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Pediatric Sepsis

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Abstract

Purpose of Review—Sepsis is the leading cause of pediatric death worldwide. In the United States alone, there are 72,000 children hospitalized for sepsis annually with a reported mortality rate of 25% and an economic cost estimated to be \$4.8 billion. However, it is only recently that the definition and management of pediatric sepsis has been recognized as being distinct from adult sepsis.

Recent Findings—The definition of pediatric sepsis is currently in a state of evolution and there is a large disconnect between the clinical and research definitions of sepsis which impacts the application of research findings into clinical practice. Despite this, it is the speed of diagnosis and the timely implementation of current treatment guidelines that has been shown to improve outcomes. However, adherence to treatment guidelines is currently low and it is only through the implementation of protocols that improved care and outcomes have been demonstrated.

Summary—Current management of pediatric sepsis is largely based on adaptations from adult sepsis treatment; however, distinct physiology demands more prospective pediatric trials to tailor management to the pediatric population. Adherence to current and emerging practice guidelines will require that protocolized care pathways become commonplace.

Keywords

protocolized care; fluid resuscitation; inotrope therapy; corticosteroid therapy

Introduction

Sepsis is the leading cause of death worldwide in the pediatric population resulting in an estimated 7.5 million deaths annually (1, 2). It encompasses the top four causes of childhood mortality as reported by the World Health Organization (WHO): severe pneumonia, severe diarrhea, severe malaria, and severe measles (3). In the United States alone, there are 72,000 children hospitalized for sepsis with a reported mortality rate of 25% and an economic cost estimated to be \$4.8 billion (1, 4, 5). Despite this tremendous impact, there has been limited focus on pediatric sepsis to date and most of our current treatment is extrapolated from adult studies.

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Physiologic factors unique to the pediatric patient rendered initial attempts to apply adult sepsis criteria futile. Adults and children differ in physiology, predisposing diseases, and sites of infection which necessitates differing diagnostic criteria and management strategies. Among children who develop sepsis worldwide, 49% have a comorbid condition that leaves them vulnerable to infection (6). The most common comorbidities in children who develop sepsis are age specific; infants have chronic lung disease or congenital heart disease, while children ages one through nine have underlying neuromuscular disease and adolescents have pre-existing cancer (6). Similar to sepsis in adults, however, a standard definition for sepsis is crucial to the incorporation of emerging research findings into clinical practice. If patients identified as septic by clinicians are different from research study participants identified as septic, results from those trials may not be applicable to clinical practice. Despite this, the Sepsis PRevalence, OUtcomes, and Therapies (SPROUT) trial recently found that there is only a 42% concordance between physician diagnosis and current diagnostic criteria used for inclusion in research studies (3). Once sepsis can be consistently diagnosed, clinical management tailored to the pediatric patient will need to be refined by large prospective multi-institutional trials. Additionally, with the advent of electronic medical records (EMR), ‘-omic’ technologies, and the ability to process *big data*, we will have a growing capacity to diagnose sepsis and identify subpopulations of patients that are most likely to benefit from certain therapies inherent to *‘personalized medicine’*.

For the same reason that pediatric sepsis requires distinction from adult sepsis, neonatal sepsis requires special distinction from pediatric sepsis. Due to the complexity of differences between these two groups, this article will exclude neonatal sepsis (7, 8).

Defining Sepsis

The dilemma with addressing sepsis in any age group is the heterogeneity inherent in this disease state and patient population. The definition of adult sepsis has undergone continuing revision to keep pace with the high volume of published research; however, it is only recently that attention has been given to the pediatric patient and the many caveats that separate the pediatric patient from the adult. Prior to 2005, there was not a standard definition for pediatric sepsis which resulted in a lack of uniformity among sepsis studies. In 2005, the Pediatric Sepsis Consensus Congress (PSCC) met to standardize the definition of sepsis (Figure 1); however, as seen with adults, the definition requires continuous reconsideration and modification as this area of research grows. Defining sepsis in the pediatric patient is made more difficult due to age specific vital signs, and their tremendous physiologic reserve which often masks the seriousness of their condition (9). The PSCC divided age into six distinct categories in order to take into account age specific vital signs as well as age specific risk factors for invasive infections which in turn affect antibiotic coverage guidelines (9). Pediatric severe sepsis is defined as (1) two or more systemic inflammatory response syndrome criteria (Table 1), (2) confirmed or suspected invasive infection, and (3) cardiovascular dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions (Table 2) (10). Determination of altered physiology is specific to age dependent vital signs.

