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Updates on pediatric sepsis

Cruz, Andrea T ; Lane, Roni D ; Balamuth, Fran ; Aronson, Paul L ; Ashby, David W ; Neuman, Mark I ; Souganidis, Ellie S ; Alpern, Elizabeth R ; Schlapbach, Luregn J

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REVIEW ARTICLE

Pediatrics

Updates on pediatric sepsis

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Abstract

Sepsis, defined as an infection with dysregulated host response leading to life-threatening organ dysfunction, continues to carry a high potential for morbidity and mortality in children. The recognition of sepsis in children in the emergency department (ED) can be challenging, related to the high prevalence of common febrile infections, poor specificity of discriminating features, and the capacity of children to compensate until advanced stages of shock. Sepsis outcomes are strongly dependent on the timeliness of recognition and treatment, which has led to the successful implementation of quality improvement programs, increasing the reliability of sepsis treatment in many US institutions. We review clinical, laboratory, and technical modalities that can be incorporated into ED practice to facilitate the recognition, treatment, and reassessment of children with suspected sepsis. The 2020 updated pediatric sepsis guidelines are reviewed and framed in the context of ED interventions, including guidelines for antibiotic administration, fluid resuscitation, and the use of vasoactive agents. Despite a large body of literature on pediatric sepsis epidemiology in recent years, the evidence base for treatment and management components remains limited, implying an urgent need for large trials in this field. In conclusion, although the burden and impact of pediatric sepsis remains substantial, progress in our understanding of

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the disease and its management have led to revised guidelines and the available data emphasizes the importance of local quality improvement programs.

KEYWORDS

antibiotic management, fluid resuscitation, pediatric, sepsis, sepsis risk factors, septic shock, severe sepsis

1 | INTRODUCTION AND EPIDEMIOLOGY

Sepsis contributes to 19% of all deaths globally, with the highest age-specific incidence in children younger than 5 years of age.^{1,2} Pediatric sepsis resulted in 0.7% of all hospital encounters, with an incidence of 2.8% in inpatients in the United States.³ Epidemiologic studies using clinical data have found an incidence of pediatric sepsis in up to 8% of all pediatric intensive care unit (PICU) admissions,⁴ contributing to 1 in 4 deaths in PICUs.⁵ Accurate estimates of pediatric sepsis are hampered by inaccuracies of diagnostic coding, resulting in gross under-reporting; at the same time, increasing sepsis awareness may lead to identification earlier in the disease process, with resultant increases in apparent survival rates.⁶ To address this, novel sepsis surveillance criteria derived from electronic health record data have been proposed.^{7,8}

Risk factors for sepsis and the most common sites and pathogens associated with sepsis are described in Tables 1^{9–11} and 2,^{3,10,11} respectively. In 1 US multicenter study, the most common pathogens affecting previously healthy children were *Staphylococcus aureus* (9.4%), streptococcal species (7.9%), and *Escherichia coli* (7.1%), whereas the most common pathogens in children with chronic diseases were *S. aureus* (11%), *Candida* (9.8%), and *Pseudomonas* (8.1%).¹² Similar patterns have been observed in recent population-based studies in

other countries and contrast with the predominance of meningococcal infections observed in previous decades.^{5,13} More than one-third of children with sepsis do not have an identifiable pathogen. This may be attributed to sepsis being caused by viral etiologies or because of the limits in detection of bacterial pathogens, particularly if the volume inoculated into blood cultures is low or if the pathogens are fastidious or have specific growth requirements. Table 3 summarizes the most common pathogens by site of infection in non-resource-limited settings.¹²

2 | DEFINITIONS

Historically, the term *sepsis* (from Greek “sepsin,” meaning “rot, make putrid”) has been used to characterize life-threatening infections usually caused by bacterial pathogens if untreated progress to shock and death.¹⁴ The 2005 International Pediatric Sepsis Definition Consensus Conference classified sepsis as infection in presence of systemic inflammatory response syndrome (SIRS), severe sepsis as sepsis in the presence of organ dysfunction, and septic shock as sepsis in the presence of cardiovascular dysfunction (Table 4).^{15–17} Although SIRS criteria have been used in many EDs to assist in the

TABLE 1 Most common comorbidities in children with sepsis in non-resource-limited settings

Condition	Prevalence range (%) ^a
Central venous catheter	31
Congenital heart disease	7–27
Neurologic	9–26
Oncologic diagnosis	11–17
Metabolic disorder	3–13
Respiratory (including ventilator dependence)	5–7
Congenital or acquired immune deficiency	4–7
Renal	2–6
Gastrointestinal	4–5
Solid organ transplant	4
Dialysis dependence	3
Bone marrow transplantation	3

^aSum >100% as ranges compiled from various studies and patients may have had multiple comorbidities.

TABLE 2 Most common sites of infection and pathogens in sepsis^a

Site	Prevalence range (%)
Respiratory	19–57
Bacteremia (primary)	19–68
Abdominal	8
Central nervous system	4–23
Genitourinary	4–22
Skin	4–3
Pathogens	Range (%)
No pathogen identified	35–57
Gram-negative bacteria	12–28
Gram-positive bacteria	16–30
Other bacteria	0.4–0.7
Fungal infections	4–13
Viral infections	11–21

^aSum >100% as ranges compiled from various studies and patients may have had multiple sites of infections or polymicrobial infections.

