 61 neonates undergoing arterial switch operation, 21 had autologous umbilical cord blood in place of reconstituted blood in the pump prime, with the volume of either type of blood in the priming fluid based on the preoperative hematocrit. Outcomes in the cord blood group were similar to clinical outcomes in the control group [99]. While more studies are needed, autologous umbilical cord blood may be an alternative to reduce homologous blood transfusions.

Case

A 200-mL circuit is primed with a combination of PRBCs, FFP, and crystalloid solution. The hematocrit during CPB is maintained at 30%. At the conclusion of CPB, modified ultrafiltration is performed, increasing the hematocrit from 29% to 39%.

Blood Product and Pharmacologic Management of CPB-Associated Coagulopathy

Transfusion of allogeneic blood products has long been a mainstay of treatment for CPB-associated coagulopathy in congenital and pediatric heart surgery. Most centers rely on a combination of three component blood products to treat coagulopathy: platelets, cryoprecipitate, and fresh frozen plasma (FFP). Replacing lost red cell mass due to bleeding or dilution may be with packed red blood cells (PRBCs) from donated blood or with the patient's own cells, either from cell salvage or ultrafiltration. Ultimately, the choice and amounts of products transfused depend upon the clinical situation.

It has been well established that platelets are both deficient and dysfunctional in children following CPB [102–104]. Both are made worse with longer CPB duration, and platelet dysfunction is greater with moderate-to-deep hypothermia (<34 °C) [102]. For this reason, platelet transfusion is a reasonable first-line therapy for coagulopathic bleeding after CPB, even if the preoperative platelet count is within the normal range. In neonates and infants, consideration may be given to the use of volume-reduced platelets, if available. Volume-reduced platelets are produced by the removal of plasma from platelet concentrates through centrifugation, resulting in a blood product that contains about twice the number of platelets per unit volume. Use of volume-reduced platelets can reduce the risk of volume overload in this population [105].

Use of FFP after CPB is more controversial. FFP has been associated with worsened viscoelastic clot parameters, increased chest tube drainage, and greater blood product administration when given empirically following CPB in pediatric patients [103]. The concentration of coagulation factors, including fibrinogen, von Willebrand factor, and factors VIII and XIII is relatively dilute in FFP, necessitating a large volume load relative to body mass to achieve adequate levels in children. In contrast, a single unit of cryoprecipitate, which is concentrated and typically consists of 5–15 mL of volume, contains about the same amount of fibrinogen as a single unit of FFP, typically ~250 ml in volume. For this reason, along with the crucial role fibrinogen plays in hemostasis, it is logical to transfuse cryoprecipitate rather than FFP following platelet transfusion in children with persistent bleeding after CPB. Expected effects of component product transfusion on laboratory parameters are described in Table 12.1.

It is important to note that storage of blood products affects their efficacy and safety, especially in infants. Undesirable alterations in PRBCs over time include increased potassium concentrations, decreased 2,3-diphosphoglycerate levels (which decreases oxygen delivery), altered deformability that impairs capillary flow, methemoglobin formation, and reduced nitric oxide concentration.

Table 12.1 Expected effect of component blood products on laboratory parameters

	Product			
	PRBC	Platelets	Cryoprecipitate	FFP
Volume	10–15 mL/kg	10–15 mL/kg	15–25 mL	10–20 mL/kg
Effect	↑ Hgb 2–3 g/dL	↑ platelet count by 30–50 K/μL	↑ fibrinogen by 100–150 mg/dL per 7 kg body weight	↑ procoagulant factors to hemostatic levels

Platelets also change during storage, becoming less functional over time [106, 107]. For these reasons, most centers reserve fresh blood products for transfusion in pediatric heart surgery patients, generally less than 7–14 days old.

In addition to component therapy from donor products, several plasma-derived procoagulants are available to replace coagulation factors without allogenic transfusion. These include recombinant factor VIIa (rfVIIa), fibrinogen concentrate, and three- and four-factor prothrombin complex concentrates (PCCs). Theoretical advantages of these agents over allogenic transfusion include:

- Potential to increase patients' clotting factors with less total volume
- Less total volume, facilitating faster administration
- Lack of need for thawing (unlike FFP and cryoprecipitate), allowing more rapid availability
- Lack of need for crossmatching
- Lower infectious risks

Among the available agents, rfVIIa has been most widely used and studied in children after CPB, despite its off-label indication in this setting. Furthermore, there is evidence in both adults [108] and children [109] that rfVIIa elevates the risk of thrombotic complications after CPB. In 2012, a Congenital Cardiac Anesthesia Society Task Force review was unable to provide evidence-based recommendations on its use but noted that observational evidence supports its utility as rescue therapy when conventional therapy has been maximized [110]. It is likely that rfVIIa is most effective not as a sole hemostatic agent but rather by increasing the effectiveness of procoagulants including platelets, fibrinogen, and other clotting factors when they are administered prior to its use.

Fibrinogen concentrate is derived from adult human plasma and purified as a lyophilized powder for injection. A randomized pilot trial compared 60 mg/kg of fibrinogen concentrate to 10 ml/kg of cryoprecipitate in 63 children (mean age 3.5 months) in whom fibrinogen concentration was less than 100 mg/dl after CPB. Post-infusion fibrinogen concentrations, blood loss, and transfusion requirements were not different between groups [111]. Based on these promising preliminary data, fibrinogen concentrate may ultimately prove to be an important adjunctive therapy for post-CPB coagulopathy.

PCCs contain factors II, VII, IX, and X, though three-factor PCCs contain negligible amounts of factor VII compared to the four-factor PCCs (4PCCs). The 4PCCs may contain either activated factor VII (FEIBA [Baxter International]) or inactive factor VII (Kcentra [CSL Behring, Marburg, Germany]). Depending on the product, they may also contain the anticoagulants protein C, protein S, and/or heparin [112]. While current FDA approval for these products is limited to congenital or acquired coagulation defects such as hemophilia or the need for warfarin reversal, there is accumulated evidence of their efficacy in off-label use after CPB in adults [113–115]. These adult studies have led to the interest in using PCCs as an adjunctive therapy for bleeding after CPB in children. Existing evidence in pediatrics is limited to case reports and nonrandomized observational studies, with little guidance in the literature regarding appropriate dosing and safety concerns such as risk for thrombosis. In one single-center study comparing the use of Confidex (Behring S.p.A., Milan, Italy), a 4FPCC, in 14 infants undergoing cardiac surgery with CPB to 11 age-matched controls who received standard therapy [116], no complications were reported, and there was less chest tube drainage and fewer transfusions in the Confidex group (although these findings did not reach statistical significance). Before routine use can be recommended, further elucidation is also needed in terms of monitoring the effects of PCCs on coagulation, which is only crudely derived from standard tests such as prothrombin time or activated partial thromboplastin time.

Donated PRBCs, which are often an important component of the CPB priming solution in children, are often not needed after CPB. This may be the result of advanced surgical and perfusion practices, use of antifibrinolytics, and

cell salvage and ultrafiltration techniques that preserve the patient's native red blood cell mass. Surgical bleeding necessitating PRBC transfusion however is still necessary for some patients, most notably those undergoing redo sternotomy (which requires dissection of tissue adhesions) or complex procedures with extensive suture lines. Coagulopathic bleeding prompting PRBC transfusion may be anticipated in patients who are younger (e.g., infants and neonates), had prolonged durations of CPB, were more hypothermic during CPB, or required massive intraoperative PRBC transfusion (which causes dilution of platelets and clotting factors).

Optimal hematocrit following CPB in children is controversial. Short-term studies indicate that a conservative transfusion strategy is safe and cost-effective compared to a liberal approach. These practices have been investigated in various patient populations [117, 118], including neonates, cyanotic patients, and those undergoing single-ventricle palliations [119]. One of the most comprehensive studies examined 162 patients undergoing biventricular or palliative repairs using either a conservative or liberal approach in each [120]. The conservative transfusion trigger was a hemoglobin level of 7.0 g/dL for biventricular (i.e., acyanotic) repairs and 9.0 g/dL for palliative procedures, but only if also accompanied by other clinical indications as judged by the critical care physician (such as tachycardia or hypotension). The triggers for transfusion in the liberal cohort were 9.5 g/dL and 12 g/dL for biventricular and palliative procedures, respectively, regardless of other clinical indications. There were no differences observed in serum lactate, estimated arteriovenous oxygen difference, or clinical outcomes between the two groups, but patients receiving the conservative strategy required fewer transfusions and smaller volumes of total blood products. As this study only examined the first 28 days following surgery, little can be concluded from it about longer-term outcomes such as neurodevelopmental milestones. This is an area of great interest currently, with many unanswered questions about what variables affect neurodevelopmental outcome, including whether perioperative blood management plays a role [121, 122].

Case

Given the small patient size, hypothermia during CPB, and the long CPB duration, the patient is assumed to require post-CPB transfusion. After the standard practice of protamine administration to reverse CPB heparinization, the patient is transfused 30 mL/kg of platelets, 1 single-donor unit of cryoprecipitate, and 30 mL/kg of ultrafresh PRBCs. After resuscitation, the Hct is 36%, platelets 156,000, and fibrinogen 110 mg/dL.

Point-of-Care Testing and Transfusion Algorithms

Cardiac surgical procedures consume 10–20% of the nation's allogeneic blood products [123]. Standard laboratory tests such as activated partial thromboplastin time, prothrombin time, and international normalized ratio do not assess coagulation in its entirety [124, 125]. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are whole-blood assays that reflect the newer cell-based model of coagulation and provide information on the viscoelastic and kinetic properties of clots, such as clot formation, stability, and firmness. These tests can distinguish how the various hemostatic factors, including coagulation factors, platelets, and fibrinogen, contribute to clot formation. TEG and ROTEM tracings are compared in Fig. 12.4.

While TEG and ROTEM both provide similar information regarding clots, each system utilizes a unique operating technique. The TEG utilizes a manually pipetted 340-microliter sample of whole blood, which oscillates in a cylinder around a pin suspended on a torsion wire. As clot strength increases, more rotation is transmitted to the wire and, after subsequent transmission to a sensor, results in a TEG tracing [126]. Due to the

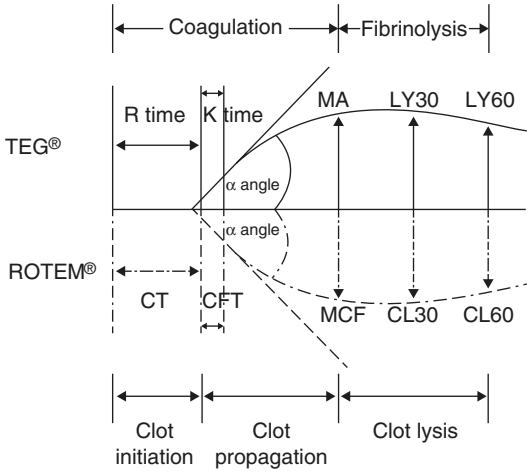


Fig. 12.4 Corresponding normal TEG vs. ROTEM tracings. (Adapted from Thiruvenkatarajan et al. [127] with permission.) Bold line, TEG tracing; dotted line, ROTEM tracing; R time Reaction time; K time Kinetic time; MA Maximum Amplitude; CL30, 60 Clot Lysis at 30 and 60 minutes; CT Clotting Time; CFT Clot Formation Time; MCF Maximum Clot Firmness; LY30, 60 Lysis at 30 and 60 min

oscillation of the sample, the TEG is exquisitely sensitive to vibration of the workspace. There are multiple types of TEG assays, each of which provides distinct information, and each machine can run two assays simultaneously. The citrated kaolin assay provides information on the intrinsic coagulation pathway. This assay can also be performed with heparinase, neutralizing heparin if desired. The functional fibrinogen assay is run with a GP IIb/IIIa inhibitor which eliminates any platelet contribution to the clot, which can help differentiate fibrinogen versus platelet contribution to the clot. A platelet mapping assay assesses platelet function. A rapid TEG is also available, which can provide results quickly, similar to the activated clotting time (ACT).

Unlike TEG, ROTEM utilizes an automatically pipetted 340-microliter sample of whole blood that does not oscillate. Rather, a pin suspended in the solution rotates. As clot strengthens, the pin rotates more slowly, and the optical system creates a ROTEM tracing. Similar to TEG, ROTEM has various assays that provide

Table 12.2 TEG vs. ROTEM parameters

	TEG	ROTEM	Measures
Time to initial fibrin formation (amplitude of 2 mm)	R time	CT	Clotting factors
Time to amplitude of 20 mm clot strength	K time	CFT	Fibrinogen
Tangential line from baseline to curve (clot formation)	α angle	α angle	Fibrinogen, platelets
Clot firmness	MA	MCF	Platelet number and function
Clot lysis	LY	CL	Fibrinolysis

R time reaction time, *CT* clotting time, *K time* kinetic time, *CFT* clot formation time, *MA* maximum amplitude, *MCF* maximum clot firmness, *LY* lysis, *CL* clot lysis

specific information about clot formation. INTEM provides information about the intrinsic coagulation pathway. EXTEM utilizes tissue factor as an activator and provides information about the extrinsic pathway of coagulation. The HEPTEM assay contains heparinase, which neutralizes heparin. FIBTEM adds cytochalasin D which inactivates platelets, thus providing a representation of fibrin contribution to clot strength. APTEM utilizes aprotinin to assess fibrinolysis. Results may be available more quickly than with a TEG due to each machine's ability to run four assays at once. The automatic pipetting also makes ROTEM less vulnerable to external movement [126, 127].

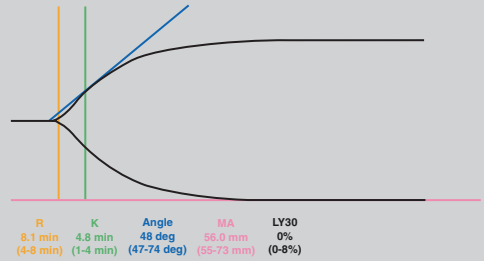
TEG and ROTEM results are described using alternative terminologies, which can be compared in Table 12.2. Each system refers to the following parameters with a different distinction: time to tracing amplitude of 2 mm, time to tracing amplitude from 2 mm to 20 mm, angle of tangential line from clot initiation to tracing slope, tracing peak amplitude (clot firmness), and tracing reduction (clot lysis) [126, 127].

Numerous studies have demonstrated the utility of these hemostatic assays in reducing transfusion requirements compared to standard transfusion practices. A prospective, double-blind randomized control trial comparing routine management versus TEG-guided transfusion management in 105 adults undergoing cardiac surgery demonstrated a reduction in overall transfusion requirements from 60% to 42%, FFP requirements from 31% to 8%, and platelet transfusion requirements from 29% to 13%, with no overall increase in mediastinal tube drainage [128]. While data in pediatric patients are less robust than in the adult population, several studies have demonstrated significant reductions in blood product transfusion when utilizing hemostatic assays [129–135]. A prospective procedure- and age-matched study comparing routine management versus TEG-guided management in 100 children undergoing pediatric cardiac surgery demonstrated reductions in overall transfusion requirements from 92% to 64%, reduction in PRBC transfusions from 78% to 58%, and reduction in FFP transfusions from 78% to 14%. Interestingly, platelets and fibrinogen were found to be underutilized, with platelet transfusions increasing from 12% to 38% and fibrinogen concentrate transfusions increasing from 2% to 16%. These data support the notion that TEG-guided management allows for more goal-directed therapy [130].

Transfusion algorithms have become standard practice in adult cardiac surgery [136–138]. Both the 2011 Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation and Clinical Practice Guidelines and the 2015 American Society of Anesthesiologists Practice Guidelines for Perioperative Blood Management recommend the use of point-of-care-guided transfusion algorithms for perioperative hemostatic management [136, 138]. The aforementioned studies in pediatric cardiac surgical patients have led to the development of such algorithms in pediatric cardiac surgery [129–133], although no standard guidelines exist. One recent 2-year retrospective study detailing transfusion requirements before and after transfusion algorithm implementation in pediatric cardiac surgery at a single center showed significant reductions in PRBC, FFP, and cryoprecipitate transfusions as well as a 75% reduction in mortality [131].

Case

After the initial resuscitation with platelets and cryoprecipitate, the patient continues to have persistent oozing from multiple surgical sites. A TEG is sent to further delineate the cause of bleeding. The TEG results show R time = 8.1 min, K time = 4.8 min, α-angle = 48°, MA = 56 mm, and LY30 = 0%.



The K time greater than 3 min suggests a fibrinogen deficiency. Another unit of single-donor cryoprecipitate is administered. The follow-up fibrinogen is 234 mg/dL, and bleeding is clinically improved. The patient is then transferred to the intensive care unit for further management.

Conclusions

Many practice variations exist across centers regarding CPB-associated coagulopathy in pediatric cardiac surgery. Though available data are often conflicting and, in many cases, insufficient to allow for widespread consensus, much has been

learned during the current era to help guide clinical practice. As more studies are published in the literature, the management of this common and potentially life-threatening complication should continue to evolve and improve.

Take-Home Points

- The cell-based model of hemostasis conceptualizes the idea that the intrinsic and extrinsic pathways function in parallel.
- Antifibrinolytics, such as aprotinin, aminocaproic acid, and tranexamic acid, reduce intraoperative and postoperative blood loss after cardiac surgery by inhibiting fibrinolysis.
- Practice variations exist in CPB management strategies, including composition of the CPB pump prime, minimization of circuit priming volume, transfusion targets, and ultrafiltration.
- Platelets are first-line therapy for post-CPB bleeding. Cryoprecipitate is a reasonable next-line therapy for persistent bleeding.
- Point-of-care coagulation tests, such as TEG or ROTEM, can help identify the causes of persistent bleeding post-CPB and can assist with developing and implementing transfusion algorithms.

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Anticoagulation for Extracorporeal Life Support

13

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Introduction

Extracorporeal life support (ECLS), or as originally named extracorporeal membrane oxygenation (ECMO), was developed initially to treat patients with severe respiratory failure over 40 years ago. In infants and children, it has been used since its inception for both respiratory failure and mechanical circulatory support (i.e., isolated cardiac failure or in conjunction with pulmonary insufficiency). Over time, the collective understanding of pathophysiology of underlying disease states has resulted in better delineation of indications for ECLS. Along with technological advancements, there has been a steady increase in the number of children treated with ECLS and the number of centers registered by the Extracorporeal Life Support Organization (ELSO). According to the ELSO registry, in the year 2015, 1072 infants and children were treated for respiratory reasons, and 807 children under 16 years were treated for cardiac reasons. Cumulatively, by 2016, over 54,000 infants and children have been treated with ECLS for either cardiac, respiratory or eCPR (ECMO initiation during cardiopulmonary resuscitation) with mean survival rates over 50%. In recent years, we have seen increased use in new patient groups such as immunosuppressed patients, bridge to lung transplant, and eCPR, which has been gaining wider use and acceptance in the pediatric population [1, 2].

There are many challenges entailed by using ECLS, not least among are those related to hemostasis, which entails balancing the risks of bleeding versus circuit and patient thrombotic complications [3]. Immediately upon exposure of the patient's blood to nonendothelial surfaces, an inflammatory response is initiated involving a multitude of cellular and humoral protein-driven cascades [3, 4]. Protein adsorption drives activation of the coagulation cascade, platelet adherence, and thrombi formation. Moreover, this exposure drives stimulation of the various arms of inflammation including the complement cascade, cytokines release, and production and recruitment of leukocytes. This environment, with multiple feedback loops, creates a hypercoagulable state and drives the need to use systemic anticoagulation. Due to this hypercoagulable and inflammatory state, the management of the patient on ECLS dictates the use of anticoagulation to maintain patency of the extracorporeal circuit without causing bleeding or thrombosis within the patient. Indeed, bleeding and thrombosis are two of the most common complications of ECLS [5, 6].

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In this chapter we will present some of the controversies surrounding current approaches to anticoagulation treatment and monitoring of patients who require ECLS. Some controversial questions that are still unanswered in this field include:

1. What is the best anticoagulant choice in ECLS?
2. How is anticoagulation monitored best in these patients?
3. What to do in cases of heparin resistance?
4. What to do if heparin-induced thrombocytopenia (HIT) is suspected?
5. Do we need anticoagulation at all?

As conclusive data to answer these questions is lacking, we will attempt to inform the reader on the current knowledge regarding some of these issues to allow for informed decision-making in a case-by-case manner. We aim to describe the rationale for the need to anticoagulate patients on ECLS, elaborate on heparin treatment and monitoring of its effects, and discuss the concept of heparin resistance. We will also proceed to expose alternatives to systemic heparin anticoagulation such as direct thrombin inhibitors (DTI) and shortly touch on issues related to bleeding prior to ECLS and its implications.

Rationale for Anticoagulation

Under normal physiological conditions, a fine balance between thrombosis and bleeding is kept by multiple prothrombotic and anticoagulant systems working through a myriad of sensory and effector arms. Upon exposure of the patient's blood to non-biologic artificial surfaces such as those of the ECLS circuit (e.g., cannulas, tubing, and oxygenator) and under turbulent and shearing conditions generated by the circuit, a complex inflammatory response is initiated that activates both protein-mediated pathways (coagulation, complement, etc.) and cellular components such as red blood cells, leukocytes, and platelets [5, 7]. The already primed inflammatory pathways in these critically ill patients are activated, leading to an increased systemic inflammatory response (SIRS), capillary leak, and derangement of the balance between thrombosis and hemorrhage. Additional processes at work include protein adsorption to the circuit (especially but not limited to albumin and fibrinogen) and endothelial cell function dysregulation. All these processes lead to a robust activation of the common pathway for coagulation, leading to generation of activated factor Xa and thrombin generation. Platelet adherence and activation ensues, and multilateral amplification loops lead to enhanced thrombi formation throughout the circuit. As anticoagulant effector arms "kick-in," a simultaneous mixture of pro- and anticoagulant states exist, leading to concurrent potential for circuit dysfunction due to thrombi and bleeding tendency in the patient.

Building from experience accumulated from use of cardiopulmonary bypass for cardiothoracic procedures and from early experiments in ECLS, it was recognized that some form of antithrombotic therapy is essential to maintaining the circuit patency and function while minimizing risks for bleeding. While heparin has traditionally been the sole option for anticoagulation at most centers, alternative agents exist and are already in clinical use. Additionally, there are circuit modifications that may allow avoiding systemic anticoagulation for short periods of time under specific conditions, and the future holds promise of ECLS mechanisms that may obviate the need for systemic anticoagulation altogether [4].

Case Scenario

A 5-year-old male is cannulated for veno-arterial (VA) ECLS using a heparin-coated circuit and heparin anticoagulation for severe myocarditis. Seven days after initiation of mechanical support and after several days of stability, thrombocytopenia develops, and 2 days later, a new thrombus is detected in the deep veins of his left leg, in which there are no cannulas. Testing for heparin-induced thrombocytopenia (HIT) has been sent and will take several days to come back. With a potential diagnosis of HIT, a discussion ensues on what should be the best course of action in terms of anticoagulation for this child.

Heparin for Anticoagulation

Historically the anticoagulant of choice for ECLS has been unfractionated heparin (UNFH). Discovered in 1916 and in clinical use since 1937, heparin is by far the most used agent for systemic anticoagulation [8], with vast amount of literature describing its use and monitoring of its effects during ECLS. Heparin works indirectly on the coagulation cascade by binding to antithrombin (AT), an endogenous anticoagulant produced in the liver. This bound complex mainly functions by irreversibly inhibiting both thrombin and factor Xa, though it also inhibits additional clotting factors (e.g., IXa, XIa, and XIIa). The heparin-antithrombin complex is 1000-fold more efficient than unbound AT.

Traditionally, therapy with UNFH is initiated upon cannulation. A bolus dose ranging from 50 to 100 units/kg is given after vessel exposure and prior to cannula insertion. Subsequently, UNFH is administered as a continuous intravenous infusion and titrated as directed by institutional protocols. Some ECLS centers have a minimum and maximum UNFH infusion rate that typically ranges from a minimum of 10–15 units/kg/h to a maximum of 40–60 units/kg/h [9].

The anticoagulant activity of UNFH is variable for several reasons: only one-third of an administered dose of UNFH has the specific sequence that binds AT; its anticoagulant profile is influenced by the chain length of the molecules; and its activity depends on endogenous AT concentrations. Moreover, there are population-specific effects. For instance, as compared to adults, neonates require higher blood concentrations of heparin to inhibit thrombin, have lower AT activity, and have larger relative volumes of distribution when connected to the ECLS circuit [10].

Among heparin's main advantages are its short half-life and potential reversibility by protamine sulfate. However, heparin use is not without complications and disadvantages, leading to controversies regarding its use. These range from its unpredictable dose-response relationship, difficulty in reliable monitoring of therapeutic targets, variable half-life, resistance to therapy (due to relative or absolute antithrombin deficiency), and heparin-induced thrombocytopenia (HIT) [11]. HIT is a rare but potentially catastrophic complication of heparin exposure: 1–5% of patients exposed to UNFH or low molecular weight heparin (LMWH) can develop an immune-mediated thrombocytopenia which is a serious prothrombotic complication with a thrombosis rate up to 53% and mortality rate upward of 30% if not recognized and treated [11]. Although clinical suspicion for HIT is usually raised by either new-onset or persistent thrombocytopenia, assisted with the use of clinical assessment tools, the diagnosis of HIT is supported with assays used to identify the presence of the syndrome. Diagnosing HIT in this context poses additional challenges as thrombocytopenia is commonly seen in critically ill patients (up to 45%). Once HIT is either considered in the differential diagnosis or confirmed with laboratory testing (some of which are challenging due to low specificity), clinicians are faced with a clinical dilemma: Which alternative anticoagulant to initiate and how to optimally titrate it in the setting of different devices?

Additional disadvantages of heparin are that it does not inhibit clot-bound thrombin or thrombin bound to the ECLS circuit. As will be detailed below, there are several new alternatives in clinical use for anticoagulation, mainly direct thrombin inhibitors (DTI). While unfractionated heparin is the most widely used anticoagulant during ECLS, prospective studies comparing the use of UNFH to DTI are lacking, and thus, the best option currently available remains unclear.

Monitoring Anticoagulation in Patients Receiving Systemic Heparin

Monitoring systemic heparinization during ECLS used to be fairly simplistic, with the activated clotting time (ACT) being the sole test used to assess anticoagulation within the circuitry. First described in 1966 and used in the identification of factor VII deficiency, ACT became the primary test for anticoagulation management of ECLS in 1975 [12]. With the evolution of more specific plasma testing of hep-

arin effect, this test has come under significant scrutiny, and yet it still remains the most frequently used point of care (POC) test for anticoagulation during ECLS [8].

Activated partial thromboplastin time (aPTT) and anti-factor Xa activity (anti-Xa) have become more commonly used to monitor heparinization during ECLS. Activated partial thromboplastin time was first described in 1953 but recognized as a viable test in 1961 [13]. In the adult population, most specifically in patients with uncomplicated cardiac or respiratory support, it is a very reliable test for heparin effect. Unfortunately, with developmental hemostasis, its reliability in the pediatric patients, especially neonates, is very poor because of globally low coagulation/anticoagulation factors in this population, most notably antithrombin (AT).

Anti-Xa testing was first described in 1973 by Denson and Bonnar but only recently has become the standard of monitoring for heparin effect in the pediatric population as it has become more readily available in clinical laboratories [12]. Specifically, it has helped to take into account the effect of developmental hemostasis and made heparinization in the neonatal population more reliable and safe.

The development of viscoelastic testing using either thromboelastography (TEG) or rotational thromboelastometry (ROTEM) is the more precise method of whole blood hemostasis testing and has been adopted by many ECLS centers. It can aid in determining next management strategies for those patients who are bleeding or having thrombotic complications during ECLS. To date, however, there are only case reports or small series published comparing its utility to conventional testing [12].

The availability of these newer tests has led to a significant increase in the number of anticoagulation tests drawn per patient on daily basis, with many being repeated multiple times per day to ensure that they are maintained within the appropriate range for what is deemed effective anticoagulation during ECLS. In fact, Dalton et al. recently described a large data collection on anticoagulation management and outcomes across several large ECLS centers in the USA and determined that the biggest cause of need for red cell transfusion was blood sampling [14]. ACT remains the most readily bedside POC test that can provide immediate results. aPTT and anti-Xa measurements are plasma tests that require laboratory evaluation, with a turnaround time of 1–2 h. TEG or ROTEM requires a stable area in which to place the sample and, because of the complexity of this equipment, must only be run by experienced personnel, which limits their availability in most centers. Currently, while viscoelastic testing POC is available, most experience with this monitoring has occurred in the cardiovascular operating theatres.

In 2014, the Extracorporeal Life Support Organization published anticoagulation guidelines after a task force reviewed center-specific guidelines from many different ECLS centers worldwide. The result was essentially a review of each of the available anticoagulation/coagulation monitoring tests described above and a recommendation that each center should use this information to determine which testing they will use to create their center-specific guidelines. Most centers have developed ECLS anticoagulation protocols that include a POC whole blood test and a plasma test, such as ACT and anti-Xa. Without literature to provide guidance on the superiority of one protocol over another, the combination of a plasma test with a POC whole blood test, at the very least, has a physiologically rationale and represents a reasonable approach to this complex clinical problem.

Case Scenario An 8-month-old treated is cannulated for veno-venous (VV) ECLS after developing severe ARDS and respiratory failure secondary to severe influenza infection. A heparin infusion is initiated, with an ACT goal of 180–220 s. In the past day, despite increased heparin infusion rates up to 60 units/kg/h, ACT and aPTT measurements are still subtherapeutic. No clots are seen on the circuit and membrane function is excellent. Should this be defined as heparin resistance and if so what is the best course of action? What other alternatives for anticoagulation monitoring should be considered?

Heparin Resistance and Antithrombin Replacement

Heparin resistance during ECLS is defined as the failure of escalating doses of heparin to achieve target ACT goals. Alternatively, heparin resistance can be better defined pharmacologically as a decreased heparin dose response (HDR) curve. Ranucci and colleagues identified five predictors of heparin response: antithrombin III (ATIII) levels less than 60%, preoperative/pre-ECMO subcutaneous or intravenous heparin therapy, platelet count greater than 300,000 cells/mm^3, and patient age >65 years [15]. Traditionally, heparin resistance has been attributed to decreased levels of AT, the major target via which heparin exerts its anticoagulant effect. Proposed mechanisms for ATIII deficiency include "normal" developmental maturation, reduced synthesis (such as in liver failure), accelerated clearance or consumption (possibly due to previous exposure to heparin, DIC), or, as is most commonly seen, mechanical consumption by the circuit [16]. On the other hand, not all heparin resistance is due to AT deficiency. Non-AT-mediated causes for heparin resistance include increased heparin binding by proteins such as chemokines, extracellular matrix proteins, and enzymes, medications such as nitroglycerin, and platelet-mediated binding.

Optimal AT level for any patient receiving UNFH anticoagulation has not been determined. In infants and children with escalating UNFH requirements and/or clinically inadequate anticoagulant effect, relative AT deficiency is assumed, and if possible, ATIII measurements are obtained. If ATIII activity is confirmed to be low, ATIII replacement may be considered [17]. Practice varies across centers, with some replacing ATIII prophylactically in patients with ATIII activity less than 50–80% (< 0.5–0.8 U/mL), while others will treat low ATIII activity only if there is evidence of reduced UNFH effect (i.e., heparin resistance). When considering replacement of ATIII, there are two main options: fresh frozen plasma (FFP) or dedicated AT concentrate. A best practice review on the subject in the context of cardiac surgery found that the treatment of heparin resistance with FFP may not increase ACT measurements to therapeutic goals [18]. Furthermore, replacement with AT concentrate has additional benefits of lower volume of administration, less risk of transfusion-related lung injury (TRALI), and lower risk of transfusion-related infections. The difference in required volume of infusion is significant: 500 IU of AT concentrate equates to a 10 ml aliquot, while FFP requires 500 ml of volume to provide 500 IU of AT, while it may not be suitable for many pediatric patients.