Although the PSSC provided a more uniform set of diagnostic criteria, the SPROUT trial found that only 42% of sepsis patients were identified as such by both the clinician and the consensus criteria (3). It is therefore important to realize that retrospective reviews based on ICD-9 codes or administrative data bases do not describe the same patient population as trials utilizing consensus criteria. Additionally, emerging research may not be applicable to patients diagnosed as septic by practicing clinicians not using consensus criteria. This alone demands the revision of diagnostic criteria to create greater uniformity within pediatric clinical practice and to facilitate the application of peer reviewed findings into clinical practice. One potential way to bridge this disconnect, and standardize diagnosis, is by utilizing checklists in EMRs. Checklists and protocols implemented via EMR have been shown to improve time to initiation of therapy (11-13); however, they have not yet been studied as a tool to provide uniformity of diagnosis.

At present, there is no single biomarker that has proven specific or sensitive enough to diagnose sepsis or prognosticate outcome in selected cohorts. Similar to studies of sepsis in adults, there is active research examining both clinical and research measurements applicable to a pediatric population. One current tool which may be available in the near future is the implementation of biomarkers or '-omic' (including genomics, transcriptomics, proteomics, and metabolomics) information that may provide diagnostic and prognostic capability early in the course of sepsis (14). This information may also help stratify this heterogeneous patient population into subgroups for more tailored therapeutic approaches (15). Already, there is evidence that genomic, transcriptomic, proteomic, and metabolomics information can be used to identify patients that will have more severe clinical courses or benefit from specific therapies (15-17). However, such technology still requires validation and development of protocols that are rapid, widely available, and cost effective. Although there are still some obstacles to overcome concerning the diagnosis of sepsis, timely recognition and institution of treatment is imperative.

Early Sepsis Recognition

Despite the dearth of prospective pediatric sepsis studies and the continued difficulty with diagnostic criteria, timely recognition and institution of therapy (within one hour) has been established as the single most crucial step in sepsis management. While timely diagnosis is crucial, it can be challenging. Unlike adults, the physiologic reserve of pediatric patients can result in a protracted state of compensated sepsis that, while detrimental, may not be as clinically apparent (18). A study from the UK found that greater than 50% of sepsis fatalities occur within 24 hours and half of these patients die before transfer to Pediatric Intensive Care Unit (PICU) care (19). Although differences in healthcare systems may limit the applicability of these findings to the United States, it clearly highlights the need for a multidisciplinary awareness since over 80% of pediatric patients present to Emergency Departments (ED) in the United States that do not have specialized pediatric care (20).

In order to combat delay in diagnosis and subsequent treatment, several EDs have implemented computerized protocols. EMRs now have the capacity to provide timely warnings based on abnormal vital signs that alert the clinician to have a heightened suspicion of sepsis. Implementation of protocol driven therapy can decrease the time to fluid

resuscitation and antimicrobial therapy (18). Although there are limitations to these types of systems, such as missed diagnosis or alarm burnout, they are proving to be an invaluable tool in diagnosing and managing pediatric sepsis.

Management

The early management of pediatric sepsis was largely extrapolated from adult sepsis studies and it is only recently that prospective pediatric sepsis studies have been undertaken. Therefore, the management guidelines for pediatric sepsis are still preliminary and require review by large multi-institutional prospective studies. Despite their limitations, adherence to current pediatric sepsis guidelines, as detailed in the pediatric section of the surviving sepsis campaign, are associated with improved outcomes (Figure 2) (10, 12, 21-23). However, multiple studies have documented low compliance (24) and in a simulated ED setting only 45% of teams correctly adhered to all six sepsis metrics (12). One method that has consistently increased adherence to published guidelines is implementation of protocols (18). Development of protocols can streamline care by developing electronic order sets and clinical pathways to expedite fluid and antibiotic administration as well as promoting nursing education which may lead to reduced mortality (9, 25). Protocol driven resuscitation bundles have been shown to decrease time to initiation of therapy (early fluids, antibiotic therapy, and vasoactive support) which is associated with improved outcomes (8, 26, 27). A retrospective cohort study incorporated a best practice alert in the ED to facilitate early recognition and found significant improvements in time-to-intervention (24). This translated to decreased incidence of AKI, need for renal replacement therapy, hospital length of stay (LOS), PICU LOS, and mortality (24).

The current guidelines for treatment are summarized in the pediatric section of the Surviving Sepsis Campaign (Figure 1) (8). Early and aggressive source control should be a top priority; this includes drainage, debridement, and surgical intervention (8). Empiric antibiotic therapy should be administered within one hour of clinical suspicion and can be administered IV, IM or PO; antibiotics should not be delayed for blood cultures but every attempt should be made to obtain blood cultures prior to the first dose of antibiotics (8). Delay of antibiotic administration is an independent risk factor for prolonged organ failure and mortality (8, 10, 28). The importance of expedited antibiotic therapy is well established in the adults (29); in fact, hourly delays have been significantly associated with increased mortality. Although positive cultures are not a diagnostic criteria of pediatric sepsis, and many cases of sepsis do not have positive blood cultures, positive cultures allow for narrowing of antibiotic usage. Narrowing antibiotic coverage not only benefits the patient, it also addresses the global crisis of antibiotic resistance (8).