TABLE 3 Most common pathogens by site of infection in children with sepsis

Organism	Bacteremia (%)	CNS (%)	UTI (%)	SSTI (%)	Pneumonia (%)	Osteomyelitis (%)
<i>S. aureus</i>	19	12	6	30	15	51
<i>S. pneumoniae</i>	2	9	1	0.2	4	1
Other Gram-positives	28	25	9	11	6	16
<i>K. pneumoniae</i>	8	2	5	1	3	2
<i>E. coli</i>	11	2	23	2	5	3
<i>H. influenzae</i>	1	3	0.3	0.4	4	1
<i>Pseudomonas</i>	7	2	5	4	13	3
Other Gram-negatives	13	9	6	3	10	2
<i>Candida</i>	9	9	5	7	7	5
<i>Aspergillus</i>	0.4	1	0.2	0.5	0.3	0
No identifiable pathogen	N/A	21	36	37	31	15

Note. Adapted from Prout et al.^{9,12}

Abbreviations: CNS, central nervous system; N/A, not applicable; SSTI, skin/soft tissue infection; UTI, urinary tract infection.

TABLE 4 Approaches to defining sepsis in children

Term	Term	Definition
2005 International Pediatric Sepsis Definition Consensus conference	SIRS	Meets ≥ 2 of the following criteria, 1 of which must be temperature or WBC count: Pyrexia ($>38.5^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$) Age-dependent tachycardia or bradycardia Tachypnea or need for mechanical ventilation Abnormal WBC count or $>10\%$ bands
	Sepsis	SIRS <i>and</i> Suspected or confirmed infection
	Severe sepsis	Sepsis <i>and</i> Cardiovascular dysfunction, respiratory dysfunction, or ≥ 2 non-cardiorespiratory organ system dysfunctions
	Septic shock	Sepsis <i>and</i> Cardiovascular dysfunction: defined as either hypotension, receipt of vasoactive medication, or impaired perfusion despite fluid resuscitation
Sepsis-3 (adults)	Sepsis	Suspected or confirmed infection <i>and</i> Presence of organ dysfunction (measured by SOFA score or qSOFA score increase in ≥ 2 points)
	Septic shock	Suspected or confirmed infection <i>and</i> Cardiovascular dysfunction defined as hypotension despite fluid resuscitation requiring vasoactive medication in presence of hyperlactatemia
Operationalization for the 2020 Pediatric surviving sepsis campaign	Sepsis	Suspected or confirmed infection <i>and</i> Sepsis-associated organ dysfunction or septic shock

Note. Adapted from Goldstein et al,¹⁵ Shankar-Hari et al,¹⁶ and Weiss et al.¹⁷

Abbreviations: qSOFA, quick SOFA; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

recognition of children who may have sepsis, SIRS vital sign criteria are poorly sensitive in identifying critically ill children.^{18,19} Recently, definitions of sepsis in adults have changed, with the 2016 Sepsis-3 consensus conference defining sepsis as infection with dysregulated host response resulting in life-threatening organ dysfunction and septic shock as sepsis with profound circulatory, cellular, or metabolic alterations associated with substantially higher mortality.¹⁶ There is

a requirement of hypotension to meet adult shock criteria, contrary to the pediatric goal of identifying compensated shock, given that hypotension is a late-stage finding for children. We refer to sepsis as sepsis-associated organ dysfunction and septic shock as sepsis with cardiovascular dysfunction (including hypotension, need for treatment with vasoactive agents, or impaired perfusion)¹⁷ in this review.

3 | SEPSIS BUNDLES AND QUALITY IMPROVEMENT INITIATIVES

Failure to recognize sepsis increases the risk of morbidity and mortality, as illustrated by the case of Rory Staunton, a 12-year-old boy who died of initially unrecognized streptococcal sepsis.²⁰ A year after Rory's death, "Rory's Regulations" were passed,²¹ requiring all New York hospitals to implement evidence-based protocols to facilitate early recognition of sepsis through screening tools, identify individuals who qualified for sepsis care, and implement guidelines for sepsis management through bundled care, consisting of protocols to assist in sepsis recognition and subsequently prompt initiation of fluid resuscitation, parenteral antibiotics, and obtaining blood cultures. Multiple studies demonstrated an improvement in in-hospital mortality rates after bundled sepsis care in both children²² and adults.²³ In addition to legislative efforts, US children's hospitals have collaborated to enhance multicenter quality improvement activities in pediatric sepsis. The largest of these efforts is the ongoing Improving Pediatric Sepsis Outcomes Collaborative through the Children's Hospital Association and involves >50 hospitals across the United States.²⁴

The benefits of early recognition, treatment, and reversal of shock using bundled sepsis care extend beyond reductions in mortality.^{22,23,25} Multiple pediatric studies have demonstrated decreased hospital length of stay after implementation of bundled care^{26,27} and reductions in the rates of acute kidney injury.²⁸ Delays in receipt of antimicrobial therapy are associated with increased mortality, with children who experienced antibiotic delays of more than 3 hours having an almost 4-fold risk of mortality in the PICU.²⁹ Other studies have found that each additional hour of persistent shock is associated with a >2-fold increased odds of mortality.³⁰ Ultimately, many pediatric studies have evaluated the relationship between the timing of antibiotic administration and fluid resuscitation through protocol-driven care and patient-level outcomes,^{22,25-28} driving ongoing revisions to institutional, national, and international guidelines.