Two commercial formulations of AT are currently available (ATryn® and Thrombate III®), neither of which is FDA-approved for acquired antithrombin deficiency or heparin resistance. As noted in the ECLS Red Book and others [9], "off label" use of AT concentrate for this indication has increased greatly over the past decade [19]. Dosing is based on plasma ATIII measurements, and the calculations used to determine dosing to a desired goal ATIII level are derived from data on hereditary AT deficiencies. Evidence for this use of AT replacement for patients on ECLS is mixed. A retrospective study of neonatal and pediatric ECLS patients revealed, as expected, measured ATIII activity increases with concentrate administration, but there were no other clinically significant changes that were noted [20]. Two other single-center retrospective studies found conflicting results: Byrnes and coworkers reported supplementation with concentrate for ATIII activity <70% resulted in higher anti-factor Xa activity but did not affect UNFH infusion rates and was associated with an increased rate of circuit failures [21], whereas Ryerson and colleagues found that supplementation with AT concentrate was associated higher anti-factor Xa activity, lower UNFH doses, and no acute adverse events [22].

Direct Thrombin Inhibitors as an Alternative to Heparin

Recently, there have been several publications detailing the use of direct thrombin inhibitors (DTI) in the context of ECLS. Several excellent reviews detailing the cumulative experience in

this context with specific recommendations have been published [3, 10, 17]. In general, DTI are not dependent on antithrombin for their effect but work by direct inhibition of both circulating and clot-bound thrombin – exposing the two major advantages over heparin. Their selective binding to thrombin makes their pharmacodynamics more predictable. A significant downside, however, is that DTI do not have a specific reversal agent, even though at least for bivalirudin the use of activated factor VII has been proposed [23]. Most of the literature on DTI use in ECLS relates to two commercially available products: bivalirudin and argatroban. In a recent survey of ECLS centers [8], most responders did not use any anticoagulation other than heparin in the months prior to answering the survey, but over 50% answered that they have used or can use DTI if indicated. Indications for DTI use include HIT, heparin resistance not responsive to antithrombin or FFP administration, and development of thrombosis while on heparin therapy.

Bivalirudin is a 20-amino acid synthetic polypeptide analog of hirudin, which binds to the active site of thrombin. It has a half-life of approximately 25 min and undergoes mostly proteolytic degradation. While metabolism is almost independent of liver and kidney function (~20% renal elimination [24, 25]), infusion doses should be adjusted according to renal function [26]. Monitoring for bivalirudin's anticoagulation effect is most often accomplished by following aPTT with a goal 1.5–2× baseline or ACT >2.5× baseline (reviewed in [3, 10]). We found no prospective studies examining the use of bivalirudin in patients undergoing ECLS, but in the past several years, two retrospective case series have been published. Ranucci et al. [26] reviewed 21 patients (9 children) on ECLS after cardiac operations, 8 of which were on heparin and 13 on bivalirudin. They reported significantly more bleeding (as measured by chest drain output), FFP requirements and platelet transfusions in the heparin group. Thromboembolic complications did not differ between the groups, and when factoring in the complications, there was a significantly lower total cost of care in the pediatric group treated with bivalirudin. In another retrospective case series, 20 adults on ECLS (both venoarterial and veno-venous) were reviewed; 10 patients were treated with heparin, and 10 patients with bivalirudin [27]. They found significantly higher variations in aPTT in the heparin group and no significant differences in bleeding or thrombosis between groups even though both major bleeding and minor bleeding were more frequent in the heparin group. Both publications concluded that DTIs are potential alternatives to heparin in patients on ECLS, with one of the groups reporting a switch from heparin to bivalirudin as the first choice for anticoagulation in patients post cardiotomy. In the context of veno-venous ECLS, a case report by Jyoti et al. [28] reports the successful switch of anticoagulation from heparin to bivalirudin. A retrospective case series reporting on 12 children [29] showed that bivalirudin can be safely used in neonates and children with maintenance dose ranges reflecting considerable inter-patient variability. Such dosing variability was observed also in adults with recommended doses to reach therapeutic targets varying more than tenfold between different reports [10, 30, 31].

Argatroban is an l-arginine derivative with a half-life similar to bivalirudin at 15 min; it undergoes hepatic metabolism which might represent an obstacle as patients treated with ECLS may have hepatic functional impairment. Monitoring and therapeutic targets are similar to bivalirudin as published in the ELSO anticoagulation guidelines. Its use for ECLS has been published in case reports and series for adult and pediatric patients with suspected or diagnosed HIT [32–38]. Of note, Cornell et al. reported successful use in five adults without complications, and similarly Beiderlinden et al. reviewed nine patients, with one critically ill patient suffering from major bleeding attributed to hepatic impairment [32, 39].

Alternative potential targets to prevent circuit clots can be found in antiplatelet agents. Inhibition of platelet activation would decrease both activation of the coagulation cascade and thrombosis within the circuit as seen in the laboratory with nitric oxide (NO)-releasing surfaces. [10]. Prostacyclin, dipyridamole, and acetylsalicylic

acid (ASA [aspirin]) have been used clinically in single-center trials and within anticoagulation protocols for specific ventricular assist devices, but the data is scarce. Similarly, new oral anticoagulants such as rivaroxaban, highly specific inhibitor of factor Xa, may be future potential targets. Oral factor IIa inhibitors, such as dabigatran, are in use in adult patients for the prevention and treatment of thromboembolism, but data in pediatric and adult ECLS are lacking.

Current Surface Modification Strategies

As systemic anticoagulation carries a set of risks, most importantly catastrophic bleeding, and as there are controversies regarding the optimal agent to use for such purposes, a potential solution might be to transition from a systemic solution to a local one confined to the circuit. Regional anticoagulation strategies such as citrate infusion which are commonly used for extracorporeal therapies such as continuous renal replacement are impractical in the context of ECLS due to the high blood flows required for the latter. However, modifications to the circuitry and oxygenator that can locally prevent coagulation and thrombi have the potential to obviate the need for systemic anticoagulation or at least markedly reduce the dosages needed.

Current surface modifications available in clinical practice can be divided into two major groups: bio-passive and bioactive (heparin and nitric oxide). Most of the available data on surface-modified circuits come from cardiopulmonary bypass-related studies. Heparin-bound circuits have been studied extensively and have been shown to improve the biocompatibility, reducing both activation of alternate complement pathway and to some extent thrombus formation in the circuitry when blood is exposed to the artificial circuit, with some evidence to suggest improvement in clinical outcomes [40–45]. A meta-analysis by Mangoush et al. further concluded that heparin-bound circuits reduce the incidence of postoperative blood transfusions, resternotomy rates, duration of ventilation, as well as ICU and hospital length of stay [46]. A subsequent report reconfirmed only the effect on ICU length of stay and demonstrated a reduction in atrial fibrillation events [47]. A recent survey has found that heparin-bound circuit use is increasing [48] as corroborated by Bembea et al. that reported that over 50% of 117 ELSO (Extracorporeal Life Support Organization) centers used partial or complete heparin-bound circuits [8]. The effect of heparin-bound circuits on the induction of HIT is more controversial [49–51] and newer coating techniques use covalent bonding which might reduce the possibility of heparin release [51].

The most common bio-passive coating, phosphorylcholine (PPC), has been shown to be thromboresistant [52–55] and non-inferior to heparin-bound circuits in pediatric patients [56]. It can also be utilized in cases of HIT where exclusion of all potential sources of heparin is needed. Furthermore, two studies by Ranucci et al. have shown that the use of phosphorylcholine coating can allow a safe reduction in systemic heparinization during intraoperative ECLS [57, 58]. However, a prospective study on the combination of phosphorylcholine and heparin coating has failed to demonstrate a significant clinical effect [59]. Of note, most data on the use of coated circuits come from CPB. The ability to extrapolate the conclusions to ECLS, in which thrombosis mechanisms differ from those during CPB in several ways [47, 51], might be limited. At this time, systemic anticoagulation remains a necessary element to ECLS. Understanding the effects of each systemic anticoagulant and monitoring for therapeutic goals remain the standard of care for management during ECLS.

ECLS Without Systemic Anticoagulation

With increasing frequency, the surface of the new extracorporeal circuits is completely coated with heparin. Moreover, a reduction of exposure to foreign surfaces is achieved by miniaturization of the ECMO system and combining specialized pumps and oxygenators with short

tubing systems [60]. These developments have led to the possibility of using ECLS for days without any systemic anticoagulation; although there are no published reports to our knowledge on this subject in infants and small children, probably due to the lower flow rates which entail a higher thrombotic risk. However, in adults there have been several publications detailing the successful use of ECLS without systemic anticoagulation for several days, mainly in the context of multi-trauma and pulmonary hemorrhage [61]. Bedeir et al. [62] conducted a systematic review on the subject of ECLS use in trauma. They identified four reports from three centers that utilized initially systemic heparin-free ECLS, whereas five reports accepted an activated clotting time (ACT) target range lower than 180 s. In general, they report a recent trend toward extending anticoagulation-free periods followed by lower ACT ranges. None of the studies identified reported complications related to systemic or pulmonary thromboembolism or morbidity related to unexpected circuit changes resulting from clotting. Even with intracranial bleeding, the risk of ECLS-related bleeding may be overestimated. Another retrospective report [63] details three patients with significant intracranial hemorrhage undergoing heparin-free ECLS for up to 5 days and also received recombinant factor VII and prothrombin complex. All three patients survived with no problems related to clotting circuits or thromboembolism. Survival ranging from 60% to 93% for patients on ECLS with intracranial hemorrhages prior to ECLS cannulation was reported. Thus, with appropriate patient selection and the new generation of ECLS setups, the benefits of an ECLS run without systemic anticoagulation might outweigh the risks.

Case Scenario A 16-year-old male is admitted to the pediatric ICU after severe multiple trauma secondary to an explosion. Blast and penetrating injuries including bilateral lung contusions and traumatic brain injury with several intracranial hematomas are observed. Several hours into his admission, with deteriorating lung function and profound hypoxemia despite aggressive ventilation, option of VV ECLS is considered. Some of the faculty argue that his intracranial injuries preclude anticoagulation and therefore the use of ECLS in this setting.

The Future of Surface Modification

Present research in surface modifications not yet transitioned to the clinical arena focus along three separate branches: passivation, biomimetics, and endothelialization. Passivation using inert materials is in developmental phases. These products use low surface tension materials to prevent protein adherence, most specifically fibrinogen. Biomimetic surfaces such as heparin-bonded circuits utilize a different strategy. Rather than target a specific portion of the anticoagulation cascade (as with the abovementioned heparin-bound circuits), this strategy tries to be more endothelial-like with elements of both platelet and thrombin inhibition. Experimental animal models have provided proof of principal; this is the next phase of circuits to come [64]. And finally the continuing work on customized endothelialization of artificial devices for support, such as an artificial lung, is reaching levels where a seeded, endothelialized surface can sustain the shear forces of flow through these systems. There is no doubt that in the next 20 years, a surface obviating the need for systemic anticoagulation will be used in the clinical arena of ECLS and implantable devices.

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Part VI

Immunologic Controversies

14

Secondary Hemophagocytic Lymphohistiocytosis, Macrophage Activation Syndrome, and Hyperferritinemic Sepsis-Induced Multiple-Organ Dysfunction Syndrome in the Pediatric ICU

Joseph A. Carcillo, Bita Shakoory, and Leticia Castillo

Introduction

In the past decade, hemophagocytic lymphohistiocytosis (HLH) has been increasingly recognized in critically ill pediatric patients. HLH can be familial or secondary, with most critically ill patients who develop this disease process having the latter. Secondary HLH (sHLH) that occurs in critically ill patients is classically referred to as macrophage activation syndrome (MAS) when triggered by drugs or when it occurs in patients with underlying rheumatologic disease and hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome (MODS) when it is precipitated by infectious etiologies. As awareness of these entities has increased, clinical intensivists have been faced with new challenges that have precipitated diagnostic and therapeutic controversies. The need for prompt and aggressive immune-modulating treatment in patients with sHLH requires early recognition and diagnosis. However, clinical and pathologic similarities between sHLH and non-hyperferritinemic sepsis, absence of optimal diagnostic tools in sHLH, and suboptimal understanding of this entity by clinicians often result in delayed or missed diagnoses.

The diagnostic challenges in sHLH are, in part, rooted in the absence of evidence-based diagnostic and therapeutic recommendations for its diagnosis and management. In fact, in most clinical settings, the diagnostic criteria and treatment protocols for familial HLH (Fig. 14.1) are also used in sHLH. In a recent review article however, it was shown that diagnostic criteria used for familial HLH do not differentiate these patients with sHLH, whether it be MAS or hyperferritinemic sepsis-induced MODS [1]. Similarly, treatment protocols for these entities vary, depending on the clinical settings: hematologists treat both familial and sHLH with the highly toxic traditional familial HLH treatment protocols, which include etoposide and dexamethasone, whereas rheumatologists have

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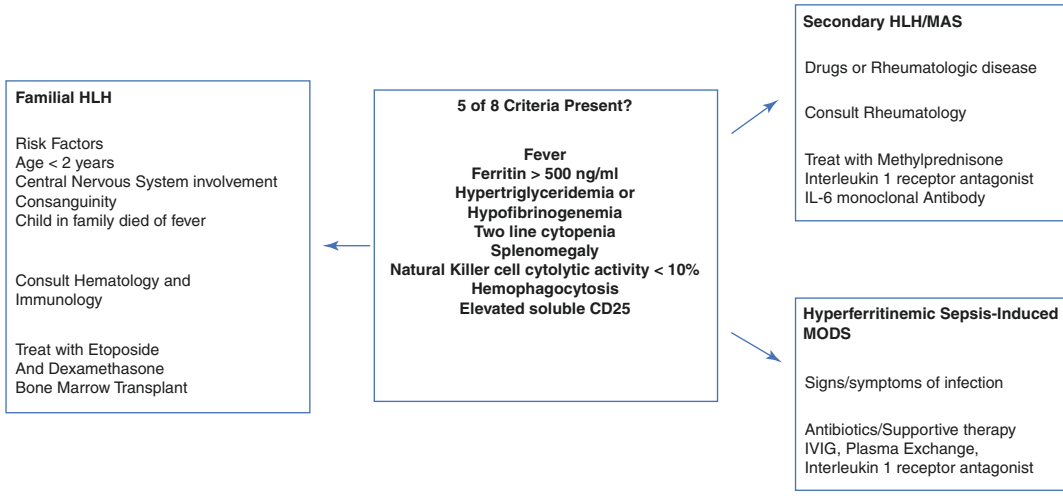

Fig. 14.1 Five of the eight criteria may represent familial hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), or hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome (MODS), each of which has a different therapeutic approach

successfully used less toxic therapies such as pulse-dose corticosteroids (e.g., methylprednisolone) in combination with cytokine-targeted therapies such as anakinra (IL-1 receptor antagonist) or tocilizumab (anti-IL-6 antibody) for MAS. Meanwhile, intensivists who encounter patients with sHLH will most often be faced with hyperferritinemic sepsis-induced MODS and generally advocate source control with antimicrobial therapy and supportive care, but adjunctive therapies such as methylprednisolone, intravenous immunoglobulin (IVIg), and plasma exchange also have a role. Such variations in nomenclature, diagnosis, and therapy emphasize the need for evidence-based data to address the clinical goals of prompt diagnosis and appropriate treatment. The purpose of this chapter is to provide intensivists with a conceptual framework to better understand and navigate these differing management principles in collaboration with their valued colleagues.

Clinical Vignette 1: Familial Versus Secondary HLH

*A previously healthy infant is admitted to a pediatric ICU after presenting with status epilepticus. The admitting intensivist elicits a history of consanguinity and another child in the family dying from "fever," both of which are risk factors for familial HLH. During the subsequent 48 h of her hospital course, she develops several clinical criteria for familial HLH (*Fig. 14.1*). A bone marrow aspirate is obtained, and the infant is started on a familial HLH treatment regimen of dexamethasone and etoposide. The child recovers and is discharged to home.*

One month later, genetic analysis confirms the diagnosis. Specifically, it reveals a homozygous UNC13D gene variant

which leads to ineffective natural killer cell eradication of virus infection and ineffective activated immune cell death. Based on these findings, the child undergoes bone marrow transplantation.

Familial HLH is typically triggered by a viral infection in a host who has a genetically determined inability to induce granzyme-perforin-mediated cytolytic killing. In these children, nonmalignant lymphoproliferation leads to high levels of lymphocyte-derived interferon-γ that activates macrophages. Treatment with dexamethasone and etoposide induces lymphocyte apoptosis and reduces macrophage activation. In contrast, secondary HLH is associated with macrophage activation in patients without hereditary predisposition to such a process, and it is typically triggered by severe systemic inflammation such as that occurs in sepsis.

Historical Context

In 1988, Suster and colleagues reviewed bone marrow, lymph node, and spleen histology from 230 consecutive intensive care unit adult autopsies and identified cases of histiocytic hyperplasia with hemophagocytosis (HHH) [2]. They reported moderate to severe HHH in 102–230 bone marrow specimens (44%), 79 of 191 lymph node specimens (41%), and 16 of 209 spleen specimens (8%). There was a strong blood transfusion dose relationship, with patients who received more than 5 transfusions nearly 60 times as likely to have HHH as compared to patients who received no transfusions. Bacterial sepsis (adjusted risk odds ratio 4.1) was also independently associated with HHH.

More recently, Strauss and colleagues [3] evaluated 107 consecutive medical ICU patient autopsies and found mild to severe HHH in 69 (65%) [3]. The authors similarly found HHH to be associated with sepsis and a number of blood transfusions. Patients with HHH were significantly less likely to have died due to cardiovascular causes (HHH 32% versus no HHH 74%) and more likely to die due to MODS (HHH 39% versus no HHH 18%), with a characteristic organ failure pattern of elevated bilirubin, liver enzymes, and disseminated intravascular coagulation. Patients with HHH were also more likely to require catecholamine infusions, mechanical ventilation, and renal replacement therapy. Autopsies with histology graded severe HHH also had more siderosis suggesting iron overload and more CD8 T cells in the bone marrow suggesting T-cell activation. These two autopsy studies associated HHH with more severe critical illness but could not determine if it was a novel and clinically relevant process or a secondary phenomenon.

Since these seminal reports were published, nomenclature for HHH has changed, with the aforementioned clinical descriptors now being used for secondary hemophagocytic lymphohistiocytosis (sHLH) – macrophage activation syndrome (MAS) for patients with sHLH precipitated by drugs or rheumatologic disease or hyperferritinemic sepsis-induced MODS, depending on the clinical setting involved [3–7].

Experimental Models of sHLH

Experimental models provide support for macrophage (i.e., histiocyte) activation associated with sHLH as an important pathway to

MODS. Steinberg and colleagues developed the sterile model of zymosan (the cell wall of the fungus saccharomyces A) plus mineral oil injected intraperitoneally to induce MODS in rodents [8]. This model results in initial hypovolemic shock followed by persistent macrophage activation. Injection of either zymosan or mineral oil alone does not induce MODS, suggesting the need for a "two-hit" insult of both toll-like receptor (TLR) stimulation by zymosan and unremitting particulate irritation by mineral oil to induce persistent macrophage activation. In another rodent model, Behrens and colleagues reported that repeated (i.e., not single time) TLR9 stimulation with CpG oligodeoxynucleotides transformed an otherwise innocuous endotoxin challenge (TLR4 stimulation) in mice into a MODS model of macrophage activation with cytopenias, splenomegaly, hyperferritinemia, and hepatitis [9]. Similarly, in another murine model of cecal ligation and perforation-induced sepsis, additional CpG injection induced cytokine production by macrophages and hepatic mononuclear cells, followed by the development of liver injury and MODS-induced mortality [10]. Importantly, the sHLH phenotype elicited with repeated TLR9 stimulation is exacerbated in knockout mice deficient in native hepatic IL-1 receptor antagonist protein production but can be ameliorated by interferon-α-induced production of IL-1 receptor antagonist protein or with direct administration of recombinant IL-1 receptor antagonist protein (anakinra) in vivo [11]. In short, liver dysfunction in this model appears to be related in part to IL-1-mediated inflammation [12].

Different Inflammation Pathobiologies in sHLH

The clinical criteria used to describe the constellation of symptoms and signs indicative of these syndromes are considered to be biomarkers for a state of uncontrolled macrophage and T lymphocyte inflammation. The NK cell, as the most important "cellular" controller of macrophage and T lymphocyte activation, is considered central to the pathobiology of these conditions. Uncontrolled inflammation can be due in part to ineffective NK cell cytolytic function. Defects or deficiencies in the ability of the NK cell to kill viruses and cancer cells and to turn off the host reticuloendothelial system, macrophage, dendritic cell, and lymphocyte activation can be related to one of the three pathologic conditions: (1) absent NK cell cytolytic activity unrelated to numbers of NK cells present (familial HLH), (2) reduced NK cell cytolytic activity unrelated to numbers of NK cells present (sHLH/MAS associated with rheumatologic disease), and (3) normal NK cell cytolytic activity per cell but NK cell cytopenia (sepsis-induced hyperferritinemic MODS). These different mechanisms are further illustrated in Fig. 14.2.

Absent NK cell cytolytic activity is the basis for familial HLH, which itself is comprised of a group of monogenic autosomal recessive or X-linked primary immune deficiency diseases characterized by the absence of crucial components of the perforin-granzyme pathway needed for NK cells to kill viruses and induce apoptosis in cancer and host inflammatory cells. Gene knockout models for this pathway result in murine HLH and death after infection with otherwise innocuous LCM (lymphocytic choriomeningitis) virus infection. In the wild-type mouse exposed to LCM virus infection, host NK and T cells respond to control the virus, whereas in the perforin knockout mouse, LCM virus infection cannot be killed leading to T-cell proliferation and activation and consequent overproduction of interferon-γ (reflected by very high levels of CXCL9, the monokine induced by interferon-γ). T lymphocyte-derived interferon-γ induces macrophage activation and organ injury. Etoposide, one of the traditional treatments for familial HLH, destroys proliferating activated T cells and reduces interferon-γ production, preventing undue macrophage activation.

Reduced NK cytolytic activity is the basis of rheumatologic or drug-induced MAS. For instance, some patients with systemic juvenile idiopathic arthritis (sJIA), a known trigger for

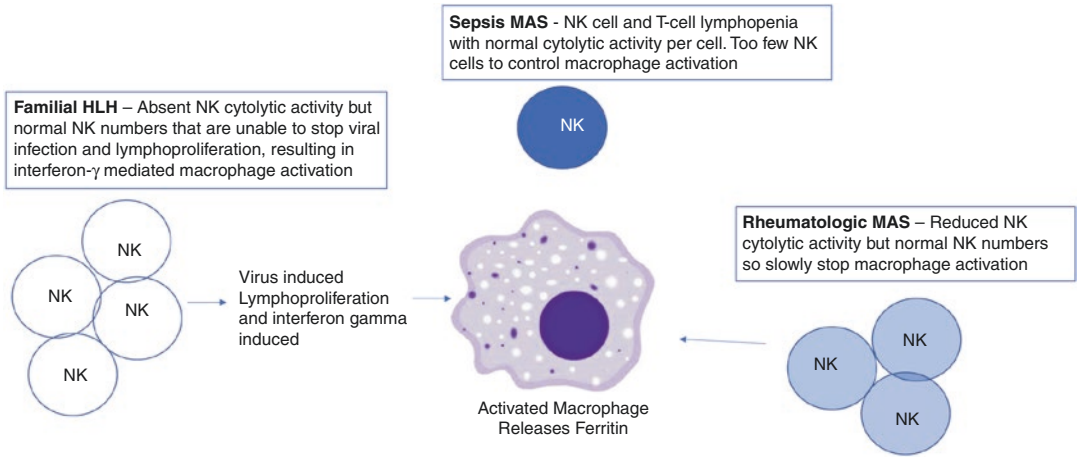

Fig. 14.2 Different natural killer (NK) cell pathobiologies: familial hemophagocytic lymphohistiocytosis (HLH) (white NK cells = absent cytolytic activity); rheumatologic disease-related macrophage activation syndrome (MAS) (light blue NK cells = reduced cytolytic activity); and hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome (MODS) (dark blue NK cells = low numbers of NK cells with normal cytolytic activity)

sHLH, are hypomorphic or heterozygotes for the perforin-granzyme pathway gene variants. As heterozygotes, these patients have some NK cytolytic activity. For the most part, these patients respond nicely to anti-inflammatory therapies such as anakinra (IL-1 receptor antagonist protein). The IL-1 receptor antagonist protein anakinra is FDA approved for inflammasome-driven conditions (e.g., sJIA). IL-18, the interferon-γ-inducible factor, is also increased in these patients. There is optimism that IL-18-binding protein (which neutralizes IL-18) as well as interferon-γ monoclonal antibody could help these patients.

Reduced number of NK cells with normal NK cytolytic activity per cell is the basis of hyperferritinemic sepsis-induced MODS. When NK cell numbers recover, then inflammation and MODS resolve. During bacterial infection, NK cells switch from an overall low cytokine-producing, high cytolytic activity phenotype to a high cytokine-producing, low cytolytic activity phenotype [13]. In hyperferritinemic sepsis-induced MODS, NK cell cytopenia and T-cell cytopenia occur with reticuloendothelial system activation but decreased to absent interferon-γ production. When the reduction in NK cell and T-cell numbers is below 10% of normal, there is a significant decrease in host ability to kill viruses and cancer cells as well as to induce apoptosis in activated macrophages. Because T cells and interferon-gamma production are already low to absent, etoposide is unlikely to be of benefit in reducing macrophage activation in these children. Indeed, etoposide may worsen outcomes in sepsis patients by preventing the recovery of lymphocyte counts needed to resolve infection. Compared to patients with other forms of HLH, those with hyperferritinemic sepsis-induced MODS have lower production of interferon-γ-inducing IL-18. The promise of interferon-γ monoclonal antibodies in treating familial HLH and MAS is therefore less likely to be realized in hyperferritinemic sepsis-induced MODS. Further, inability to produce interferon-γ is associated with increased mortality in experimental models of sepsis.

Two interferon-γ-independent pathways that induce macrophage activation-related hyperferritinemia in patients with sepsis-induced MODS are free hemoglobin and DNA viremia. These pathways are depicted in Fig. 14.3 [14]. Endotheliopathy in sepsis leads to hemolysis, particularly in patients with gene variants related to atypical hemolytic uremic syndrome (HUS) and low to absent inhibitory complement production. The released free hemoglobin complexes

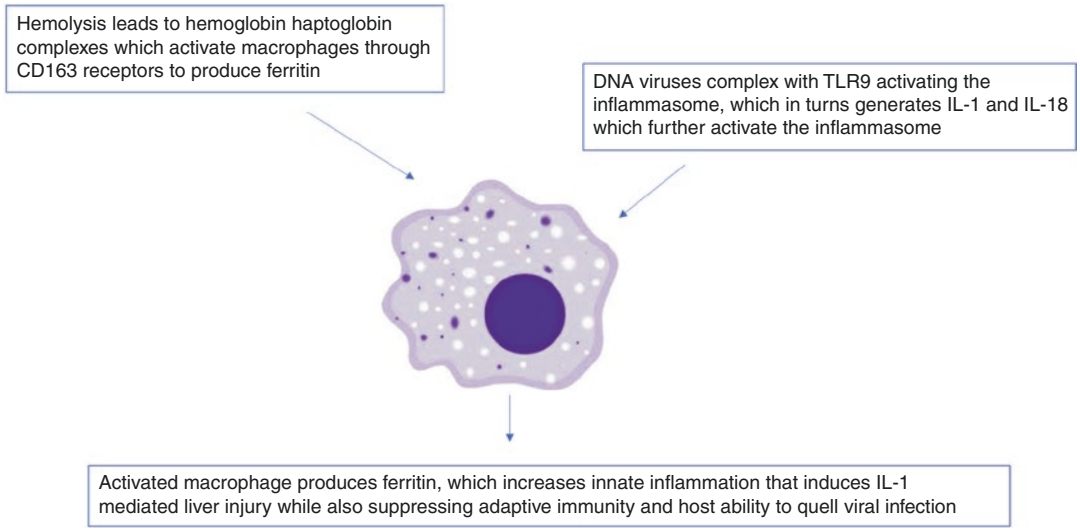

Fig. 14.3 Interferon-γ-independent pathways to macrophage activation during sepsis include free hemoglobin from hemolysis or blood transfusions, as well TLR9 stimulation from DNA viral reactivation

with haptoglobin and binds to the macrophage CD163 receptor, which is internalized, leading to the production and release of extracellular ferritin. Extracellular ferritin activates liver stellate cells causing pro-inflammatory cytokine-mediated liver injury. Ferritin also increases toll-like receptor (TLR) expression including TLR9 on innate immune cells while inhibiting the adaptive immune response by preventing lymphopoiesis. DNA viremia, enabled in part by lymphopenia-induced viral reactivation, complexes with the macrophage TLR9 receptor resulting in inflammasome activation and production of IL-1, IL-18, and more extracellular ferritin. This cascade results in a feed-forward positive feedback inflammation loop with more liver injury, innate immune cell inflammation, and adaptive immune cell depression [14]. Plasma exchange can be used in these patients to remove free hemoglobin and extracellular ferritin as well as to replace inhibitory complement. Intravenous immunoglobulin (IVIg) can also be given to neutralize DNA viremia and to block further TLR9 stimulation. Interestingly, IL-1 receptor antagonist protein is effective in reversing both ferritin and TLR9-induced liver injury while inducing a delayed type 1 interferon response to combat DNA viremia.

Diagnosis and Therapeutic Options for Secondary HLH

Despite different pathobiologies, familial HLH and both forms of sHLH – MAS induced by rheumatologic disease and hyperferritinemic sepsis-induced MODS – are all characterized by uncontrolled macrophage activation and are traditionally diagnosed by the presence of five of eight clinical criteria that include ferritin >500 ng/ml, two-line cytopenia, organomegaly, hypertriglyceridemia, hypofibrinogenemia, elevated soluble CD25, absent natural killer (NK) cytotoxic activity, and hemophagocytosis (Fig. 14.1). Importantly, though these criteria were initially created to diagnose familial HLH, there are some clinical data supporting approaches to the treatment of sHLH using this diagnostic methodology [4–7]. Additionally, Demirkol et al. evaluated different therapies for Turkish children who met criteria for sHLH in a cohort study [15]. They excluded children who were under 2 years, had a history of consanguineous parenting, or had a previous young family member who died from fever because these children were more likely to have familial HLH. Mortality in these excluded children, who were treated by hematologists with etoposide and dexamethasone, was 50%. All the included

children (i.e., without these familial HLH risk factors) were diagnosed with sHLH and had five of the aforementioned eight clinical criteria and had five to six organ failures. Centers in one treatment cohort administered the familial HLH protocol of dexamethasone and/or etoposide along with daily plasma exchange to these children with sHLH and observed a 50% mortality rate, whereas centers in the other treatment cohort administered a less immune suppressive regimen of methylprednisolone with or without intravenous immunoglobulin (IVIG) with daily plasma exchange and observed a 0% mortality rate. Based on the above data, though it may be appropriate to use the diagnostic criteria for familial HLH to diagnose sHLH, the traditional familial HLH protocol of dexamethasone and etoposide should be replaced by less toxic treatment strategies for patients with sHLH.

Clinical Vignette 2: sHLH Induced by Systemic Juvenile Arthritis

A febrile 7-year-old child presents to an ICU with rash, leukocytosis, arthritis, and laboratory data concerning for sHLH. The intensivist calls the rheumatologist, who believes the presentation is consistent with systemic juvenile arthritis-related MAS. She recommends treatment with methylprednisolone and the IL-1 receptor antagonist anakinra. Other laboratory testing is sent to rule out systemic lupus erythematosus, sarcoidosis, scleroderma, Sjogren's syndrome, and Kawasaki's disease.