Fluid resuscitation should be aggressive and administered as boluses of 20 ml/kg crystalloid given over 5-10 minutes via intravenous or intraosseous access (8). Due to the remarkable physiologic reserve of pediatric patients hypotension often does not occur until the patient is nearing cardiovascular collapse. Therefore, blood pressure is not an adequate endpoint for resuscitation and resuscitation of patients with severe sepsis should be titrated to increasing urine output, level of consciousness, and attaining normal capillary refill without inducing hepatomegaly or rales (8). Early and aggressive fluid resuscitation has been shown to

decrease mortality (11, 15, 26). Conversely, delayed fluid resuscitation has been associated with longer ICU stay and hospital LOS and an increased incidence of AKI (24, 30). Although total volumes of fluid resuscitation were not considerably different, a shorter time to implementation resulted in decreased incidence of AKI and its associated morbidity and mortality (24). Despite this evidence, the benefits of current fluid resuscitation guidelines have recently been called into question and further study has been demanded (31). If the patient remains hypotensive once these clinical benchmarks have been achieved, inotropic support should be initiated and has been shown to decrease mortality (8). Inotropes can be started peripherally until central access is obtained (8). Furthermore, 25% of children with septic shock have adrenal insufficiency and will benefit from corticosteroid treatment; purpura, prior steroid therapy, and known pituitary and adrenal abnormalities should prompt a heightened level of clinical suspicion (8). When clinically necessary, corticosteroids therapy should not be delayed; early implementation (< 8 hours) of corticosteroids has been associated with decreased mortality, while delay in corticosteroid treatment (<72 hours), was associated with increased adverse events without the same mortality benefit (32-34). Additionally, ECMO has been shown to increase survival in the setting of refractory shock despite adequate fluid resuscitation and inotrope therapy (8). ECMO can also be used in cases of respiratory failure associated with sepsis (8). ECMO use for sepsis has a survival rate of 39% for children and 73% for newborns (8).

Cardiovascular treatment endpoints, as defined by the Surviving Sepsis Campaign, include normalization of vitals and mental status among other criteria (Table 2); importantly, laboratory values are not included as children often have less derangement of serum markers such as lactate (8).

The heterogeneity of both the patient population and the etiology of severe sepsis require an approach to the syndrome of sepsis as well as an appreciation for the individualization of clinical approaches. Personalized medicine, either in the form of genetic determinations or proteomic, transcriptomic or metabolomics measures will soon be a part of the EMR. This ‘-omic’ revolution will be combined with clinical data from EMR resulting in large quantities of data termed ‘*big data*’. Efforts are currently underway to make this data clinically applicable. All one needs to do is watch television and see the advertisements from large information warehouses, like IBM, General Electric, Google and Microsoft. As this information database grows and the tools to extract biological information from this data improve, we will see the advent of personalized medicine where treatment is tailor-made to the individuals unique physiology (14). Although this technology seems far off, there are already genomic markers that can identify which patients will benefit from corticosteroid therapies (15).

Outcomes

There is only limited information on chronic morbidity and long-term mortality in the septic pediatric patient population. The applicability of early studies that utilized inconsistent definitions of sepsis is limited; however, survivors of sepsis are recognized to often have long-term neuropsychological and neurocognitive morbidity (35-38). Retrospective chart review, dependent on ICD-9 codes, estimated mortality to be 10-20%; however, recent

prospective studies that relied on consensus criteria found a mortality rate of 25% for severe sepsis (30, 33, 34). Improvement in the early treatment of adult sepsis has led to decreased acute mortality only to unmask a chronic phenotype of persistent inflammation, immunosuppression and catabolism syndrome (PICS) that is associated with indolent death (39). Although limited by its retrospective design and inclusion of neonates, one study demonstrated that almost half (47%) of pediatric sepsis survivors were readmitted at least once, and half of deaths occurred after discharge from primary admission (40). Therefore, future pediatric sepsis studies should take care to include long-term morbidity and mortality.

Future Directions

A recent study showed a large mismatch between physician diagnosed sepsis and consensus criteria sepsis which highlights the short-comings of our current definitions and prior retrospective ICD-9 code based studies. A definition of sepsis that is more inclusive of what is considered septic by the clinician will need to be developed. The treatment and outcomes of this population will then need to be evaluated in large prospective studies to determine the maximally effective treatment regimen. The development of this information will require a great deal of resources. The SPROUT trial estimated that an interventional trial that could detect a 5% reduction in mortality would require 2,118 children with severe sepsis; they further estimated that it would require 3 years and 58 PICUs (5). Therefore, other clinically significant outcomes need to be evaluated in addition to in-hospital mortality. In addition to acute outcomes, long-term morbidity and mortality also require investigation.

