Objectives

- Describe current diagnostic sepsis criteria and the resultant dilemmas facing pediatric critical care clinicians and researchers
- Identify novel new diagnostic techniques for sepsis and severe sepsis that can enhance our ability to diagnose patients earlier and more reliably
- Detail current management strategies for pediatric severe sepsis and septic shock and describe novel approaches on the clinical and research horizon

Key words: pediatric severe sepsis, pediatric septic shock, sepsis, early goal directed therapy, sepsis bundles

Sepsis is the leading cause of death in infants and children worldwide. In the United States alone, approximately 42,000 cases of severe sepsis occur annually, and in-hospital mortality is estimated at 10.3%.\(^1,2\)

Defining Severe Sepsis and Septic Shock

Both pediatric and adult studies have demonstrated an association between delayed, inadequate, goal-directed resuscitation and increased mortality\(^3,4\); therefore, early detection of sepsis is key to successful treatment of septic patients.\(^5\) Particular attention must be paid to identifying “the start of sepsis,” as many sepsis management bundles are predicated on initiation of time-sensitive therapies within the first 1, 6, and 24 hours of sepsis. Because many US states now require institutions to provide data on their compliance with these time-sensitive management strategies, identification of the start of sepsis has many potential clinical and medicolegal consequences. Accurate detection is predicated on definitions that are both useful to all clinicians who may be first responders for these patients and robust enough to discriminate patients with simple infection from those with severe sepsis or septic shock, particularly for effective research study implementation. Of note, because of complex diagnostic criteria for sepsis in children, many research studies default the start of sepsis to the time of emergency department triage or the time when clinicians recognize the presence of sepsis. Neither of these conventions has been proposed for use by the American College of Critical Care Medicine (ACCM) nor do they necessarily accurately correlate with the physiological starting time of sepsis as defined by international criteria.

The 2016 Third International Consensus Definition for Sepsis and Septic Shock (aka Sepsis-3) intends to offer the bedside clinician easy steps to identify adults with sepsis, now defined as infection plus a dysregulated host response leading to life-threatening organ dysfunction. A diagnosis of sepsis requires a change in a patient’s Sequential Organ Failure Assessment (SOFA) score of more than 2 points, while the term *septic shock* is reserved for patients with clinical sepsis plus persistent hypotension that requires vasopressors and lactate levels higher than 2 mmol/L after adequate fluid resuscitation. For first responders in the field, a “quick SOFA” (qSOFA) score was developed that initiates sepsis diagnosis for patients with at least 2 of the following: respiratory rate 22 breaths per minutes or more, altered mentation, or systolic blood pressure lower than 100 mm Hg.\(^6\)

Sepsis-3 definitions exclude children, so the task in our field is to assess the 2005 International Pediatric Sepsis Consensus Conference definitions for sepsis and organ dysfunction in pediatrics\(^7\) and adapt these definitions both for clinical use and for compliance with the Surviving Sepsis Campaign and the ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. For children, a diagnosis of sepsis requires evidence of systemic inflammatory response in the
presence of, or as a result of, suspected or proven infection. Severe sepsis is defined as sepsis that entails at least 1 of the following conditions: (a) 2 or more organ dysfunctions, (b) cardiovascular organ dysfunction, or (c) acute respiratory distress syndrome. Septic shock is diagnosed by sepsis and cardiovascular dysfunction that persists after fluid resuscitation with 40 mL/kg of fluid or more in the first hour.

Currently, diagnosing sepsis relies on objective and age-adjusted clinical and laboratory measurements; however, these may not always be reliable based on certain patient characteristics. The Sepsis Prevalence, Outcomes, and Therapies Study (SPROUT) researched nearly 7,000 pediatric ICU patients for the presence of severe sepsis at 128 sites across 26 countries. Interestingly, this study showed that less than half of patients were identified by both physician and consensus criteria. Although further research is needed to understand the variability in physician diagnosis, the use of tools such as biomarkers may play a role in the early detection and stratification of pediatric patients with sepsis.