Patients with autoimmune rheumatologic disease have increased inflammasome activation and reduced NK activity ***without lymphoproliferation****. Accordingly, rather than etoposide and dexamethasone regimens, methylprednisolone and anakinra are typically recommended to control inflammasome activation associated with rheumatologic disease. Other biologics and chemotherapeutic regimens, however, such as cyclophosphamide, methotrexate, tocilizumab, or etoposide as well as plasma exchange, are considered if the patient remains recalcitrant.*

Because three of the eight clinical criteria (e.g., soluble CD25 levels, NK cytotoxicity, and hemophagocytosis) used to identify patients with HLH are not easily accessible tests, rheumatologists have sought to redefine sHLH with other criteria sets that use more readily available laboratory tests. For example, utilizing current literature, Ravelli and colleagues have provided a consensus statement defining sHLH in a child with known systemic juvenile idiopathic arthritis (sJIA), a common trigger of macrophage activation, based on the presence of fever, ferritin >684 ng/mL, and any two of the following: platelet count <181 K, ALT >48 IU/L, triglycerides >156 mg/dL, and fibrinogen <360 mg/dL [16]. Though recommended for patients with MAS secondary to sJIA, these criteria can be applied to patients with MAS secondary to other rheumatologic diseases as well.

Shakoory and colleagues have offered another method for simplifying the diagnosis of and treatment of sHLH [17]. Specifically, they suggested that the combination of hepatobiliary dysfunction and disseminated intravascular coagulation (DIC) can be representative of sHLH including hyperferritinemic sepsis-induced MODS. Further, they hypothesized that if the combination of these two organ dysfunctions represents sHLH, then treatment with IL-1 receptor blockade should improve sepsis-related macrophage activation as it does in the previously mentioned experimental model [10] and in children with sJIA-related MAS [15–17]. In their secondary analysis of an adult with severe sepsis IL-1 receptor blockade trial, Shakoory and colleagues compared patients with combined hepatobiliary dysfunction (HBD) and DIC (HBD + DIC) to those without this combination (non-HBD + DIC) [17]. The investigators found the following: (1) 5.6% of severe sepsis patients had HBD + DIC; (2) patients with HBD + DIC had a higher incidence of shock (HBD + DIC = 95% versus non-HBD + DIC = 79%) and acute kidney injury (HBD + DIC = 61% versus non-HBD + DIC = 29%), but not acute respiratory

Table 14.1 Simplified clinical criteria used to diagnose rheumatologic or drug-related secondary hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) and hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome (MODS)

Familial HLH: five of eight criteria	Rheumatologic/drug-induced MAS	Hyperferritinemic sepsis-induced MODS
• Fever • Ferritin > 500 ng/ml • Hypertriglyceridemia • Hypofibrinogenemia • Two-line cytopenia • Splenomegaly • Natural killer cell cytolytic activity < 10% • Hemophagocytosis • Elevated soluble CD25	• Fever • Ferritin > 684 ng/mL • With any two of the following: Platelet count < 181,000 Alanine transferase > 48 IU/L Triglyceride > 156 mg/dL Fibrinogen < 360 mg/dL	• Hepatobiliary dysfunction • Disseminated intravascular coagulation • +/- ferritin > 500 ng/mL

distress syndrome (HBD + DIC = 21% versus non-HBD + DIC = 26%); and (3) IL-1 receptor blockade significantly increased 28-day survival in patients with HBS + DIC (IL-1 blockade = 65.4% versus placebo = 35%), while 28-day survival in non-HBD + DIC did not change (IL-1 blockade = 71% vs placebo = 71%). It can be, therefore, extrapolated that sHLH diagnosed by the presence of HBD and DIC constitutes a small but significant subset among severe sepsis patients; death attributable to superimposed sHLH can be remedied in some patients with adjunctive therapy with IL-1 receptor blockade.

More recently, Hellenic and Swedish investigators reported outcomes in adult patients with hyperferritinemic sepsis-induced MODS, though they described these patients as having sepsis and concomitant "macrophage activation-like syndrome (MALS)" [18]. In this study, they found that the degree of hyperferritinemia was most predictive of mortality. As a result, they concluded that the presence of hyperferritinemia (ferritin >500 ng/dL), hepatobiliary dysfunction, and disseminated intravascular coagulation can be used to diagnose sHLH and feasibly be used to identify patients with sHLH or hyperferritinemic sepsis-induced MODS for "early clinical trials" of inflammation-modulating therapies [5–7, 15, 17, 18]. The simplified approaches to the diagnosis of MAS and hyperferritinemic sepsis-induced MODS are summarized in Table 14.1.

Clinical Vignette 3: Hyperferritinemic Sepsis-Induced MODS

A 3-year-old patient is admitted to the ICU with a presumed diagnosis of sepsis. Antibiotics and source control are implemented. Shock, acute respiratory distress syndrome, and acute kidney injury subsequently develop, along with hepatobiliary dysfunction and disseminated intravascular coagulation. Serum ferritin is 1120 ng/dL. Diagnosis of hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome (MODS) is made.

An exhaustive search for the diagnosis is also performed, including bacterial sources (mycoplasma, rickettsia, legionella, chlamydia, brucella, and borrelia), fungi and parasites (histoplasmosis, babesia, leishmaniasis, pneumocystis, aspergillus, toxoplasmosis, cryptococcus, and candida), and viruses (EBV, CMV, HSV, HIV, HHV8, HHV6, parvovirus, adenovirus, and influenza) so that appropriate antimicrobial therapy can be ensured.

Plasma exchange, IVIG, and anakinra are considered for treatment. (methylprednisolone can also be considered if the patient does not have a contraindicated infection, e.g., HSV.) In patients with hyperferritinemic sepsis-induced MODS, improvement occurs when NK cell and T lymphocyte counts, which are reduced, recover.

ICU Management of Secondary HLH for the Pediatric Intensivist

Patients arriving to the pediatric ICU with a diagnosis of familial HLH will most commonly be receiving etoposide and dexamethasone, while patients arriving with a diagnosis of MAS will be receiving methylprednisolone with biologics such as anakinra (IL-1 receptor antagonist) or tocilizumab (anti-IL-6 antibody). For these children, supportive ICU care is most often necessitated by cardiopulmonary instability or organ failure often associated with HLH. The approach to organ support therapies for these children would be no different for any other child admitted to a pediatric ICU with sepsis, ARDS, and MODS.

More commonly, patients will present to an intensivist without a preceding diagnosis of HLH or MAS but rather with a diagnosis of sepsis-induced MODS. Indeed, most of these patients have sepsis-induced MODS. In addition to standard management for sepsis and multiple-organ failure, intensivists should have a high index of suspicion for sHLH. Though some centers have developed multidisciplinary hyperferritinemia interest groups to help the intensivist with this differential diagnosis, most depend on the intensivist to recognize signs and symptoms of this sHLH (Fig. 14.1) and call for specialty consultation. Of note, history of consanguineous parenting or family history of children dying from fever, especially in a patient presenting less than 2 years of age with significant CNS pathology, should raise suspicion for familial HLH. For patients with subacute arthralgia or arthritis, rheumatologic disease with MAS should be considered, although sHLH in patients with septic arthritis will be more likely to be hyperferritinemic sepsis-induced MODS.

For any patient presenting to the pediatric ICU with sepsis, CRP and serum ferritin can be measured on presentation. If ferritin is greater than 500 ng/dL and other signs or symptoms of sHLH are present, especially DIC or hepatobiliary dysfunction, the diagnosis of hyperferritinemic sepsis-induced MODS should be made. We also recommend monitoring systemic inflammation associated with macrophage activation at the bedside by measuring C-reactive protein (CRP) and serum ferritin at least twice weekly. CRP is a pattern recognition receptor made by the liver in response to bacterial infection or necrotic tissue. CRP binds to C-components of microbes or the externalized phosphatidylcholine moiety of necrotic cells, complexes with complement, and attaches to the CRP receptor on the macrophage for internalization, degradation, and presentation to the adaptive immune system. Ferritin is released by macrophages in response to free hemoglobin and to DNA viremia. Hyperferritinemia occurs in iron overload states and can also be released by dying cells during necrosis. Mortality risk increases as the circulating CRP and serum ferritin increase. The goal of therapy is to subdue the inflammatory response for which CRP and serum ferritin are surrogate biomarkers. If CRP increases while serum ferritin decreases, this combination is a harbinger of new or worsening infection and warrants attention to better source control and reduction in immune suppression. If ferritin does not come down or increases, then ongoing iron overload and/or macrophage activation (possibly associated with DNA viremia) is likely. Attention should be given to reducing hemolysis, quelling macrophage activation, and neutralizing DNA viremia. This approach to monitoring is illustrated in Fig. 14.4.

As for any patient admitted to an ICU with sepsis, source control and organ support are paramount for patients with hyperferritinemic sepsis-induced MODS. Empiric antibiotics should be started within 1 h of presentation, and patients should be managed according to current sepsis guidelines [20]. For patients presenting with erythroderma, one must consider toxic shock from Group A *Streptococcus* or *Staphylococcus aureus*, which warrants therapy with clindamycin to prevent toxin production and an antimicrobial drug which kills both of these pathogens such as vancomycin. We do not use linezolid because hepatobiliary dysfunction reduces its safety window; specifically, linezolid can become a host mitochondrial toxin when blood concentrations increase due to poor clearance. We recommend immunomodulation with corticosteroids

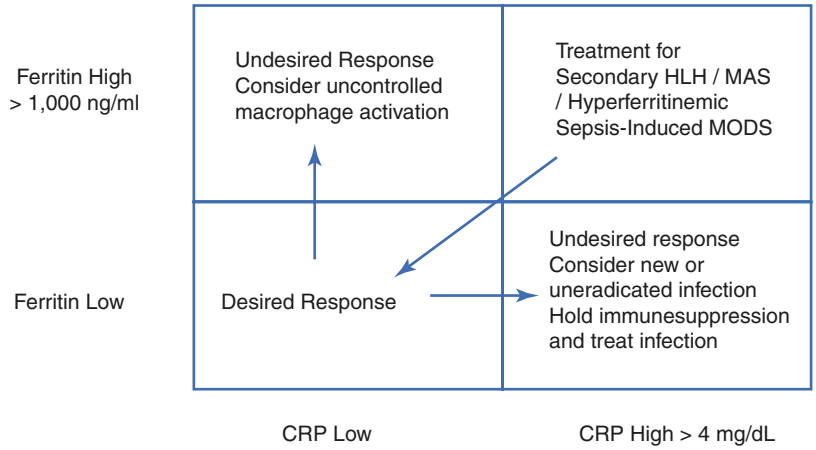

Fig. 14.4 An approach to monitoring inflammation and infection response during initiation of therapy for hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and hyperferritinemic sepsis-induced multiple-organ dysfunction syndrome (MODS) by observing changes in C-reactive protein (CRP) and ferritin. C-reactive protein reflects bacterial infection, whereas ferritin reflects macrophage activation

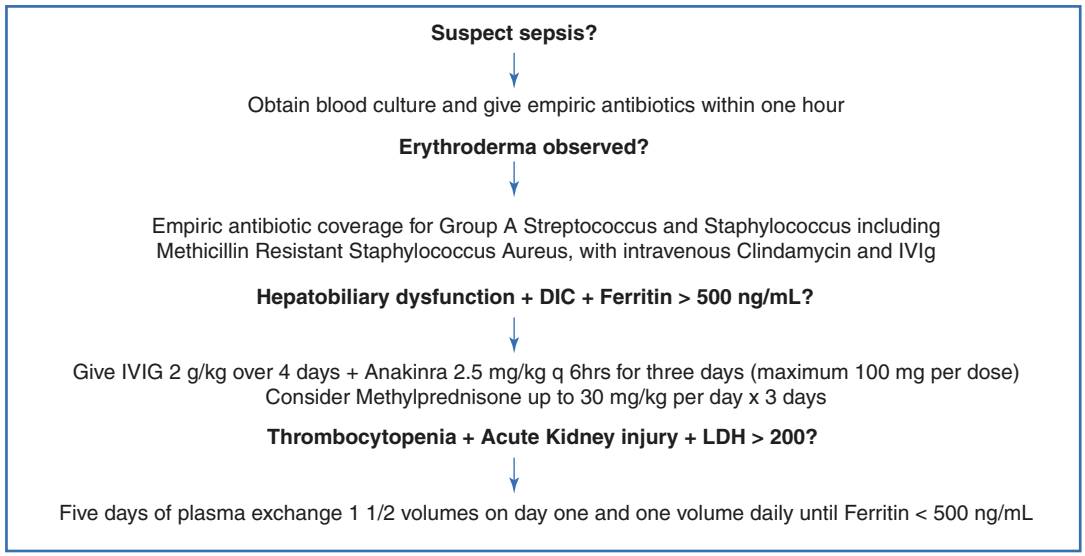

Fig. 14.5 Recommended approach to hyperferritinemic sepsis-induced multiple-organ dysfunction (MODS)

(30 mg/kg per day of methylprednisolone × 3 days) and IVIG (2 g/kg over 1–4 days). If the patients have evidence of acute kidney injury, thrombocytopenia, and elevated lactate dehydrogenase, we recommend daily plasma exchange 1.5 × blood volume on day 1 followed by 1 × volume daily until serum ferritin decreases to less than 500 ng/mL. In addition, we recommend the IL-1 antagonist anakinra (2.5 mg/kg q6h to maximum of 100 mg q6h) for 3 days. This treatment pathway is summarized in Fig. 14.5.

Summary and Conclusion

The prompt recognition and appropriate treatment of familial and secondary HLH present important challenges to clinical intensivist. Differentiating between these clinical scenarios is the first step toward outlining the most appropriate clinical strategies, which is only possible through increasing our understanding of underlying immunopathogenesis that drives the clinical presentation. As our knowledge and

understanding of the familial and secondary HLH evolve, evidence-based recommendations will better assist the clinical intensivists in their endeavors. Most importantly, a collaborative approach with hematology and rheumatology colleagues is likely the best means of securing a favorable outcome in patients who develop this challenging disease process.

Conflict of Interest Statement On behalf of the authors, there are no conflicts of interest.

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15 Diagnosis and Management of Fungal Infections in the Pediatric Intensive Care Unit

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Introduction

Invasive fungal disease (IFD) contributes significantly to morbidity, mortality, and healthcare costs in hospitalized pediatric patients [1, 2]. This is particularly true for critically ill patients, where risk factors such as complex underlying medical conditions and states of immunodeficiency, invasive procedures, and indwelling foreign catheters are prevalent and predispose patients to opportunistic infections [3]. As the number of patients with underlying malignancies, autoimmune disorders, and chronic infections survive longer into their illness, the ability to rapidly diagnose and treat invasive fungal infections becomes of increasing importance.

Historically, the early diagnosis and management of invasive fungal infections have been difficult to make using conventional culture-based approaches. This was associated with treatment delays and subsequent increased mortality [4]. Advances such as the use of biomarkers for early disease detection provide a promising opportunity for earlier diagnosis and therapeutic monitoring. Additionally, a recent focus on prospective, multicenter studies is allowing for an improved understanding of pediatric-specific epidemiology, outcomes, and optimal therapeutic strategies [5].

Despite this, there remain significant challenges for the clinician. Consider the following patient scenario: *You admit a 6-year-old female with short gut secondary to necrotizing enterocolitis (NEC) in infancy, on chronic total parenteral nutrition (TPN), following surgical repair of a small bowel obstruction. Her postoperative course is complicated by gram-negative bacteremia for which she is started on piperacillin-tazobactam with resolution of fever and improvement in clinical status. Approximately 7 days into her antibiotic regimen, she develops new-onset fevers to 39.3°, with associated tachycardia and hypotension. Blood cultures are drawn, and the patient's antibiotic regimen is broadened to include vancomycin. Forty-eight hours into the new antibiotic regimen, the patient remains highly febrile. Blood cultures at this time are no growth to date.*

Is this patient at risk for fungal infection and at what point did it become more likely? What testing should be sent to assess for fungal infection? Should she be treated presumptively in the interim? Though sure to evolve, an emerging literature aims to address these questions and improve the outcomes for our patients.

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Epidemiology

The majority of fungal disease in the pediatric intensive care unit (PICU) results from infection with invasive candidiasis (IC) or invasive aspergillosis (IA) [1, 6], with an overall increase in recent years. While different in their risk factors, virulence patterns, diagnostic challenges, and treatment options, both contribute significantly to morbidity and mortality and pose management challenges for the intensivist [3, 7].

Candida Species

Candida (*C.*) species are the leading cause of fungal infections and the third most common cause of healthcare-associated bloodstream infections in the United States [1]. The incidence among PICU patients varies widely by study and is cited from 3.6 to 43/1000 admissions [8–10]. While *Candida albicans* remains the most frequently isolated species, recent epidemiologic studies demonstrate an emergence toward non-albicans species. The largest prospective, multicenter pediatric study to date enrolled 434 patients from 24 sites; 44% of isolates were *C. albicans*, and 56% were non-albicans species. The non-albicans species included 22% *C. parapsilosis* and 11% *C. glabrata* [7].

Risk factors for the development of IC are reported in Table 15.1 [8, 9, 11, 12]. Colonization is a frequent occurrence in PICUs, with one study demonstrating a rate of 69%. This was four times more likely if a central venous line (CVL) was present [8]. Though multiple risk factors exist, presence of CVL appears to confer the highest risk, with a reported increased odds ratio of 30.4 on multivariate analysis [11]. Mortality attributable to IC is difficult to estimate given the severity and comorbidities of underlying illness. Attributable mortality has been estimated at 16.7% [13], with mortality rates as high as 44%, significantly higher than in matched PICU controls [14].

Table 15.1 Risk factors for invasive fungal disease in children

Aspergillosis	• Hematologic malignancies – Acute myelogenous leukemia (AML), high-risk acute lymphoblastic leukemia (ALL), relapsed ALL • Hematopoietic stem cells transplant (HSCT) recipients • Neutropenia • Immunosuppressive therapy including corticosteroid use
Candidiasis	• Admission to pediatric intensive care unit (PICU) • Presence of central venous line • Use of parenteral nutrition • Immunosuppression, malignancy • Colonization • Vancomycin and anaerobic antibiotic use
Mucormycosis	• Hematologic malignancies – AML, ALL • HSCT recipients • Use of parenteral nutrition • Admission to PICU • Diabetes mellitus • Neutropenia • Iron overload • Burns and traumatic wounds

Aspergillus Species

Aspergillus species cause approximately 75% of invasive mold disease in pediatrics [15], with *Aspergillus (A.) fumigatus* and *A. flavus* the most frequent isolates. In the largest retrospective review of IA performed in pediatric patients, *A. fumigatus* was isolated in 52.8% of cases followed by *A. flavus* at 15.7%, *A. terreus* at 4.7%, and *A. niger* at 4.7% [16].

Epidemiologic studies report an incidence ranging from 0.4% when evaluating all hospitalized immunocompromised children [17] to upward of 6.2% when evaluating specifically in pediatric cancer patients receiving high-dose chemotherapy [18].

Risk factors for development of IA are reported in Table 15.2 [16, 17, 19]. Notably, IA is seen almost exclusively in severely immunocompromised children, specifically those with

Table 15.2 Diagnosis of possible and probable invasive fungal disease

	Host factor	Clinical factor	Mycological testing
Possible	Recent neutropenia Allogeneic stem cell transplant Steroid use >3 weeks Use of T cell immunosuppressive medication Severe immunodeficiency	Lower respiratory tract disease Tracheobronchitis Sinonasal infection CNS infection Disseminated candidiasis	
Probable	Recent neutropenia Allogeneic stem cell transplant Steroid use >3 weeks Use of T cell immunosuppressive medication Severe immunodeficiency	Lower respiratory tract disease Tracheobronchitis Sinonasal infection CNS infection Disseminated candidiasis	Direct test Cytology, direct microscopy, culture Indirect test Aspergillosis: Galactomannan Others: (1 → 3)B-D-glucan

Adapted from DePauw et al., Clin. Infect. Dis. 2009

hematologic malignancies or those that have undergone bone marrow transplantation [19]. Mortality rates of 30–52.5% have been reported in pediatric patients with aspergillosis [15, 16]. When evaluating children with malignancy and IA, their relative risk of mortality was 13.5 times that of matched children with malignancy and without IA [17].

Mucorales Species

The epidemiology of infection caused by *Mucorales* spp., including *Rhizopus*, *Mucor*, *Lichtheimia*, *Cunninghamella*, and *Saksenaea*, is not well described in the pediatric literature even though they constitute the third most common cause of invasive fungal disease in children [3, 20]. Although seen more frequently in patients with underlying malignancy, *Mucorales* infection also occurs in the immunocompetent host [21]. Mortality is also quite heterogeneous. An evaluation of two large international databases reported an overall mortality of 33%. When evaluating by underlying disease, mortality was as high as 66% in the presence of malignancy and as low as 16.6% when no underlying condition was present. Mortality was also significantly higher if disseminated disease was present, which occurs in a significant number of cases [3]. Risk factors are reported in Table 15.2 [3, 20, 21].

Diagnosis

The critical nature of PICU patients and comorbidities associated with invasive procedures make the gold standard diagnosis of invasive fungal disease, detection of fungus by histological or culture results, clinically challenging. To overcome limitations in diagnostic options, a consensus group of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) created a definition for establishing proven, probable, or possible invasive fungal disease, with a later revision in 2008 [22, 23].

Both probable and possible invasive fungal diseases require the presence of both a host factor and a clinical factor, as outlined in Table 15.2. The distinction between probable and possible infection occurs based on the presence of mycological criteria, with probable infection requiring either a positive direct or indirect test [23]. Both galactomannan (GM) and (1→3)-β-D-glucan (BDG) can fulfill criteria as indirect tests. Additional assays for biomarkers besides GM and BDG exist, including *Candida* mannan antigen, anti-mannan antibody, and fungal polymerase chain reaction (PCR). While all pose promising adjuncts for the diagnosis of IFD, except for GM, none are validated in children.

Given the potential for earlier diagnosis, options for therapeutic monitoring, and decreased morbidity and mortality, there is a significant focus on better understanding the role of biomarkers in children [24].

Galactomannan Assay

GM, which is a component of the cell wall specific to *Aspergillus* spp. and released during the growth phase, is designed for the diagnosis of IA. It is the most widely studied fungal biomarker in children [24]. When used in patients meeting EORTC/MSG criteria for proven invasive fungal disease, GM has a sensitivity of 76% and specificity of 86% [25]. In the sole study performed on non-hematologic pediatric ICU patients, it was found to have a sensitivity of 90% and specificity of 35.6% [26]. The sensitivity of GM is lacking in certain patient populations, however, including non-neutropenic solid organ transplant recipients and those with certain primary immunodeficiencies [27, 28]. Its utility for aiding in the diagnosis of IA for patients taking mold-active antifungal prophylaxis has also been questioned. Current recommendations advise against use of GM in these patients due to nullification of the GM signal and subsequent false negative testing [29].

Additionally, its positive predictive value (PPV), when evaluated in a systematic review of patients with cancer who underwent hematopoietic stem cell transplantation (HSCT), was <75% in most studies and <50% in half of studies [30]. The other major concern surrounds high false-positive rates, much higher in pediatric compared to adult populations [31]. This is particularly true for premature infants [32]. Its strength appears to be in its consistently high negative predictive value (NPV) among high-risk patients [26, 30].

Recommendations regarding use of GM as a screening tool are therefore controversial without a consensus. In a subset of high-risk patients, those with certain cancers or undergoing HSCT, the European and US guidelines are conflicting. The European guidelines suggest screening is warranted; however, the most recent US guidelines, revised in 2017, recommend consideration against routinely testing serum GM levels in patients with persistent febrile neutropenia [33, 34]. This is based on its poor PPV, and fact that the high NPV does not rule out other non-aspergillus molds [34].

The utility of GM as a screening tool is greatest in high-risk patients with significant concern for aspergillosis. It is possible that its use in non-serum samples, particularly those from a bronchoalveolar lavage, when used in addition to serum samples, may increase the overall sensitivity and specificity [35]. Adult studies have also demonstrated that initial levels may be predictive of outcome and that follow-up levels can be utilized to correlate for improvement in extent of disease [36]. Thus while a positive marker coupled with risk factors and clinical condition may assist in diagnosis, significant caution needs to be taken when interpreting a negative result to ensure the clinician isn't led into excluding fungal disease as an etiology of a patient's deterioration.

BDG Assay

BDG is a major cell wall component of various medically important fungi. The BDG assay is therefore more broadly applicable and used to detect *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Trichosporon* spp., *Saccharomyces cerevisiae*, *Acremonium* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Sporothrix schenckii*, and *Pneumocystis jirovecii*. Sensitivity and specificity in pediatric specific studies vary broadly. Reported sensitivities range from 50% to 82% and specificity from 46% to 82% [24]. In the one study performed on PICU patients without hematologic disease, sensitivity was reported at 53.3% and specificity at 63.2% [26].

One of the major issues surrounding the use of BDG in pediatric patients is a lack of standard cutoff value in which to interpret a positive result. Studies suggest the adult cutoff of 80 pg/mL is likely too low and that baseline BDG are higher in children than adults [37]. Two pediatric studies

demonstrated dramatically higher median BDG levels in cases compared to controls (480 pg/mL vs. 61 pg/mL and 372 pg/mL compared to 57 pg/mL); healthy pediatric controls were also found to have levels as high as 473 pg/mL [26, 38]. Using the data from one of these studies, receiver operating characteristic (ROC) curves were constructed and demonstrated a level of 177 pg/mL provided an optimal sensitivity of 78% and specificity of 91% [38].

The PPV of BDG is poor, with values ranging from 33.3% to 46.67% [26, 38]. A significant number of medications and medical products used in the critical care setting have been shown to increase false-positive rates. Examples of these with frequent use include albumin infusions, IVIG, piperacillin-tazobactam, ampicillin-clavulanate, alcohol swabs, and active antifungal use [39].

The BDG assay is therefore not recommended in any pediatric specific guidelines for routine use in screening or treatment management, and further studies are needed to determine optimal cutoff values for children. Its value appears to be in its consistently high NPV, with values as high as 93% [38], and thus the exclusion of invasive fungal disease. Additionally, it has been shown to be of value in guiding length of treatment, particularly in CSF, where a case series demonstrated reversion to negative levels in all nine patients [40].

Fungal Polymerase Chain Reaction

To date, fungal PCR has been evaluated most frequently in the diagnosis of IC and IA, with studies demonstrating sensitivities of 63–100% [24]. The largest pediatric study evaluating the utility of PCR for candidemia looked at 54 children hospitalized in the ICU setting with suspected infection. The study utilized a multiplex PCR, designed to detect multiple targets simultaneously for the seven most causative *Candida* strains. A total of 15% of patients had positive blood cultures, and 24% of patients had positive PCR results (including all eight patients with positive cultures). PCR testing was negative in all 28 controls. Additionally, PCR results were available within 24 h compared to 48–96 h with respect to blood culture results. Detection limit was found to be 4 CFU/mL as compared to 10 CFU/mL needed for blood cultures [41].

The largest pediatric study evaluating the utility of PCR for aspergillosis was conducted in patients with hematologic or solid tumor malignancy. Using EORTC/MSG 2008 criteria, 125 patients were classified as either proven, probable, or no IFD. When comparing GM, BDG, and PCR, PCR had the highest sensitivity, specificity, and PPV at 82.7%, 54% and 72.9%, respectively. When various combinations were used, all parameters increased and were uniformly highest with the combination of PCR and GM, with a sensitivity of 87.7%, specificity of 64%, PPV of 73.9%, and NPV of 73% [42].

Fungal PCR represents a promising avenue that may allow for more timely diagnosis, with increased specificity and sensitivity. Currently, the lack of standardization or validation of clinical technique prevents its recommendation in routine use [23]. It is likely that future recommendations will include a combination of biomarker and PCR testing; currently there is not enough known about pediatric specific values and cutoffs to allow for accurate interpretation.

Candida Mannan Antigen and Anti-Mannan Antibody Assay

Mannans are also main cell wall components of *Candida* spp. Studies evaluating *Candida* antigen testing in non-neonatal pediatric patients are few [24]. The one study in PICU patients demonstrated sensitivities of 100% and 60% for the mannan antigen and anti-mannan antibody assay, respectively. A high false-positive rate of 23% was also reported [43]. While neonatal studies have also demonstrated high sensitivities, the test has demonstrated a consistent inability to detect *C. parapsilosis* [24], which, as discussed previously, composes the majority of non-albicans candida infections [7].

Role of Imaging

The role of imaging in diagnosis of IFD is not well described, as pediatric specific studies are lacking. Though proposed as a useful adjunct in high-risk populations for diagnostic work-up and treatment response, findings are often non-specific [44]. Furthermore, classic adult findings are not necessarily applicable to children. In an evaluation of pediatric aspergillosis, the most common pulmonary finding on chest CT was nodules (59%). The classic adult findings of "air crescent" and "halo" signs were only seen in 2.2% and 10.9% of pediatric patients, respectively [16]. Despite this, chest CT is currently recommended in children at high risk for aspergillosis with prolonged fever and neutropenia despite antibiotics [34].

Conclusions

Many PICU patients have significant risk factors with respect to invasive fungal disease. Biomarkers represent a promising tool in the diagnosis of IFD in children, especially those in which clinical status precludes invasive testing. Further studies are needed to better understand applicable patient populations, age-specific cut-offs, and pediatric-specific validation of tests with attention paid to testing combinations. There are currently no US-based guidelines for routine use of biomarkers, though the most recent EORTC/MSG guidelines utilize them for the diagnosis of "probable" infection. Clinicians must therefore use judgment with respect to individual patients and risk factors, being mindful of the sensitivity, specificity, and predictive values of the various tests. Imaging studies, though mostly non-specific, can assist in establishing both extent of disease and treatment response.

Management: When and How to Treat

Given the high morbidity and mortality associated with invasive fungal disease, prompt initiation of appropriate antifungal therapy is crucial to optimizing outcomes. Medications with sufficient data in children, their mechanisms of action, toxicities, and dosage recommendations are summarized in Table 15.3 [29, 45–49]. What follows includes a broad overview of management for the most commonly encountered invasive fungal disease in the PICU; for specifics, the authors recommend referencing the most recent Infectious Diseases Society of America (IDSA) practice guidelines, endorsed by the Pediatric Infectious Diseases Society [29, 49]. While first-line treatment recommendations are consistent among adult and pediatric patients, caution must be applied to dosing due to considerable pharmacokinetic variation between neonates, children, and adults.

Treatment of Invasive Candidiasis

The treatment of IC is separated into treatment of neutropenic and non-neutropenic patients. For both, echinocandins are the recommended first-line therapy. Amphotericin B can be considered as well, particularly in those patients with suspected resistance. With either treatment regimen, transition to fluconazole is recommended within 7 days in those patients that are both clinically stable and with proven azole sensitivity. Fluconazole can also be considered first-line therapy in non-critically ill patients and without prior azole exposure, which would make resistance more likely. In all cases of IC, azole sensitivity testing is recommended [49].

