CRRT in the Septic Patient

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Case Vignette

A 12-year-old (48 kg) previously healthy male presents to your hospital in acute respiratory failure and overwhelming suspected septic shock. He is intubated in the emergency department, received broad spectrum antibiotics (vancomycin and ceftriaxone), fluid resuscitated with 4 L of normal saline, placed on an epinephrine infusion and titrated to 0.4 mcg/kg/min, and brought to your intensive care unit. Initial labs obtained in the emergency department demonstrate thrombocytopenia, anion gap metabolic acidosis, transaminitis (AST 650, ALT 525), and an elevated creatinine at 2.5 mg/dL. He is febrile at 40.1, and has had no urine output in the 2 h since his arrival in the emergency department. He is given another 2 L of normal saline, loaded with steroids for vasopressor refractory shock, and given two additional anti-staphylococcal drugs. He is becoming increasingly hypoxic, requiring increases in ventilator settings, with a pattern consistent with pulmonary edema seen on a repeat chest radiograph. Echocardiogram demonstrates poor cardiac contractility, and in consultation with pediatric surgery, nephrology, and blood bank, the decision is made to place the patient on ECMO to gain stability to provide CRRT and plasma exchange.

Infections and their complications are the number one cause of pediatric mortality worldwide. Accordingly, sepsis and septic shock are two common reasons why children are admitted to the pediatric intensive care unit (PICU). While in adults, the mortality associated with septic shock is between 30 and 40%, in children it has been thought to be much lower (in the 5–10% range) based on previous studies [1, 2].

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However, a recent point prevalence study of pediatric severe sepsis over 128 sites in 26 countries demonstrated a prevalence of 8.2% of 6925 patients with 25% mortality [3]. One potential reason for the higher mortality in this study was the frequent presence of multiple organ dysfunction syndrome (MODS), which from previous work we know is associated with higher mortality rates [4]. MODS was present in 67% of the patients on the day of sepsis recognition and 30% of those with MODS went on to have additional organ failures. With the progress in medical science, there are very few diseases in the pediatric population which have such high mortality rates, and thus pediatric sepsis is a common target for attempting to reduce childhood mortality. Attempts at improving sepsis outcomes over the last decade have targeted prevention (immunization), early recognition (sepsis scoring systems, community pediatrician and family education, etc.), and standardized practice (sepsis bundles, mandated antibiotic choices, etc.). Many have met with some degree of success, however this remains a pressing public heath focus.

At the bedside in the PICU, one must acknowledge that caring for the patient with sepsis not only involves treatment of the causative infection, but also managing the multiple other organ dysfunctions that are common in pediatric sepsis. With advanced technologies, such as continuous renal replacement therapy (CRRT), we have available to provide organ support and replacement. As a result, the outcome for a septic child is less related to the ability to eradicate the inciting infection, and more dependent on the clinician's ability to support the patient's other organ failures until they recover. This chapter will review the use of one of those therapies, CRRT, during sepsis. Chapter 22 in this textbook covers the use of multiple extracorporeal therapies together to support a patient with multiple organ failure. An important notation is that while the last decade has provided us with some evidence on how best to perform CRRT, many questions remain and there is a lack of evidence to answer them conclusively. Pediatric specific evidence will be covered if available, and if not, I will present data from adult trials and leave it to the reader to balance whether that data is applicable to the pediatric population. As we described in Chap. 22, in this field, expert opinion remains a common source of information and additional clinical trials are needed in order to best define the optimal practice of CRRT in pediatric sepsis patients.