**Next Steps in More Accurate and Early Diagnosis of Sepsis**

The heterogeneity of demographics, comorbidities, biological mechanisms, and severity of illness often leads to difficulty in determining which patients are at highest risk of mortality. Although sepsis is highly heterogeneous from both a clinical and a biological standpoint, the therapeutic approaches we use, at least within the first hours of severe sepsis, are homogeneous. In addition, current research trial design is extremely challenged in identifying relevant areas of patient heterogeneity at study enrollment, which can severely affect both the trial and patient clinical outcomes. Hence, it is not surprising that our literature is saturated with clinical trials that have failed to demonstrate efficacy despite being based on sound preclinical data. Given these obstacles, the field of critical care medicine is in need of stratification tools and biomarkers that may provide help for clinical decision making and predicting sepsis-related outcome.

**Biomarkers of Inflammation: Cytokines and Acute Phase Proteins**

Once an inflammatory response is initiated, immune cells release a wide range of mediators, such as interleukins (ILs) and tumor necrosis factor alpha (TNF-alpha), into the circulation. These cytokines result in production and secretion of acute phase proteins, and the potential of these proteins to serve as sepsis biomarkers has been explored.

**C-Reactive Protein and Procalcitonin**

The most used biomarkers in the clinical setting are the acute phase proteins C-reactive protein (CRP) and procalcitonin (PCT). The synthesis of CRP in the liver is triggered by IL-6 in response to tissue damage or inflammatory and/or infectious stimuli. A notable increase in CRP is seen after 4 to 6 hours, which doubles every 8 hours and peaks 36 to 50 hours after infection, inflammation, and/or infectious stimulus. Cost-effectiveness and timeliness of CRP are potential benefits; however, it does not effectively allow distinction between infectious and noninfectious stimuli.

PCT is a prohormone of calcitonin that is released by parenchymal cells, including liver, kidney, muscle, and adipose tissue, after systemic infection. Levels increase 2 to 4 hours after toxin release and peak at 14 hours. PCT is seen as a biomarker for bacterial infection, although elevations can be seen in trauma, surgical procedures, renal impairment, and pancreatitis. In the pediatric population, PCT has shown to be a better diagnostic marker for sepsis than CRP. Several studies showed that PCT levels were significantly elevated in bacterial sepsis but were not significantly increased in viral, fungal, or culture-negative infections. More important, PCT potentially can serve as a tool to guide antibiotic therapy.

**Interleukin 8**

The IL-8 gene has been found to be differentially regulated in sepsis survivors and nonsurvivors. IL-8 measurements could predict
a 95% probability of survival with standard care. One potential role for IL-8 could be to exclude children from future interventional clinical trials as a means of improving the risk to benefit ratio of a given therapy.22

**Cell Surface Receptors and Their Soluble Forms**
Expression of various proteins (e.g., cell surface receptors) is upregulated and activated in immune cells and could serve as a potential biomarker in septic patients.3 Examples include the transmembrane receptor of advanced glycation end products (RAGE), soluble triggering receptor expression expressed on myeloid cells 1 (TREM-1), soluble CD14 subtype (CD14-ST), urokinase-type plasminogen activator receptor (uPAR), and human leukocyte antigen-DR (mHLA-DR).5

**Biomarkers of Tissue Dysfunction and Organ Failure**
The breakdown of endothelial barrier function is thought to be an important mechanism in the development of organ dysfunction. Potential biomarkers of endothelial integrity that have been evaluated include angiopoietin 1 and 2 (Ang-1 and -2), cytokeratin 18 (cCK-18), and heart type fatty acid binding protein (hFABP).5

**Genetics and Sepsis**
Genetic variations are likely present within multiple candidate genes that affect how a host responds to an infectious response.22 Polymorphisms are the regular occurrence (>1%) of 2 or more alleles at a particular chromosomal location and consist of the majority of gene associations involving pediatric critical care.23 The most common type is a single nucleotide polymorphism: a substitution, deletion, or insertion of a single nucleotide occurring in approximately 1 per 1,000 base pairs of human DNA that can result in an altered protein, a change in the amount of normal protein expression, or no discernable change in protein function.22