Conclusion

Pediatric sepsis continues to have a tremendous impact worldwide. The continued evolution of how we define sepsis will enable a more facile incorporation of emerging research findings into clinical practice. Treatment of sepsis begins with correct and timely diagnosis; best practice alerts and the implementation of protocols have repeatedly demonstrated faster time-to-first intervention. Early and aggressive care with IV fluids, antibiotics, and vasoactive medications are the most important facets of sepsis treatment (26) and result in improved outcomes. The future of pediatric sepsis research should focus on prospective randomized trials that evaluate both in-hospital outcomes as well as long-term outcomes.

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Abbreviations

ED	Emergency Department
EMR	Electronic Medical Record
PICU	Pediatric ICU
LOS	Length of stay
ECMO	Extracorporeal membrane oxygenation
WHO	World Health organization
ICD	International classification of diseases

SPROUT Sepsis PRevalence, OUtcomes, and Therapies

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Key Points

Protocol driven care results in more timely care and improves outcomes.

Timely recognition and institution of therapy (<1 hour) is the single most crucial step in sepsis management.

Future management of pediatric sepsis will be tailored to the individual's unique genomic signature.

Fig 1.
Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock.

Reproduced from reference 8

Fig 2. Surviving Sepsis Campaign Pediatric Treatment Protocol

Table 1

Age-specific vital signs and laboratory variables

Age Group	Pediatric SIRS Criteria (1 of the criteria from Column 1 <u>AND</u> Column 2)								Cardiovascular Dysfunction
	Column 1 (1 of the below criteria)				Column 2 (1 of the below criteria)				
	Core Temperature (°C)		Leukocyte Count (Leukocytes ×10 ³ /mm) ³		Heart Rate (Beats/Min) ¹		Respiratory Rate ² (Breaths/Min)	Systolic Blood Pressure (mmHg)	
	Hypothermia	Hyperthermia	Leukopenia	Leukocytosis	Bradycardia	Tachycardia			
0 days to 1 wk	<36	>38.5	NA	>34	<100	>180	>50	<65	
1 wk to 1 mo	<36	>38.5	<6	>19.5	<100	>180	>40	<75	
1 mo to 1 yr	<36	>38.5	<6	>17.5	<90	>180	>34	<100	
2-5 yrs	<36	>38.5	<6	>15.5	NA	>140	>22	<94	
6-12 yrs	<36	>38.5	<4.5	>13.5	NA	>130	>18	<104	
13 to <18 yrs	<36	>38.5	<4.5	>11	NA	>110	>14	<117	

¹Tachycardia, defined as a mean heart rate 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, -blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.

²Mean respiratory rate 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.

³Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or 10% immature neutrophils.

Adapted from reference 9

Table 2
Organ dysfunction criteria

<u>Cardiovascular dysfunction</u> (1 of the following despite administration of isotonic intravenous fluid bolus 40 mL/kg in 1 hr)	
•	Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age ¹
•	Need for vasoactive drug to maintain BP in normal range (dopamine >5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
•	2 of the following
–	Unexplained metabolic acidosis: base deficit >5.0 mEq/L
–	Increased arterial lactate >2 times upper limit of normal
–	Oliguria: urine output <0.5 mL/kg/hr
–	Prolonged capillary refill: >5 secs
–	Core to peripheral temperature gap >3°C
<u>Respiratory</u> ² (1 of the following)	
•	PaO ₂ /FIO ₂ <300 in absence of cyanotic heart disease or preexisting lung disease
•	PaCO ₂ >65 torr or 20 mm Hg over baseline PaCO ₂
•	Proven need ³ or >50% FIO ₂ to maintain saturation 92%
•	Need for non-elective invasive or noninvasive mechanical ventilation ⁴
<u>Neurologic</u> (1 of the following)	
•	Glasgow Coma Score 11
•	Acute change in mental status with a decrease in Glasgow Coma Score 3 points from abnormal baseline
<u>Hematologic</u> (1 of the following)	
•	Platelet count <80,000/mm ³ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
•	INR >2
<u>Renal</u>	
•	Serum creatinine 2 times upper limit of normal for age or 2-fold increase in baseline creatinine
<u>Hepatic</u> (1 of the following)	
•	Total bilirubin 4 mg/dL (not applicable for newborn)
•	ALT 2 times upper limit of normal for age

blood pressure (BP), alanine transaminase (ALT), International normalized ratio (INR)

¹ Please see Table 1;

² acute respiratory distress syndrome must include a PaO₂/FIO₂ ratio 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO₂/FIO₂ ratio must be 300 mm Hg;

³ proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required;

⁴ in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

Adapted from reference 9