4 | DIAGNOSIS

Early diagnosis is critical to reversing shock. Barriers to recognition include age-related variation in vital signs (resulting in failure to recognize abnormal vital signs), hypotension being a late manifestation, a relatively low prevalence of pediatric sepsis in EDs in high-income countries, and alternative explanations for abnormal vital signs (fever or crying contributing to tachycardia or tachypnea). There are also associated challenges in identifying which children meeting SIRS criteria may be at risk for sepsis. As such, we review triage-based and laboratory-based tools that may optimize sepsis recognition.

4.1 | Triage-based recognition

Rapid, systematic identification of children with sepsis is paramount to initiating timely interventions. Without this critical step, delays in

care may impact morbidity and mortality. In 2017, the American College of Critical Care Medicine (ACCCM) on Pediatric and Neonatal Sepsis emphasized the importance of triggers or screening tools to rapidly identify patients with septic shock.³¹ In 2020, the first Pediatric Surviving Sepsis Campaign (SSC) international guidelines extended the goal of identification to non-cardiovascular dysfunction.¹⁷

The clinical signs of those at risk for pediatric sepsis are largely based on the presence of suspected infection and abnormal physical examination findings such as perfusion abnormalities, altered mental status, hypotension, temperature abnormality (fever or hypothermia), and tachycardia.^{31,32} A pragmatic screen/alert should be based on these readily identifiable and available parameters. Incorporating a sepsis screen into the triage process is efficient and identifies most patients with sepsis.²⁵ In 1 ED study, moving from a paper-based to an electronic health record process significantly decreased time to recognition.³³

The significant mortality and morbidity associated with pediatric sepsis drives the inherent balance of sensitivity versus specificity of all screening models to favor sensitivity at the cost of specificity. However, this results in a low positive predictive value, and balancing measures related to false positive alerts and the potential for alert fatigue need to be considered. Design should consider institution-specific characteristics (ie, tertiary/quaternary vs rural or community setting, acuity, healthcare workers awareness/sensitivity to sepsis)^{17,34} and can include temperature-corrected heart and/or respiratory rate,^{35,36} age-based vital sign adjustments,^{33,36-39} and the inclusion of high-risk conditions.^{25,33,37}

Some of the earliest adopters of sepsis screening in pediatric EDs primarily leveraged vital sign abnormalities to identify patients with possible sepsis (Table 5).³⁵⁻⁴⁰ An ideal pediatric sepsis screening process should be efficient, initiated at first contact with the patient, incorporate reassessment/identification throughout the visit, and harness the strength of the electronic health record. The screen should incorporate pertinent vital sign and clinical parameters, recognize children with high-risk conditions, involve a care team huddle/bedside assessment, and be monitored by a dedicated quality improvement team. Because clinician assessment can significantly improve screening performance, a 2-step process consisting of a screening tool prompting timely medical evaluation has the potential to combine the advantages in terms of the sensitivity and specificity of both steps.^{37,41} Performing a 2-step screening process is well aligned with other care processes in the ED setting and is effective.^{25,37} The first step is nurse driven, involves responding to an electronic alert determined by the presence of abnormal vital signs and/or clinical parameters, and takes into consideration the presence of high-risk conditions. If the screen is positive, a bedside care team huddle is performed to assess the patient and determine if sepsis pathway management is appropriate.

Successful implementation and subsequent administration of a pediatric sepsis screening process is a large quality improvement effort requiring a dedicated and engaged workgroup. Screening pathways require adherence and performance monitoring with modifications to improve compliance and optimize sensitivity and specificity.

TABLE 5 Emergency department sepsis screens and performance characteristics

Authors	Components					Performance	
	Integrated into EHR	Vital signs, \pm temperature adjustment	Clinical signs	Bedside huddle	High-risk conditions included	Sensitivity (%)	PPV (%)
Cruz et al (2012) ³⁵	+	+, internally derived	+	+	+	81	4
Sepanski et al (2014) ³⁶	+	+, modified SIRS	+	–	+	97	49
Lane et al (2016) ²⁵	+	–, modified PALS	+	+	+	99	20
Balamuth et al (2017) ³⁷	+	+, modified PEWS	+	+	+	86	25
Lloyd et al (2018) ³³	+	+, modified PALS	+	+	+	NR	NR
Powell et al (2018) ⁴⁰	–	–, PEWS	+	+	+	NR	NR

Note. –, heart rate not adjusted for pyrexia; +, heart rate adjusted for pyrexia.

Abbreviations: EHR, electronic health record; NR, not reported; PALS, pediatric advanced life support; PEWS, pediatric early warning signs; PPV, positive predictive value; SIRS, systemic inflammatory response syndrome.

4.2 | Laboratory-based diagnostics

A WBC count $\geq 15,000$ cells/ μ L was historically used to identify febrile young children at higher risk of occult bacteremia.⁴² However, studies conducted in the post-pneumococcal conjugate vaccine era have demonstrated that WBC count has poor test characteristics for bacterial infections across age groups and that no single cut-off value has a sufficient sensitivity or specificity for clinical utility.^{43–46} Although elevated absolute band count > 1500 cells/ μ L has high specificity ($> 90\%$) for bacterial infections, the sensitivity is very low ($< 30\%$).^{45,47} Similarly, an absolute neutrophil count $> 10,000$ cells/ μ L has moderate to high specificity (78%–88%) but poor sensitivity ($< 50\%$) for bacterial infection when used in isolation.^{44–46} The absolute neutrophil count is part of the step-by-step approach and Pediatric Emergency Care Applied Research Network (PECARN) prediction rule to identify febrile infants ≤ 60 days of age at low risk of bacterial infections (Table 6).^{48,49}

C-reactive protein is often integrated into identification of febrile infants with bacterial infections. A C-reactive protein cut-off of 2 mg/dL has moderate sensitivity (88%) and specificity (60%) for identification of febrile children with bacterial infections, with higher levels (eg, > 8 mg/dL) having higher specificity.⁵⁰ Other studies have found lower diagnostic utility for C-reactive protein used in isolation to identify septic children.^{51,52} Yet all of these laboratory parameters have low positive predictive value for predicting sepsis.