Additional recommendations for the management of patients with IC include dilated ophthalmological exams, within the first week for non-neutropenic patients and at resolution of neutropenia for neutropenic patients. Neonates should undergo a more extensive work-up given the high risk of dissemination, including CNS disease; therefore a lumbar puncture and abdominal imaging (computed tomographic or ultrasound) are part of the initial work-up. There are a strong recommendation for removal of central lines in neutropenic patients and consideration in non-neutropenic patients [49]. In patients for which removal of central access in not feasible, consideration

Table 15.3 Treatment options for invasive fungal disease in children

Medication	Class	Mechanism of action	Toxicity	Indication	Pediatric dosing
Amphotericin B deoxycholate	Polyene macrolide	Binds to ergosterol → changes in cell permeability and death	Nephrotoxicity, hepatotoxicity, hypokalemia, anemia, GI intolerance	-First-line therapy for IA in neonates when voriconazole not tolerated[a] -First-line therapy for IC in neonates when resistance suspected -First-line therapy for zygomycosis	0.6–1.5 mg/kg IV every 24 h
Liposomal amphotericin B	Polyene macrolide	Binds to ergosterol → changes in cell permeability and death	Nephrotoxicity (less), hepatotoxicity, hypokalemia, anemia	-First-line therapy for IA when voriconazole not tolerated -Second-line therapy for IC -First-line therapy for zygomycosis	3–5 mg/kg IV every 24 h
Fluconazole	First-generation triazole	Inhibits cell wall ergosterol production, an essential part of fungal cytoplasmic membrane	GI intolerance, hepatotoxicity, SJS syndrome, headache	-First-line therapy for IC when no concern for resistance -Caution with *C. krusei* and *C. glabrata*, unless susceptibilities are available -Empiric therapy in high risk, immunocompromised patients	12 mg/kg PO/IV every 24 h
Itraconazole	First-generation triazole	Inhibits cell wall ergosterol production, an essential part of fungal cytoplasmic membrane	GI intolerance, hepatotoxicity	-First-line therapy for IC when no concern for resistance, or resistance only to fluconazole	2.5 mg/kg PO every 12 h (only available as oral formulation)
Voriconazole	Second-generation triazole	Inhibits cell wall ergosterol production, an essential part of fungal cytoplasmic membrane	Hepatotoxicity, vision changes, photophobia, rash, CYP450 drug interactions	-First-line therapy against IA -Effective against all species of *Candida*, including *C. krusei* and *C. glabrata*	<40 kg: 8–9 mg/kg IV every 12 h >40 kg: 400 mg IV every 12 h × 2 doses and then 200–300 mg every 12 h
Caspofungin	Echinocandin	Inhibits synthesis of the glucose homopolymer BDG synthase	Hepatotoxicity, hypotension, GI intolerance, fever, headache, rash, shock, shivering, respiratory failure	-First-line therapy in neutropenic patients with IC -Salvage therapy in IA	1–17 years: 70 mg/m^2 IV on day 1 followed by 50 mg/m^2 IV every 24 h

(continued)

Table 15.3 (continued)

Medication	Class	Mechanism of action	Toxicity	Indication	Pediatric dosing
Micafungin	Echinocandin	Inhibits synthesis of the glucose homopolymer BDG synthase	Hepatotoxicity (less), leukopenia, neutropenia, hemolytic anemia, GI intolerance, fever, headache, mucositis, hypokalemia	-First-line therapy in neutropenic patients with IC -Salvage therapy in IA	<40 kg: 4–5 mg/kg IV every 24 h >40 kg: 50–150 mg IV every 24 h

[a]Utilization is advised only in the neonatal population to avoid renal dysfunction; liposomal amphotericin is recommended in all other age groups

should be given to antifungal lock therapy, as an emerging body of literature demonstrates feasibility and efficacy [50].

Treatment should continue for at least 2 weeks following resolution of symptoms and negative culture results. In the case of hepatosplenic candidiasis, treatment should continue through resolution of abdominal lesions [49].

Though prophylaxis is recommended in certain adult populations [49], there are currently no recommendations for prophylaxis in pediatric patients. Utilization of validated clinical prediction tools in adult ICUs has been helpful for identifying at-risk patients [51]. Though a pediatric model was proposed, it failed validation in further studies [11, 27].

Treatment of Invasive Aspergillosis

During the past decade, there has been a notable increase in the development of antifungals effective against IA; however, only voriconazole, a second-generation triazole, and amphotericin B deoxycholate, a polyene and its lipid formulations, are FDA-approved in the United States for primary treatment. Though pediatric patients are treated with the same antifungals as adults, dosing varies and in some cases is not yet known, resulting in potential underdosing with consequent clinical failure. For example, voriconazole, a first-line treatment against IA, has a linear pharmacokinetic profile in children and nonlinear in adults. Moreover, high inter-patient variability has also been reported, making dosing recommendations difficult [48, 52]. Therapeutic drug monitoring is currently recommended, though notably, it is unclear if higher levels correlate to clinical efficacy. A rational approach suggests aiming for levels above the MIC of the organism (>0.5 mcg/mL) and below toxic levels [48].

Amphotericin B deoxycholate, and its lipid derivatives, is recommended as first-line treatment against IA when voriconazole cannot be administered [29]. The clinician should be mindful of the increased treatment response and survival benefits of voriconazole compared to amphotericin B when making this decision [53]. Amphotericin B can also be used as salvage therapy, with a preference for the lipid derivatives given higher tissue concentrations and decrease in nephrotoxicity [29, 48]. Echinocandins, individually or in combination, are an alternative for salvage therapy [29]. Combination therapy, currently without a sound evidence base but widely used, remains a debated topic with need for further clinical trials, specifically in pediatrics.

For patients at high risk for IA with prolonged neutropenia, prophylaxis is strongly recommended, with continued prophylaxis, while patients remain immunosuppressed. Options include posaconazole, voriconazole, and micafungin [29].

Empiric Therapy for PICU Patients

In those PICU patients with underlying malignancy or who have undergone HSCT, the recommendation for empiric antifungal therapy is clear,

and it is to start empiric echinocandin or liposomal amphotericin B when these high-risk patients remain febrile and neutropenic past 96 h into their antibiotic course [34].

It is the subset of patients without underlying malignancy but with significant risk factors that pose the greater diagnostic challenge. Given the available evidence to date, the authors recommend restricting empiric antifungal therapy to those patients with known risk factors (i.e., broad-spectrum antibiotics, prolonged neutropenia, presence of indwelling central line) with fever and SIRS/sepsis who fail to respond to broad-spectrum antibiotic therapy within 72 h. Given the high risk of *Candida* infection, an echinocandin would be the treatment of choice.

Take-Home Points

- Despite significant advances in diagnostic and therapeutic options, invasive fungal disease remains a major contributor to morbidity and mortality, particularly in PICU patients.
- The diagnosis of invasive fungal disease requires a high index of suspicion, and testing should be limited to those patients with known risk factors. Biomarkers, while promising, have yet to be widely validated in the pediatric population.
- Clinicians should be mindful of pharmacokinetic variation and dosing variability when implementing treatment in the pediatric population.

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Part VII

Endocrinologic Controversies

Corticosteroid Therapy for Septic Shock and Pediatric ARDS

16

Lauren Jacobs, Hector Wong, and Kusum Menon

Overview and Epidemiology of Sepsis

Despite efforts aimed at reducing the morbidity associated with pediatric sepsis, it remains a leading cause of pediatric intensive care admissions and carries a relatively high risk of mortality worldwide [1]. Pediatric sepsis rates have been increasing over time, with a large 2015 study reporting a worldwide point prevalence of 8.2% for severe sepsis, with significantly higher rates in Africa (23.1%) and South America (16.3%) [2]. The same study described a 24% overall mortality rate, rising to 41% in patients with malignancy and 48% in those with either solid organ or stem cell transplants. Other work estimates pediatric intensive care unit (PICU) mortality from sepsis ranging from 9% to 23% [3–5], with death most commonly secondary to refractory shock [6].

As sepsis remains a significant public health concern, the 2016 Surviving Sepsis Campaign reissued strong recommendations for rapid diagnosis and source control, early targeted antimicrobial therapy, and aggressive fluid resuscitation followed by initiation of vasoactive support should intravascular expansion fail to raise mean arterial blood pressure to targeted goals [7]. They offer a weak recommendation to trial intravenous hydrocortisone for patients remaining in septic shock despite institution of vasoactive medications. The following section will evaluate the evidence to support the routine use of corticosteroids for fluid and vasoactive refractory septic shock.

Case Example

A 2-year-old previously healthy female presents with 3 days of fever and decreased energy. On initial exam, temperature is 39.6 °C, heart rate is 180 beats/min, blood pressure is 70/30 mmHg, respiratory rate is 30 breaths/min, and oxygen saturation is 96% in room air. Extremities are cool and clammy and pulses are weak with capillary refill of 4 s. The patient appears listless with poor response to noxious stimuli. Laboratory studies reveal a total WBC of 21 K/μL with 85% neutrophils and 10% bands and lactic acid of 5.0 mmol/L. Blood and urine cultures are drawn, she is given broad-spectrum antibiotics, and 60 mL/kg of normal saline is rapidly infused. However, her vital signs and exam remain

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relatively unchanged. She is therefore given an additional 40 mL/kg of Ringer's lactate, started on epinephrine at 0.1 mcg/kg/min, and admitted to the PICU. In the PICU, a central venous catheter and arterial line are placed, and epinephrine is escalated to 0.3 mcg/kg/min with minimal improvement in blood pressure to 80/32 mmHg. Norepinephrine is added at 0.1 mcg/kg/min as the physician considers starting intravenous hydrocortisone.

Overview of Pathogenesis of Sepsis

Sepsis is an inherently heterogeneous syndrome, with any number of infectious stimuli triggering robust immunologic and inflammatory cascades. The activation of both the innate and adaptive immune systems results in an initial pro-inflammatory response mediated by the release of cytokines and small inflammatory molecules [8–11]. Although critical to stemming the infection, a hyperactive immune response can be paradoxically harmful, causing direct host damage and worsening the clinical course [12, 13].

Given this pathophysiology, it is proposed that corticosteroids could dampen host-mediated injury. The literature suggests vast immunologic variability from patient-to-patient, as well as fluctuations in immune function during an individual patient's course. There is evidence to support a multiphasic immunologic response during sepsis, characterized first by hyper-immunity, followed by hypo-immunity, and then either a return to baseline or persistent hypo-immunity with resultant secondary infection [14]. In the latter case, corticosteroids could be potentially detrimental.

In addition to concerns about the immunosuppressive properties of corticosteroids, there is a debate about their use as adrenal replacement therapy in the critically ill. Studies suggest that a subset of critically ill patients demonstrate critical illness-related corticosteroid insufficiency (CIRCI) [15–18], but a consensus definition of CIRCI has yet to emerge, with the 2017 guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine offering no opinion on how best to diagnose CIRCI – whether low total serum cortisol or an inadequate increase in cortisol level in response to synthetic adrenocorticotropic hormone (ACTH) should be considered the reference standard [18].

A few studies have attempted to quantify the frequency and impact of corticosteroid insufficiency in pediatric critical illness. The first, a small prospective single-center study conducted in the developing world, defined relative adrenal insufficiency as an incremental increase in cortisol of less than 9 g/dL after low-dose ACTH stimulation and found the prevalence of CIRCI to be 30% [19]. A larger prospective multicenter study conducted at tertiary care PICU's in Canada used the same definition of adrenal insufficiency and also reported 30% prevalence of CIRCI [17]. Patients in this study with CIRCI required more fluid boluses as well as higher doses and more days of catecholamine therapy. Interestingly, half of the study participants were tested on both the first and second days of admission. By the second day, the prevalence of corticosteroid insufficiency was down to 20%, with only 38% of patients with insufficiency on day 1 also being insufficient on day 2. Although the study assessed all critically ill patients, this observation also held true for the septic shock subgroup, implying that adrenal insufficiency in septic shock may be a transient, self-resolving phenomenon.

Corticosteroids are often proposed for septic shock due to their hemodynamic effects. Endogenous or exogenous cortisol contributes to maintenance of hemodynamic stability via several mechanisms. It exerts immediate non-genomic effects by decreasing reuptake of norepinephrine [20], as well as augmenting β-adrenergic receptor sensitivity in the heart and increasing calcium availability in myocardial and vascular smooth muscle cells [21], leading to increased myocardial contractility and vasoconstriction. Cortisol also exerts delayed effects (several hours) through its genomic actions [22], including inhibition of prostacyclin and nitric

oxide synthetase production leading to increased vascular tone [23], stimulation of intercellular adhesion factor from vascular smooth muscle with a resulting decrease in capillary leak [23], and increasing the number of β-adrenergic receptors in the heart, thereby increasing myocardial contractility [22]. Therefore, lack of sufficient cortisol at the cellular level may contribute to hemodynamic instability by limiting myocardial contractility while encouraging vasodilation and/or capillary leak syndrome [24, 25].

There are even further intricacies at the cellular level which likely influence a patient's response to corticosteroids. Endotypes are subclasses of diseases differentiated at the genomic level or by other biological processes. Using genome-wide expression profiling in septic pediatric patients, Wong et al. identified two distinct endotypes: A and B [26–28], which are displayed as gene expression mosaics in Fig. 16.1. They discovered 100 endotype-defining genes, corresponding to adaptive immunity and glucocorticoid receptor (GCR) signaling. The majority of these endotype-defining genes were repressed in endotype A as compared to B. When contrasted with endotype B, endotype A patients tended to be younger, had fewer PICU-free days, and had higher Pediatric Risk of Mortality (PRISM) scores, number of organ failures, and mortality [27]. After controlling for illness severity, comorbidities, and age, odds of mortality and complicated course (defined as continued failure of two or more organs at day 7 of illness) were both 2.7 times higher in endotype A patients (95% CI for mortality, 1.2–6.0; 95% CI for complicated course, 1.5–4.8) [28]. Furthermore, corticosteroid administration was associated with increased mortality among the endotype A patients [28].

Further work supports patient-to-patient variability in GCR gene expression. Quax et al. established that response to corticosteroids depends, in part, on functional polymorphisms in the GCR gene [29]. Cvijanovich et al. studied three functional GCR polymorphisms in pediatric septic shock patients, finding that patients who were homozygous for the wild-type allele

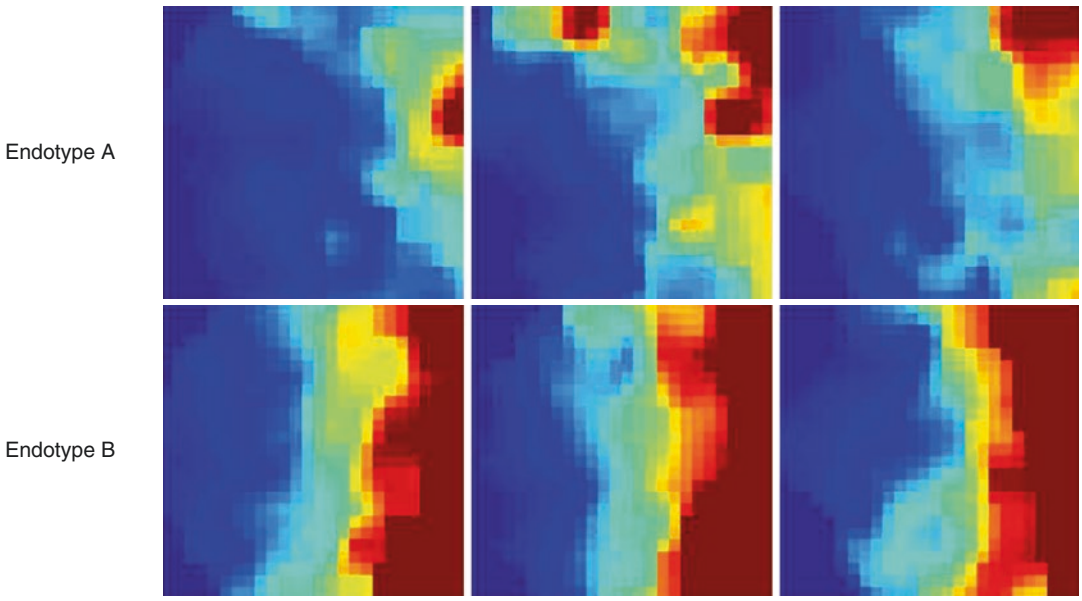

Fig. 16.1 Pediatric septic shock endotypes: The images are gene expression mosaics of the 100 endotype-defining genes corresponding to adaptive immunity and glucocorticoid receptor signaling. The degree of red intensity corresponds to increased gene expression, and the degree of blue intensity corresponds to decreased gene expression. Examples of three individual endotype A patients are shown in the upper panel, and examples of three individual endotype B patients are shown in the lower panel. See text for associations between endotype assignment and outcome and endotype assignment and response to corticosteroids

had a higher risk of complicated course if exposed to corticosteroids, even after adjusting for PRISM score [30]. In a prospective cohort study in critically ill children evaluating the relationship between GCR expression in peripheral white blood cells and illness severity, patients with cardiovascular failure, higher PRISM scores, and higher degree of organ failures all had significantly lower GCR expression in both CD4+ and CD8+ lymphocytes [31]. Thus, the heterogeneity of sepsis and the response to corticosteroids start at the genomic level. These intricacies make standardizing treatment strategies challenging.

In Support of Corticosteroids for Sepsis

The majority of evidence to support corticosteroid administration stems from the adult literature. In 2002, Annane et al. performed a placebo-controlled randomized double-blind study involving almost 300 adult patients with fluid-refractory septic shock [32]. Enrollment occurred within 8 h of diagnosis, excluding patients receiving etomidate in the prior 6 h. Subjects were randomized to either the placebo arm or the treatment arm, consisting of hydrocortisone 50 mg every 6 h and fludrocortisone 50 μg daily for 7 days. Seventy-seven percent of subjects had corticosteroid insufficiency, as diagnosed by a low-dose ACTH stimulation test. Compared to the placebo group, the corticosteroid group had a trend toward decreased 28-day mortality (OR, 0.65; 95% CI, 0.39–1.07) and ICU mortality (OR, 0.61; 95% CI, 0.37–1.02) and significantly faster cessation of vasopressor therapy (HR, 1.54; 95% CI, 1.10–2.16). Within the treatment arm, hydrocortisone conferred the greatest survival benefit among patients who failed to respond to an ACTH stimulation test. Additionally, there was no difference in adverse events between the groups.

Park et al. performed a retrospective analysis of adult patients receiving low-dose corticosteroids for septic shock to evaluate the relationship between survival and time to corticosteroid initiation [33]. The cohort was comprised of 178 severely ill patients, as evidenced by a high median Sequential Organ Failure Assessment (SOFA) score of 11, 70% mechanical ventilation rate, 33% renal replacement therapy rate, median vasopressor (norepinephrine or equivalent) dose of 0.5 μg/kg/minute at the time of corticosteroid initiation, and 44% 28-day mortality. Just over half of the subjects underwent a low-dose cortisol stimulation test. Within this subpopulation, 81% failed to respond. The median time to corticosteroid administration was 8.5 h, with multivariate analysis showing increased lag time to corticosteroid initiation associated with higher likelihood of mortality.

Most recently, Annane et al. published a follow-up trial evaluating the impact of hydrocortisone plus fludrocortisone therapy on mortality in over 1200 adults with septic shock [34]. Subjects in the treatment arm had lower mortality at 90 days (49% versus 43%, p-value 0.03) and 180 days (53% versus 47%, p-value 0.04), as well as at the time of ICU and hospital discharge. Subjects receiving study drugs also had a greater number of vasopressor-free (17 versus 15 days, p-value <0.001) and organ failure-free days (14 versus 12 days, p-value 0.003) within the first 28 days of enrollment. The latter findings are supported by a recent large randomized trial of 3800 adult subjects [35]. Subjects in the treatment arm exhibited shorter time to resolution of shock [median 3 days (IQR, 2–5 days) versus 4 days (IQR, 2–9 days); HR, 1.32 (95% CI, 1.23–1.41)] and duration of mechanical ventilation [median 6 days (IQR, 3–18 days) versus 7 days (IQR, 3–24 days); HR, 1.13 (95% CI, 1.05–1.22)].

There is a relative paucity of support for corticosteroid use in pediatric septic shock within the pediatric literature. A recent meta-analysis evaluated the findings of eight randomized controlled trials (RCT) of corticosteroids in pediatric shock [36]. The analysis revealed differing corticosteroid protocols, small sample sizes (n = 22–98), and a lack of generalizability to tertiary care populations as many studies were conducted in patients with dengue hemorrhagic shock. Two studies showed statistically significant mortality reduction with corticosteroid administration, but

the pooled meta-analysis results did not support that finding. No studies to date have defined a subpopulation of septic shock patients who may benefit from corticosteroid administration.

Enrichment strategies may better identify which children with septic shock are most likely to benefit from corticosteroids. Enrichment refers to the selection of patients in whom an intervention is more likely to be beneficial, compared to unselected patients. Although initially promising, the corticotropin stimulation test, regardless of dose used, does not appear to be a sufficiently robust enrichment strategy to select patients most likely to benefit from corticosteroids [32, 37].

A recent post hoc analysis combined prognostic and predictive enrichment to identify a subgroup of children with septic shock more likely to benefit from corticosteroids [38]. The pediatric sepsis biomarker risk model (PERSEVERE) was used for prognostic enrichment by assigning a baseline mortality probability [39–41]. Predictive enrichment was carried out by assigning patients to endotype A or B, as described above. Corticosteroids were associated with a more than tenfold reduction in the rate of complicated course among endotype B subjects with an intermediate to high PERSEVERE-based mortality risk [38]. Endotype B subjects with low PERSEVERE-based mortality risk and all endotype A subjects, regardless of baseline mortality risk, received no such benefit [38].

Against Corticosteroids for Sepsis

The oft-cited counterargument to the initial findings of Annane et al. [32] is the 2008 work of Sprung et al. [37]. This randomized, double-blind placebo-controlled study included nearly 500 adult patients in septic shock. Subjects were eligible for enrollment up to 72 h after diagnosis and then randomized to either placebo or treatment. Of note, exposure to etomidate was not an exclusion criterion, and nearly 20% of subjects had received etomidate prior to enrollment. The treatment group received hydrocortisone 50 mg every 6 h for 5 days, followed by a taper over an additional 6 days. Following a stimulation test, low cortisol levels were present in 47% of all subjects and 60% of patients exposed to etomidate. Regardless of baseline adrenal status, there was no survival benefit with corticosteroids. The corticosteroid group, and especially those with no response to an ACTH stimulation test, did have a significantly quicker resolution of shock (cessation of vasopressor requirement); although the proportion of patients achieving shock reversal was no different. Additionally there were higher rates of superinfections among subjects in the treatment arm, raising the question of safety. The most recent 3800 patient trial [35] also did not demonstrate a survival benefit with hydrocortisone administration (28% mortality treatment arm versus 29% placebo) (OR, 0.95; 95% CI, 0.82–1.1). Notably, both of these trials enrolled patients up to 72 h post-diagnosis, whereas Annane's studies required enrollment within 24 h, suggesting that time to initiation of corticosteroids may play a role in corticosteroid responsiveness.

Pediatric-specific data regarding the role of corticosteroids in septic shock are substantially less robust. A meta-analysis of randomized controlled pediatric studies conducted in developing countries showed no difference in mortality between placebo and corticosteroid groups [36]. Atkinson et al. retrospectively evaluated the relationship between corticosteroids and mortality in almost 500 pediatric patients with septic shock [42]. Initial analysis revealed an association between corticosteroid use and increased mortality (OR, 2.3; 95% CI, 1.3–4), but patients who received corticosteroids had higher PRISM scores, more organ dysfunction, and increased vasoactive support needs. The authors then employed prognostic enrichment, stratifying patients by PRISM score and PERSEVERE-derived mortality risk to elucidate which, if any, groups would benefit from corticosteroids. Neither PERSEVERE- nor PRISM-based stratification yielded any evidence of survival benefit associated with corticosteroid usage, regardless of degree of risk. Additionally, an observational study using data from the RESOLVE trial (double-blind placebo-controlled trial evaluating activated protein C for pediatric sepsis) found a 41%

incidence of corticosteroid administration among 477 subjects, with multivariate analysis determining corticosteroids offered no survival benefit [43].

Beyond potentially incurring little survival benefit, there is the larger concern that corticosteroids could actually be harmful. At the genomic level, pediatric subjects with septic shock display early repression of genes associated with the innate immune system [44]. Compared to corticosteroid-naïve septic patients, those exposed to corticosteroids have an even higher degree of repression of those genes, potentially compromising their ability to fight infection [44]. A retrospective cohort study evaluated the association between corticosteroid use and mortality using the Pediatric Health Information System (PHIS) database [45]. The authors gathered data from 27 hospitals, capturing almost 6700 pediatric patients (≤ 17 years) with severe sepsis, defined as presence of infection with the need for mechanical ventilation and vasoactive medications. Forty-eight percent of patients received systemic corticosteroids, and the use of corticosteroids was significantly associated with mortality (OR, 1.9; 95% CI, 1.7–2.2). However, the study included a population with a 24% mortality rate, and did not control for illness severity. An additional retrospective study of 70 children with fluid-refractory, catecholamine-dependent septic shock found that even after adjustment for PRISM score, corticosteroid therapy was independently associated with mortality [46].

Summary of Corticosteroids for Sepsis

Currently, there is only marginal evidence that corticosteroids improve mortality or morbidity associated with pediatric septic shock. Pediatrics is bereft of a large, randomized controlled trial, which is absolutely essential to furthering our understanding of the response to corticosteroids in children. To that end, Menon et al. recently conducted a randomized, double-blind, placebo-controlled feasibility study involving 49 pediatric patients in Canada [47]. Septic patients were enrolled within 8 h of diagnosis. If randomized to the treatment arm, patients received hydrocortisone 2 mg/kg IV bolus, followed by hydrocortisone 1 mg/kg every 6 h until they no longer required fluid boluses or increased vasoactive support. This study demonstrated that a large, randomized, controlled pediatric corticosteroid trial is feasible, and although not powered for a robust analysis, there were no significant differences in PICU mortality, time to cessation of vasoactive agents, fluid requirements, or length of stay between groups, even after controlling for illness severity.

In summary, corticosteroids may be helpful in targeted populations, but unless these populations can be identified in a rapid, cost-efficient manner, there remains only minimal clinical utility.

Overview and Epidemiology of Acute Respiratory Distress Syndrome (ARDS)

In an effort to "speak the same medical language," practitioners sought to redefine the acute respiratory distress syndrome (ARDS) in order to facilitate more accurate diagnosis, risk stratification, and research. The Berlin definition, published in 2012, standardized the diagnosis of ARDS in adults and stratified it based on severity of oxygenation impairment (Table 16.1) [48]. Extrapolating this definition to pediatric patients proved challenging, though, as invasive arterial monitoring is less common. Therefore, in 2015, the pediatric acute lung injury consensus conference (PALICC) exacted pediatric-specific modifications to the definition of ARDS (Table 16.1) [49, 50].

Pediatric ARDS (PARDS) and acute lung injury (ALI) are quite prevalent, with 9–16 per 1000 PICU admissions attributable to either of these diagnoses [51]. Other epidemiologic studies suggest an incidence of 2–13 per 100,000 person-years [49, 52–55]. Similar to adults, the etiology of PARDS is most commonly pneumonia, non-pulmonary sepsis, aspiration, and trauma [52, 54–58]. Recent studies suggest

Table 16.1 Comparison of diagnostic criteria for pediatric and adult ARDS [48–50]

	Adult ARDS			Pediatric ARDS			
Timing	Within 7 days of known insult			Within 7 days of known insult			
Radiographic findings	New bilateral opacities on chest x-ray or CT scan consistent with bilateral pulmonary edema			New infiltrate on chest imaging Consistent with pulmonary parenchymal illness			
Oxygenation	**Mild**	**Moderate**	**Severe**	Noninvasive MV	Invasive MV **Mild**	Invasive MV **Moderate**	Invasive MV **Severe**
	PaO_2/FiO_2 >200 ≤ 300 With PEEP ≥5	PaO_2/FiO_2 > 100 ≤ 200 With PEEP ≥5	≤ 100 With PEEP ≥5	CPAP ≥5 PaO_2/FiO_2 ≤ 300 SpO_2/FiO_2 ≤ 24	4 ≤ OI ≤ 8 5 ≤ OSI ≤ 7.5	8 ≤ OI ≤ 16 7.5 ≤ OSI ≤ 12.3	OI ≥ 16 OSI ≥ 12.3
Exclusion criteria	Respiratory failure explained by heart failure or fluid overload			Perinatal-related lung injury			

mortality ranges from 13% to 38% [52, 54–56, 59–65] and up to 60–70% in immunocompromised pediatric patients [66, 67]. Higher mortality is also associated with degree of hypoxemia [68, 69], higher PRISM III score [70], larger tidal volume [70], multi-organ dysfunction [71], and non-pulmonary sepsis [52]. As management continues to evolve, outcomes have improved, with overall mortality decreasing over the past decade [51].

The remainder of this section will evaluate the evidence to support the routine use of corticosteroids for PARDS.

Case Example

A 7-year-old boy presents to the emergency room with 1 week of cough and rhinorrhea and 3 days of worsening fever and fatigue. Vital signs include temperature of 38.7 degrees Celsius, heart rate of 110 beats/min, blood pressure of 100/60 mmHg, respiratory rate of 24 breaths/min, and oxygen saturation of 90% in room air. On exam, he appears tired and diaphoretic, and lung exam is notable for decreased aeration and faint crackles in the right lower and middle lobes. Chest x-ray reveals right-sided lobar consolidation with an associated parapneumonic effusion. The patient is placed on 4 L/min of oxygen by nasal cannula, given a normal saline bolus, started on intravenous ceftriaxone and vancomycin, and admitted to the PICU. On arrival, his breathing becomes more labored, so noninvasive positive pressure ventilation is started, and a right-sided pigtail catheter is placed, which drains 300 mL of pus. Within 12 h, his work of breathing worsens, and his oxygen saturation is 91% on bi-level positive airway pressure (BiPAP), with an inspiratory pressure of 24 cm H_2O, expiratory pressure of 12 cm H_2O, and fraction of inspired oxygen (FiO_2) of 1.0. Chest x-ray reveals a smaller effusion, but with new bilateral multifocal opacities. Given his degree of hypoxemic respiratory failure, the patient is endotracheally intubated and mechanical ventilation is initiated. Initial settings on synchronized intermittent mandatory ventilation (SIMV), with pressure-regulated volume control (PRVC), are as follows: positive end expiratory pressure (PEEP) 12 cmH_2O, tidal volume 7 mL/kg, pressure support 10 cm H_2O, respiratory rate 16 breaths/min, inspiratory time 0.9 s, and FiO_2 1.0, yielding peak inspiratory pressure of 35 cm H_2O and mean airway pressure of 20 cm H_2O. The clinical team begins discussing possible adjunctive therapies that could be helpful to this patient.

Overview of Pathogenesis of ARDS

The pathologic hallmarks of ARDS are interstitial and alveolar edema, endothelial and epithelial disruption, and heavy cellular infiltrate [72]. As with sepsis, there is dysregulation of the immune system which furthers lung injury, with studies showing that the degree of inflammation corresponds with illness severity and worse outcome [73, 74]. Alveolar cell death and increased vascular permeability result from this inflammatory response, followed by pulmonary fibroblast activation and hyaline membrane formation [58, 72, 75]. This primary state begets either a secondary inflammatory response with fibroproliferation or recovery with cellular resorption [57, 72]. Development of fibrosis is also associated with worse outcome [76, 77]. Compared to a static lung in adults, pediatric lungs are still maturing and therefore respond differently to injury [78]. Additionally, the pediatric immune system is not fully constituted, so the inflammatory response in PARDS is inherently different than that in adult ARDS [78]. In support of this notion, sepsis is the leading risk factor for development of adult ARDS, compared with pneumonia in PARDS [79, 80].

Despite a general understanding of the pathophysiology of ARDS, there is still much unknown about what leads to phenotypic variation. For example, two patients may present with pneumonia from the same organism, but only one develops ARDS, while the other improves. Once ARDS is diagnosed, there may be genetic differences that place certain patients at higher risk of fibrosis. Indeed, nuclear factor-κB (NF-κB), a pro-inflammatory transcription factor, and glucocorticoid receptor α (GCRα), a receptor activated by glucocorticoids, show differential activity in adult patients with ARDS whom either improve or fail to improve [81]. Subjects who improve have lower NF-κB binding (with decreased transcription of pro-inflammatory molecules) and increased GCRα activity [81]. Other adult studies show differential expression in metabolites of fatty acid oxidation and ethanol degradation, as well as proteins involved in fibrosis, in the bronchoalveolar lavage (BAL) fluid of ARDS survivors and non-survivors [82, 83].