26.1 Septic Acute Kidney Injury

Acute kidney injury (AKI) is a common manifestation of injury seen in both adult and pediatric critically ill patients in the intensive care unit and occurs from a variety of pathologic insults. While AKI is commonly recognized at the bedside, consistent definitions have limited research into this important topic in the past. Over the last decade, advances have been made in this area and other chapters in this text cover comprehensively the intricacies of the diagnosis, consensus definitions, severity scoring systems, and outcomes associated with AKI. In a similar manner, sepsis has had the same problems—a disease easily recognizable at the bedside, but suffering from a lack of consistent formal definitions that would facilitate worldwide

research. Over the last decade, the sepsis community has collaborated and developed consensus definitions for both adult and pediatric patients [5, 6]. The copresence of AKI during an episode of sepsis defines the condition known as septic AKI. Estimates of the prevalence of septic AKI have been published in the adult population and range from 22 to 53% depending on the method of the study and definitions used [7, 8]. In pediatrics, a subanalysis of the SPROUT study demonstrated a 21% prevalence of septic AKI [9].

The pathophysiology of septic AKI is not completely understood, but the pathways involved appear to be quite different from traditional renal insults due to drug induced, hypoxic/ischemia mechanisms, and rhabdomyolysis induced injuries. Previously, the major theories surrounding the causes of septic AKI revolved around changes in blood flow to the kidney during times of either low global blood pressure or due to the renal perfusion effects of the vasopressors used to support the global blood pressure, and that these changes in perfusion led to acute tubular necrosis. There is increasing evidence, both on the bench and at bedside, that this model is partially incorrect. A combination of studies have demonstrated acute tubular necrosis plays a lesser role in septic AKI injury, and that renal perfusion is much more dynamic during sepsis than first thought, and may actually be increased during certain phases of sepsis. Increasing understanding of the immune and coagulation systems during the body's response to sepsis have allowed further insight into the both the AKI, as well as led to some observations which may explain the higher levels of chronic kidney disease in AKI survivors. The implication of the immune and coagulation systems in septic AKI also provides plausible pathophysiologic pathways that could be involved in the injury of other organs and subsequent development of MODS. While some two organ dysfunction syndromes, such as hepato-renal, are established, new models of organ cross talk, such as cardio-renal syndrome, have been proposed based on this new paradigm [10]. A thorough understanding of these pathways is important, especially for those caring for the septic pediatric patient, who as described above, is most likely to present with established MODS. Detailed reviews of the underlying pathways implicated in septic AKI have been published, and they are covered more extensively in Chap. 6 [11–13].

Similar to AKI, fluid overload (FO) is common during sepsis, from a combination of resuscitation fluids given empirically to support blood pressure, as well as to provide adequate oncotic pressure (and thus intravascular volume) during periods of vascular leak that are commonly seen in sepsis. Fluid overload has been associated with mortality in multiple clinical conditions in the pediatric population, in both single and multiple center studies. The association of fluid overload with poor outcomes in a multitude of conditions resulting in pediatric critical illness has been reviewed elsewhere in this textbook, however, it is worth reviewing a few newer examples of the evidence specifically in pediatric sepsis. While the original work on fluid overload and outcomes in children receiving CRRT came from the United States in the 2000s, more recent work has replicated the findings in other settings. In Venezuela, Naveda recently retrospectively reviewed 149 pediatric patients with an average age of 6 years, with 60% having sepsis as the etiology for their shock. In this septic group, the overall mortality was 25.5%, and fluid overload was identified

as an independent risk factor (OR 1.5, CI = 1.2–4.9) for the development of kidney failure [14]. Similarly, in China, Chen evaluated 202 children with severe sepsis, finding a 30.2% mortality rate and a 23% rate of fluid overload [15]. They found the previously described correlation between increasing degree of fluid overload and increasing mortality risk. While this correlation usually has been reported as starting at >10% FO, they evaluated a novel concept of early fluid overload being defined as >5% FO in the first 24 h of ICU admission. This test predicted mortality with a sensitivity of 67% and specificity of 80% (ROC 0.74, CI 0.65–0.82). In both of these studies, a significant portion of the fluids given were due to fluid boluses. No discussion of fluid boluses in the treatment of sepsis would be complete without mentioning the findings of the FEAST trial. While fluid overload was not specifically calculated, the FEAST trial is one of the largest pediatric sepsis trials, having evaluated 3141 children with sepsis in limited resource settings in Africa. It found that saline fluid boluses at the time of admission to the hospital were associated with a significant increase in mortality at 48 h (10.5% saline, 7.3% control, RR 1.44, CI 1.09–1.9) [16]. While one must determine if the results of this study are generalizable to the patient population and diseases that you care for at your center, it certainly has introduced controversy into a mainstay of pediatric sepsis care. Fluid overload, especially in sepsis, remains a potentially modifiable risk factor for poor outcome and thus is a tempting target for intervention.