Procalcitonin (PCT) has the most favorable test characteristics for the identification of children with bacterial infections, particularly for invasive bacterial infection (IBI) (bacteremia and/or bacterial meningitis).^{45,53} Among febrile infants ≤ 60 days of age, a PCT level of < 0.5 ng/mL should be used in combination with other clinical and laboratory parameters to identify infants at low risk of IBI (Table 6).^{48,49} For febrile older children, a PCT level of > 0.5 ng/mL has low sensitivity (55%) and moderate specificity (85%) for bacterial infections, although its sensitivity is higher for IBI (82%).⁵³ A PCT level of > 2 ng/mL has low sensitivity (61%) for IBI but high specificity (94%) and can be used to identify febrile children at higher risk of sepsis.⁵³ PCT use in adults with suspected sepsis has demonstrated

TABLE 6 Step-by-step approach and PECARN prediction rule for identification of well-appearing febrile infants with bacterial infections

	Step-by-step approach	PECARN prediction rule
Age range	≤ 90 days	≤ 60 days
History	No source of fever	Gestational age ≥ 36 weeks No antibiotics in preceding 48 hours No soft-tissue infections No chronic medical conditions Not critically ill
Criteria	1. ≤ 21 days 2. Ill appearing 3. +leukocyturia 4. PCT ≥ 0.5 ng/mL 5. CRP > 20 mg/L 6. ANC $> 10,000/\text{mm}^3$	1. Positive urinalysis 2. PCT > 0.5 ng/mL ^a 3. ANC $> 4000/\text{uL}$ ^a
Low risk	None of the above present	None of the above present
Test characteristics for bacterial infections	Sensitivity: 97.8% (95% CI, 96.1–98.8) ^b Specificity: 58.3% (95% CI, 55.9–60.6) ^b	Sensitivity: 98.2% (95% CI, 94.8–99.6) ^c Specificity: 58.1% (95% CI, 55.7–60.6) ^c

Note. Adapted from Gomez et al⁴⁸ and Kuppermann et al.⁴⁹ The majority of patients with bacterial infections in these studies did not have organ dysfunction.

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; PECARN: pediatric emergency care applied research network.

^aRoit iunded cut-off values.

^bSensitivity and specificity calculated using data from the validation study.

^cSensitivity and specificity calculated from combined derivation and validation data using rounded cut-off values.

mixed results.^{54,55} Further data are needed on the role of PCT in children with suspected sepsis. A major limitation of currently available evidence relates to the fact that serious bacterial infection rather than sepsis, or infection with organ dysfunction, was used as the outcome in diagnostic accuracy studies.

Serum lactate >2 mmol/L (>18 mg/dL) is a component of the Sepsis-3 definition of septic shock in adults.¹⁶ Studies have reported that increasing lactate levels, both venous and arterial,⁵⁶ are associated with a higher risk of organ dysfunction and mortality in children with infection, in particular if >4 mmol/L (>36 mg/dL).^{57,58} Although a normal lactate does not exclude a sepsis diagnosis in children, high levels should raise suspicion for sepsis and septic shock in the appropriate clinical context and prompt aggressive resuscitation.³¹

4.3 | Novel biomarkers and sepsis phenotypes

The complexity of pediatric sepsis makes it unlikely that any single biomarker in isolation will have sufficient diagnostic or prognostic capability. Consequently, most successful strategies in sepsis biomarker development have taken a multimarker approach. Because sepsis pathophysiology can affect multiple organ systems, particular interest has been paid to mechanisms spanning organ systems including immune, vascular, and bioenergetic dysfunction.

Novel biomarkers can define pediatric sepsis endotypes. Wong et al⁵⁹ identified 5 markers for the Pediatric Sepsis Biomarker Risk Model (PERSEVERE) biomarker risk model: C-C chemokine ligand 3 (*CCL3*), interleukin 8 (*IL8*), heat shock protein 70 kDa 1B (*HSPA1B*), granzyme B (*GZMB*), and matrix metalloproteinase 8 (*MMP8*). These markers in combination were associated with 28-day mortality. Addition of the platelet count (PERSEVERE II)⁶⁰ and elements of the tumor protein 53 pathway (PERSEVERE-XP) allowed more precise prediction of 28-day mortality.⁶¹ Wong et al⁶² identified higher pathogen burden in children with higher PERSEVERE II scores. One important caveat is that this work focused on children in the ICU with established sepsis diagnoses who were already severely ill at time of biomarker assessment. The performance of PERSEVERE or similar ICU-based markers in a more undifferentiated population of children with possible sepsis, where the aim is to identify those about to deteriorate, remains unknown.