Calfee et al. employed latent class analysis, a statistical method that models data with the assumption that a given dataset inherently has subgroups, to better understand these phenotypic variations [84]. The authors identified two distinct subphenotypes of ARDS in adult patients: phenotype 1, which was more commonly associated with trauma and less likely related to sepsis, and phenotype 2, which displayed higher levels of inflammatory cytokines, more acidosis and shock, higher rates of mechanical ventilation, increased vasoactive medication use, and higher mortality rates. Of note, phenotype delineation was independent of both ARDS and illness severity. Another adult study evaluated the cellular differences between direct ARDS (e.g., pneumonia, aspiration) and indirect ARDS (e.g., non-pulmonary-related sepsis, burns, trauma) [85]. Direct ARDS subjects had higher levels of biomarkers of lung epithelial injury but lower levels of markers of endothelial injury. Subjects with indirect ARDS had higher vasopressor use and illness severity. These studies identify subgroups of patients who have discernibly different patterns of injury and degree of inflammation, suggesting that identification of an individual's phenotype and a more personalized approach are feasible and may be necessary for optimization of therapy.

In Support of Corticosteroids for ARDS

The majority of evidence in support of corticosteroid use stems from adult studies. Several small studies in the early 1990s demonstrated clinical improvement of ARDS with corticosteroids [86–89], leading the way for the prospective, randomized, double-blind placebo-controlled study conducted by Meduri and colleagues evaluating the safety and efficacy of a prolonged methylprednisolone course for adults with unresolved ARDS [90]. Subjects (n = 24) were enrolled if they met all ARDS consensus criteria, had been mechanically ventilated for ≥7 days, had ARDS for <3 weeks, were not already receiving corticosteroids, and had not developed a new ventilator-

associated pneumonia. Subjects were randomized to receive either placebo or treatment, consisting of 2 mg/kg methylprednisolone load followed by an additional 32 days of tapered dosing. If no clinical improvement was apparent by day 10 of therapy, subjects were crossed over into the opposite arm. Those treated with corticosteroids showed improved PaO_2/FiO_2, decreased lung injury and mean pulmonary artery pressure by day 5, and improved multi-organ dysfunction by day 7. All patients in the initial treatment arm showed some improvement by day 10, but among subjects receiving placebo, two died, and four failed to improve and were thus crossed over to the corticosteroid arm. Of the crossover cohort, only one survived. Compared with placebo, subjects receiving corticosteroids had significantly shorter duration of mechanical ventilation, improved multi-organ dysfunction, and decreased mortality, even after controlling for confounding variables. In addition, all the deaths in the placebo group were related to unremitting ARDS, in contrast to the two deaths in the treatment group which were not directly related to ARDS and occurred following ICU discharge. There was no difference in adverse events between the groups. These results are compelling but must be interpreted with caution given the very small sample size.

An interesting finding of the Meduri study was that institution of corticosteroids after 10 days provided no benefit. This prompted a larger adult study, published in 2007, looking at the effects of corticosteroid initiation within 72 h of the diagnosis of ARDS [91]. The treatment protocol involved lower doses (i.e., maximum of 1 mg/kg methylprednisolone per day) and shorter duration (i.e. 28 days as compared to 32). Compared to the placebo group, subjects in the treatment group had significant improvement in lung injury, PaO_2/FiO_2 ratio, multi-organ dysfunction, and C-reactive protein (CRP) and were more likely to be breathing independently by day 7. The rate of adverse events was similar between groups. The authors suggest that corticosteroids improve ARDS by downregulating systemic inflammation, as evidenced by decreased CRP and multi-organ dysfunction score.

A 2016 meta-analysis of individual patient data (IPD) compiled results from 322 adult patients drawn from 4 randomized controlled trials [92]. There was variability in both corticosteroid dosing and treatment duration across these studies. Subjects receiving corticosteroids were more likely to be successfully extubated, had a shorter time to extubation, and had a significantly lower hospital mortality rate, without an increased occurrence of adverse events.

Pediatric research is very limited. Most studies have been retrospective and observational, and the few prospective, randomized trials have been small and generally not favorable. One notable double-blind, placebo-controlled randomized trial examined differences in both clinical outcomes and biomarkers related to PARDS pathogenesis in patients relegated to either treatment or placebo [93]. Eighteen patients received placebo, and seventeen patients were given a 2 mg/kg methylprednisolone load within 72 h of ARDS diagnosis, followed by a tapered continuous infusion over 14 days. At the biological level, matrix metalloproteinase-8 (MMP-8, a marker of neutrophil activity) decreased in the corticosteroid but not placebo group, and soluble intercellular adhesion molecule-1 (sICAM-1, a marker of endothelial injury) increased in the placebo but not the corticosteroid group, with no differences in the levels of biomarkers of coagulation or epithelial injury. In terms of clinical outcomes, there were no differences in duration of mechanical ventilation, ICU or hospital length of stay, or mortality between groups. However, patients receiving corticosteroids had improved PaO_2/FiO_2 ratio by day 8 and were less likely to require supplemental oxygen at the time of transfer out of the ICU.

Corticosteroids may ameliorate lung injury, thereby improving compliance and oxygenation. But we would argue that temporal, non-sustained clinical improvement is not proof of corticosteroid efficacy; rather, the true metrics of utility ought to be survival and long-term morbidity, neither of which shows demonstrable improvement in any study other than Meduri's original work. There remains insufficient evidence to support the routine prescription of corticosteroids for PARDS.

Against Corticosteroids for ARDS

A 2006 prospective double-blind study randomized 180 adult patients to either placebo or treatment, consisting of a 2 mg/kg methylprednisolone load followed by a corticosteroid taper of at least 21 days [94]. Patients could be enrolled between 7 and 28 days from diagnosis of ARDS. Similar to other studies, the treatment group had significantly higher ventilator-free and ICU-free days at day 28 and shorter time to extubation. But there were two novel observations of concern. First, patients in the corticosteroid arm were significantly more likely to require re-intubation. Second, there was no survival benefit seen with corticosteroids, and for those subjects enrolled beyond day fourteen of ARDS onset, there was a significantly higher mortality rate among the treatment group. These results – a lack of trend toward survival benefit, and possibly even harmful effects if instituted later in the clinical course – are in opposition to other studies.

A retrospective study analyzing a large (n = 607) cohort of adults with ARDS related to H1N1 conferred similar findings [95]. Forty-six percent of patients received corticosteroids, for a median of 7 days, with initiation at a median of 0 days from the onset of critical illness and 1 day from intubation. Univariate analysis revealed that subjects who received corticosteroids had higher hospital mortality and fewer ventilator-free and ICU-free days at day 28 of illness. After propensity matching, corticosteroid exposure was no longer independently associated with mortality risk (OR, 1.52; CI, 0.9–2.58), but they incurred no survival benefit.

Results from pediatric studies are relatively similar. Yehya et al. conducted a prospective observational study examining outcomes in 283 pediatric patients with ARDS and either ≤24 h of corticosteroid exposure (typically a peri-extubation dose) or >24 h of corticosteroid exposure [96]. Both multivariate and propensity-matched analyses revealed that longer corticosteroid exposure and total dose were independently associated with fewer ventilator-free days and longer duration of mechanical ventilation. The unadjusted analysis found an association between corticosteroid use and mortality, but this relationship did not persist in multiple regression analysis. Interestingly, the authors evaluated subgroups of patients they postulated would have greater benefit from corticosteroids: immunocompromised patients (with likely prior corticosteroid exposure), patients with reactive airway disease or chronic lung disease, patients with shock requiring vasoactive medications, and patients with multi-organ dysfunction (≥3 non-pulmonary organ failures). Corticosteroids provided no survival benefit in any of these groups. Of note, this study differs from the randomized adult trials in that more patients received hydrocortisone than methylprednisolone, and some patients were prescribed dexamethasone or a combination of more than one corticosteroid.

Drago et al. published a pediatric randomized placebo-controlled pilot study in 2015 that mirrors prior adult studies [97]. Thirty-five patients were randomized into the placebo or treatment arm within 72 h of PARDS diagnosis. The therapeutic course consisted of a 2 mg/kg methylprednisolone load followed by a tapered continuous infusion over an additional 14 days. Despite higher illness severity in the placebo group, there was no difference in the duration of mechanical ventilation, ventilator-free days, oxygenation index, and PICU or hospital length of stay. As this was only a pilot study to evaluate feasibility of future larger studies, the authors did not discuss mortality risk, nor did they perform multivariate analyses.

Summary of Corticosteroids for ARDS

Due to a paucity of pediatric-specific evidence proving corticosteroids are beneficial in PARDS, clinicians are often forced to apply adult data and protocols to children. Despite the disparate results on the utility of corticosteroids in even large adult trials, pediatric intensivists are ready prescribers, with upward of 60% of patients receiving corticosteroids for PARDS [52, 61, 98].

Some would argue the benefit of corticosteroids hinges on the timing of initiation. Early ini-

tiation could temper the inflammatory response, but if fibroproliferative changes have ensued, the patient has potentially reached the "point of no return." The results of the H1N1 adult study and the available pediatric studies are antithetical to that notion, as even early institution of corticosteroids failed to decrease mortality risk [95–97]. Others might contend that given the robust heterogeneity of this disease process, it is imperative to identify patients most likely to benefit from corticosteroids. Even though Yehya et al. [96] showed no improvement in certain higher-risk subgroups, perhaps the identification and therefore stratification of patients must occur at the genomic level. Recently, the PERSEVERE biomarkers were adapted to estimate the risk of mortality among children with PARDS [99], offering a new approach to better select high-risk patients and target research toward these populations.

In summary, there is a lack of evidence that corticosteroids improve clinical course or provides survival benefit for pediatric acute respiratory distress syndrome. Early initiation of corticosteroids appears unassociated with an increased likelihood of adverse events, while late initiation is likely futile and, at the very worst, harmful. But to suggest that clinicians should routinely employ corticosteroids for early PARDS because it is non-injurious and has theoretical benefits overlooks the role that genotypic and phenotypic variations play in this disease process – an avenue which researchers are just starting to explore.

Conclusions and Future Directions

Despite the advances made in the field of pediatric critical care, investigation into the role of corticosteroids for both sepsis and ARDS is in its relative infancy. Adult studies for both disease processes are discrepant, and there is no definitive pediatric evidence to support the routine use of corticosteroids in either case. Future directions for studying corticosteroid use in these conditions should be focused in two realms. Firstly, bench and translational research is needed to better identify which subgroups of patients would benefit from corticosteroids. Secondly, large, randomized clinical trials must be conducted in pediatric populations, with an emphasis on the subgroups with purported greater benefit. Until further proof of both benefit and a lack of harm exists, pediatric intensivists should practice caution when prescribing corticosteroids for sepsis or ARDS.

Take-Home Bullet Points

- Pediatric sepsis and pediatric acute respiratory distress syndrome (PARDS) are heterogeneous disease processes.
- Sepsis is increasingly prevalent with a relatively high mortality rate among children in ICUs.
- PARDS has a high rate of ICU mortality, up to 70% in immunocompromised patients.
- There is a paucity of pediatric research evaluating the role of corticosteroids in sepsis and ARDS.
- Adult studies on corticosteroid use in both sepsis and ARDS often report discrepant results, and cannot be extrapolated to pediatric populations.
- Based on the available literature, there is a lack of evidence to support the routine use of corticosteroids for pediatric sepsis or ARDS.
- Further research is needed to identify subphenotypes which would benefit from corticosteroids.
- Large prospective, randomized, double-blind placebo-controlled pediatric trials are needed to evaluate the efficacy and safety of corticosteroids.

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Management of Diabetic Ketoacidosis

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Laura Kitzmiller, Courtney Frye, and Jeff Clark

Scenario

A 12-year-old girl with type I diabetes mellitus is brought to the emergency department with 12-h history of abdominal pain and vomiting. She had been previously well but this morning began throwing up and became less interactive. She denies other symptoms including fever. Her mother states that her blood sugar has been under good control, but recently she has been allowing her daughter more responsibility in monitoring her diet and blood sugar. The patient denies missing any insulin or deviating from her prescribed diet. On exam, she is sleepy but arousable and appropriately interactive. She is tachypneic and hyperpneic with labored breathing, and she is mildly dyspneic. Her heart rate is 160 bpm, RR is 34 per minute, BP is 128/63 mmHg, and SpO_2 is 97% breathing room air. Her peripheral perfusion is diminished, and her extremities are cool. Her oral mucosa appears dry. Her lungs are clear, and her cardiac exam is unremarkable. Her abdomen is mildly diffusely tender without rebound or guarding. Her pupils are 4 mm and reactive and she does not have focal neurologic deficits.

Introduction

Diabetes is the most common endocrine disorder in the pediatric population [1]. The estimated incidence of diabetes, both type 1 and type 2, in children in the United States is 24.3 per 100,000 children. A frequent complication of diabetes is diabetic ketoacidosis (DKA), which results from a relative or absolute insulin deficiency. This is accompanied by a concomitant increase in counter-regulatory hormones and is often triggered by infections, trauma, or poor compliance with a home insulin regimen [2, 3]. DKA, although preventable, remains the leading cause of morbidity and mortality among those with type 1 diabetes, the mortality rate ranging anywhere from 0.15% to 0.30% [3–5]. DKA also accounts for about 100,000 hospital

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admissions each year [6]. Patients with both type 1 and type 2 diabetes are at risk for developing DKA [7]; and an estimated 15–70% of patients with diabetes will develop DKA at some time in their life [8].

Risk factors for developing DKA include those with newly diagnosed diabetes, very young children, lower socioeconomic background, poor compliance, and adolescent girls [8]. Timely and appropriate diagnosis and management of DKA is critical, as each episode can be life-threatening. The highest mortality occurs in association with cerebral edema (CE), which occurs in only about 1% of DKA episodes but can account for 50–60% of diabetes-related deaths in children [5]. In addition, life-threatening metabolic and electrolyte abnormalities can occur in DKA. However, little data exist as to optimum management of these complications, and significant controversy exists as to the exact mechanisms and ideal management of each. In part due to this lack of data, it is important to have a strong working knowledge on the pathophysiology and management of DKA.

Her bedside blood glucose test is above the upper limit of detection. She has a capillary blood gas that shows the following: pH 6.9, PCO_2 13 torr, and bicarbonate 7 mEq/L. Her urinalysis shows a specific gravity of greater than 1.030, ketones of "high," and glucose of "high." Her serum glucose is found to be 797 mg/dL.

Pathophysiology and Clinical Manifestations

DKA is defined as a blood glucose concentration greater than 200 mg/dL (11 mmol/L), ketonuria/ketonemia, and acidosis with a pH less than 7.3 [2, 8]. The primary abnormality is caused by a relative or absolute insulin deficiency. Hyperglycemia results from this as well as increased gluconeogenesis, glycogenolysis, and poor peripheral glucose utilization. This lack of adequate intracellular glucose leads to ineffective energy production and cellular metabolic dysfunction. An osmotic diuresis ensues as serum glucose levels exceed the renal threshold for glucose reabsorption (180 mg/dL in the healthy kidney). This diuresis causes both dehydration and electrolyte abnormalities. Counter-regulatory hormones including glucagon, catecholamines, and cortisol are produced, which can worsen acidosis and dehydration. These hormones contribute to the metabolic dysfunction by increasing hyperglycemia by augmenting hepatic glucose production and decreasing peripheral glucose uptake from the serum. The catecholamines also promote lipolysis and the production of ketones by the activation of hepatic beta-oxidation of free fatty acids to form ketone bodies. This accumulation of ketones leads to the anion gap metabolic acidosis seen in DKA [8].

There are several significant electrolyte abnormalities that occur in DKA. Patients with DKA present with a total body deficiency of both potassium and phosphate as both intracellular ions are transferred from inside the cell into the serum in exchange for a hydrogen ion; the exchanged potassium and phosphate are then excreted in the urine. It is therefore recommended to replace both of these electrolytes during treatment for DKA [9].

Hyperglycemia increases serum osmolarity causing flux of water into the extracellular space and leading to dilutional hyponatremia [10]. Calculation of undiluted sodium concentrations can help in the estimation of dehydration and metabolic dysfunction. The relationship that sodium is lowered by 1.6 mEq/L for each 100 mg/dL rise in glucose greater than 100 mg/dL helps estimate undiluted serum sodium concentrations that should result once hyperglycemia resolves [11]. If a normal or high sodium is observed, this is suggestive of more severe dehydration [8]. Sodium replacement via intravenous fluids should be initiated at the onset of DKA therapy. The serum sodium should increase as the serum glucose decreases. Of note, if the serum sodium levels do not increase with therapy, this may be a potential sign of imminent cerebral edema [9].

The clinical presentation of diabetes and DKA is well-described; symptoms include polyuria, polydipsia, and weight loss. DKA often presents with a history of these symptoms (in a child who has not been previously diagnosed with diabetes) in addition to symptoms of abdominal pain,

Table 17.1 Risk factors for the development of cerebral edema in diabetic ketoacidosis

New-onset diabetes mellitus
Age younger than 5 years
Lower pH at presentation
Lower bicarbonate concentration at presentation
Higher blood urea concentration at presentation

dehydration, hyperventilation, and altered mental status. Physical exam findings often include tachycardia, poor capillary refill, dry mucus membranes, poor skin turgor, tachypnea with Kussmaul breathing, and altered mental status.

Cerebral edema in the setting of pediatric DKA is a rare but life-threatening complication, and risk factors associated with development of edema are listed in Table 17.1. Although its incidence is about 1%, it is responsible for the majority of deaths and poor neurologic outcomes of patients with DKA [4]. Signs and symptoms include headache, worsening mental status, incontinence, relative bradycardia, and focal neurologic signs such as pupillary asymmetry. Signs of cerebral edema must be identified quickly, and management initiated to prevent neurologic injury or death. The mechanism of edema is thought to be multifactorial. Cytotoxic or cellular edema may exist, and mechanisms that lead to this may include metabolic failure of neurons or blood-brain barrier (BBB) cells, ischemia due to underperfusion of the brain from dehydration, severe acidosis, severe hyperventilation with cerebral vasoconstriction, and possibly neuroinflammation [12]. However, some studies suggest that vasogenic edema exists, possibly due to loss of cerebrovascular autoregulation or failure of blood-brain barrier cells [13, 14]. The distinction potentially has clinical significance in that preventative therapies that allow manipulation of cerebral blood flow and volume may be beneficial in the setting of one, but not the other. As an example, does osmotherapy, which is a common therapy for cerebral edema, worsen vasogenic edema by increasing circulating volume or increasing delivery of osmotic substances across a permeable blood-brain barrier? In the setting of DKA, the answer is not known.

Table 17.2 Initial lab values for clinical scenario

Serum sodium	132 mEq/L
Serum potassium	6.1 mEq/L
Serum chloride	101 mEq/L
Serum bicarbonate	8 mEq/L
Blood urea nitrogen	22 mg/dL
Plasma creatinine	0.8 mg/dL
Serum calcium	10.6 mg/dL
Serum magnesium	1.5 mg/dL
Serum phosphorus	5.1 mg/dL
B-Hydroxybutyrate	4 mmol/L

In addition to cerebral edema, additional treatable causes of encephalopathy need to be evaluated. Stores of water-soluble vitamins can be quickly depleted in the setting of anorexia and osmotic diuresis such as occurs with DKA. Thiamine deficiency has been described in the setting of diabetes and DKA in children and can present with acute encephalopathy [15, 16]. Thiamine is a critical cofactor in carbohydrate metabolism. The mechanism for encephalopathy with acute depletion is not as well understood as that with chronic thiamine deficiency (e.g., Wernicke's encephalopathy) but may be related to loss of blood-brain barrier function, cerebral edema, or decreased in production of excitatory neurotransmitters [17]. Although testing for thiamine deficiency is not routine and blood levels that correlate with clinical symptoms are not well established, supplementation is relatively easy and may prove beneficial when other causes of encephalopathy have been ruled out.

The remainder of her lab work has returned and is shown in Table 17.2. *The patient receives a bolus of normal saline followed by the initiation of an insulin infusion at 0.1 U/kg/h. She is placed on IV fluids using 0.45% NS at a rate to include maintenance plus correct for 10% dehydration over 24 h. Three hours later, she is still tachycardic with HR 140. Her perfusion is improved but her respiratory effort is unchanged. She is more somnolent and is difficult to arouse. She will awaken and answer yes and no appropriately but is otherwise unresponsive to voice or tactile stimulation. She does withdraw appropriately to pain. Her pupils are now 7 mm and reactive. Her bedside glucose testing is now 280 mg/dL.*

Management of DKA

The initial management of severe diabetic ketoacidosis involves the re-establishment of adequate circulating volume, initiating insulin therapy in order to treat hyperglycemia and improve ketoacidosis and correcting electrolyte imbalances [3]. Necessary baseline lab work for suspected DKA includes serum blood glucose, blood gas analysis, urinalysis, urinary and/or plasma ketones, serum electrolytes, renal function, calcium, phosphate, and often a CBC. Lab work often reveals hyperglycemia, hyponatremia, hypokalemia, hypophosphatemia, anion gap metabolic acidosis, low bicarbonate, and ketonuria/ketonemia [3, 8]. In addition, management of other complications as they arise often begins in the initial phase of treatment.

Establishing adequate intravascular volume is paramount in the initial management of DKA. Although dehydration due to osmotic diuresis is expected, it can easily be overestimated. The increase in extracellular osmolarity causes shifting of fluid from the intracellular to extracellular spaces, which can cause skin turgor to appear worse than expected for the degree of dehydration. In addition, Kussmaul respirations that accompany significant metabolic acidosis may cause mucosal surfaces to appear excessively dry. Tachycardia is standard for patients in DKA, but hypotension as a sign of severe dehydration is rare, in part due to the increase in serum osmolarity and relative sparing of dehydration of the intravascular space. Studies evaluating the degree of dehydration in pediatric DKA show that most children with severe DKA are not more than 6% dehydrated [18]. Appropriate estimation of dehydration is potentially important as the total volume and type of fluid administered potentially affect the likelihood and degree of CE formation. Volume expansion is often necessary in the initial stages of treatment, but judicious administration is advised. Often a single 10 mL/kg or 20 mL/kg bolus is adequate to establish adequate circulating volume, allow adequate delivery of oxygen and insulin therapy, and treat and/or prevent lactic acidosis. Ongoing fluid administration is aimed at correcting dehydration over 24–48 h and keeping up with ongoing losses such as osmotic diuresis. This is generally done using isotonic IV fluids such as 0.9% saline.

Improvement in acidosis and administration of insulin both will lower serum potassium. Potassium supplementation should be added to IV fluids once adequate renal function has been established and serum potassium levels fall below 5.0 mEq/L. In addition, dextrose is often added once serum glucose levels fall below 200–300 mg/dL, to prevent hypoglycemia in the setting of continued insulin therapy. This is preferable to weaning insulin in order to promote ketone metabolism. Although many of the tenets of treatment are widely accepted, there continue to exist a few controversies regarding several aspects of DKA treatment.

Upon arrival to the PICU, the bedside nurse caring for her asks when is the appropriate time to resume her subcutaneous insulin, especially the long-acting analog.

Long-Acting Insulin Administration

The use of long-acting insulin analogs has become standard of care for basal therapy in the setting of chronic diabetes type 1 management. The use of long-acting insulin analogs in the management of DKA is more controversial. Administration of IV regular insulin for DKA is a hallmark of treatment with guidelines recommending 0.05–0.1 U/kg/h for patients in DKA. There is some variation in practice for both infusion dosing as well as transitioning to subcutaneous insulin. Cutaneous perfusion may be impaired early on in moderate to severe DKA making absorption of subcutaneous insulin unreliable. Unfortunately, rebound hyperglycemia and acidosis can occur when transitioning from infusion to intermittent dosing of regular or short-acting insulin. This provides a theoretical window in which long-acting subcutaneous insulin may have a treatment advantage. While the most recent pediatric DKA clinical management guidelines [19–21] do not address the use of long-acting insulin in the acute management of DKA, it has been described as part of a subcuta-

neous regimen once corrected. The 2011 Joint British Diabetes Societies guidelines for the management of adult DKA concluded that continuation of home basal insulin in the acute period is unlikely to be detrimental and could facilitate easier transition to subcutaneous insulin while preventing rebound hyperglycemia and ketogenesis [22]. Several adult and pediatric studies evaluate the use of long-acting insulin analogs in acute diabetes management.

A randomized, mixed cohort prospective study of 61 adults evaluated the rate of rebound hyperglycemia after insulin drip discontinuation. A variety of conditions requiring insulin infusion were studied (surgery, type 1 and type 2 diabetes) including treatment of DKA. The intervention group received 0.25 units/kg of glargine within 12 h of initiation of insulin infusion compared to standard insulin drip therapy. There was significantly less rebound hyperglycemia in the intervention group ($p < 0.001$) with no episodes of hypoglycemia [23]. Another prospective, randomized trial evaluated 40 adult DKA patients over a 6-month period. The intervention group received 0.3 units/kg of glargine within 2 h of DKA diagnosis in addition to standard insulin drip therapy. The time to closure of anion gap and hospital LOS was less in the intervention group, but not statistically significant. There were no differences in incidents of hypoglycemia [24].

In 2007, a retrospective review of 71 pediatric patients treated for DKA compared standard DKA management to standard DKA management plus the administration of 0.3 units/kg of glargine in the first 6 h of diagnosis. There were no incidents of hypoglycemia or adverse neurologic outcomes in either group. The intervention group had statistically significant improvement in time to correction of acidosis, length of insulin infusion, and total IV insulin required. PICU length of stay (LOS) decreased with a trend toward shorter hospital LOS [25].

In 2017, Harrison et al. published a retrospective chart review of 149 episodes of pediatric DKA in patients greater than 2 years old. The intervention group received 0.3 to 0.5 units/kg of glargine more than 4 h prior to discontinuation of the insulin drip. The control group received the same dose of glargine less than 2 h prior to insulin drip termination. The study separately analyzed new (50) and pre-existing (99) type 1 diabetic patients. There were no differences in the rates of hypoglycemia. Two cases of cerebral edema occurred in the control group, but none in the intervention group. A statistically significant increase in hypokalemia occurred in the treatment group of new-onset diabetics (minimum potassium 3.1 mmol/L) with no adverse outcomes in either group. Interestingly, the treatment group had a longer length of insulin infusion and duration of acidosis, but no change in hospital LOS [26].

These studies evaluate long-acting insulin analog use in acute diabetes management of both pediatric and adult patients focusing mostly on DKA. As a whole, they show no consistent improvement in DKA resolution or LOS. Although they do confirm less rebound hyperglycemia after discontinuation of continuous insulin therapy, they do not inform optimal time frame for administration of subcutaneous, long-acting insulin. In general, the studies are limited by small sample size and study designs introducing bias indicating that a larger, prospective study may be necessary to thoroughly answer these questions. There were no adverse outcomes noted except clinically insignificant hypokalemia in new-onset type 1 diabetic patients reinforcing the safety of this intervention.

Fluid Management and Prevention of Cerebral Edema

The degree to which fluid therapy contributes to the development of (CE) in the setting of DKA is undetermined [5, 27]. However, therapies that are known or suspected to increase CE in other clinical settings are usually avoided in the treatment of DKA. Preventing a low or rapidly declining serum osmolarity is a mainstay of safe therapy. As two of the primary determinants of serum osmolarity, this can be accomplished by controlling the rate of fall of serum glucose and sodium concentration. This is the rationale for administering isotonic fluids during the early stages of

DKA resuscitation and treatment. As discussed, serum sodium should increase during the treatment of DKA due to the fall in serum glucose. Failure of rise or even decline in serum sodium during treatment is associated with an increased risk for CE formation; however causality is unproven [28, 29]. This, along with our current understanding of fluid shifts during serum osmolarity changes, has led to the general recommendation that isotonic fluids be administered during the early stages of treatment of severe DKA [9]. Whether this decreases the incidence or severity of edema is unknown. However, considering the morbidity of CE relative to hyperchloremic metabolic acidosis, prudence supports the use of isotonic fluid until such time as the risk for cerebral edema is past, or additional data regarding the type of edema may also help clarify optimum fluid management in DKA.

Utilization of isotonic fluid during rehydration may help promote the rise in sodium and decrease the likelihood of edema formation but also includes the administration of chloride. This increased chloride load eventually needs to be eliminated via the kidneys and can result in hyperchloremic metabolic acidosis. Although its significance is debated, this new- and late-onset acidosis may increase the length of hospitalization and need for additional therapy [9].

The next hour, she is difficult to arouse with painful stimuli. Her HR is now 117 bpm, BP is 138/82 mmHg, RR is 23 per minute, and SpO_2 is 95% without supplemental oxygen. Her pupils are 8 mm and less briskly reactive. Her withdrawal to pain is now non-specific in all extremities. Her respiratory pattern now shows less hyperpnea and is less regular. Her bedside blood glucose test shows 155 mg/dL, and serum labs are shown in Table 17.2.

Treatment of Cerebral Edema

In the setting of suspected or documented edema and increased intracranial pressure (ICP), traditional osmolar therapies are often employed. Mannitol, which has been used for decades in the treatment of CE, and, more recently, 3% hypertonic saline boluses have been advocated [9]. Mannitol is a typical osmotic agent that increases serum osmolarity, draws water out of the brain, and is typically followed by an osmotic diuresis as mannitol is filtered and excreted in the kidney. In addition, it may have additional beneficial rheologic and regional blood flow effects. Hypertonic saline also increases serum osmolarity and decreases brain water content but may have less osmotic diuretic effect, thus maintaining intravascular volume and cardiac output better than mannitol. This is the rationale for preference of hypertonic saline over mannitol in the treatment of CE in the setting of DKA and intravascular volume depletion. However, a retrospective review of osmolar therapy and outcome demonstrated an association of 3% saline with increased mortality for the treatment of cerebral edema in DKA [30]. Although a physiologic rationale exists for the use of hypertonic saline over mannitol in this setting, the ideal osmotic agent is unclear. Therefore, suspicion and recognition of cerebral edema and prompt treatment, using osmotic agents as necessary, are key. In addition, attention to other factors that can influence CE and increase intracranial pressure is vital to optimizing outcome, such as maintenance of adequate ventilation, temperature control, and possible surgical intervention. Surgical options can include decompressive craniotomy, intracranial pressure monitor placement, and external ventricular drain placement in severe cases.

As her mental status has continued to decline, a blood gas is obtained that shows a severe metabolic acidosis with a pH of 6.7 and a bicarb of 9 mEq/L. She is not withdrawing to pain. Her pupils remain 8 mm and are sluggishly reactive. Her blood pressure has also decreased to 86/42.

Use of Bicarbonate

Acidosis is one of the hallmarks of DKA. This acidosis slowly corrects as fluid resuscitation and insulin therapy result in improving perfusion and cessation of ketogenesis [31]. Because the level of acidosis can be severe, bicarbonate was once a

mainstay of therapy and thought to improve outcomes, reduce mortality, and decrease length of stay in the hospital. However, the administration of bicarbonate therapy to treat acidosis in the setting of DKA remains controversial as multiple studies have failed to show any significant benefit, and some have shown an association with increased risk. A multicenter study sought to define risk factors for the development of CE [29]; while studying a patient cohort, it was found that the only therapeutic intervention that was associated with increased risk of the development of CE was administration of bicarbonate therapy. Additional studies showed no difference in the rate of complications or time to metabolic recovery between patients given bicarbonate and those who were not [32]; in fact, the data suggested that bicarbonate may provide more risk than benefit as those patients were found to have prolonged hospital stays.