26.2 Why CRRT During Sepsis?

AKI and FO are both common during sepsis, and renal replacement therapy is often needed to mitigate the consequences of the renal injuries. When evaluating options for providing renal replacement therapies, the three most common options in pediatrics are intermittent hemodialysis (IHD), CRRT, and peritoneal dialysis (PD). Looking at the epidemiology of which therapy is chosen, we often see a predominance for CRRT use in the pediatric population. For example, Westrope recently reviewed the Pediatric Intensive Care Audit Network (PICANet) database which collects data on all children <16 years old who receive care in a PICU in the United Kingdom [17]. They found that 2.9% of PICU admissions received renal replacement therapy, and that about 50% received CRRT only, 45% received PD, and 4% received IHD. Similar findings have been seen in other countries, and for the sickest population of patients—those on ECMO—CRRT use is >90% [18]. With these varying options for providing renal replacement therapy, why is CRRT often the predominant form used?

Increased rates of hemodynamic instability with the use of IHD in septic patients are a common reason given for the primary use of CRRT. In the pediatric population, there are very little data comparing hemodynamic parameters between these two groups. In adults, John examined 30 septic AKI patients who were randomized to CRRT or IHD and found patients treated with CRRT had increased blood pressure and decreased HR at 2 h and an increased systemic vascular resistance at 24 h compared to those who received IHD [19]. Avoiding the need for systemic

anticoagulation, usually with heparin, is another frequent reason cited for choosing CRRT over IHD in the septic population, since many regional anticoagulation strategies have been published (see Chap. 17). With the increased prevalence of disseminated intravascular coagulation and thrombocytopenia that often coexist in septic shock patients, this concern of bleeding complications is certainly warranted. Similarly, this concern of hemorrhagic complications with catheter placement often is cited as a reason to not perform acute PD in the septic patient. Seen more commonly in the smaller pediatric patients, the diaphragmatic loading associated with infusion of PD fluids into the abdominal cavity leads to a reduction in functional residual capacity and may make adequate oxygenation and ventilation more difficult. Other experts share concerns that clearance may be inadequate when using PD due to increased metabolic demands seen during sepsis. It should be pointed out that while CRRT use predominates, many centers are able to use IHD and PD successfully in septic patients, and that while each of these above concerns are valid in general, since there is no convincing evidence of superiority that choice of renal replacement modality should be individualized to meet the needs of each patient best utilizing the skills and equipment available at a particular center.

Advocates for using CRRT for septic AKI generally point to several key advantages of using a continuous therapy modality. The first is that in sepsis, cellular metabolism is greatly increased and rapidly changes throughout the day with increases in fever, dosing of anti-infectives, and blood products. Use of a continuous renal replacement therapy allows a slow, but steady correction of acidosis and electrolyte abnormalities back to their prescribed baseline and provide a more normal homeostasis when compared to the saw tooth shaped clearance of IHD or to a lesser degree PD. Increased clearance of middle-sized molecules, including cytokines, chemokines, and other immune-derived molecules has been another proposed benefit of the use of continuous renal replacement therapies. Understanding that the underlying pathophysiology of septic AKI is likely to be related to a dysregulation of host immune response, has led to the desire to use continuous therapies in order to blunt the agents causing the dysregulation. In the early 2000s, Ronco proposed the "peak concentration hypothesis" that states that high levels of both inflammatory and anti-inflammatory mediators are associated with both the end-organ damage seen in MODS as well as the increased mortality rates [20]. This has led to the introduction of "blood purification" techniques that attempt to lower the peak levels of such mediators and regain the usual immunologic homeostasis. To achieve this goal, continuous therapies are favored over intermittent ones, and CRRT was the first of these therapies to be used. Clearance of the mediators of sepsis have been described in multiple studies, however the exact amounts and types of mediators cleared varies by dose of CRRT, filter variables (pore size, surface coatings, material, frequency of replacement, etc.), and timing of initiation. For those wishing to follow this path, Honore et al. provide a recent pragmatic review of the variables involved and a strategy for choosing equipment and dosing for patients with septic AKI [21]. In addition to CRRT-based clearance, hemoperfusion columns are also available that can remove mediators and are added to a CRRT system. The polymyxin B-based systems are the most commonly used (>100,000 cases in Japan