**Gene Association Studies**
A selected group of gene association studies in pediatric sepsis have evaluated plasminogen activator inhibitor 1, Toll-like receptors, and TNF-α. Although no specific gene has been found to directly affect pediatric sepsis, more work is needed to translate this to the bedside.22

**Gene Expression Profiling Studies**
Expression profiling involves the use of microarray technology to measure the abundance of messenger RNA transcripts in biological specimens.24,25 This information could provide effective patient stratification and novel therapies that could enhance our current clinical protocols.

Expression profiling studies in children with septic shock have documented early and persistent repression of genes directly related to or dependent on zinc homeostasis as well as low serum levels of zinc.23,26-29 A phase 1 trial involving intravenous zinc supplementation in critically ill children (NCT01062009) has recently completed. IV zinc supplementation at 500 mcg/kg/day safely restored zinc levels to the 50th percentile. Clinical efficacy remains to be proven.123 Other genes evaluated in children with septic shock include matrix metalloproteinase 8 (MMP-8), a neutrophil-derived protease that cleaves extracellular matrix collagen and exhibits elevated expression in septic patients. TREM-1 is crucial for amplification of the inflammatory response to pathogen and has been shown to be repressed in neonates with septic shock.30

**The Pediatric Sepsis Biomarker Risk Model (PERSEVERE and tPERSEVERE)**
One approach to address the heterogeneous nature of sepsis is to develop clinically applicable stratification tools.31 The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) incorporates a panel of biomarkers and age into a decision tree estimating the baseline risk of mortality in children with septic shock.31 The PERSEVERE biomarkers are measured in the blood on day 1 of presentation to the ICU with septic shock, and a temporal version (tPERSEVERE) evaluates how these biomarkers change over time and their relationship to outcomes.32 The biomarkers included in
PERSEVERE were selected objectively based on extensive genome-wide expression studies and subsequent classification and regression tree (CART) analysis.\textsuperscript{32,33} PERSEVERE has recently been adapted for adults with septic shock.\textsuperscript{34} In pediatric patients, granzyme B (GZMB), heat shock protein 70 kDa 1B (HSPA1B), C-C chemokine ligand 3 (CCL3), IL-8, and matrix MMP-8 contribute to the predictive capacity of the decision tree.\textsuperscript{9} The CART-derived decision trees separate patients into terminal nodes that provide mortality probabilities for patients diagnosed with septic shock or severe sepsis.\textsuperscript{35} The tPERSEVERE model could serve as a monitor for therapeutic efficacy in combination with traditional clinical parameters.

**Management Recommendations**

Despite major advances in the understanding of sepsis, management relies on anti-infective treatments and restoration of cardiovascular and respiratory function.\textsuperscript{9,36} Throughout the years, many pharmaceutical and physiological interventions have been tested to improve outcomes; however, many have failed to show definitive improvement in outcomes. This review intends to highlight the universal therapies as well as some adjunctive therapies for sepsis.

**A Word on Sepsis Bundles**

The 2014 ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock support recommendations made in the 2002 and 2007 versions. These recommendations primarily focus on first-hour management directed at early fluid resuscitation and the administration of antibiotics and vasoactive medicines with the goals of restoring heart rate, blood pressure, and perfusion. ICU-level management includes providing adequate antibiotics, achieving source control, and attaining hemodynamic goals of central venous oxygen saturation (SCVO\textsubscript{2}) of 70% or higher and cardiac index of 3.3 to 6 L/min/m\textsuperscript{2}. Unlike previous versions, the 2014 guidelines call for sepsis to be addressed at an institutional level, with each institution developing recognition bundles, resuscitation and stabilization bundles, and performance bundles to ensure compliance.