There are several physiologic reasons for why bicarbonate therapy should not be used. First, increasing serum bicarbonate leads to increased carbon dioxide formation, which easily crosses the blood-brain barrier and can lead to paradoxical CNS acidosis [8]. Sodium bicarbonate administration has also been shown to be associated with hypokalemia due to the correction of acidosis and intracellular shift of potassium. In a study by Viallon et al. [33], patients with DKA were divided into two groups: those that received bicarbonate and those that did not. Not only was there no difference in the time to resolution of laboratory parameters, but the patients that received bicarbonate required more frequent potassium replacement than those patients who did not. An additional concern of bicarbonate administration is it may cause impaired tissue perfusion and oxygenation due to a leftward shift of the oxyhemoglobin dissociation curve. Because of these factors, bicarbonate administration is no longer recommended on a routine basis; however, the controversy remains as there may be utility for its use in patients with severe acidosis (pH < 6.9). It is known that severe acidosis affects myocardial function and impairs tissue perfusion; bicarbonate may help attenuate these effects by correcting the pH more toward normal in a subset of patients. However, a study in adults show that administration of bicarbonate to patients in DKA with an initial pH less than 7.0 did not decrease time to improvement of acidosis or decrease hospital length of stay [34], and current recommendations are that sodium bicarbonate not be given routinely in pediatric patients with DKA except in the case of extremely severe acidosis and refractory hemodynamic instability [9, 35]. As the data remains unclear and inconclusive, the only known indication and recommendation for bicarbonate administration in the clinical setting of DKA is life-threatening hyperkalemia.

Conclusion

Diabetes mellitus is the most common endocrine disorder among pediatric patients. Patients with both type 1 and type 2 diabetes are at significant risk of developing DKA at least one time in their lives. Patients with DKA develop dehydration and electrolyte abnormalities and are at risk of developing cerebral edema. Cerebral edema remains the most common cause of morbidity and mortality among those patients with DKA. The mainstays of DKA therapy are insulin, fluid resuscitation, and electrolyte replacement. There remain significant controversies regarding the specifics of fluid resuscitation, the prevention and treatment of cerebral edema, and the efficacy of bicarbonate administration.

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Part VIII

Neurologic Controversies

Optimizing Sedation in the Pediatric ICU

18

Rita V. Alvarez and Chani Traube

Introduction

> Compared to what we ought to be, we are half awake.
>
> —William James

As pediatric intensivists, we strive to facilitate patient comfort in the PICU, despite daunting odds [1]. In the past, we have employed a sedative-hypnotic approach during a physiologically taxing period, to decrease the patient's fear, anxiety, discomfort, and pain. The intended goal of minimizing these negative experiences has been dual, ensuring the safety of the patient and decreasing the suffering each person experiences [2, 3].

Finding the right balance in analgesia and sedation has proven to be a challenge. Fear of risking patient safety, along with a misplaced belief that amnesia is achievable and protective, has been well intended but likely misguided practices [4]. Preventing patients from appropriately perceiving negative experiences leads to inability to communicate pain and interferes with the ability to incorporate accurate memories [5]. Suboptimal pain control contributes to organ system dysfunction in the critically ill [6, 7]. Distorted perceptions of the environment lead to feelings of fear and anxiety and increase delirium rates [6–9]. Delirium in children is associated with significantly poor outcomes including increased mortality [10–14]. Delusional memories and uncontrolled pain also lead to long-term psychological morbidity, including symptoms of post-traumatic stress [6–9].

Traditional sedation protocols have used a sedative-first approach with added opioids as needed for pain [15, 16]. In recent years, we have begun to see the benefits of minimizing sedation (particularly in those mechanically ventilated), prioritizing pain control, and recognizing delirium [10, 17, 18]. This analgesic-first method (termed analgosedation) offers many benefits (Fig. 18.1). Here we advocate for this practical approach: address pain, sedation, and delirium as three distinct processes in the critically ill child. Overall goals of comfort care should be optimizing pain control, minimizing sedation, and preventing delirium.

Pain

There has been an evolution in our understanding of pediatric pain. Early on it was believed that neonates were unable to feel pain and that most of the interventions in critical care were benign. We now know that children experience pain due to

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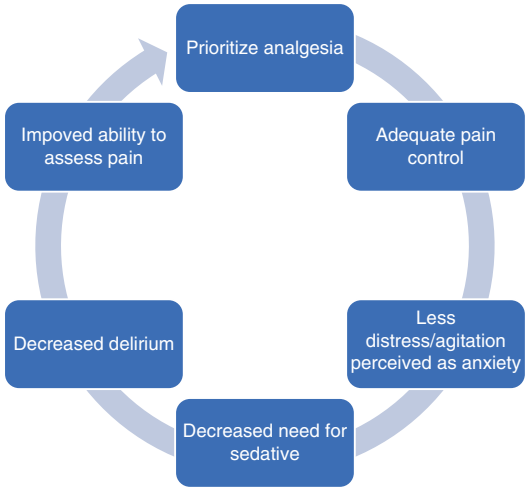

Fig. 18.1 An analgesic-first approach minimizes sedative use in mechanically ventilated patients, minimizing sedative-induced delirium

underlying disease, catheters, surgeries, immobility as well as routine cares such as suctioning and turning. Psychological stressors such as sleep deprivation and delirium can amplify pain perception [19–23]. Acute pain that is poorly controlled may lead to development of chronic pain [24].

Pain and anxiety activate the autonomic nervous system leading to a surge in catecholamines and stress hormones. These lead to vasoconstriction and compromised tissue perfusion. Additionally, there is increased myocardial oxygen demand, activation of the renin-angiotensin-aldosterone axis, increased cytokine production, altered glycemic control, enhanced catabolic state, hypercoagulability, and immune system dysfunction [25, 26]. Conversely, well-controlled pain is associated with decreased energy consumption, postsurgical catabolism, and hyperglycemia, along with improved immune function. Adequate analgesia is linked to decreased length of mechanical ventilation, ICU length of stay, and mortality [5].

Pain not only has physiologic effects that contribute to acute illness, it also results in serious psychological sequelae. Patients are at risk for chronic pain, anxiety, depression, and post-traumatic stress disorder (PTSD). Uncontrolled pain contributes to anxiety and delirium [5, 6, 19, 21, 27, 28].

The literature reports that pain is common, under-recognized, and undertreated in the ICU [5, 19, 21, 27, 28]. The American Academy of Pediatrics (AAP) released a Task Force on Pain in Infants, Children, and Adolescents. The AAP noted that pain is inherently subjective and is intertwined with developmental and sociocultural factors. Suffering occurs when the pain is overwhelming and chronic or when the patient feels out of control. The goal of analgesia is to create insensibility to pain without loss of consciousness [29].

Barriers to treatment of pediatric pain include false beliefs (such as the myth that children do not feel pain the way adults do) and clinician fears (including fear of adverse respiratory and hemodynamic effects of analgesics and concerns over addiction). With improved education of pediatric providers, frequent assessment and reassessment for pain, and timeliness of treatment, we can optimize pain control in critically ill children [29].

Excellent pain control begins with timely recognition of pain. In order to achieve this, standardized assessment tools for pain should be employed routinely [30]. There are many well-validated tools including the numeric rating scale (NRS); visual analogue scale (VAS); Faces, Legs, Activity, Cry, and Consolability (FLACC) Observational Tool; and COMFORT scales [31–44]. A child must not be oversedated; research shows that sedation may impair a patient's ability to communicate pain. Unfortunately, when unrecognized pain results in agitation, the patient may be given even more sedation which perpetuates this process. A sedated patient – although she/he may look asleep – can still experience pain [5, 45].

Opioid analgesics remain a mainstay of pain treatment in the PICU [3]. Active at opioid receptors in the hypothalamus, striatum, periaqueductal gray matter, and the spinal cord, opioids hyperpolarize the neuronal membrane and block neurotransmitter release. These drugs are highly effective for many types of pain but have associated side effects. Cardiovascular effects include decrease in heart rate and blood pressure. Respiratory effects include suppression of ventilatory drive and cough (this can be

a beneficial side effect in mechanically ventilated patients). In addition to pain control, neurologic effects include sedation, meiosis, nausea, and pruritus. Opioids increase smooth muscle tone which can lead to constipation and urinary retention. Despite these well-known side effects, opioids are highly effective and useful analgesics [3].

A multimodal approach to treatment of pain appears to be most effective. An underappreciated analgesic is acetaminophen. By inhibiting central cyclooxygenase, it has potent analgesic and antipyretic effects. It works synergistically with opioids, causing an "opioid-sparing" effect. Availability of an intravenous form of acetaminophen allows for effective use in nearly all critically ill patients (although it must be avoided in those with significant hepatic insufficiency) [3].

Another highly effective class of non-opioid analgesics are the nonsteroidal anti-inflammatory drugs, including ibuprofen and ketorolac. These inhibit peripheral cyclooxygenase, with strong analgesic, antipyretic, and anti-inflammatory effects. The potential hemostatic (antiplatelet) effects are infrequently seen clinically. NSAIDs must be avoided with significant renal impairment [3]. Anecdotally, we have found that mechanically ventilated children who are treated with acetaminophen and ketorolac routinely achieve greater comfort on lower doses of opioids.

Other non-opioid analgesics include the alpha agonists, such as clonidine and dexmedetomidine. Postsynaptic alpha receptors are activated in the CNS leading to decreased sympathetic activity via inhibition of norepinephrine release. Sedation occurs with decreased firing at the locus coeruleus in the brainstem; analgesia results from binding in the spinal cord [46–50]. In adults, the use of alpha agonists has been associated with reduced need for opioids, benzodiazepines, and propofol [50, 51]. In children, limited literature indicates alpha agonists may decrease amount of benzodiazepines and opioids needed in those mechanically ventilated [53]. Regarding clinically significant adverse effects, bradycardia is reported with dexmedetomidine and hypotension with clonidine [46–48, 50–57].

Another possible option is low-dose ketamine, an NMDA receptor antagonist. As NMDA receptor activation mediates opioid tolerance, a low-dose ketamine infusion (when given alongside an opioid) may delay the development of tolerance. These drugs also have sedative properties, which can be a beneficial side effect in mechanically ventilated children [3, 5]. However, there is evidence (in vitro and in young animal models) that has suggested a link between NMDA receptor antagonism and a toxic influx of intraneuronal calcium, leading to increased reactive oxygen species and neuronal cell death. This may lead to alterations in brain development, with disturbed motor function, learning, and memory [58–60]. Research is needed to determine the applicability of these studies in young children.

Lastly, regional anesthesia (such as nerve blocks and epidural catheters) is highly effective at optimizing pain control with minimal systemic effects. The increased availability of regional anesthesia in the PICU over recent years has been a huge asset for improving pain control [61–69].

Nonpharmacologic analgesia may be especially useful in children. Studies suggest that massage, acupuncture, and distraction (e.g., music therapy) can be beneficial [70–79]. Further research is needed to demonstrate the effectiveness of adjunctive nonpharmacologic analgesia in critically ill children.

Sedation

As trainees we are taught that sedation is employed to facilitate care, to prevent dislodgement of catheters and monitors, as well as to decrease the stress response triggered by the perception of anxiety and pain. In the past, sedation was considered an absolute necessity when caring for critically ill patients, especially when invasive therapies such as mechanical ventilation were employed. However, decades of research have suggested significant consequences associated with overuse of sedative agents [4]. Animal studies have shown widespread neuroapoptosis and decreased neurogenesis with administration of sedatives and anesthetics [80–88], including

benzodiazepines. There is growing evidence that this neurotoxicity occurs in premature infants [89–94]. In adults and children, there is mounting literature showing an association between benzodiazepines, delirium, and poor outcomes [10, 12–14, 52, 95–108].

Since sedation is potentially associated with poor outcomes, it is important to re-examine the reasons why we sedate children. There are several common misconceptions regarding sedation of critically ill children [4]. There is the belief that sedated children are more comfortable; in fact, as noted previously, oversedation is a major reason for inadequate analgesia [5]. There is also the myth that sedatives facilitate sleep. Although a deeply sedated child may appear to be sleeping, sedatives (particularly benzodiazepines) completely disrupt sleep cycles and interfere with the body's ability to consolidate restorative sleep [1, 109, 110]. There is also misplaced compassion – those at the bedside may want the child to "rest and not remember" the traumatic hospitalization. Unfortunately, children who are sedated are not completely amnestic; they often lay down delusional memories which paradoxically increase the chance for psychological morbidity in survivors [111]. Finally, bedside providers may presume that a sedated child will be easier to manage. In fact, oversedation often leads to delirium, and delirious children are notoriously difficult to care for [4, 112].

In 2011, the Society of Critical Care Medicine (SCCM) released Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients. The SCCM guidelines recommend light sedation for ICU patients, with a preference for propofol or dexmedetomidine rather than benzodiazepines [10]. In the adult literature, oversedation is associated with poor outcomes including prolonged mechanical ventilation and ICU length of stay, greater incidence of delirium, and death. On the contrary, minimizing sedation is associated with decreased respiratory depression, diaphragmatic atrophy, ventilator-associated pneumonia, and prevalence and duration of coma. Benzodiazepine use in particular has been associated with development and duration of delirium, increased length of mechanical ventilation, and increased length of ICU stay [4, 17, 105, 113–117].

In children, recent studies have demonstrated similar outcomes in association with benzodiazepine-based sedation. Benzodiazepines have been independently associated with pediatric delirium, with odds ratios ranging from 2.2 (in a multinational study including 994 children and 25 different PICUs) to OR 3.8 in a cardiac ICU (n = 99 patients) and OR 5.2 in a single-center ICU study including more than 1500 children [11–13, 95]. Benzodiazepines have not merely been independently associated with delirium; benzodiazepines have also been linked to outcome measures. Smith et al. showed that greater benzodiazepine exposure was associated with lower likelihood of ICU discharge (HR 0.65, P = 0.01) and longer delirium duration (IRR 2.5, P = 0.005) in 300 children ages 6 months to 5 years old. This study showed that dexmedetomidine increased likelihood of ICU discharge (p = 0.008) [118]. Modi et al. established a causal inference between benzodiazepines and pediatric delirium. In 580 subjects, a temporal relationship was demonstrated, where benzodiazepines were highly and independently associated with transition from normal mental status to delirium. Data showed a dose-response effect, with probability of transitioning to delirium increasing with dose of benzodiazepine given during the previous day. Sophisticated marginal structural modeling was used to carefully control for time-dependent confounders including cognitive status, opioids, and mechanical ventilation. This pseudo-randomized sample revealed that benzodiazepines independently increased subsequent delirium risk by 333%. These data suggest that alternatives to benzodiazepine-based sedation (prioritizing dexmedetomidine) may be beneficial in critically ill children.

Although we have suggested that much of the sedation currently provided in the PICU is unnecessary, there are clearly clinical situations where sedation is absolutely warranted. For example, it is reasonable to sedate children for procedures, facilitate patient-ventilator synchrony, allow for

tolerance of monitors and catheters, and decrease metabolic demand (i.e., in the setting of shock or intracranial hypertension). Just as systematic assessments and reassessments are necessary for optimizing management of pain, the same is true for sedation [30]. We recommend the use of the Richmond Agitation-Sedation Scale (RASS), an intuitive tool that allows for assignment of sedation targets in ventilated and non-ventilated children of all ages, and titration of medication to achieve sedation goal [119]. Please see case study for an example.

In contrast to the literature in critically ill adults, daily sedation interruption (DSI) with spontaneous breathing trials (SBT) has not been proven effective in pediatrics. Vet et al. compared DSI to a standard sedation protocol in a randomized controlled trial including 129 children in three PICUs in the Netherlands. In the DSI group, children were on continuous protocolized sedative infusions; sedation was held once daily to allow the child to emerge for an attempt at spontaneous breathing; the child was then sedated again. In the control group, children were maintained on protocolized sedation. In this study cohort, DSI was not beneficial; there was no change in ventilator-free days, length of stay, or cumulative amount of sedation received. There were higher rates of agitation reported in the DSI group and an overall increased mortality [120]. Many PICUs are adopting a different approach: rather than continuous sedation with DSI, keep children as lightly sedated as possible throughout the day, and proactively wean the ventilator [121].

Pediatric evidence shows that an analgosedation approach is feasible in critically ill children (Fig. 18.2). In 2011, Seattle Children's Hospital employed a morphine-based "comfort" protocol in mechanically ventilated patients, with sedation added only if needed. In a cohort of 166 children, they demonstrated a significant decrease in sedation days (7 versus 5 days, $p = 0.026$) and a trend toward shorter time on mechanical ventilation (HR 0.81, $p = 0.06$). There was also a trend toward decreased ICU length of stay (HR 0.81, $p = 0.058$). Importantly, there was no increase in accidental extubations with this sedation-sparing approach [122]. Another groundbreaking study was published from Advocate Children's Hospital, where 70 children after cardiothoracic surgery were randomized to either continuous sedation (morphine and midazolam infusions) or placebo (a saline infusion). Both groups were allowed as-needed open-label doses of morphine and midazolam. Significantly, there was no difference in the number of intermittent doses required between the two groups. Children without background sedation required no more "breakthrough" doses than children on continuous infusions. This decrease in sedation exposure led to a significantly shorter hospital length of stay in the placebo group (4.9 days versus 8.4 days, $p = 0.04$) [123].

Delirium

Delirium is an acute neuropsychiatric syndrome with altered cognition and consciousness. It is an acute encephalopathy that always represents a change from baseline [124]. Its neuropathophysiology is complex and incompletely understood. Dopaminergic, serotoninergic, glutaminergic, and cholinergic pathways in the cerebral cortex, striatum, substantia nigra, and thalamus have been implicated. Imbalance in the synthesis, release, and inactivation of neurotransmitters can result in altered cognitive function, behavior, and mood [108]. It is likely that delirium in the ICU is a result of multiple factors inherent to the patient, the presenting illness, and the ICU care [125]. Associated risk factors (Table 18.1) as well as short-term outcomes (Table 18.2) associated with delirium in children have been described in the growing literature [11–14, 95, 106, 112, 121, 125–140]. Pediatric delirium has been associated with increased length of stay, costs, time to extubation, and excess mortality.

Delirium is a common occurrence in critically ill children. High prevalence rates have been reported in the general PICU (17–38%), the pediatric cardiac ICU (49–57%), and the postoperative PICU population (66%) [11, 13,

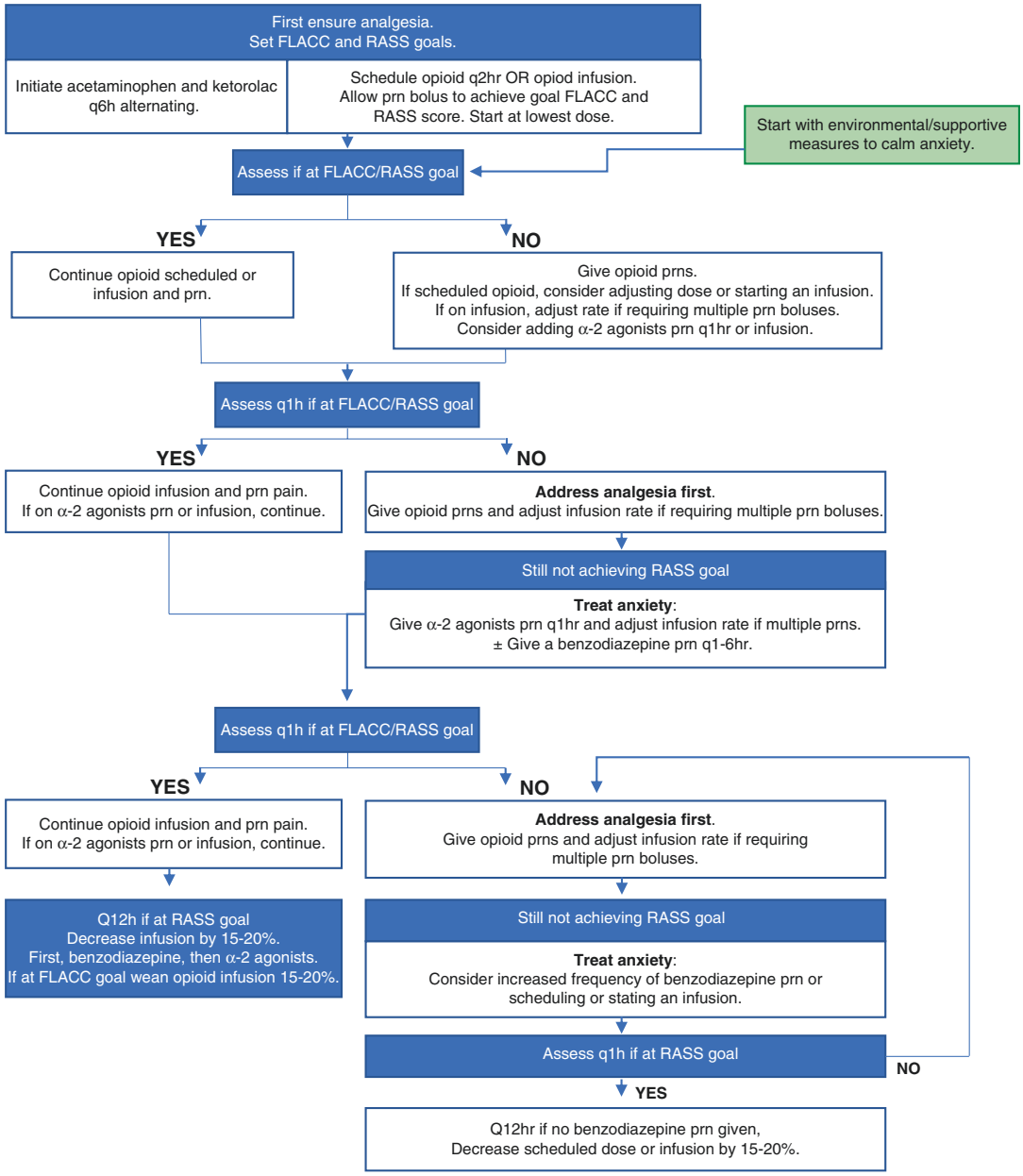

Fig. 18.2 Sample analgosedation protocol for mechanically ventilated patients. Prn, as needed

95, 106, 127, 140]. Delirium can be classified by subtypes as defined by the level of psychomotor activity. The pediatric literature supports that the hypoactive subtype is most common (46–56%) and may present as a sluggish, lethargic, apathetic, and even stuporous child. Following in frequency (43–45%) is mixed type in which patients may have a normal level of psychomotor activity or fluctuating level of activity. Lastly, hyperactive delirium is seen as mood lability, agitation, and restlessness and is the least common subtype described (5–8%) [11, 12, 14]. Adult literature supports that of all the subtypes, the

Table 18.1 Risk factors associated with delirium

Predisposing	Precipitating Presenting illness	Iatrogenic
Young age < 5 year	Severity of illness	Benzodiazepines
Cognitive impairment	Mechanical ventilation	Anticholinergics
Prior emotional/behavioral problems		Deep sedation
Poor nutritional status		Physical restraints
Cyanotic heart disease		Immobility
		Social isolation
		Sleep deprivation

Table 18.2 Outcomes associated with delirium

Increased PICU length of stay
Increased hospital length of stay
Increased duration of mechanical ventilation
Higher cost of care
Increased mortality

hypoactive patient is associated with the worst outcomes [141, 142]. This has yet to be explored within pediatrics.

SCCM has released clinical practice guidelines recommending widespread delirium screening in adults, as well as treatment to decrease duration of delirium and ameliorate its long-term effects [10]. There are now validated tools available for use at the bedside to screen for delirium in children of all ages [106, 129, 143]. The European Society of Paediatric and Neonatal Intensive Care (ESPNIC) has recommended that all children in the PICU be monitored for delirium routinely using the Cornell Assessment of Pediatric Delirium [30].

Importantly, we have evidence that delirium is amenable to intervention [10]. Simply by implementing routine screening for delirium, we can decrease delirium burden in at-risk children. Widespread screening results in earlier recognition of delirium and allows for intervention and decrease in delirium duration. Widespread delirium screening also improves staff knowledge about delirium and creates opportunities for unit-wide implementation of preventive strategies. A single-center experience describes a decrease in delirium rates from 46% to 35% in children on invasive mechanical ventilation over a 2-year period, simply by increasing awareness of delirium and targeting light levels of sedation [12, 144]. Another exciting study showed a stepwise decrease in delirium rates with a bundled approach: institution of unit-wide delirium screening, followed by protocolized sedation, and then an early mobilization initiative. Delirium rates decreased 39% over the course of the study [139].

Conclusion: A Changing Paradigm

> Progress is impossible without change, and those who cannot change their minds cannot change anything.
>
> —George Bernard Shaw

Traditional sedation protocols have used a sedative-first approach with added opioids as needed for pain. These protocols are more likely to be associated with oversedation, which is in turn linked to masking of pain and delirium, increased length of mechanical ventilation, ICU length of stay, and health-care costs. An analgosedation approach in critically ill adults has led to decreased delirium, shorter lengths of mechanical ventilation, and ICU length of stay [15]. Emerging data in pediatrics suggests similar effects. The pediatric critical care community is on the cusp of a culture shift. In the next decade, we may see the pendulum swing toward an analgesic-first approach to sedation, with incorporation of delirium prevention into our daily PICU practice. This is an opportunity to potentially improve outcomes in our pediatric patients.

Conclusions

- There is a complex interplay between pain, sedation, and delirium in critically ill children.
- A shift in historical sedation-first practices to an analgesia-first approach is feasible in pediatrics. Early data suggest strong clinical benefits.
- Historically, the mainstay of sedation in the PICU has been benzodiazepines. A large body of evidence suggests that an alternative approach may be beneficial. Further research is needed to explore alternatives to benzodiazepine-based sedation in children.
- Randomized controlled trials are needed to test interventions to treat and prevent pediatric delirium.
- Optimization of pain control, minimization of sedation, and recognition of delirium will likely improve outcomes in critically ill children.

Case Study

> Intellectuals solve problems, geniuses prevent them.
>
> —Albert Einstein

Alex[1] is a 6-year-old previously healthy boy with acute hypoxemic respiratory failure requiring mechanical ventilation due to influenza virus pneumonitis and superimposed bacterial pneumonia. Soon after intubation, he requires moderate ventilator settings, with a PEEP of 8. His hemodynamics are stable. Here we contrast two approaches to sedation:

Traditional Approach

Alex is started on fentanyl and midazolam infusions. Within hours of intubation, he awakens from sedation and appears agitated; he is given bolus doses of fentanyl and midazolam, and infusion rates of both drips are escalated. This cycle repeats itself multiple times over the first 24 h. By the second day of intubation, he is on a fentanyl infusion of 3 mcg/kg/h, and midazolam has been increased to 0.3 mg/kg/h. His bedside nurse notes that he is "impossible to sedate" and fears for the stability of his endotracheal tube. Restraints are ordered; opioid and benzodiazepine drips are steadily increased. He has some hypotension associated with sedation boluses and requires several fluid boluses over the next several days. His A-a gradient increases over the first 3–4 days before plateauing. Despite high-dose sedatives, he has periods of emergence with extreme agitation. Intermittent doses of paralytic are employed to maintain patient-ventilator synchrony. He is edematous and bedbound.

After 7 days on mechanical ventilation, and 24 h of diuresis, his chest radiograph and peak inspiratory pressures have improved. Attempts at lightening sedation to facilitate ventilator wean result in patient agitation. Staff recognizes symptoms of hyperactive delirium. Haloperidol is given and patient is started on methadone to manage opioid withdrawal. After 3 more days, sedatives and ventilator have been weaned, and the patient is ready for an extubation trial.

Analgosedation Approach

Alex is started on intermittent acetaminophen and ibuprofen and morphine every 2–3 h. A goal FLACC score of ≤ 3 (mild discomfort) is determined to be optimal analgesia. He is assigned a sedation level target of zero (awake and calm) using the RASS scale. Within 1 h of intubation, he awakens from procedural sedation and appears agitated; his FLACC is 7 (severe discomfort/pain) and RASS is +2 (agitated) so he is given several extra loading doses of morphine and calms. This cycle repeats itself two times over the next several hours. (His bedside team recognizes that it is not likely that he has developed opioid tolerance in this short period of time. They provide extra loading doses of morphine but refrain from increasing the standing morphine dose.) Although he has improved FLACC of 3 (mild discomfort), he still appears anxious (RASS +1, restless). A dexmedetomidine drip is initiated and

[1] "Alex" is not an actual patient; he is an amalgam of several different patients that the authors have treated successfully with an analgosedation approach.

titrated to effect. Alex is able to sleep for several hours but then awakens and communicates pain when his nurse suctions his endotracheal tube. A plan is made for preemptive morphine prior to suctioning.

Despite moderate ventilator settings, he is awake and reasonably cooperative. This allows for early mobilization, and although he refuses to ambulate, he can be moved to his bedside chair for a 30-min period. He is interactive with parents and staff and watches a movie with his mom. He is exhausted from the exercise and is able to sleep for 5 h at night (especially once his parents provide his special blanket and stuffed animal from home). Twice daily delirium screening occurs; when his delirium score (using the Cornell Assessment of Pediatric Delirium) begins to rise, the medical team reviews his medication list and discontinues unnecessary anticholinergic medication; they also remove his Foley catheter. His subsequent delirium scores improve.

Over the first 3 days, his A-a gradient increases. His RASS target is changed to −1 (drowsy) to facilitate patient-ventilator synchrony; he receives several boluses of dexmedetomidine and an increase in his dexmedetomidine infusion to achieve target sedation. By day 4 of mechanical ventilation, his chest radiograph and peak inspiratory pressures have improved. His sedation target is changed back to RASS 0 (awake and calm) and his medication adjusted accordingly. He begins to tolerate a slow ventilator wean. He participates in physical therapy twice daily and is kept cognitively stimulated during the day to facilitate nighttime sleep. As he has been spontaneously breathing and exercising for most of his ICU stay, he has not experienced significant deconditioning. He weans quickly and is successfully extubated after 6 total days of invasive mechanical ventilation.

Discussion

Our "traditional" approach to sedation allowed for a still and quiet patient, which may be soothing to the observer – however, the sedated patient may still be experiencing pain, fear, and anxiety [145]. Alternatively, managing this patient with an analgosedation approach allowed for prioritization of adequate pain control first, followed by added anxiety control with dexmedetomidine as needed. The benefits of verbal communication and environmental comforts described here are often overlooked; it may be time to employ various therapeutic methods in real time instead of waiting for PTSD to develop [7–9]. Pediatric intensivists have reported success with active parental involvement and incorporation of child life, physical, occupational, and speech therapists into routine PICU care. This remains an area for much needed research.

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19 Diagnosis of Brain Death and Organ Donation After Circulatory Death

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Abbreviations

AAP	American Academy of Pediatrics
CPR	Cardiopulmonary resuscitation
DCD	Donation after circulatory determination of death
DND	Donation after neurologic determination of death
DNR	Do not resuscitate
OPO	Organ procurement organization
PICU	Pediatric intensive care unit
SCCM	Society of Critical Care Medicine
UAGA	Uniform Anatomical Gift Act
UDDA	Uniform Determination of Death Act
WLST	Withdrawal of life-sustaining therapies

Introduction

Understanding how death is determined and the associated ethical conflicts is paramount to the pediatric critical care provider charged with caring for critically ill children, determining death, and providing continued, humanistic support to families that want their child to be an organ donor. *Death* conceptually is the permanent cessation of biological function. While this basic notion has endured over time, the methods by which death is determined have evolved and adapted to changing social values and advances in biomedical technology. Historically, death was determined by the cessation of vital functions such as respiration and heartbeat. Advances in modern medical care allow certain physiologic functions to be artificially maintained for prolonged periods of time, such as mechanical ventilators that can breathe for patients and mechanical assist devices that can provide artificial circulation. With these advances, application of traditional means to determine death by the absence of breathing and circulation was no longer clear nor fully satisfactory. Medical innovations such as organ transplantation also necessitated re-examination of how death could be determined. The recovery of vital organs for transplantation mandated legal, ethical, and clinical precision to determine when and how death could be appropriately established in circumstances where breathing and circulation were artificially

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maintained. Importantly, during the process of dying, the event of declaring death does not signify complete biologic death of every cell in an organ or the body. Death is regarded not only as the cessation of biologic function but also the corresponding loss of individuality. The essence of mind, individuality, or person is biologically interrelated to cortical neuronal function. Thus, following a severe neurologic injury with loss of neurologic function resulting in brain death, medical therapies can sustain an individual's body despite irreversible neurologic injury and absence of personhood.