alone) in both adult and pediatric patients. Shimizu provides a recent review of this technology and application [22]. When used in combination with CRRT, it can further reduce mediators of sepsis. Among others using this combined approach, Zheng recently reported significant reductions in high mobility group box protein 1 (HMGB1) levels and improved 30 days survival in an adult population of septic AKI [23].

26.3 Practical Issues with CRRT During Sepsis

Using CRRT in the septic patient is not without potential risks and issues. The first question in prescribing CRRT is to determine when the patient should receive this therapy. The timing of CRRT initiation is a complicated subject, and remains the subject of research investigation. There are proponents in the medical literature from the extremes of initiating CRRT only once the "traditional" indications of dialysis (acidosis/pulmonary edema/hyperkalemia/etc. that have failed medical management and are life threatening) have been met to the other extreme of initiating it in certain populations, such as extracorporeal membrane oxygenation, empirically on all patients even in the absence of evidence of renal injury in an attempt to prevent fluid overload and other electrolyte complications. It should be mentioned that the current KDIGO guidelines recommend a global assessment of the patient's current condition and trend of changes, and not relying on absolute numbers to trigger CRRT initiation. While a few studies have been attempted to evaluate issues of "early" versus "late" initiation of CRRT, their interpretation for the pediatric community are complicated by being done prior to the consensus definitions of AKI, differing in definitions of "early" and "late" between studies, and mostly involving adult patients with disease processes that differ from what is seen in children. Two new studies, IDEAL-ICU and STARRT-AKI, will address the issue of timing in the adult population. Additional studies in pediatrics are now being developed to better define optimal care for this important question.

Once to the decision has been made to initiate CRRT, the question of optimal prescription is the next to be addressed. Other chapters in this textbook address in other clinical settings the different modes of CRRT that can be used (continuous veno-venous hemofiltration, continuous veno-venous dialysis, and continuous veno-venous hemodiafiltration) and the potential associated benefits and issues. This information is applicable to sepsis patients as well, with some expert opinion favoring convective modalities of clearance. Many centers standardize on one mode and utilize one type of filter for all CRRT procedures regardless of indication, since there is little substantial evidence of outcome benefit demonstrated for tailoring this therapy more specifically. While not an evidence-based statement, the concept of doing one thing and doing it well will likely serve the patient better (by reducing interruptions in therapy due to complications, and maximizing the delivered dose) than introducing new modes or filters in these unstable sepsis patients. The dose of therapy has been a controversial topic, for both adults and children.