Sepsis bundle creation and compliance are not new. Compliance with bundles generally has resulted in improved patient outcomes, particularly in adults, even if compliance entailed only a portion of bundle components. In a study of 15,022 adults across 165 sites, bundle compliance started at 18.4% and increased only to 36.1% yet resulted in improved unadjusted mortality (from 37% to 30.8%; \(P < 0.001\)) and improved adjusted odds ratios for mortality.\textsuperscript{37} Not surprisingly, bundle compliance is difficult and can be challenged in times of high patient volume, during night shifts versus day shifts, and whether senior nurses and house staff are primary managers of these patients or not.\textsuperscript{37-41} Interesting and multifaceted approaches are now underway at many institutions and in many countries to improve bundle compliance.\textsuperscript{42} Some strategies include nurse initiation of sepsis bundles, electronic health record alerts, and social media “tweet” reminders.\textsuperscript{43-45}

**Antibiotics**

Antibiotic administration along with aggressive fluid resuscitation can be considered the cornerstone of therapy for patients with severe sepsis and septic shock.\textsuperscript{46} Numerous studies have exhibited compelling evidence that timely administration of antibiotics is associated with improved mortality. In a large retrospective analysis of 17,990 patients with severe sepsis or septic shock, a linearly increasing risk of mortality was associated with each hour delay in appropriate antibiotic administration.\textsuperscript{47} Similar results were demonstrated in another large, retrospective, multicenter study of adults with septic shock.\textsuperscript{48} In this study, the overall in-hospital mortality for this cohort was 56.2%. However, for patients who received appropriate antibiotics within the first hour of hypotension, in-hospital mortality was reduced to 20.1%.\textsuperscript{48} Mortality was found to increase by an average of 7.6% for every hour untreated following hypotension over the subsequent 6 hours. The FINNSEPSIS study group found that a delay in antibiotic administration beyond 3 hours was the
most significant early treatment variable associated with increased mortality.  

Pediatric literature, although not to the same scale as adults, also supports that delayed administration of antibiotics is associated with mortality. In a study of 130 pediatric patients with severe sepsis or septic shock, delay in antimicrobial therapy beyond 3 hours after recognition of sepsis was an independent risk factor for mortality and prolonged organ failure. In addition, a trend was found for an escalating risk of mortality with delays of 1 and 2 hours from sepsis recognition to antimicrobial administration. Collectively, these data highlight the importance of timely administration of antibiotics, which continues to be an area for quality improvement. One study showed that implementation of a protocol to optimize antibiotic administration in children with signs of sepsis presenting to the emergency department greatly reduced time to antibiotic administration. Prior to protocol implementation, the median time from initial triage to antibiotic administration was 130 minutes. The median time from initial triage to antibiotic administration decreased to 38 minutes after protocol implementation, indicating that a protocol-based system is relevant to the treatment of sepsis.

**Fluid Resuscitation**

More than 20 years ago it was reported that in children with septic shock, fluid resuscitation in excess of 40 mL/kg within the first hour of presentation was associated with improved survival without an increase in the risk of cardiogenic pulmonary edema or acute respiratory distress syndrome. Since that time, aggressive fluid resuscitation has been the mainstay in the management of septic shock, and subsequent studies have further supported this practice. Interestingly, these data have been questioned and critiqued recently, and cohort studies have reported an association between positive fluid balance and mortality. The Fluid Expansion as Supportive Therapy (FEAST) study compared 20- to 40-mL/kg fluid boluses versus no bolus in more than 3,000 acutely ill African children. The FEAST study reported a significantly increased mortality risk in the group randomized to the fluid bolus arm. However, the unique clinical characteristics of this study need to be mentioned: 57% of the patients in the FEAST study had a positive blood test for malaria, 32% of the participants had a hemoglobin concentration less than 5 g/dL, and many were significantly malnourished. Despite recent questioning, fluid resuscitation remains crucial, especially in the early stages of septic shock; however, determining the optimal amount of fluid remains a key topic.