Historical Background

Controversy regarding the definition of death and recovery of organs for transplantation were initially highlighted in 1967 after the first successful cardiac transplantation from donor Denise Ann Darvall to recipient Louis Washkansky in Cape Town, South Africa [1]. Unlike cadaveric renal donation for transplantation performed in the decades prior, this seminal event was the first procedure performed from a donor whose death had been neurologically determined but whose heart continued beating with artificially supported respiration. In response to concerns regarding how death was defined, an ad hoc committee from Harvard Medical School provided a definition for brain death as *irreversible coma* in 1968 [2]. Brain death, described by the Harvard Committee, represented the loss of total brain function established by the absence of responsiveness and lack of receptivity noted by absent movement, breathing, and brain stem reflexes where a cause of coma had been identified. In the following years, individual states adopted laws with varying definitions of circulatory and neurologic death. The need for a uniform definition and path for determining death was vital to ensure consistent legal and medical standards for pronouncing death and provide clarity for legal consequences including organ donation, inheritance, taxes, criminal trials, and utilization of resources such as discontinuing medical treatments and artificial support [3]. Concurrently, the legal framework for organ donation was being developed and incorporated into the Uniform Anatomical Gift Act (UAGA) of 1968, which was subsequently adopted as law in every state and remains the legal standard governing organ donation [4]. The UAGA provides the legal structure for how organ donation after death can be authorized but does not define death nor provide any related standards other than the requirement that the physcian declaring death may not also be involved in transplanting the gifted organs. This was designed to remove a potential conflict of interest.

The first attempt at legal harmonization of determining death was made in 1981 with the President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research [5]. The commission concluded that an individual has died if there is either "(1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brain stem." They further commented that, "a determination of death must be made in accordance with accepted medical standards." This definition was adopted into the Uniform Determination of Death Act (UDDA) that has been accepted as the legal standard in every state in the country [6]. Subsequently, this definition of death was reviewed and accepted by multiple national organizations including the American Medical Association, the American Bar Association, National Conference of Commissioners on Uniform State Laws, American Academy of Neurology, American Academy of Pediatrics, Society of Critical Care Medicine, and Child Neurology Society.

While the President's Commission and UDDA largely agreed with the Harvard Committee's definition of death, concerns were raised by some in the medical community regarding the term "coma," presence of persistent spinal reflexes, metabolic imbalances potentially interfering with death determination, and disagreement on the timeframe between two distinct examinations to confirm neurologic death. The American Academy of Neurology outlined guidelines for the determination of neurologic death in adults in 1995 with a subsequent revision in 2010 [7, 8].

The President's Commission unfortunately failed to adequately address unique considerations regarding determination of neurologic death in the pediatric population resulting in the 1987 task force guidelines for the determination of brain death in children. These guidelines were revised by the Society of Critical Care Medicine (SCCM), American Academy of Pediatrics (AAP), and Child Neurology Society in 2011 [9, 10]. The revised multi-society guidelines continued to emphasize that neurologic death for infants and children is a clinical diagnosis based on the absence of neurologic function with a known irreversible cause of coma [10].

Transplantation medicine has continued to evolve since the highly publicized 1967 heart transplant. The growing need for transplantable organs is evident by the increasing gap between donated organs and transplant recipients despite significant increases in the number of organs donated and transplanted [11]. In 2018, waitlisted individuals for organ transplantation in the United States exceeded 115,000, with nearly 75,000 active candidates. Children account for more than 1.5% of those waitlisted individuals. In 2017, 16,488 organ donors provided 34,772 transplanted organs of which 82% were deceased donors (with pediatric donors accounting for 0.7% of all donors). This represents the highest number of donors and organs transplanted ever achieved in the United States and a 20% increase over the previous 5 years. Nonetheless, approximately 7000 individuals on the waiting list (~6%) die annually waiting for an organ transplant [12]. Additionally, candidates are removed from the waiting list and die because they become too sick to transplant while waiting for a lifesaving organ. The AAP supports all efforts to facilitate and increase organ donation. The opportunity for organ donation is rare in the pediatric population, but the need is significant [13]. The sheer volume of individuals, including children, awaiting transplantation and their associated waitlist mortality stress the importance of advocating for and preserving the option for organ donation as a means to save lives. A timeline of important historical events related to death determination and organ transplantation is presented in Figs. 19.1 and 19.2. This information helps frame further discussion about controversies related to determination of death and organ donation in this chapter.

Case Presentation: Part 1

A 7-year-old child is admitted to your pediatric intensive care unit (PICU) following a motor vehicle collision. The child was an unrestrained, front seat passenger, ejected from the vehicle and found pulseless by the emergency medical personnel. The child was intubated on the scene and received cardiopulmonary resuscitation (CPR) for >30 min before return of spontaneous circulation. After initial stabilization in the emergency department, the child was noted to have minor orthopedic injuries, dermal injuries, and fixed, dilated pupils. Neuroimaging reveals the loss of gray-white matter differentiation, effacement of cerebral and cerebellar cortical tissue, and grossly restricted diffusion consistent with global anoxic injury and intracranial hypertension. After 2 days of medical management in the PICU, the patient remains mechanically ventilated without observed spontaneous respiratory effort, perfusion is maintained with minimal dose of vasoactive agents, no electrical activity is noted on the electroencephalogram, no reaction to painful stimuli is elicited, and pupils remain fixed and dilated. Since admission, the child has not received any sedative or neuromuscular blocking agents.

Your colleague has been the primary provider for this patient and is concerned the child's examination is consistent with neurologic death. The designated organ procurement organization (OPO) has been contacted as required by federal regulation [15]. The family is informed about proceeding with testing to determine neurologic death. They express their desire to have their child's organs donated, and your colleague provides this information to the OPO. The first examination is consistent with neurologic death. Your colleague expresses concern that continuing any medical therapies for this child who is likely brain dead is unethical if only for the purposes of organ donation and asks if you are willing to

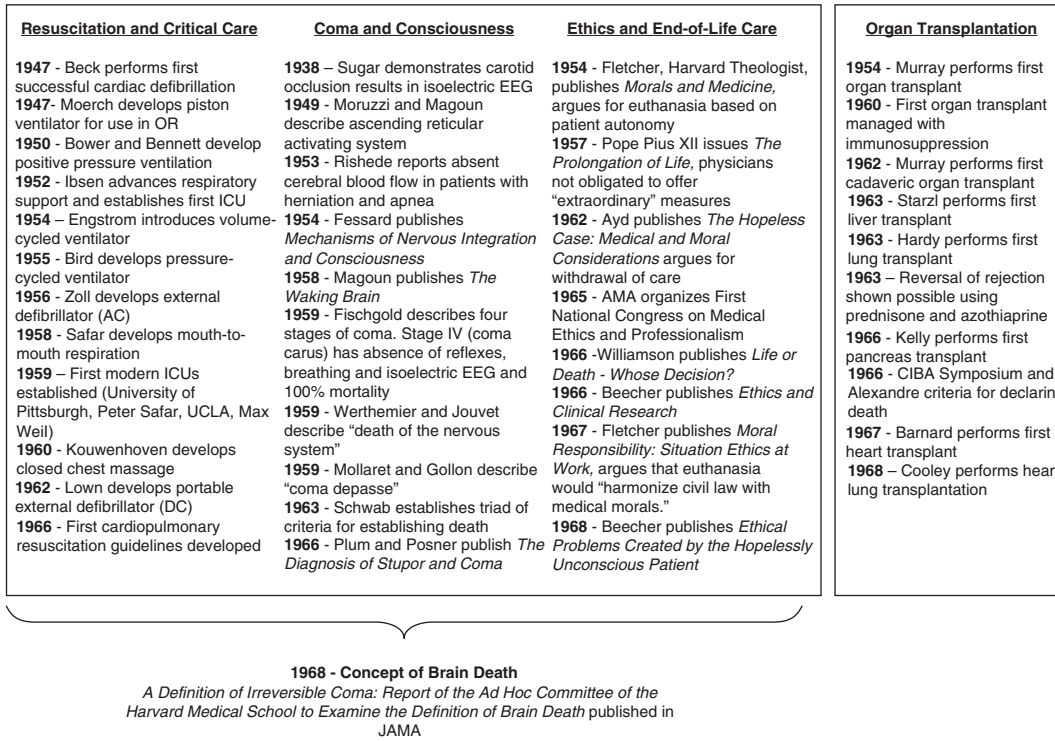

Fig. 19.1 Parallel developments that converged in the formulation of the concept of neurologic death. (Used with permission from De Georgia [14] and Elsevier)

assume care of this patient. A do not resuscitate (DNR) initiative is established for this child.

Case Discussion: Part 1

The critical care provider expressed internal conflict providing medical care to a child with impending neurologic death and familial request to proceed with donation after neurologic determination of death (DND). Pediatric critical care is fraught with parallel and, at times, competing interests that may result in the feeling of conflict for the provider [15–17]. First and foremost, the physician is obligated to provide medical care to the critically ill child. In the case of the dying child, ensuring palliative or end-of-life care and supporting a family's request for donation must be balanced. Continuing to treat the patient in the face of unclear medical benefit in part for purposes of preserving the potential for organ donation raises the ethical concern of whether such practices present an unacceptable conflict of interest. Closer examination of the issue reveals that the goals of caring for the child and the facilitation of organ donation are often congruent.

A conflict of interest is generally defined as having three elements: (1) two incompatible interests (2) where the possibility of benefiting one's interest could influence the course of action (3) to the detriment of the other interest. While there are a number of interests involved in this case scenario, the two primary interests are the patient and the potential organ transplantation recipients. Continued critical care of this patient will serve two separate goals by potentially benefiting different patients. Continued critical care benefiting donation may also medically benefit the patient by saving their life or at a minimum not cause harm [15]. Further, the maintenance of a patient in these circumstances to preserve the opportunity for donation is required by the law [4, 18]. The two interests can thus be viewed as in alignment rather than incompatible.

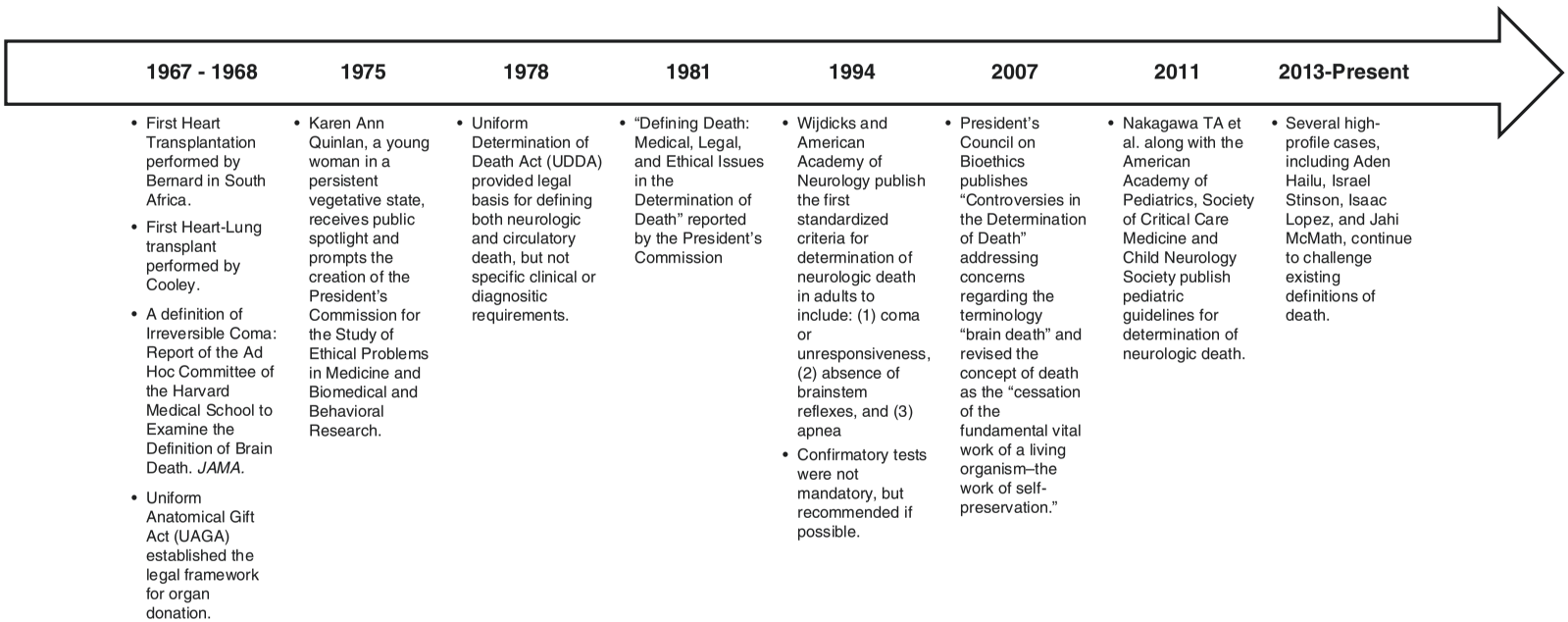

Fig. 19.2 Timeline of events following the 1968 Ad Hoc Harvard Medical School Committee to examine the definition of brain death

The second element of a conflict focuses on the possibility of personal benefit influencing a course of action. In the case scenario, the physician's ethical duty to the patient is primary but not exclusive from other legitimate purposes (such as supporting the patient's family or providing donor management) to the extent both interests can be served in a compatible manner. The responsibility for healthcare professionals to deliver care that might not medically benefit the patient is not unique to donation. Examples of this include maintaining a patient on artificial support at the family's request to allow for family members to gather and say "goodbye." This is viewed as consistent with and not incompatible with good patient care. Physicians manage multiple interests frequently including personal financial interest (payor arrangements) and hospital resource allocation ("right of the last bed"). There is nothing unique with balancing multiple interests when considering a course of patient care. The treating physician who continues medical care of patients with catastrophic brain injuries does not have the potential for personal or financial gain. The potential benefit from organ donation accrues to the donor's family, recipients, and society, not the treating physician.

The third element of a conflict is in regard to a disadvantage to other interests. Yet, there is no clear detriment to the patient in these cases. To the contrary, there are known benefits to the donor families' experience of grief. For families who do not want to pursue donation, providing the opportunity to make that decision does not represent harm. Accordingly, in most cases, the continued treatment of a patient to preserve the opportunity for donation does not present an actual conflict, and the treating physician should feel comfortable that the goals for the patient, family, and potential transplant recipients are compatible. Therefore, the physician's ethical duty to the patient is primary but not exclusive from care that facilitates or optimizes organ donation.

Best practices and federal regulation require that only trained requestors approach families for donation authorization [15]. In most instances OPO staff fill that role, but it may also be hospital staff trained by the OPO. Data indicate authorization rates for organ donation are improved when trained requestors are the primary interface with families [18]. This does not preclude a collaborative approach for authorization with the OPO representative and medical team as may be desirable and effective particularly for pediatric donors [19–21]. The clinician who has built a unique bond with a family during the process of providing care to their critically ill and dying child is potentially the most ideal individual to discuss this sensitive topic with a grieving family [22]. A coordinated plan with the OPO for the most appropriate approach under the circumstances of the case should be agreed upon in advance. Discussions regarding donation should always occur in a private and respectful manner [23, 24]. If a provider believes a conflict of interest exists or is uncomfortable caring for a child who will become an organ donor, the institution should provide an alternative, willing provider to assume care of the patient. In extreme circumstances, although not ideal, the institution can arrange for patient transfer to a facility where the family's wishes can be honored. Pediatric donation is unique because parental authorization is required since the child cannot provide their consent to be an organ donor. Importantly, an adult (18 years of age or older) can make his or her own legally binding donation prior to death through a donor registry or other signed document (such as a living will) [4]. If the patient is 18 years of age or older and has registered as a donor, the parents will be approached to discuss the donation process, but additional authorization will not be requested, and the law does not allow for family to override the patient's donation decision [4].

Case Presentation: Part 2

Twelve hours after your colleague completes the first neurologic death examination, you perform the second examination. Your findings are consistent with neurologic death. As you update the family, they state that they do not believe in brain death and fully expect medical treatment will continue until their child recovers. The family

indicates that any attempt to stop medical care at this time would result in legal ramifications.

Case Discussion: Part 2

A recent high-profile case from California exemplifies an increasingly common, controversial, and unfortunate circumstance for both a grieving family and the medical community [25]. The case involved a young girl who suffered a cardiac arrest after a tonsillectomy for obstructive sleep apnea. Severe neurologic injury occurred, and she was declared dead by neurologic criteria consistent with well-established medical and legal standards [10]. The family petitioned the court to prevent withdrawal of medical support which the court granted. The patient was deceased under the law, and the hospital was not obligated to perform any further medical interventions such as a tracheostomy or gastrostomy as requested by the family. Artificial support continued for the deceased child for 22 days until an agreement was reached allowing the family to arrange transfer of this deceased child to a facility in New Jersey. Despite a legal death certificate issued from the state of California, artificial support for this deceased child continued until rcent cardiac arrest and asytole. In a similar case, a mother in Kentucky petitioned the court to prevent the hospital from removing the ventilator and feeding tube from her child who had been declared dead by neurologic criteria [26]. The mother argued that a child's parents, not the hospital, has the right to make decisions about the medical treatment of the child including withdrawal of artificial support after death determination. The judge ruled because the child was dead in accordance with medical standards and the law, no parental right survives, and medical therapies were discontinued. These two controversial, high-profile cases are examples where families disagree with the medical team regarding continued medical treatment following death. Notably, these cases open an important discussion about the rights of parents regarding continued medical support for a deceased child when there are no specified legal state exceptions.

Individual state laws recognize an individual whose entire brain function has ceased is dead, but how the cessation of total brain function is determined is a matter of medical practice, consistent with the UDDA [6]. Once death is declared, there is no further legal or ethical duty to continue medical treatments including mechanical support on a decedent. The law has never generally required healthcare providers to provide treatment to deceased patients. Exceptions exist in the circumstance of authorization for organ donation or in states permitting religious and moral exceptions to neurologic death. Three states have such exceptions, with New Jersey and New York accepting religious or moral exceptions and California requiring a "reasonably brief period of accommodation" to families after declaration of brain death from any objection, moral, religious, or otherwise [3, 25]. If there are disagreements regarding the determination or definition of death, the court system may consider a temporary restraining order to allow for a second opinion on the medical determination of death based on neurologic criteria and assessment of harms.

Medical providers work with families preparing them for the potential or eventual death of their child in situations where medical therapies can no longer cure or restore health. Physicians are obligated to provide support and guidance to families as they attempt to understand what has happened to their child and face difficult end-of-life decisions. Appropriate emotional support for the family should be offered, including adequate time to grieve with their child after death has occurred. There are no existing guidelines to prescribe a reasonable or optimal duration for continuation of care to accommodate a grieving family after determination of neurologic death. Qualitative studies have shown that parental presence at the time of death, provision of adequate information from the healthcare team, and a sympathetic environment cultivate the provider-family relationships and end-of-life decision-making and enable healthy grieving [27, 28]. Special attention to decoupling or separating the brain death examinations from discussions regarding donation

could assist the provider in determining the needs, beliefs, or accommodations for individual families. Although grieving families should be provided adequate, respectful time and space to grieve after determination of neurologic death, intensive care services are a limited resource, and, therefore, the clinician and institution must triage beneficence with non-maleficence in postmortem accommodations.

These cases demonstrate the importance of a careful, humanistic, and guided response to scenarios where a family requests exception or accommodation after neurologic determination of death. Ideally, disagreements should be identified prior to brain death examinations and are best suited for discussion in a multidisciplinary care conference with healthcare team members who are trained in end-of-life care. The option for a second opinion could be arranged by the institution to allow for a third-party evaluation or confirmation of determination of death. In the case of highly confrontational interactions, risk management, hospital administration, and medical ethics committees can provide insight and guidance with a goal of removing the medical team from the center of controversy. Guidance should be provided to the critical care team for ongoing medical care such as documentation of vital signs, suctioning, positioning, and other routine ICU procedures for the decedent. A well-thought-out plan should be established to communicate a consistent message with the family that their child has died while assisting them with the death of their child in a timely and efficient manner. Finally, it must be reiterated to a patient's family that respectful, compassionate care will continue for their child regardless of the medical outcome or trajectory including palliative medical therapies, withdrawal of life-sustaining medical therapies, or authorization for organ donation.

Case Presentation: Part 3

After considerate and respectful discourse between the medical team and the family, you allow for a 24-h accommodation to facilitate travel for out of town family members. Compassionate support continues for this grieving family. At the end of the 24-h period, the family realizes their child has died and wishes to proceed with donation after neurologic death (DND). As the process of donation proceeds, the donor develops hemodynamic instability. Telemetry is consistent with ventricular tachycardia, and chest compressions with advanced life support are initiated. Some members of the medical team are concerned that CPR is being performed on a child that has an established DNR order.

Case Discussion: Part 3

Preserving the option of donation following neurologic death is essential once authorization for donation has occurred. Treatment of cardiac arrest for the donor should be viewed as a part of active donor management. While ethical concerns of violating a previous DNR order may surface, the donor is no longer a patient once death is declared; therefore issues related to CPR become irrelevant [29, 30]. Continued support of the donor including the use of CPR preserves the option of donation helping to fulfill the family's request for their child to be an organ donor [21]. The use of extracorporeal support for the brain-dead donor has been considered and used in extreme cases including dialysis for fluid removal and correction of severe electrolyte disturbances [31]. The use of extracorporeal support to limit warm ischemic time for donation after circulatory determination of death (DCD) donors should be avoided as re-establishing anterograde circulation in this specific patient is in direct conflict with circulatory determination of death [32].

Case Presentation: Part 4

Your team achieves return of spontaneous circulation after a brief period of CPR for this donor. During continued preparation for donation, the mother makes an explicit request to

hold her child in her arms until the heart stops beating. The father asks you if it is still possible for their child to be a donor under these circumstances.

Case Discussion: Part 4

Organ donation continues to remain a possibility to fulfill both wishes of this family. Although the more controlled organ procurement process achieved by DND allows for optimal organ perfusion and decreased ischemic time, organ donation from a neurologically deceased patient can be accomplished through a DCD process following circulatory arrest in this scenario.

In 2017, 1879 (18.3%) of deceased donors represented cases of DCD of which 138 (7.3%) were children [11]. While the total number of organs available for recovery from a DCD donor might decrease, the ability to recover and transplant DCD organs such as the kidney, liver, and lungs helps provide the most needed organs for children awaiting a transplant. Transplantation outcomes data appears comparable for organs recovered from both types of donors. A recent systematic review for renal transplant outcomes found there was delayed initial graft function from DCD donors compared to DND, but no differences in long-term graft function or patient survival [33]. Similar data for hepatic, renal, and visceral transplant would suggest comparable graft function and survival in some cases [34].

Case Presentation: Part 5

As the OPO prepares for a DCD donation process by requesting laboratory-antigen testing, organ function and size calculations, and heparinization of the patient, your team members express concern that the DCD donor may feel discomfort during these assessments or during recovery of organs. Additionally, they are troubled by performing procedures and medical therapies that provide no direct benefit to the patient prior to determination of circulatory death despite the fact this child has been pronounced dead by neurologic criteria.

Case Discussion: Part 5

In this particular scenario, the patient has already died with death determined by neurologic criteria. The team members should be reminded the DCD process is being facilitated to meet the parents' request and all procedures performed in preparation for donation in this case are on a deceased person. However, in other DCD circumstances, where the patient has in fact not been declared dead by neurologic criteria, the criteria for determination of circulatory death are met when examination is consistent with the absence of circulatory function observed for a minimum of 2–5 min depending on the medical protocol and hospital DCD policy. However, some question if a patient is truly deceased after 2 min of circulatory arrest. Electrical activity of the brain measured by electroencephalography (EEG) has been used as a surrogate to determine brain function. Potential DCD donors have been compared to patients suffering from acute cardiac arrest where cessation of cerebral activity measured by EEG occurs within 15–30 s following loss of circulation [35–38]. Withdrawal of medical therapies for a potential DCD donor rarely results in immediate circulatory arrest. Rather, the donor experiences a gradual reduction in blood pressure ultimately reaching a point of inadequate cerebral perfusion pressure prior to complete circulatory arrest. During the process of dying, cerebral blood flow falls below a threshold of adequate perfusion ultimately affecting cerebral cellular activity before complete circulatory arrest occurs. Importantly, when withdrawal of life-sustaining medical therapies occurs, suitable comfort measures including administration of analgesic and sedative agents are provided to the patient as medical therapies cease.

The UDDA states that death occurs when there is irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem [6]. Function describes the fundamental purpose of what an organ is supposed to do. Function is therefore different from activities as defined by physiologic properties of cells or groups of cells that can be measured by laboratory

means [39]. The presence of electrical activity indicating activity of cells does not necessarily correlate with function of the organ. In circulatory death, death is declared following mechanical asystole defined as the loss of perfusion pressure. Perfusion pressure is an indicator of contractility of the heart muscle to provide anterograde circulation to the body. Residual electrical activity of the heart may continue after mechanical asystole has occurred. In sum, electrical activity is not a measure of organ function or, in the case of DCD, contractility [32].

Although two standards are stated separately in the UDDA, the loss of circulation and respiration and the loss of entire brain function are essentially a single standard based on cessation of brain function. Cessation of brain functions follows quickly after the loss of circulatory and respiratory function in the absence of medical intervention. If resuscitative measures such as CPR or other mechanical or pharmacologic support restore circulation and respiration before all brain functions are eliminated by the lack of circulating oxygenated blood, the patient could not be determined dead. Cessation of circulation and respiration can be viewed as a valid means for establishing cessation of brain function and therefore death [32].

The American Academy of Pediatrics and other major organizations have adopted policy statements for the DCD process including identifying and providing guidance to bioethical concerns [40, 41]. The UAGA provides a legal framework for gifting of organs after death following authorization by either the individual him- or herself if an adult or by surrogate decision-makers in a specified priority [42]. Parents are the prioritized decision-makers to authorize donation from a pediatric donor with the option for other surrogate decision-makers if there are no parents or they are unavailable [4]. Authorization for DCD occurs prior to the withdrawal of life-sustaining therapies (WLST) and declaration of death does not alter the legal requirements. The UAGA permits surrogates to make the donation decision at the same time as the decision to WLST [4]. Although both are required to coordinate a DCD, each component follows different legal frameworks – informed consent for the withdrawal and authorization for the donation under the UAGA [43–45].

After permission to proceed with DCD, antemortem medical therapies are employed that have no direct patient benefit and may pose potential harm such as anticoagulation and immunomodulation therapy. Anticoagulation is administered antemortem to reduce the risk of thrombosis from altered perfusion during the dying process. Nonbeneficence and potential maleficence in antemortem treatment are outweighed in DCD by the altruistic goals of the family wishing to donate on their child's behalf [45]. Prohibiting parents from carrying out donation of organs on their child's behalf would be an unethical restriction of autonomy and to the detriment of society in general and those awaiting transplantation specifically. Some OPOs may utilize regional perfusion techniques using extracorporeal membrane oxygenation after circulatory death to the thorax or abdomen [39]. While perfusion techniques may continue localized circulation and oxygenation to create more viable organs for procurement, in the context of the DCD donor, the restoration of circulation, even if regional, could be viewed as contrary to circulatory death determination and therefore unethical [31, 32, 46].

Supplemental Discussion

Anencephalic infants have historically not been accepted as donors because of continued brain stem activity preventing determination of neurologic death. The anencephalic infant donor gained national attention in the late 1980s after a successful heart transplant occurred following recovery of organs from an anencephalic infant. A case series assessing feasibility of organ donation in this population concluded anencephalic infants supported with intensive care measures could not be used as organ donors because they did not progress to neurologic death [47]. The authors suggested modification to neurologic death, and organ donation criteria were required if anencephalic infants were to be considered organ donation

candidates. However, in 1992 the American Academy of Pediatrics affirmed that anencephalic infants were not appropriate organ donors and rejected arguments advocating for modification of the medical criteria of neurologic death and legal standards of pronouncement of death [48].

We have examined the progression of ethical standards, accepted criteria, and legal aspects of DCD donation. Neurologic death in neonates continues to be a rare occurrence; however organs recovered from neonates after DCD, including organs from anencephalic infants, have been recovered and transplanted with success [49]. In the case of anencephalic infants, consistent quality end-of-life care and comfort measures must be provided and titrated to palliative relief of suffering. Specific premortem procedures including elective intubation and mechanical ventilation, and administration of pharmacologic agents as previously noted, have been used in this patient population to successfully recover organs despite ethical concerns [45]. While ongoing debate continues, the increasing prevalence of neonatal DCD suggests that anencephalic children can also be potential DCD donors. While DCD for anencephalic infants remains controversial for some, so too was neurologic death in 1968.

Conclusion

The ethical, legal, and clinical controversies regarding appropriate determination of death and facilitation of donation after death represent a continually evolving dialogue between society and the medical community. It is vital for the pediatric critical care provider to recognize ethical controversies and potential conflicts of interest while offering humanistic care to a dying child and their grieving family. The positive benefits a legacy from donation can bring to the grieving process combined with the lifesaving impact for those awaiting transplantation stress the need for the pediatric medical community's awareness of donation opportunities and close collaboration with OPOs, to respectfully shepherd families through the most difficult time in their life.

Key Points

- Death using circulatory or neurologic criteria is *defined* by the Uniform Determination of Death Act enacted through individual state laws.
- Neurologic death is *determined* by accepted medical standards supported in pediatrics by the American Academy of Pediatrics, Society of Critical Care Medicine, and child neurology society guidelines for the determination of brain death in infants and children.
- Providers performing examinations to determine death should have sufficient experience and be cognizant of historical legal and social controversies as described in this chapter.
- Once a child is determined to have died consistent with neurologic criteria, the hospital and provider have no ethical or legal obligation to continue medical therapies of any kind unless organ donation is planned. Specific time-limited accommodations can be provided to family members after declaration of death to allow for grieving.
- DCD remains an option for families of children where DND is not possible and should be carefully managed in collaboration with local OPOs.

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Ms. Glazier: None

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Therapeutic Hypothermia in the Pediatric ICU

20

Jessica S. Wallisch and Ericka L. Fink

Introduction

Acute neurologic injury accounts for 16% of all patients admitted to the pediatric intensive care unit (PICU) [1] and is a causative factor in 65% of PICU deaths [2]. In a multinational point prevalence study, the three most common types of acute neurologic injury in critically ill children studied were cardiac arrest, traumatic brain injury (TBI), and status epilepticus [1].