Ronco performed the first randomized trial with dosing divided between 20, 35, and 45 mL/kg/h and demonstrated improved survival with 35 mL/kg/h compared to 20, but no difference in mortality between the 35 mL/kg/h and 45 mL/kg/h groups [24]. Later subgroup analyses of the septic AKI patients in the ATN and RENAL trials also showed no difference in dose [25, 26]. Based on this study, the "standard" dose for all patients has been 20–30 mL/kg/h. Several other adult trials have attempted "high dose" (~70–100 mL/kg/h) CRRT in the setting of sepsis, attempting to maximize the mediator clearance with some demonstrated success in that outcome, but with no difference seen in mortality [27, 28]. It is important to note that in many of these studies, increased clearance of antibiotics is also demonstrated, which raises particular concern in the septic patient. Clearance, both of anti-infectives, but also nutrition must be taken into consideration in the patient on CRRT, and frequent drug and nutritional monitoring must be performed to ensure optimal dosing. Guidelines and best practice reviews have been published to aid with appropriate anti-infective and nutrition prescribing and monitoring for the patient with septic AKI [29, 30]. Finally, choosing an anticoagulation strategy is important for the septic patient. While it can be performed safely, considering the coagulopathy and disseminated intravascular coagulation that often coexists during septic shock, there are advantages to avoiding heparin-based strategies that require both the patient and the CRRT circuit to be anticoagulated in order to reduce bleeding complications. Regional anticoagulation techniques, for example with citrate, have been reviewed in other chapters and are ideal for use in septic AKI patients. Frequent monitoring of, and avoiding low patient ionized calcium levels is necessary in these sepsis patients, so as not to impair cardiac function. This occurs more prominently in the youngest pediatric patients whose immature myocardium is more dependent on extracellular calcium concentrations to promote contractility. A more novel approach for these septic children is to use low dose prostacyclin infusions to provide short duration, localized platelet inhibition within the CRRT circuit as a source of anticoagulation [31]. Potential benefits of this approach in septic AKI are avoiding hypocalcemia induced hypotension or dysrhythmias as well as citrate lock.

As seen above, while many patients' hemodynamics improve in the first few hours after initiating CRRT, the first few minutes after connection can often be more precarious. First described during intermittent hemodialysis, the correlation between bradykinin release and subsequent vasodilatory induced hypotension with exposure of blood to membranes has also been described in CRRT use. While often attributed to only AN69 membranes, the phenomenon has also been described in patients with polysulfone membranes [32, 33]. Various techniques have been described to mitigate this problem, and should be considered in patients on high amounts of cardiovascular support or who are already unstable at CRRT initiation. During CRRT, circuit and filter life is variable and not predictable in patients with sepsis. Similarly, the total duration of CRRT needed for septic AKI remains variable, and clinical criteria of when to stop in order to evaluate for recovery of native renal function are poorly defined.

26.4 Outcomes in Septic AKI

As has been discussed, there are many different approaches to prescribing CRRT for the septic AKI population. There is an increasing amount of outcome data, mostly from large adult trials, however many of the basic components of optimal renal replacement therapy remain incompletely defined. A brief review of some of the major controversies in renal replacement therapy during sepsis follows.

With regard to choice of therapy, adult trials demonstrate similar mortality, renal recovery, and complication rates when using IHD, slow low-efficiency dialysis (SLED), and CRRT [34, 35]. Similarly, in total, there appear to be similar outcomes when evaluating convective versus diffusive clearance modes [35]. The mode of CRRT has been found to change outcome in one, single-center, randomized prospective study, published in 2006 which demonstrated improved 90 day survival with CVVHDF as compared to CVVH (hazard ratio 0.59, CI 0.40–0.87) [36]. No subsequent prospective study has evaluated this specifically. Two retrospective studies, from Canada and Croatia (which specifically evaluated septic AKI) have been subsequently published demonstrating no difference in survival between these modes [37, 38]. Timing of CRRT initiation was addressed in the recently published AKIKI study, which involved 31 adult ICUs in France [39]. The study randomized patients to CRRT initiation within 6 h of meeting stage 3 AKI or using a set of "standard" indications for CRRT. There was no difference in mortality between the two groups, and interestingly almost half of the "standard" indication patients never received CRRT. There was an additional single-center trial, that was able to demonstrate a mortality difference (39.3% vs. 54.7%, hazard ratio 0.66, CI 0.45–0.97) with randomization within 8 h of meeting stage 2 AKI versus within 12 h of meeting stage 3 AKI [40].

Anticoagulation during CRRT is always a controversial topic, and potential benefits and harms are frequently reviewed in the medical literature. Many of the more recent reviews make statements such as, "regional citrate anticoagulation can be recommended as the therapy of choice for the majority of critically ill patients requiring CRRT" [41]. While avoiding heparin anticoagulation for CRRT in septic AKI has some potential benefits, at least in the adult population, it is important to remember that there is data suggesting that using IHD or CRRT with systemic heparin anticoagulation in septic patients can have low complication rates. In a subanalysis to the CONVINT study which randomized patients between IHD and CRRT and had a 66% rate of septic AKI, there was a low rate of death from bleeding complications (3.6%) and no complication rate difference between IHD and CRRT [42].