RNA expression profiling also has been proposed as a tool to distinguish pathogen type in children. Blood cultures lack sensitivity (false negatives with sporadic bacteremia or low blood culture volumes) and specificity (contaminants) and are slow to result. A large multicenter study identified gene expression patterns associated with bacterial versus viral infection in febrile young infants,⁶³ and others have identified candidate markers in older children as well.⁶⁴⁻⁶⁶

5 | ED MANAGEMENT: THE 2020 PEDIATRIC SSC GUIDELINES

In February 2020, the SSC published the new guidelines (Figure 1)¹⁷ for the management of children with sepsis. Of the 77 statements, 6 were strong recommendations and 9 were best practice statements (BPS) (Table 7).¹⁷ For most of the guidelines, there were inadequate data to make strong recommendations in support of or against various interventions, reflecting the paucity of randomized trials in the field of pediatric sepsis. The guidelines are based on systematic literature review followed by rigorous evaluation of the evidence and discussion in the

expert panel to provide guidance for most scenarios relevant to ED management.

5.1 | General management

The guidelines emphasize the role of systematic screening for sepsis while acknowledging that there is no best screening/recognition tool and that implementation of screening procedures requires careful consideration of the local epidemiology and processes, with regular calibration and evaluation. Building on a body of retrospective and prospective observational studies that report on improved outcomes related to timely protocolized treatment, the new guidelines recommend the implementation of institutional protocols for the management of sepsis. Sepsis bundles should consist of the following 6 steps: obtain intravenous/intraosseous infusion access, collect blood cultures and lactate, initiate of empiric broad-spectrum antibiotics early, administer fluid bolus if shock is present, and consider vasoactive agents if shock persists.

5.2 | Antibiotic management

Empiric antibiotic therapy should be initiated as quickly as possible for children with sepsis. Empiric broad spectrum parenteral agents should be administered based on the child's age, presenting features/focus of infection, comorbidities such as immunocompromise, and local epidemiology in relation to disease prevalence and antimicrobial resistance patterns. One approach for empiric antibiotics based on the presumed site of infection and a child's comorbid medical conditions is described in Table 8.^{17,67-69}

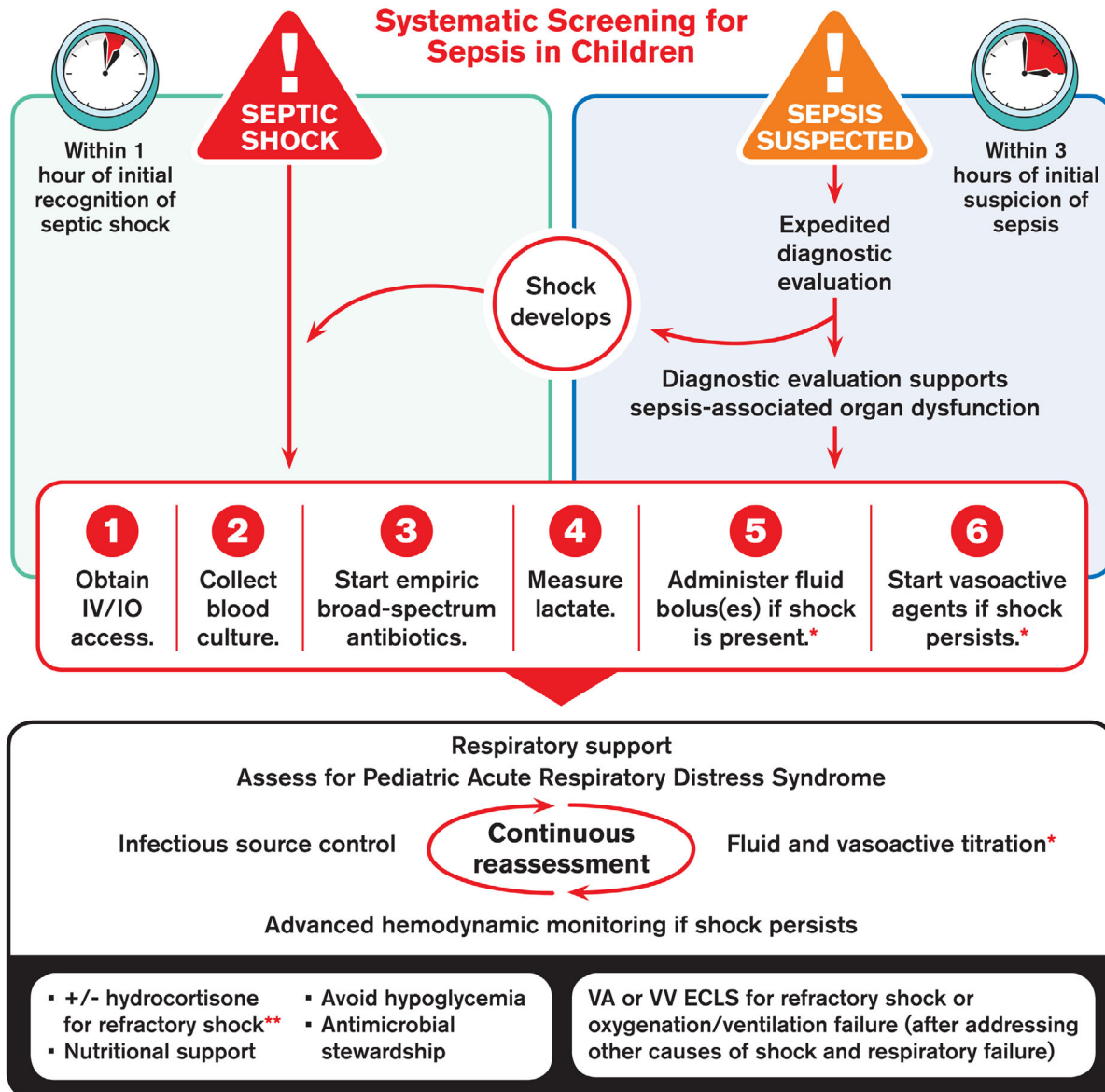
Antibiotics should be administered as soon as possible, ideally within an hour of the recognition of septic shock.¹⁷ This recommendation is based on the observational data demonstrating improved survival associated with early antibiotics in cohorts of children with a predominance of septic shock.^{22,29,70,71} Antibiotic administration should follow blood culture sampling, but not be delayed while awaiting the collection or results of diagnostic testing, including lumbar puncture, in children with shock. In practice, however, many children presenting to EDs being evaluated for sepsis are not in shock, and sepsis may represent one of several diagnostic options. In children without shock, the SSC panel considered the benefits of rapid antibiotic administration with balancing measures related to the exposure of non-septic children to potentially unnecessary antibiotics.⁷² In children with sepsis without shock, the 2020 SSC recommends starting antimicrobial therapy after appropriate evaluation and within 3 hours of recognition.

