Early Recognition and Emergency Treatment of Sepsis and Septic Shock in Children

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Abstract: Early diagnosis and treatment of sepsis and septic shock in children results in improved outcomes. However, diagnosis is hampered by lack of specific diagnostic tests and relies on the recognition of the alterations of vital signs and protean systemic manifestations associated with infections, signs that mimic many critical illnesses. As a result, the early diagnosis of sepsis is usually presumptive and is based on the suspicion or presence of an infection in combination with the systemic changes. Suspicion should be heightened in vulnerable risk groups such as those with immune compromise due to underlying disease or medication use. Thus, on many occasions, treatment of sepsis is initiated on clinical suspicion pending the outcomes of ongoing evaluations and laboratory findings.

What is of relevance to the emergency clinicians is the initial recognition, resuscitation, and treatment in the first few hours of presentation. To best accomplish these tasks, contemporary guidelines suggest that the use of a "recognition bundle" containing a trigger tool for rapid identification, a "resuscitation and stabilization bundle" to enable adherence to best practice, and a "performance bundle" to identify and overcome barriers to best practice be used.

Although there are no universally acceptable tools to accomplish these tasks, the various iterations used in quality improvement initiatives have consistently demonstrated better care processes and outcomes. In this article, we outline the contemporary approach to sepsis in the first hours after presentation.

Key Words: sepsis, pediatric sepsis, recognition, septic shock, treatment, critical illness

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TARGET AUDIENCE

This article is intended for pediatric emergency physicians, emergency physicians, pediatricians, family physicians, and other health care providers caring for children in emergency departments and urgent care settings.

LEARNING OBJECTIVES

After reading this article, the reader should better be able to:

1. Discuss sepsis and septic shock in children,
2. treat sepsis or septic shock in children,
3. evaluate care processes and outcomes of care in sepsis.

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Sepsis is defined as a life-threatening organ dysfunction caused by a severe infection. Septic shock refers to sepsis with cardiovascular dysfunction that persists despite fluid resuscitation. It is a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities associated with a greater risk of mortality.[1] The most common sites of infection leading to sepsis are respiratory, abdominal/urinary tract, or skin infections. The etiological agents involved in sepsis vary depending on geographic location and may include bacterial, viral, mycoplasmal, and fungal infections, individually or in combination.[2] Commonly, the primary source of infection is not apparent.[3]

Sepsis confers a huge burden globally, with an estimated incidence of 3 million cases of sepsis in neonates and 1.2 million cases in children.[4] Sepsis is also a major contributor to death and disability in children, with wide variation on outcomes and case fatality rates of 19% in developed countries and 32% in developing countries.[5] Recognition of the enormity of this burden in both children and adults resulted in sepsis being designated a global threat and a key health care priority by the World Health Organization.[6] Based on this document, the salient global priorities relevant to children, including timely recognition and emergency care, were outlined.[7]

In North America, data from 2013 show that around 100,000 children present to the emergency department (ED) with severe sepsis, which would translate in 20 cases of severe sepsis per average-sized ED per year.[8] In Canada, sepsis accounted for 4000 admissions and 200 deaths nationwide per year, with 75% of cases being neonates and infants younger than 2 months. The most common type of organ failure associated with sepsis was respiratory failure, and an increasing number of organs failing was associated with an increasing mortality.[9]

Of relevance to emergency clinicians are the initial recognition, resuscitation, and treatment in the first few hours of presentation. To best accomplish these tasks, contemporary guidelines suggest that the use of a "recognition bundle" containing a trigger tool for rapid identification, a "resuscitation and stabilization bundle" to enable adherence to best practice, and a "performance bundle" to identify and overcome barriers to best practice be used.[10] The strength of a bundle lies in linking of interventions that will be followed in total. Bundles consist of evidence-based practices, which together give much improved outcomes.[11] Guidelines and "bundles" are not interchangeable concepts, and there is evidence that use of both can lead to improvement in care process and outcomes when followed.[12]

RECOGNITION OF SEPSIS AND SEPTIC SHOCK IN CHILDREN

Sepsis and septic shock are not distinct entities but represent a continuum of increasing physiological instability in response to

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a systemic infection. Children also have tremendous compensatory reserve, and hence, when the signs of shock are apparent, there is little time for deliberation, and treatment should be given emergently. This ability to compensate, the heterogeneity of the pediatric population, protean clinical symptoms and signs, and the greater burden of infectious diseases in children presenting for emergency evaluation highlight the importance of having a robust plan to address sepsis.

RECOGNIZING SEPSIS

Timely treatment relies on early recognition. In some instances, the child may present with subtle clinical derangements, and there is time for evaluation to progress in the traditional manner of history taking and physical examination leading to a differential diagnosis. However, the child can also present in extremis, which leaves little time for deliberation, and hence, resuscitation efforts take precedence or occur in tandem with history taking.