Considering the dose of CRRT, the current KDIGO guidelines recommend 20–25 mL/kg/h based on the finding of Grade 1A evidence in the medical literature. As discussed earlier, in the realm of septic AKI, other investigators have attempted higher dosing in an attempt to alter outcomes. Park et al. randomized 212 adult patients with septic AKI between 40 mL/kg/h and 80 mL/kg/h and evaluated the effect on mortality and cytokine levels [28]. They found no difference in 28 day mortality between the two groups. While the higher dose CRRT group significantly reduced multiple pro- and anti-inflammatory mediators, the standard dose did not.

This and other studies demonstrate that while you can clear these mediators via high dose CRRT, that the end effect may not be enough to change clinical outcomes such as survival.

We briefly examined the potential role of polymyxin B-based hemoperfusion columns in septic AKI when used in conjunction with CRRT. Previous smaller studies have been promising and the results of the much larger and now recently completed EUPHRATES randomized trial of polymyxin B hemoperfusion columns in septic shock have not been formally reported yet, but a press release stated that there was a reduction in mortality between groups (36.9% and 31.9% with the device) that did not reach statistical significance. There are some interesting subgroup analyses that are ongoing looking at the sickest population with MODS, where a post hoc analysis demonstrated a 10.7% reduction in mortality was seen [43]. Further evaluation and publication of the entire clinical trial data and outcomes will be necessary in order to fully understand these findings.

26.5 Role of Multiple Organ Support Therapies in Sepsis

Understanding the pathophysiology of the development of MODS as described above, it is becoming increasingly common in the ICU to be supporting patients with 4–5 organ failures. It is interesting that the pathophysiology of MODS appears to be a common end pathway to many different inciting injuries. With 66% of septic pediatric patients presenting with MODS, it is not unusual for the intensivist to be taking care of a patient for the first few days with no clearly defined diagnosis of the underlying disease that got the patient there. For the sickest of patients, organ support therapies provide a lifesaving bridge to give time to figure out the underlying cause, give time for therapies such as antibiotics or immune suppression to work, or allow surgeries to obtain source control of infections that would otherwise be lethal. Extracorporeal therapies, such as ECMO, CRRT, and plasma exchange, play major roles in supporting these patients. While Chap. 22 discusses the practical side of getting these various devices to work together from a clinical and biomedical engineering standpoint, a brief focus on the framework of how we use these devices at our center to provide multiple organ support is warranted.

The patient presented at the beginning of this chapter represents a common scenario that is seen in the pediatric ICU. In summary, the patient shows up with overwhelming shock that is thought to be septic in nature, but no definitive organism has been identified yet. As is seen with many septic patients, this patient presents in four organ MODS, with respiratory, cardiac, hepatic, and hematologic organ dysfunctions. He is rapidly declining since his admission to the ED and initial efforts at support are failing to meet goals of adequate oxygen delivery and organ support. This is a patient that not so long ago, would have been treated by escalating inotrope/vasopressor infusions and ventilator settings until they have reached center-based "maximum" doses and often resulted in complications from therapy (pneumothorax, dysrhythmias, etc.) and death within the first 24 h of therapy. While diagnostic labs were sent, often the results would return post-mortem.

Currently, these unstable and rapidly decompensating patients are managed at our center by a multidisciplinary team that can bring organ support therapies to the bedside and initiate them in a short period of time (<1 h goal). The underlying pathophysiology that these patients have in common is often an initial insult that leads to organ damage, and then through the immunologic and coagulation pathways described above leads to damage of other organs and the rapid progression into MODS. Many of the traditional therapies that are used (mechanical ventilation, high dose inotropes/vasopressors, diuretics, blood products, etc.) cause injury to the very organs they are being used to support, and often lead to increasing other organ damage due to these "cross talk" pathways, and the vicious cycle of increasing multiple organ damage escalates eventually ending in death. A detailed review of the problems associated with our traditional therapies are out of the scope of this chapter, but are derived from evaluating the advances that cardiac intensivists and surgeons have made with the introduction of early mechanical support for heart failure over traditional therapies and the long held understanding of the negative effects of mechanical ventilation (currently >8000 articles in PubMed).