5.3 | Initial fluid and inotrope resuscitation, and hemodynamic monitoring

Although intravenous fluid boluses remain a cornerstone of the resuscitation of children with septic shock, an increasing number of publications have highlighted the increased morbidity and mortal-

Initial Resuscitation Algorithm for Children

Surviving Sepsis Campaign®



*See fluid and vasoactive algorithm. Note: Fluid bolus should be omitted from bundle if a) fluid overload is present or b) it is a low-resource setting without hypotension. Fluid in mL/kg should be dosed as ideal body weight.

**Hydrocortisone may produce benefit or harm.

www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients

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FIGURE 1 Surviving Sepsis Campaign algorithm for the initial resuscitation of children with suspected sepsis. Used with permission from the Surviving Sepsis Campaign. ECLS, extracorporeal life support; IO, intraosseous infusion; IV, intravenous; VA, veno-arterial; VV, veno-venous

TABLE 7 Surviving Sepsis Campaign international guidelines for the initial management of pediatric septic shock and sepsis-associated organ dysfunction: strong recommendations and best practice statements applicable to the emergency department setting

Category	Recommendation
Recognition	Implement systematic screening for timely recognition of septic shock and other sepsis-associated organ dysfunction ^a
	Implement a protocol for management of sepsis-related organ dysfunction (BPS)
	Obtain blood cultures before starting antimicrobial therapy if this does not delay antimicrobial administration (BPS)
Antimicrobial therapy and antimicrobial stewardship	Administer antibiotics within 1 hour of recognition to children with septic shock and within 3 hours of recognition in children with sepsis-associated organ dysfunction without shock
	Start with empiric broad-spectrum antibiotics to cover all likely pathogens (BPS)
	Narrow antimicrobial coverage after culture and susceptibility data are available (BPS)
	Narrow coverage or discontinue antimicrobials if no pathogen is identified, considering site of infection, clinical improvement, and patient risk factors (BPS)
	Optimize antimicrobial drug dosing based on pharmacokinetic data (BPS)
	Reassess daily for antimicrobial de-escalation (BPS)
Source control	Determine antimicrobial duration based on site of infection, etiology, clinical response, and ability to obtain source control (BPS)
	Remove intravascular access devices if confirmed to be source of sepsis after alternative access is obtained
Fluid therapy	Emergently achieve source control if possible (BPS)
	If intensive care support is available, administer up to 40–60 mL/kg in bolus fluids during the first hour and monitor for signs of fluid overload
	If intensive care support therapies are unavailable, ^b administer bolus fluids only in the presence of hypotension
Hemodynamic monitoring	Avoid starches (hydroxyethyl starch) or gelatin in acute resuscitation
	Use advanced hemodynamic monitoring, if available, in addition to bedside clinical variables to guide resuscitation
Respiratory support therapy	Use trends in blood lactate levels to guide resuscitation
	Consider a trial of non-invasive mechanical ventilation in children responding to resuscitation without clear indication for intubation (weak). No recommendation regarding intubation in children with fluid or catecholamine-resistant septic shock
Endocrine and metabolic	Follow ARDS treatment recommendations including prone positioning, neuromuscular blockage, and high PEEP, do not routinely use iNO
	Do not use IV hydrocortisone in children with septic shock responding to fluids and/or vasopressor therapy. No recommendation regarding the use of IV hydrocortisone in refractory shock
	Do not use insulin to target lower blood glucose levels
	Consider early enteral nutrition

Note. Adapted from Weiss et al.¹⁷

Abbreviations: ARDS, acute respiratory distress syndrome; BPS, best practice statements; iNO, inhaled nitric oxide; IV, intravenous; PEEP, positive end-expiratory pressure.

^aWeak recommendation, very low-quality evidence.

^bIn most US settings, intensive care support therapies such as inotropes or ventilation can, at least temporarily, be administered in the emergency department and ward environments even in facilities with no on-site ICU; this recommendation is indicated for settings where no such support can be provided.

ity associated with aggressive fluid administration. At present, the only high-grade evidence relates to the Fluid expansion as supportive therapy (FEAST) study,⁷³ which observed substantially higher mortality in children in Africa with infection and organ dysfunction receiving fluid boluses. The challenge in ascertaining the relevance of these findings for high-income settings where critical care support to deal with the side effects of fluid overload (such as respiratory failure) remains. The SSC panel therefore made a recommendation that takes the health care setting into account. In settings where intensive care interventions such as ventilation and inotropes can be provided (which is the case, at least currently, for most EDs in the United States), 40–60 mL/kg isotonic fluid boluses should be administered during the first hour in increments of 10–20 mL/kg. Fluid administration needs to be titrated to signs of perfusion and

organ dysfunction and should be discontinued if signs of fluid overload develop. In contrast, in settings where intensive care is not available, fluid resuscitation should be restricted to children with hypotension using more judicious fluid amounts of 10–20 mL/kg during the first hour.