**Corticosteroids**

Although corticosteroids have been considered as potential adjunctive therapy in sepsis for decades, their use remains controversial. Adult and pediatric studies suggest a form of hypothalamic-pituitary-adrenal axis impairment in critical illness and sepsis. The mechanisms are thought to include both deficiency of cortisol production and tissue resistance to cortisol. Some retrospective, pediatric-specific data on the use of steroids in pediatric shock are available. An analysis of more than 6,000 pediatric severe sepsis cases in the Pediatric Health Information System administrative database attempted to determine correlates of outcome in regard to corticosteroid use and determined that the use of corticosteroids was an independent predictor of mortality (Relative Risk 1.7; 95% CI, 1.7-2.2). Similar to this observation, a post hoc analysis of the RESOLVE database, which is derived from the largest interventional clinical trial in pediatric severe sepsis conducted to date, could not find any evidence to support the efficacy of adjunctive corticosteroids in pediatric severe sepsis.

So, which patients do we treat with steroids? For children with septic shock who are at risk for adrenal insufficiency, such as those receiving...
chronic steroids, or patients with hypothalamic, pituitary, or adrenal disease, adjunctive corticosteroids are clearly recommended. However, for the general pediatric patient with septic shock, the current evidence does not definitively support the use of adjunctive corticosteroids, and it should be kept in mind that the risk of steroids is not negligible. Data based on gene expression profiles of pediatric patients with sepsis demonstrated that the subclass of patients with the highest illness severity and mortality had genes that were associated with repressed glucocorticoid receptor signaling pathway.

Blood Purification Strategies and Extracorporeal Support
The use of blood purification techniques in the ICU has increased dramatically in recent years. The clearance of a plethora of soluble mediators and toxins thought to be involved in the pathobiological process of sepsis could be a potential avenue for intervention. Hemofiltration, hemoadsorption, and plasmapheresis are strategies that have been used for this purpose.

Hemofiltration
Given that cytokines are responsible for many of the pathological events during sepsis, it would seem prudent to find a way to remove them. Cytokines are small, water-soluble proteins; thus, hemofiltration via continuous renal replacement therapy (CRRT) has been studied as a nonspecific mediator removal technique based on the convective filtration properties of CRRT. Studies of adults have failed to show any significant differences in clinical outcomes following hemofiltration, and results in pediatric studies are similar. One possibility is that the hemofiltration rate is not sufficient to clear inflammatory mediators from the blood compartment.

The Prospective Pediatric Continuous Replacement Therapy Registry Group evaluated children receiving CRRT and failed to demonstrate the efficacy of CRRT as a blood purification strategy in pediatric sepsis. The High Volume in Intensive Care (IVOIRE) trial, a large, randomized, multicenter trial comparing ultrafiltration rates of 35 versus 70 mL/kg/h in adult patients with septic shock and acute kidney injury, demonstrated no change in 28-day mortality and did not show earlier improvements in hemodynamic or organ dysfunction. The Adult International Consensus Statement, published in 2010, recommended against the use of high volume hemofiltration (HVHF) in patients with sepsis in the absence of acute kidney injury, citing a lack of “strong, scientific rationale” and “reproducible, proof-of-principle efficacy” in existing clinical trials.

Hemoadsorption
Also of interest are the adsorptive properties of various hemofilters as a potential mechanism for mediator removal. Studies have shown decreases in mediator concentrations approximately 1 hour after CCRT initiation and with frequent filter changes, suggesting initial efficacy through adsorption, with subsequent membrane saturation. A similar principle has led to the use of polymyxin B–coated filters as a means to remove endotoxin in patients with sepsis. The Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS) trial randomized 64 adults, who had septic shock and required emergency surgery for intra-abdominal infection, to conventional therapy or conventional therapy plus 2 sessions of polymyxin G hemoperfusion. The group undergoing polymyxin B hemoperfusion showed significant improvements in hemodynamics, improvements in organ dysfunction, and decreased mortality. A systematic review of the literature showed that 28 publications, including 9 randomized trials, lend further support for the potential efficacy of this approach. Pediatric data are lacking; however, one report described the successful application of polymyxin B hemoperfusion in a child with sepsis. This therapy remains experimental and requires more clinical investigation.