A cornerstone of our approach is acknowledging that breaking this cycle of traditional therapy induced injuries is vital. This starts with evaluation of the cardiorespiratory system. ECMO is commonly used as a platform to gain control over the cardiorespiratory system and gain enough stability to be able to provide the other organ support and medical therapies. While veno-arterial (VA) ECMO, which provides both cardiac and respiratory support, would at first thought be the ideal modality in this situation, it has significant issues associated with it, including, but not limited to, need for carotid cannulation, higher risk of embolic stroke and cerebral hemorrhage, and ineffectiveness in high output cardiac failure often seen in vasodilatory septic shock. The benefit of it is that it provides excellent forward blood flow when a replacement for cardiac failure is needed in a classic cold shock setting. Our approach is to try venovenous (VV) ECMO first to avoid the complications associated with VA ECMO, with an understanding that this will not be effective for all patients. A review of the outcomes of septic, noncardiac, pediatric patients in the Extracorporeal Life Support Organization's (ELSO) registry demonstrated improved outcomes with VV ECMO [44]. From a surgical standpoint, the surgeons open the neck and isolate and control both the internal jugular and carotid artery. We then proceed with venovenous (VV) cannulation and turn down the ventilator to minimal levels. Often the adequate supply of oxygen from the ECMO circuit combined with the ability to reduce the intrathoracic pressures caused by high ventilator settings (which have substantial cardio-pulmonary interactions with respect to venous return and transmural pressure) are sufficient to allow both gas exchange and a rapid weaning of various inotropes/vasopressors. It is not unusual for patients to be on 2–3 high dose inotropes/vasopressors prior to VV ECMO, and be completely off of them within the first 15–30 min of ECMO. During that time, the surgeons and the intensivists remain at bedside and if rapid improvement is not seen, then cannulation of the carotid artery occurs and the patient is transitioned to veno-arterial ECMO. Now that cardiorespiratory stability has been achieved, either natively on VV or mechanically via VA ECMO we move to adding additional organ support.

Over the last decade at our center in the PICU, our approach has been that CRRT is provided for all ECMO patients at the time of ECMO initiation. From a practical standpoint, it is usually started within 0.5–1 h of cannulation immediately after cannulas have been confirmed in an appropriate position and secured. A review of the reasons behind this is discussed in Chap. 22, as well as the KIDMO series of papers that are cited there. In brief, essentially all of these septic patients meet criteria for >10% fluid overload and > 50% of them have > stage 2 AKI, and we wish to both prevent that fluid overload from worsening, as well as to correct it when hemodynamically improved, providing renal replacement therapy for electrolyte and acidosis control, and allowing improved nutrition [45]. The previously mentioned KIDMO data has demonstrated that the risk of mortality is best associated with stage of AKI and not solely the use of CRRT. Considering the degree of acidosis often present in these patients, we often initially start with a replacement fluid with a higher base concentration to more rapidly correct the acidosis which will help improve cardiac function. Initial fluid balance prescription is usually to be fluid neutral including insensible losses. In this setting, one also needs to consider water losses from the oxygenator which will be related to the amount of sweep gas flow used across the oxygenator. A reasonable estimate of oxygenator water losses for the adult Quadrox D™ membrane is 50–60 mL/day per liter of sweep gas [46, 47]. Diuretics are not used in these patients after CRRT initiation, even in the absence of urine output. Anuria is commonly seen and may persist for the duration of CRRT, however renal recovery of survivors is not affected by this in children. Using this approach, our center's survival and renal recovery rates are similar to the overall worldwide ELSO data [48].