While these etiologies have diverse pathophysiologies and mechanisms of injury, one uncontroversial common thread is that all of these conditions have strong preclinical data showing a benefit of therapeutic hypothermia (TH) on outcome. Work in preclinical models has helped to elucidate the multiple mechanisms of action and efficacy of neuroprotection afforded by TH. First, TH leads to a reduction in oxygen consumption and cerebral metabolic demand with targeted brain cooling [3]. Additionally, TH ameliorates elements of the secondary injury cascade including excitotoxicity [4–10], apoptosis [11–13], free radical generation [14], and inflammation [15–24]. However, these results have not yet translated into clinical care. Thus far, results from studies in critically ill children have ranged from no clear benefit to potentially contributing to worse outcome. Some explanations provided for this failure to translate include heterogeneity in patient characteristics and injury presentation, methods of application of TH, and choice of outcome measures [25]. One of the challenges of pediatric critical care medicine and performing high-quality research in particular is the diverse patient population, range of pathophysiologies, and age variation that spans from neonates to adults. Thus, clinicians often attempt to generalize the findings in other populations and indications with varying degrees of success. Despite the controversy surrounding TH, one point is robustly clear: fever after acute neurologic injury is detrimental and is associated with worse outcome [26–34]. For this reason, active fever prevention using targeted temperature management (TTM) has become standard of care. In this chapter, we aim to review the controversies on TTM, which includes both TH and controlled normothermia, and attempt to provide guidance on its clinical application.

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Case Scenario 1

A 2-month-old full-term previously well female found apneic and unresponsive was transported by paramedics after she reportedly "rolled off the bed." Her exam was notable for bruising and bulging fontanelle, Glasgow Coma Score (GCS) of 7, and brain computed tomography (CT) imaging that showed bilateral subdural hematomas. Intracranial pressure (ICP) was persistently elevated at 30 mmHg despite management strategies such as sedation and neuromuscular blockade, $PaCO_2$ 34 mmHg, and serum sodium 150 mmol/L on 3% saline infusion. As you are considering additional therapies to manage her intracranial hypertension, a medical student asks "Does the literature support the use of therapeutic hypothermia in this patient with TBI?"

Use of TTM for Traumatic Brain Injury

TTM aimed at controlled normothermia for the prevention of fever has been supported by several studies in adult and pediatric TBI and should be incorporated into clinical practice [26, 28–32, 34]. Therefore, the use of TTM for TBI is not controversial and will not be discussed further in this chapter.

Along with preclinical data, early studies of TH in adult TBI patients generated excitement for a new modality of neuroprotection [35, 36]. Subsequent adult and pediatric TBI study results however were not as promising. Four randomized controlled trials (RCTs) including 405 children with severe TBI (GCS less than 9) evaluated the efficacy of TH, defined as TTM to 32–33 °C, on outcome (Table 20.1) [37–40]. Notably, all four RCTs utilized different durations of TH as well as different rates of rewarming. Not only were these studies unable to show improved outcome with TH, but there was a suggestion of potential harm with this strategy. For example, Hutchinson and colleagues, whose trial utilized a shorter duration of TH with a faster rewarming rate, reported a trend toward worse 6-month functional outcome and increased mortality [40]. Likewise, the "Cool Kids" trial, which utilized an adaptive rewarming protocol in which patients with elevated ICP at 48 h remained on TH for an additional 24 h, observed a nonsignificant increase in mortality in the TH group compared to normothermia (15% vs 5%, respectively, $p = 0.15$) [38]. Importantly, hypotension and lower cerebral perfusion pressure were more frequent in patients receiving TH, which are confounders that may have played a role in the worse outcomes. The most recent RCT by Beca et al. attempted to address these factors by protocolizing adequate cerebral perfusion pressure, but this phase II trial did not detect a difference in outcome [39].

While TH has not been shown to improve outcomes following severe TBI, TH may have a role in controlling ICP. In the trial by Hutchinson and colleagues, the beneficial effect of TH on decreasing ICP during the active cooling phase was negated throughout rewarming, during which patients in the TH arm of the study subsequently had higher ICP [40]. Adelson et al. also reported a reduction in ICP early in the TH phase with subsequent and rebound intracranial hypertension during rewarming [37]. Pertinent to application of this literature is the fact that TH was applied prophylactically in both of these RCTs as opposed to only targeting patients with refractory intracranial hypertension.

Thus, the 2012 pediatric severe TBI guidelines provide a level II recommendation to avoid moderate TH to 32–33 °C for short durations $\leq$24 h. In addition, the guidelines recommend that moderate TH should be considered for the management of intracranial hypertension when initiated within 8 h of injury and maintained for up to 48-h duration [41]. Slow rewarming (rate < 0.5 °C/h) should be employed with the use of TH. There is no guidance to support the duration of time to actively prevent fever after severe TBI.

Controversies remain surrounding the approach to TTM in children who sustained non-accidental TBI, a cohort with a high frequency of morbidity and mortality that were excluded from research

Table 20.1 Key pediatric TBI therapeutic hypothermia randomized controlled trials

RCT	TH target temp (°C)	Control temp (°C)	Timing of TH initiation	Duration of TH	Rate of rewarming	Outcome results	Comments
Adelson (2005)	32–33	36.5–37.5	<6 h from injury	48 h	1.0 °C every 3–4 h	Trend toward improved survival with TH (mortality 8% vs 16%, $p = 0.44$) Significantly lower ICP decreased and less time (%) greater than 20 mmHg within the first 24 h with TH No difference in rates of coagulopathy, arrhythmia, or infection Lower rate of post-traumatic seizures with TH	First multicenter trial in pediatric TBI Phase II trial – not powered to detect differences in survival or outcome Low multicenter enrollment rate (22% of children with severe TBI) 65–70% of patients had a temperature protocol deviation (average: >2 °C per patient) Rebound intracranial hypertension after rewarming in TH group Post hoc analysis found no difference in functional or neurocognitive outcomes by treatment group
Hutchinson (2008)	32.5	37.0	< 8 h from injury	24 h	0.5 °C every 2 h	Higher mortality in TH group (21% vs 12%, $p = 0.06$); adjusted HR, 2.36 (95% CI, 1.04–5.37) Trend toward higher rate of unfavorable outcome (PCPC) at 6 months with TH (31% vs 22%, $p = 0.14$); adjusted OR, 2.33 (95% CI, 0.92–5.93) Lower ICP during cooling but higher during rewarming with TH	Mean time to cooling 6.3 ± 2.3 h after injury and time to target temp 3.9 ± 2.6 h 97% of norm patients adhered to target temp Significantly more normothermia patients received hypertonic saline (46% vs 31%) More hypotension and lower CPP in TH patients during rewarming ($p < 0.001$)

(continued)

Table 20.1 (continued)

RCT	TH target temp (°C)	Control temp (°C)	Timing of TH initiation	Duration of TH	Rate of rewarming	Outcome results	Comments
Adelson (2013)	32–33	36.5–37.5	< 6 h from injury	48–72 h (additional 24 h maintained if ICP was elevated at 48 h)	0.5–1.0 °C every 12–24 h	Trend to increased mortality at 3 months (15% TH vs 5% norm, $p = 0.15$) No difference in functional outcome (GOS and GOS-E Peds) at 3 months by treatment group	Early termination for futility after 77 patients enrolled 75% of patients enrolled at three sites (out of 15 participating centers) Mean time to cooling 5.1 ± 0.9 h after injury and time to target temp 3.2 h) Higher rate of decompressive craniectomy in norm (45%) vs TH (18%), $p = 0.02$
Beca (2015)	32–33	36–37	<6 h from injury	Minimum of 72 h	≤0.5 °C every 3 h with control of hypotension and ICP	No difference in mortality (13% TH vs 4% norm, $p = 0.34$) No difference in functional outcome	30% of norm patients had temperature elevations >38 °C No differences in MAP and CPP during cooling or MAP, ICP, or CPP during rewarming but more episodes of hypotension in TH group during rewarming (17% vs 0%, $p = 0.05$)

Abbreviations: CPP, cerebral perfusion pressure; GOS, Glasgow Outcome Scale; GOS-E, Glasgow Outcome Scale-Extended; ICP, intracranial pressure; PCPC, pediatric cerebral performance category; RCT, randomized controlled trial; TH, therapeutic hypothermia; TBI, traumatic brain injury

studies discussed above due to delays in care and challenges with consent. These infants and toddler-aged children, like the patient described in the first case study, frequently have injuries compounded by hypoxic-ischemic injury [42]. Ongoing comparative effectiveness trials may help to bring more clarity on these topics [43], and new pediatric TBI guidelines are expected in 2018.

Case Scenario 1 Considerations

As the literature suggests, we would not advocate for prophylactic initiation of therapeutic hypothermia for this patient to affect a favorable outcome. However after establishing that there has been no expansion of the intracranial hemorrhage with repeat imaging, we would suggest consideration of TH as a third tiered therapy if refractory intracranial hypertension persisted despite maximal medical management (e.g., sedation, neuromuscular blockade, hyperosmolar therapy, mild hyperventilation, treatment of seizures, and barbiturate coma) in the absence of the option for or while awaiting surgical intervention such as drainage or diversion of cerebrospinal fluid or decompressive craniectomy (Fig. 20.1). While there is no evidence to support the tempo at which to add therapies, we advocate for aggressive escalation to target ICP < 20 mmHg.

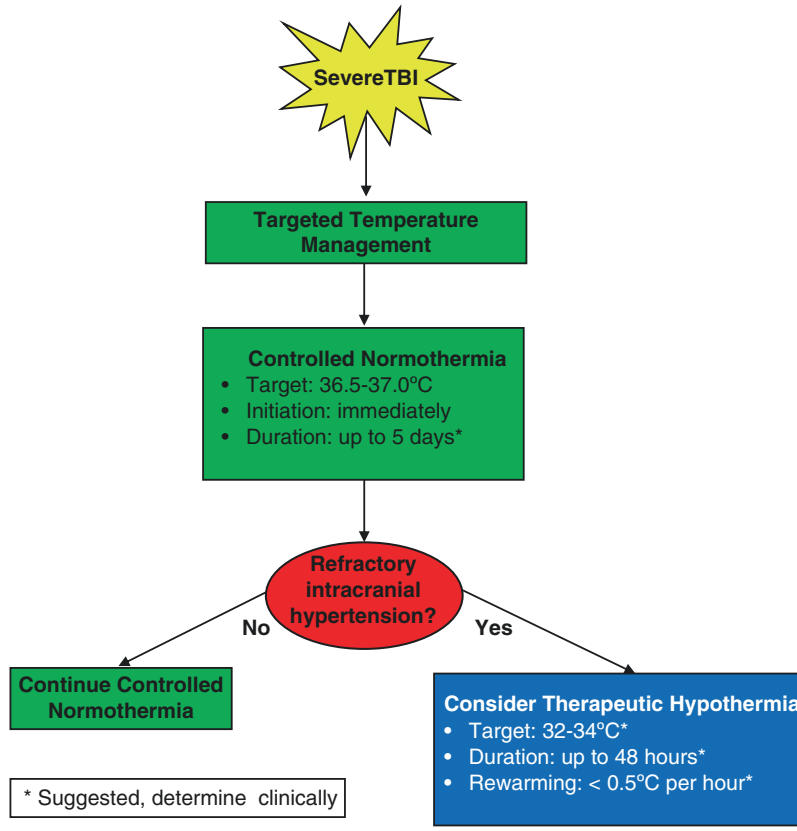

Fig. 20.1 Targeted temperature management in pediatric severe TBI. Controlled normothermia is recommended as part of targeted temperature management in all patients who sustain a severe TBI (GCS ≤ 8). Patients with refractory intracranial hypertension (unresponsive to maximal medical management) may benefit from improved ICP control with therapeutic hypothermia, while consideration is given for decompressive craniectomy or in cases deemed not to be surgical candidates. Abbreviations: TBI, traumatic brain injury; GCS, Glasgow Coma Scale; ICP, intracranial pressure

Key Points

- TTM should be used to prevent fever in the early post-TBI period.
- Prophylactic TH has not been shown to improve outcomes after severe pediatric TBI.
- TH has a role in treating refractory intracranial hypertension in children with severe TBI, with a cautious rewarming protocol.

Case Scenario 2

A 15-year-old male who collapsed while playing basketball received bystander cardiopulmonary resuscitation (CPR). An automated external defibrillator (AED) placed by paramedics noted ventricular tachycardia (VT) and provided two defibrillation shocks, resulting in return of spontaneous circulation (ROSC) after 15 min of CPR. He presented to your ICU comatose (withdrawal to pain without localization). What is the role if any of TH for this patient?

Use of TTM for Hypoxic-Ischemic Injury

TTM aimed at controlled normothermia has been proven as an effective neuroprotective strategy and should be incorporated into clinical practice [31]. Therefore, the use of TTM for this indication is also not controversial and will not be discussed further in this chapter.

TH has had great success and implementation into clinical care for neonates with perinatal hypoxic-ischemic encephalopathy (HIE) [44]. TH also provides a 30% survival benefit and increased likelihood of favorable neurological outcome in the most recent Cochrane review meta-analysis for adults surviving out-of-hospital cardiac arrest (OHCA) due to ventricular fibrillation, but not for non-cardiac etiologies or in-hospital cardiac arrest events [45].

Evidence has been less supportive of TH in children after cardiac arrest. First, observational non-randomized studies did not detect differences in outcome with the use of TH [46–50]. While these reports did not collectively find a benefit, they showed that the general use of TH was unprotocolized and was more often provided for children with the worst prognoses. These limitations supported the need for an RCT in this population.

To date, three RCTs of TH after cardiac arrest have been completed in the pediatric population (Table 20.2). The Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) OHCA study was a multicenter RCT of 260 infants and children who remained comatose after cardiac arrest [49]. Patients were randomized to TTM (36.8 °C for 120 h) vs TH (33 °C for 48 h followed by slow rewarming over 16 h to 36.8 which was maintained for the duration of 120 h). The primary outcome of survival with good functional outcome at 1 year was not statistically different among treatment groups, 20% for patients receiving TH versus 12% for patients receiving controlled normothermia (p = 0.14). Twelve-month survival was 38% vs 29%, respectively (p = 0.13). Intriguingly, survival duration was longer for the TH vs normothermia group (mean survival from time of injury 149 vs 119 days, respectively, $p = 0.04$), but this difference did not meet the prespecified secondary outcome threshold for statistical significance. Subgroup analyses were underpowered to make robust conclusions, including for arrests associated with shockable vs non-shockable rhythms.

Next, the THAPCA in-hospital cardiac arrest (IHCA) trial evaluated 257 children utilizing the same treatment protocol as the OHCA trial. The IHCA study was terminated early prior to reaching full enrollment based on interim analysis that revealed lack of efficacy in demonstrating survival with favorable functional outcome at 1 year (36% for TH vs 39% for normothermia, $p = 0.63$) [51]. Critiques of this study noted a relatively short median "no-flow" time (period from cardiac arrest to initiation of CPR) paired with a long duration of cardiopulmonary resuscitation, which may result in a less severe neurologic injury that is less modifiable by TH [52, 53]. A single-center pilot RCT just published compared serum brain biomarker profiles to 24 vs 72 h of TH (33 °C) in children comatose after resuscitation from cardiac arrest [54]. Serum neuron-specific enolase (NSE) and S100b concentrations had previously been shown to be associated with patient outcome after cardiac arrest [55, 56]. Here, serum S100b and NSE were increased (worse) at specific time points within the first week post-arrest in patients only receiving 24 h of TH. In multivariate analysis, there was an association of shorter TH duration and higher (worse) serum S100b at 1 week post-arrest. This study highlighted the need for additional investigation into the optimal duration of TH as well as the potential utility for biomarkers in measuring outcome and patient response to therapy.

The 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (ILCOR) Pediatric Basic Life Support and Pediatric Advanced Life Support (PALS) Treatment Recommendations suggest that TTM be used as part of the post-cardiac arrest care for infants and children following out-of-hospital cardiac arrest (OHCA) [57]. The guidelines parallel findings in THAPCA, citing a range of 32–34 °C for TH for 48 h or 36–37.5 °C for controlled normo-

Table 20.2 Key pediatric cardiac arrest therapeutic hypothermia randomized controlled trials

RCT	TH target temp (°C)	Norm control (°C)	Timing of initiation	Duration of TH	Rate of rewarming	Results	Comments
THAPCA-OHCA Moler (2015)	32–34 °C	36–37.5 °C	<6 h after ROSC	48 h followed by Norm for remainder of 120 h	≥16 h	No difference in survivors with good neurobehavioral outcome at 12 months with TH (20% vs 12%, $p = 0.14$) Better survival analysis trend for TH group (149 ± 14 vs 119 ± 14 days, $p = 0.04$); 12-month survival not statistically different between groups (38% vs 29%, $p = 0.13$)	Median time to cooling 5.9 h and time to target temp 2.6 h TH group more likely to develop hypokalemia (23% vs 14%, $p = 0.04$) and thrombocytopenia (10% vs 1%, $p = 0.001$) but less likely to receive RRT (2% vs 7%, $p = 0.03$)
THAPCA-IHCA Moler (2017)	32–34 °C	36–37.5 °C	<6 h after ROSC	48 h followed by Norm for remainder of 120 h	≥16 h	No difference in survival with good neurobehavioral outcome at 12 months (TH 36% vs Norm 39%) No difference in 12-month survival (TH 49% vs Norm 46%)	Early termination for futility after 329 patients enrolled Median time to cooling 4.9 h and time to target temp 2.1 h Median time from cardiac arrest to CPR 0 min; median duration of CPR 22 min
Fink (2018)	33 ± 1 °C	N/A	At clinician discretion	24 h vs 72 h followed by Norm for remainder of 120 h	0.5 °C every 4 h	Nonsignificant decreased mortality in 72 h group (24% vs 47%, $p = 0.3$) No difference in rate of unfavorable outcome (65% for 24 h vs 59% for 72 h) Serum NSE, MBP and S100b all elevated after CA NSE and S100b significantly increased at day 7 in 24 h as compared to 72 h group Shorter duration of TH remained independently associated with elevated S100b at 7 days in multivariate analysis	Included patients with both IHCA and OHCA that had TH initiated by clinical team Partly concurrent with THAPCA (prioritized enrollment) included children that did not qualify for THAPCA First study to include biomarkers 24 h group had temperature elevations >38 °C during Norm period (after rewarming) 72 h group had more females, more patients with cardiac etiology for arrest (18% vs 6%), and trend to longer duration of CPR (25.5 min vs 17.0 min, $p = 0.10$)

Abbreviations: IHCA, in-hospital cardiac arrest; MBP, myelin basic protein; NSE, neuron-specific enolase; Norm, normothermia; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; RCT, randomized controlled trial; RRT, renal replacement therapy; S100b, S100 calcium-binding protein B; TH, therapeutic hypothermia

thermia as acceptable goal temperatures, with ongoing TTM for fever prevention for up to 5 days. While no explicit evidence was provided for TTM in pediatric IHCA, fever should be prevented.

In summary, while the evidence and guidelines have changed over time, TTM has become standard of care in both pediatric and adult post-cardiac arrest care. Guidelines keep options open for TH and controlled normothermia post-CA for children. Future research with a personalized medicine approach utilizing biomarkers, EEG, imaging, and other tools may help guide application, duration, and response to treatment with TTM.

Case Scenario 2 Considerations

PALS guidelines include controlled normothermia or therapeutic hypothermia as TTM options to consider in post-arrest pediatric patients. While the number of patients with cardiac arrest due to VT did not allow for subgroup analysis in the THAPCA trials, this population may see benefit based on the adult literature. Additional support comes from the updated American Academy of Neurology practice guidelines which recommend TH (32–34 °C for 24 h) for adult comatose patients with "shockable rhythm" of ventricular tachycardia (VT) or ventricular fibrillation (VF) following OHCA [58]. Notably, the duration of TTM recommended in adults (24 h) is shorter than what has been studied in the pediatric population (48 h). Extrapolating from the literature, we would support the use of TH in this patient for 24–48 h followed by controlled normothermia up to 5 days post-arrest (Fig. 20.2).

Key Points

- TTM should be used to prevent fever in the early post-ROSC period.
- Evidence in other patient populations may inform the use of TH in the PICU.

Other Indications

TH has been explored as a neuroprotective therapy in preclinical models and patient case series for refractory status epilepticus to reduce seizure burden [59–61], secondary cerebral edema, and immune activation [60]. While the Pediatric Neurocritical Care Research Group completed a feasibility study on TH in this population, validation studies are pending [62]. In France, 270 critically ill adults with convulsive status epilepticus were randomized to 24 h of 32–34°C vs standard care [63]. While there was no statistical difference in the primary outcome of good functional outcome (GOS = 5) at 90 days, less patients receiving TH had "EEG progression." Thus, similar to TBI, TH may have a therapeutic role in improving symptomatology (e.g., ICP, EEG derangements), but thus far, not on patient outcome.

Case series and reports describing teenagers and one neonatal patient with spinal cord injury suggest an improvement in functional status with the use of systemic TH [64, 65]. While high-quality evidence does not support routine use in clinical practice at this time, an RCT is currently enrolling adults with acute cervical spinal cord injury to evaluate the safety and efficacy of TH (33 °C) on neurologic and functional status [66].

TTM for stroke has not been prospectively studied in children. A recent French expert-led panel recommended consideration of TTM (36–37.5 °C) to control ICP in children with subarachnoid hemorrhage, extrapolating data from the adult literature [67]. A prospective cohort study of TH (34.5 °C) in adult ischemic stroke patients who had successful recanalization showed less cerebral edema, hemorrhagic transformation, and better outcome with TH treatment [68]. RCTs thus far have evaluated the safety and feasibility in this population, but the trials that were poised to answer whether TH improves outcome in this population were terminated early [69, 70].

The nuances of the application and efficacy of TH in these different conditions support the need for ongoing study particularly in the

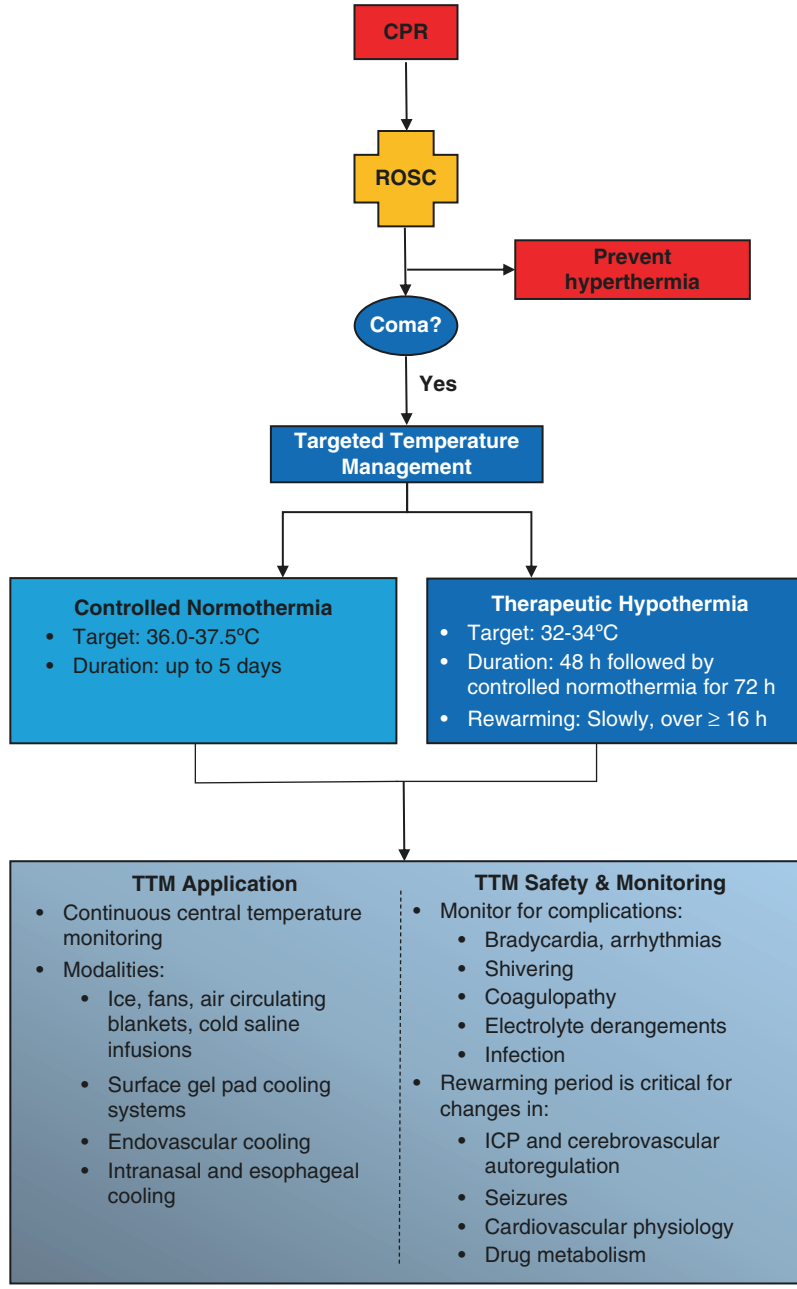

Fig. 20.2 Targeted temperature management in pediatric hypoxic-ischemic injury. Fever avoidance is recommended in all patients following hypoxic-ischemic injury. Targeted temperature management should be employed for patients who remain comatose following hypoxic-ischemic injury with consideration given to both controlled normothermia and therapeutic hypothermia. Abbreviations: CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TTM, targeted temperature management; ICP, intracranial pressure

pediatric population. Given the different pathophysiologic considerations of these cohorts, it remains controversial for clinicians to extrapolate the evidence for application in other populations, and we would not recommend the use of TH in these situations at this time.

Controversies in the Logistics and Modalities of Patient Monitoring and Treatment

The optimal provision of TTM requires accurate temperature monitoring and close provider attention. In pediatrics, core temperature is best

estimated using the rectal or esophageal route; peripheral (e.g., oral, axillary, or temporal) monitoring has been shown to be inferior [71]. The neurocritical care guidelines recommend continuous central temperature monitoring, preferably with an esophageal or bladder temperature probe [72]. In practice, patients may require two central probes, one each for monitoring and feedback of the temperature-modulating device.

Clinicians have a menu of options for techniques to achieve TTM, but limited data exist comparing their performance characteristics. Among the most readily available are surface application of ice, fans, air-cooling blankets, and intravascular infusions of cold saline (4 °C). However, advanced temperature-modulating devices have been found to achieve target temperature more rapidly and reliably [73–75]. Several studies which have directly compared modalities of cooling support the use of endovascular cooling and surface gel pads for rapid induction and more reliable maintenance of TH [74–77]. The neurocritical care guidelines advocate the use of a servo-controlled body wrap surface-cooling device in neonates with hypoxic-ischemic encephalopathy and the use of intravascular catheters or surface-cooling gel pads in older populations [72]. Endovascular cooling devices are only FDA-approved for use in adult patients at this time. Novel intranasal and esophageal cooling devices are currently being studied but have not yet reached the same level of support in the literature [78, 79].

The rewarming period is critical for the emergence of complications and modulation of the beneficial effect of TH. Preclinical studies have found that a rewarming rate of 0.5–1 °C/h did not affect the benefit of TH, but faster rewarming negated this effect [80, 81]. Rapid rewarming is tied to increases in ICP and changes in cerebrovascular autoregulation [82–84]. The rewarming period has also been associated with the emergence of interictal epileptiform discharges, seizures, and status epilepticus [85, 86]. Indeed, the American Clinical Neurophysiology Society consensus statement on continuous EEG in critically ill adults and children cites acute supratentorial brain injury with altered mental status including during and after TH as an indication for continuous EEG monitoring [87]. Furthermore, there are clear changes in cardiovascular physiology during rewarming that result in shifts in blood pressure and heart rate resulting from redistribution of blood flow secondary to peripheral vasodilation [88]. Patients are at increased risk of hyperkalemia during rewarming due to cellular shifts and iatrogenic replacement of hypokalemia during TH [89]. Altogether, the rewarming phase is one that necessitates close monitoring with gradual and controlled temperature modulation to prevent overshooting or rapid temperature correction.

Complications

Shivering

Shivering is a frequent complication that may impede efficacy of TTM application as shivering increases metabolic demand and cerebral energy consumption [90]. A first line of prevention or treatment includes the non-pharmacologic intervention of surface counter warming with an air-circulating blanket; however, in practice, acetaminophen, sedation, and neuromuscular blockade are routinely added in a stepwise approach [72, 91–94].

Cardiovascular Complications

TH can have a number of effects on cardiovascular physiology, including bradycardia and arrhythmias. These effects can be particularly detrimental to patients who may have compromised function post-CA [95–97]. Due to higher systemic vascular resistance index in patients who are cooled to 33 °C vs 36 °C, cardiac index may be adversely affected and, combined with the associated bradycardia, can result in decreased organ and tissue perfusion, hyperlactemia, and increased requirements for vasoactive support [95, 98].

Metabolic Derangements

In addition to hyperlactemia and metabolic acidosis, serum potassium levels decrease during

active cooling, with as high as 76% of patients undergoing TH developing hypokalemia [89]. Subsequently, serum potassium levels rise with cellular shifts during the rewarming phase, such that 15% of patients develop hyperkalemia, necessitating close monitoring throughout all phases of TTM [89]. Similarly, hypophosphatemia and hypomagnesemia are also frequently encountered during cooling [99]. TH is associated with higher mean blood glucose, increased blood glucose variability, and higher insulin requirements during active cooling phases due to changes in insulin sensitivity and pancreatic function [100].

Cold diuresis is characterized by increased urine output during the induction phase of TH [101]. It occurs as a result of the increased systemic vascular resistance, which increases venous return leading to activation of atrial natriuretic peptide release and, in turn, suppression of antidiuretic hormone secretion [102, 103]. This diuresis can quickly result in hypovolemia and can be aggravated by other treatments including hyperosmolar therapies.

Coagulopathy

Coagulopathy is a known complication of TH due to its effect on platelet and clotting factor function [103]. Monitoring with thromboelastography during mild TH has revealed differing findings ranging from a delay in the initiation of coagulation and altered fibrinolysis to no effect of TH on coagulation [104–106]. The occurrence of TH-associated coagulopathy can be confounded by trauma-induced coagulopathy in patients with TBI, which may develop after admission and initiation of TTM [107]. Despite these laboratory and in vitro differences in coagulation, the literature has not found an increase in the incidence of new hemorrhage, transfusion requirement, or bleeding complications with TH [108–110]. Thus intracranial hemorrhage associates with TBI or HIE are not contraindications to TH.

Infection

The risk of infection in TTM has been long debated. Evidence suggests suppression of leukocyte count and migration as well as phagocytosis with TH [103, 111]. A meta-analysis of adults treated with TH for any indication found an increased risk of pneumonia and sepsis, though variability and controversy regarding the definition of infection make these results difficult to interpret [112]. Monitoring for infection can include observation of water temperature on servo-controlled devices (with decreasing water bath temperature as a suggestion of patient tendency for hyperthermia) as well as surveillance blood cultures; however there is no evidence to support the utility or efficacy of these practices. In our practice we do not monitor daily screening cultures but reserve testing when clinical suspicion would warrant based on a combination of patient condition and risk factors, laboratory values, and water bath temperature trends.

Drug Metabolism

TH affects pharmacokinetics and pharmacodynamics of many medications commonly used in the PICU. In general, TH can affect absorption, distribution, and excretion as well as protein binding, enzymatic activity, and receptor modulation, all to the degree that can have an impact on dosing, duration of activity, and side effects [113]. These effects may be time dependent, with longer duration of TH having a larger impact on drug effects. Complicating matters further are the potential for different clinical responses to some drugs during active cooling and rewarming phases of treatment. Notable classes of medications impacted by TH include benzodiazepines, opiates, neuromuscular blockers, anti-epileptic drugs including barbiturates, and those cleared by the cytochrome P450 enzyme system [113–118]. Close monitoring of drug levels where available and for signs of toxicity is especially important in this population.

Conclusions

TTM, especially fever prevention after acute brain injury, has become standard of care in the PICU. Heterogeneity of the PICU population and varied approaches to optimal implementation of TTM impedes adequate power for study in subgroups of children who may benefit over generic application. New innovative research and analytical methods may assist in providing clarifying evidence for optimal TTM application in this population of children having a vital need for advances in neuroprotection.

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