Plasmapheresis
Plasmapheresis is an extracorporeal approach to blood purification that is based on separation, removal, and replacement of the plasma component of blood. A series of adult studies showed significant improvement in mortality when plasmapheresis was used in patients with
disseminated intravascular coagulation and multiple organ dysfunction syndrome, including acute renal failure. Eighty-two percent of these patients survived, compared with a historical rate of 20% with similar clinical characteristics. Another study reported an absolute 28-day mortality risk reduction of 20% and a 0.6 relative risk of death in the plasmapheresis group compared with a group receiving standard therapy. Recently, the use of plasmapheresis in sepsis has been focused on the concept of thrombocytopenia-associated multiorgan failure (TAMOF), which has been described as being similar to thrombotic thrombocytopenic purpura. In thrombotic thrombocytopenic purpura, plasmapheresis has become the standard of care due to its ability to eliminate the inhibitory ADAMTS-13 factor and replace with ADAMTS-13. Current American Society of Apheresis guidelines describe the use of plasmapheresis in “sepsis with multiorgan failure” as a category III recommendation (optimum role of plasmapheresis is not established and decision making should be individualized) with a 2B grade (weak recommendation, moderate-quality evidence). The use of plasmapheresis may have value, but more pediatric clinical trials are needed.

Extracorporeal Membrane Oxygenation
A study involving a large, multicenter cohort of children with septic shock in pediatric ICUs showed that the use of extracorporeal membrane oxygenation (ECMO) has significantly increased since 2009. The study further showed that this increase may be related to increasing support in the literature for the use of ECMO in patients with comorbidities as well as the inclusion of ECMO in sepsis guidelines. Mortality rates in pediatric septic shock patients receiving ECMO have decreased over time, including patients with malignancy. Survival rates in neonates (~80% survival) and children (~50% survival) are similar in other indications for ECMO.

Although mortality rates with the use of ECMO may be similar in sepsis compared with other indications, thrombotic complications such as ECMO-induced hemolysis can be more common in sepsis, and thus efforts to reduce hemolysis are warranted because it may lead to microvascular thrombosis, reversal of portal blood flow, and multiple organ failure.

Novel Therapies for Sepsis
Modulation of the Immune System
Because sepsis is characterized by dysregulated host responses to stress, including inappropriate responses of the hypothalamic-pituitary-adrenal and vasopressin axes and the autonomic system, some research has focused on ways to manipulate these systems to find an optimal treatment strategy.

Corticosteroids
Investigations of corticosteroids continue, and current adult trials are looking at the benefits and risks of using hydrocortisone alone versus a combination of hydrocortisone and fludrocortisone.

Vasopressin
Plasma vasopressin levels during sepsis demonstrate a progressive decline, and thus vasopressin has been proposed as an adjunct therapy in a broad variety of conditions, including postoperative vasodilatory shock, septic shock, cardiac arrest, and cardiogenic shock. However, no compelling evidence is available to support the use of vasopressin as first-line therapy in septic shock.

β-Adrenergic Receptor Blockade
Based on the knowledge that β₁ stimulation induces the release of proinflammatory mediators and that β₂ agonists may downregulate innate immune response and prolong cell life, research has investigated β-adrenergic receptor blockade as a potential therapeutic modality. One study showed improvement in cardiac function, lactate clearance, and survival after treatment with esmolol. Another study showed that a combination of milrinone and esmolol was associated with survival benefit in patients treated with both agents compared with patients who received milrinone alone. No pediatric studies to date have tested this concept.
Polyclonal and Monoclonal Immunoglobulins
Polyclonal and monoclonal antibodies as well as immune stimulants have been investigated as potential therapeutic interventions. Intravenous polyclonal and monoclonal immunoglobulins have been investigated, but their use in sepsis remains controversial. So far, the evidence is insufficient to recommend the routine use of intravenous immunoglobulins for the management of septic shock.