Having addressed the respiratory, cardiac, and renal systems rapidly, we turn to the hematologic and hepatic systems. At this point, it is important to try to figure out the underlying cause of the patient's shock. Rapid diagnostics, such as infectious PCR-based methods, echocardiography, and labs that can be run at your center are often helpful in providing a provisional diagnosis. Carcillo has recently published a mental framework for classifying these MODS children, which can lead to the next therapeutic options for supporting the remaining organ systems [49].

In brief, often patients fall into three clinical and laboratory syndromes. An "immunoparalysis syndrome" is described which is characterized by persistent and new infections that are difficult to clear with traditional therapy, with prolonged lymphopenia and decreased response of leukocytes to stimulators such as tumor necrosis factor alpha or endotoxin. These patients may benefit from immunomodulation techniques, reduction of immunosuppressants (if used), and addition of granulocyte macrophage colony stimulating factor (GM-CSF). The second syndrome describes patients with "TAMOF" (thrombocytopenia associated multiple organ failure). These patients are characterized by having a thrombotic microangiopathy due to failure to clear von Willebrand factor after endothelial injury due to reduced ADAMSTS13 levels. Excessive inflammation in these patients is also associated with complement activation and has similarities in pathophysiology to disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. These

patients benefit from aggressive and immediate plasma exchange to both replace missing ADAMSTS13 and to remove any autoantibodies to ADAMSTS13. This procedure also corrects the coagulopathy that is commonly seen in sepsis, helping restore both hematologic and hepatic homeostasis. Like the case presentation patient, approximately 75% of our rapidly decompensating previously healthy children with new onset MODS have the TAMOF syndrome. The final syndrome is described as "SMOF" or sequential multiple organ failure with new hepatobiliary dysfunction. This syndrome is clinically seen with patients who usually start out with respiratory failure and then develop rapid onset of hepatic and then other organ failures. Massive increases in inflammation are often present, leading to extremes of cardiac instability associated with lab findings of severe liver failure, hyperferritinemia, cellular hypoxia, and inability to clear viral infections. Diseases such as hemophagocytic lymphohisticytosis, post-transplant lymphoproliferative disorder, and macrophage activation syndrome are examples of conditions that often carry the SMOF phenotype. Immune modulation in this group can be useful, and anti-inflammatory cytokine-based strategies such as anakinra (IL-1 receptor antagonist) has shown potential for benefit in small studies.

While these syndromes of multiple organ failure do not identify a specific disease, taking this approach to classification and empiric therapy along with total organ support provide adequate stability for the underlying diagnosis to be identified and specific therapy initiated prior to death. Serial evaluations of underlying organ function and disease status is important during multiple organ support therapy, because patients who present as hyperinflammatory may revert to the immunosuppressed phenotype later in their course and changes in approach will be necessary. Trading traditional approaches to life support to an extracorporeal-based system is not without its own set of complications, and the team must be fastidious in care for each of these systems to prevent complications. Although this approach is being performed in a few high volume centers in the United States with reasonable results, additional work is needed with multicenter studies to see if these techniques can ultimately improve outcomes of this most unstable group of patients.

26.6 Summary of CRRT During Sepsis

Septic AKI is a commonly encountered problem for the pediatric intensivist and nephrologist. Our understanding of the underlying pathophysiology of septic AKI has changed over the last decade, and is beginning to influence the way we approach, diagnose, and treat this disease. As our technology improves, we are being faced with sicker and more complicated patients than ever before. We have an increasing amount of both pediatric and adult literature to guide some of the decision-making surrounding renal replacement for these patients. Use of multiple extracorporeal organ support therapies during sepsis is occurring successfully at several large pediatric centers. However, controversies and much work remains, with many questions about how to provide optimal care for this complex, unstable, and heterogeneous population.

Key Learning Points

- Septic acute kidney injury is common in the pediatric population.
- CRRT, with changes in technique, can be used to support these patients to recovery.
- Multiple extracorporeal support therapies can be used together to support patients with multiple organ dysfunction syndrome.

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