Normal saline, lactated Ringer's, and to a lesser extent PlasmaLyte are the most commonly used isotonic fluids in pediatric sepsis. The administration of normal saline results in a hyperchloremic metabolic acidosis that can exacerbate the acidosis already common in sepsis and has been associated with decreased renal perfusion and increases in morbidity.^{74–76} Balanced fluids have been demonstrated to reduce acute and persistent kidney injury and mortality in adults with sepsis.⁷⁷ For these reasons, the new pediatric SSC recommendations suggest using balanced fluids for initial resuscitation, acknowledging that

TABLE 8 Empiric antimicrobial coverage in children with sepsis^a

Group	Regimen	Notes
Previously healthy	Third-generation cephalosporin + vancomycin	Can use cephalosporin monotherapy in regions with minimal MRSA or resistant pneumococci; consider adding an aminoglycoside in regions with substantial ceftriaxone resistance among Gram-negative organisms
Immunocompromise	Vancomycin + anti-pseudomonal cephalosporin (eg, cefepime) or extended-range PCN/Beta-lactamase combination (eg, piperacillin-tazobactam) or a broad-spectrum carbapenem (eg, meropenem)	Vancomycin and cefepime has been associated with less AKI in adults than vancomycin combined with an extended-range PCN/Beta-lactamase combination
Central venous catheter	Vancomycin + anti-pseudomonal cephalosporin (eg, cefepime) or extended-range PCN/Beta-lactamase combination (eg, piperacillin-tazobactam) or a broad-spectrum carbapenem (eg, meropenem)	Recognize predominance of Gram-negative enterics in TPN-dependent children with intestinal failure and risk of pseudomonal sepsis in febrile neutropenic children
Neonates	Ampicillin + third generation cephalosporin + acyclovir	Ampicillin for <i>Listeria</i> coverage
Musculoskeletal source ^{bc}	Vancomycin	Add Gram-negative coverage if immunocompromise or after penetrating trauma; if history of MSSA, add cefazolin or nafcillin
Suspected hospital-acquired pneumonia	Vancomycin + (piperacillin/tazobactam or cefepime or ceftazidime or carbapenem)	If high risk of mortality or recent receipt of broad-spectrum antibiotics, consider administration of 2 antibiotics with Gram-negative coverage, trying to avoid giving 2 beta-lactam agents together (for risk of marrow suppression, AKI)
Intra-abdominal source ^c	Extended-range PCN/Beta-lactamase combination or carbapenem, or addition of metronidazole or clindamycin	Requires more robust anaerobic coverage (eg, piperacillin-tazobactam)
Influenza-like illness	Oseltamivir, peramivir, or other influenza treatment; consider Gram-positive coverage	Biphasic illness with influenza concerning for bacterial superinfection (<i>Staphylococcus aureus</i> , streptococcal species)
Toxic shock ^c	Addition of clindamycin or lincomycin	Limits toxin production
Necrotizing fasciitis ^c	Vancomycin + piperacillin/tazobactam (or vancomycin + carbapenem); alternative: ceftriaxone + metronidazole	PCN + clindamycin for group A <i>Streptococcus</i> (<i>Streptococcus pyogenes</i>)
Travel history	Consider treatment for malaria or rickettsial diseases	

Abbreviations: AKI, acute kidney injury; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PCN, penicillin; TPN, total parenteral nutrition.

^aVariables to consider in the selection of antimicrobial agents include local epidemiology and antibiotic resistance patterns, a child's prior cultures, risk factors for specific infections, and potential drug toxicities.

^bIncludes septic arthritis, osteomyelitis, or pyomyositis.

^cRole for early surgical intervention for source control and to obtain culture data to facilitate targeted antibiotic coverage.

further pediatric data are needed to ascertain the optimal fluid for resuscitation of children with sepsis.⁷⁸ The group recommended against the administration of blood products for non-bleeding children who were not anemic (hemoglobin ≥ 7 g/dL), as data do not support empiric administration of packed RBCs, platelets, or plasma in improving outcomes in this group.

Epinephrine or norepinephrine are recommended as first-line vasopressors over dopamine for fluid-refractory sepsis, with insufficient data to recommend either one specifically. Vasopressor administration initially can be through either peripheral intravenous, intraosseous, or central venous catheter (CVC). Limited data existed to suggest maximum rates to administer peripherally. Vascular access should not delay inotrope administration. The decision to place a CVC in the ED using point-of-care ultrasound should be made in conjunction with ICU col-

leagues, depending on the expertise of the ED healthcare workers in the placement of CVCs, risk of infection in a CVC placed under potentially suboptimal conditions of sterility, clinical stability of the child, and how long the child is anticipated to remain in the ED. Trending lactate levels can be used to guide resuscitation. Hydrocortisone can be considered for fluid-refractory and vasopressor-refractory shock, but there is no recommendation to administer intravenous hydrocortisone in the new guidelines. Finally, extracorporeal membrane oxygenation (ECMO) remains an option for children in septic shock refractory to conventional support, acknowledging that ECMO is only available at specialized centers and optimal patient selection remains challenging.⁷⁹

The previous ACCCM recommendations³¹ differentiated between warm shock (bounding pulses, flash capillary refill, warm extremity

temperatures, wide pulse pressure) versus for cold shock (thready pulse, slow capillary refill, cold extremities, narrow pulse pressure, mottled appearance) to select vasoconstrictors versus inotropes. However, vital signs and clinical evaluation poorly differentiate between cold and warm shock and inaccurately identify children with cardiac dysfunction.⁸⁰ Therefore, the new pediatric SSC guidelines recommended against the use of clinical parameters to categorize children as being in warm versus cold shock. Advanced hemodynamic monitoring (eg, arterial blood pressures, central venous oxygen saturations) in addition to clinical assessment may provide more reliable guidance in relation to systemic vascular resistance, filling, and cardiac output, but is operator dependent and often unavailable in the ED.