Immune Stimulants
Interferon gamma (INF\(_\gamma\)) has been used to boost the immune system after the initial proinflammatory phase and to prevent the immunoparalyzed state after sepsis; however, after initial success in 9 patients, no additional clinical data have become available to support the use of INF\(_\gamma\). Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have been investigated for several years. A recent systematic review suggested that these treatments were not associated with survival benefit in sepsis.

Targeting Cytokines
Cytokines are powerful proteins that generate tissue injury secondary to a cytokine storm and subsequent inflammatory cascade, including favoring a prothrombotic state. Elevated levels of TNF-\(\alpha\) and IL-1 have been predictive of organ failure and poor patient outcomes. The proinflammatory state is followed by high levels of circulating anti-inflammatory cytokines (IL-10, IL-13) with subsequent compensatory anti-inflammatory response syndrome. Observations in animal models have demonstrated that antibodies to TNF-\(\alpha\) or IL-1 or deletion of their gene function leads to improved survival, hence paving the way for the initiation of clinical trials. Despite evidence of the destruction caused by dysregulated cytokines, several clinical trials using TNF-\(\alpha\) and IL-1 antibodies have failed to show clinical benefit. Alternative approaches are available to target the activities of proinflammatory cytokines such as macrophage migration inhibitory factor, MIF, HGMB-1, IL-8, and IL-17. However, these treatments may have beneficial effects in certain population subsets.

Nonactivated Protein C
In 2011, human activated protein C was removed from the market given its lack of efficacy and the increased risk of bleeding associated with its administration. A study of 22 pediatric cancer patients with sepsis showed that nonactivated protein C administration reduced mortality in patients and had no drug-related side effects. More research is needed in this area, but perhaps these results are secondary to the unique nature of septic patients with cancer and represent evidence of the need for patient-individualized treatment in sepsis.

Amino Acids and Vitamins

Vitamin C
Low plasma levels of vitamin C are a consistent feature in septic patients, varying inversely with the incidence of multiple organ failure and directly with survival, and are associated with disrupted proinflammatory and procoagulant cascades. A phase 2 trial is underway evaluating whether the use of parenteral augmentation of vitamin C (ascorbic acid) by intravenous infusion will attenuate sepsis-induced lung injury (5U1HL116885-02).

Citrulline
A clinical study is underway to evaluate the use of the amino acid citrulline in septic-induced lung disease (5R34HL105869-03). This investigation is based on the fact that urea cycle dysfunction is a key part of the inflammatory and oxidative stress cascades in sepsis and that the administration of citrulline can reestablish autoregulation of nitric oxide synthase and homeostasis of the urea cycle and therefore reduce inflammation and oxidative stress.

Vitamin D
Vitamin D deficiency is common in critically ill patients and has associations with increased mortality and morbidity in the ICU. Correction of vitamin D deficiency in critical illness has been recommended, and ongoing clinical trials are investigating the effect of repletion on...
Using Ultrasonography in Sepsis

As previously elucidated, many questions remain unanswered regarding resuscitation for pediatric sepsis. What is the ideal fluid volume? What is the time period for fluid administration? What therapeutic targets should be used to titrate fluid therapy? A recent report indicates that the use of ultrasonography to assess fluid status of patients offers an opportunity to determine fluid responsiveness based on inferior vena cava collapsibility, extravascular lung volume, and cardiac index. Potential benefits of this type of guided therapy include avoiding overzealous fluid administration and allowing quicker identification of cardiac causes of shock. Further, ultrasonography allows clinicians to understand the hemodynamic situation. In another study, bedside echocardiography provided crucial information leading to the recognition of septic myocardial dysfunction and uncorrected hypovolemia that was not apparent on clinical assessment. Ultrasonography has even been proposed to play a role in early identification of the source of infection in adult septic patients treated in an emergency department. In a recent study, point of care ultrasonography identified the source of sepsis in 89% of enrolled patients, with a sensitivity greater than 90% for pneumonia, almost 80% for soft tissue infection and cholecystitis, and about 60% for diverticulitis and appendicitis. Ultrasonography may allow a faster diagnosis while enabling clinicians to tailor more appropriate antibiotic therapy.

REFERENCES