5.4 | Near-infrared spectroscopy

The microcirculatory changes of sepsis precede diversion of blood from end-organs and cannot necessarily be predicted from macro-hemodynamic values such as vital signs. Detecting these early micro-circulatory changes could lead to earlier diagnosis and improved outcomes⁸¹; however, microcirculation is difficult to monitor. Micro-circulatory tests such as lactic acid, acid-base status, and central venous oxygen saturation levels are invasive, not always available, and do not offer the advantage of continuous monitoring.

Near-infrared spectroscopy (NIRS) is a non-invasive, real-time, easily applied tool that continuously monitors microcirculation and regional tissue oxygen saturation (StO₂) without requiring a pulsatile signal. NIRS uses the absorption of infrared light emitted from a probe that passes through skin or bone into underlying tissue, giving a venous weighted hemoglobin saturation in tissue.⁸² NIRS-derived cerebral StO₂ correlates with central venous oxygen saturation.⁸³⁻⁸⁶ Abnormal NIRS values have been shown to identify perfusion deficits earlier than lactate or base deficit.⁸⁷ A systematic review and meta-analysis of adults showed that patients with severe sepsis or septic shock have lower levels of StO₂ with survivors having higher levels of StO₂ compared with non-survivors.⁸⁸ However, the utility of StO₂ in pediatric sepsis has not been well studied. The potential for StO₂ as a resuscitation target in sepsis and incorporation into a risk score along with other predictor variables are possible avenues for future investigation.

5.5 | Respiratory support

Many children will respond to initial sepsis therapy. If signs of respiratory distress or failure develop, a trial of non-invasive positive-pressure ventilation can be considered for children who lack clear indications for intubation.¹⁷ Although the guidelines do not specifically recommend airway management, intubation should be considered for children with fluid-refractory and catecholamine-refractory shock. Etomidate as an induction agent should be avoided, as small studies have found significant adrenal suppression in adults with sepsis intubated with etomidate as opposed to other agents.⁸⁹ Although there are limited data on optimal induction agents for children, the use

TABLE 9 Risk factors for mortality in pediatric sepsis in high-resource settings

Category	Risk factor
Demographic	Age < 1 year
Comorbidities	Congenital heart disease
	Hematology/Immunology
	Malignancy
	Immunosuppression
Organ system dysfunction	AKI
	Hypotension
	Cardiac arrest
	Ventilatory support
	Shock at ICU admission
	ECMO
Laboratory or microbiologic parameter	Elevated lactate
	Bacteremia
	Pneumococcal infection

Abbreviations: AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation.

of ketamine or fentanyl (the latter potentially administered at lower doses in children with hypotension) may facilitate intubation without causing adrenal suppression. Once intubated, children with acute respiratory distress syndrome and sepsis may require higher (>10 cm H₂O) positive end-expiratory pressure to prevent alveolar collapse and optimize oxygenation, and best practices for pediatric acute respiratory distress syndrome including prone positioning and consideration for ECMO in cases of refractory respiratory failure should be followed.⁷⁹

6 | OUTCOMES

Recent studies from high-income countries indicate that ≈3%–7% of children with sepsis presenting to EDs die, with mortality rates increasing to up to 20% for those with septic shock treated in PICUs.^{1,9,90} In resource-limited settings, mortality rates as high as 50% remain a daily reality.⁴ The majority of pediatric sepsis deaths occur within 48 hours of presentation, and specific risk factors for mortality have been identified (Table 9).^{10,11,91-93} Early deaths are usually attributed to refractory shock, whereas late deaths are more often associated with multiorgan system dysfunction.⁹⁴

In recent years, the relevance of long-term outcomes beyond the hospitalization of children with sepsis received increasing attention. Of concern, more than one-third of pediatric survivors had not regained their baseline health-related quality of life one year after an episode of community-acquired sepsis.⁹⁵ Lower quality-of-life scores were associated with multiorgan dysfunction, renal replacement therapy, ECMO or cardiopulmonary resuscitation, and duration of mechanical ventilation and inotropes.⁹⁶ Similar findings were observed internationally.¹¹

Given that most children with sepsis are younger than 10 years of age, the long-term impact of sepsis sequelae on children, their families, and society cannot be emphasized enough.

7 | CONCLUSIONS

Sepsis remains a leading cause of death in children in the United States and globally, and its toll on short-term and long-term outcomes for this vulnerable patient group is substantial. Yet the relative rarity of sepsis in comparison to common febrile infections, combined with often non-specific early manifestations, can make prompt recognition in EDs challenging. The use of clinical decision support and sepsis protocols have been shown to reduce morbidity and mortality in children with sepsis and should be implemented and audited as best practice to save lives and improve outcomes for children with sepsis.

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