The presenting history can be indistinct, especially in neonates and infants, or children with developmental delay. Poor feeding, lethargy, poor tone, irritability, and signs of upper airway infection are common presentations. In older children, some days of febrile illness followed by deterioration in their status such as somnolence, lethargy, and/or poor oral intake can be the only clue. Interestingly, a physician's "gut feeling" has shown to be a discriminator of serious infection and should not be ignored.[13] Parents' perception of their child's illness may also be an indication of severity, although the role of their perception in sepsis evaluation is unsettled.[14]

Both benign infections that commonly present to the ED and early sepsis can present with temperature changes, tachycardia, and local signs of infection. If, in addition, the child shows signs of systemic infection, such as tachypnea and mental state changes, or looks generally "unwell," the diagnosis of sepsis should be considered. Sepsis screening should be done for all patients presenting with inappropriate heart rate for age (most commonly tachycardia, but bradycardia may be present especially in neonates and infants) and signs of infection. Different screening tools have been developed based on the recommendations by the American College of Critical Care Medicine. An example of the screening tool developed by British Columbia Child Health is included (Fig. 1), and others are referenced.[15,16]

HIGH-RISK GROUPS

There are certain high-risk groups where extra vigilance in identifying early sepsis is required. These are children with risk factors making them prone to develop sepsis, risk of unorthodox presentation, and/or high risk of rapid deterioration. The clinical presentation may be subtle in infants younger than 3 months, or in patients with significant developmental delay. Seventy-five percent of patients presenting with sepsis are younger than 3 months and are especially vulnerable if they are very-low-birth-weight infants. The immune system of premature neonates is characterized by poor innate and adaptive function.[17] All patients with immunocompromise, for instance, with neutropenia under cancer treatment, or those with an immunodeficiency syndrome, are at a higher risk of developing an invasive infection. Even patients with chronic diseases (cardiac, respiratory, neuromuscular), patients with indwelling devices/access devices, or patients after a recent hospitalization are at increased risk of septic events.

SEPTIC SHOCK

Septic shock implies cardiovascular dysfunction as evidenced by signs of inadequate tissue perfusion, such as prolonged capillary refill (>3 seconds), mottled and cool extremities, altered mental status, oliguria, and/or hypotension. The presence of hypotension indicates loss of compensatory reserve but is not required to diagnose septic shock in children. Indeed, increasing severity of hemodynamic abnormalities is associated with increasing mortality: *normotension* with a capillary refill >3 seconds was associated with 7% mortality, whereas *hypotension* with capillary refill >3 seconds showed a 33% mortality.[18]

DIFFERENTIAL DIAGNOSIS

Because of the nonspecific nature of the clinical signs of sepsis in children, the differential diagnosis is broad. Differential diagnoses include congenital heart disease and metabolic disease in newborns, myocarditis, malignancies, hemophagocytic syndromes, poisoning, anaphylaxis, adrenal insufficiency, hypovolemia, or pulmonary embolism. Although the history and physical examination will usually give clues when to suspect other diagnoses, these may be difficult to differentiate initially. They should be considered if the patient's presentation is atypical or not responding to the treatments initiated for sepsis. Congenital heart disease can present when the duct between the pulmonary artery and the aorta closes, and should be considered in any neonate presenting with circulatory failure or respiratory distress. Hepatomegaly, a cardiac murmur, or differential blood pressures or pulses between the upper and lower extremities should lead to the initiation of prostaglandin treatment until congenital heart disease is ruled out. Adrenal insufficiency is usually diagnosed through newborn screening, but secondary insufficiency can present as circulatory collapse with severe electrolyte disturbances. This will need urgent treatment with glucocorticoids. Failure to address new findings or continuously reevaluating the patient may lead to misdiagnosis.

RECOGNITION BUNDLE

A sepsis screening tool should be included in a recognition bundle to aid clinicians evaluating children with possible sepsis. No screening tool has proved to be superior to another; however, implementing a tool adapted to local context is most effective to ensure adherence by all involved in sepsis care. For these tools to be effective, all children presenting to the ED should be screened for sepsis. Most tools emphasize the use of clinical parameters rather than laboratory tests in North American EDs to identify sepsis.[19] A previously referenced example of a screening tool has been given in Figure 1.

Recognition should lead to activation of emergency treatment as outlined in a "resuscitation and stabilization" bundle.

LABORATORY TESTS AND PEDIATRIC SEPSIS

Laboratory tests results should not dictate or delay treatment and may not be available in resource poor settings. No biomarker, including white blood cell counts, has been shown to be reliable to diagnose sepsis or predict prognosis. As soon as sepsis is suspected, appropriate cultures should be obtained, but they should not delay the start of antibiotic treatment. The cultures should always include at least one set of blood cultures, and if the patient has an indwelling vascular device, cultures should be drawn both from the device and from peripheral blood. The cultures have an important role in determining the causative agent and to promote antibiotic stewardship further on in the treatment course. In addition to blood cultures, the clinical context will dictate the necessity of obtaining other cultures. Usually, urine cultures and a tracheal or nasopharyngeal aspirate may be needed. Cerebrospinal fluid or wound cultures can be indicated. Because viral infections are common and are the most important differential diagnosis, a nasopharyngeal viral polymerase chain reaction and viral serology can be sent. Pneumococcal

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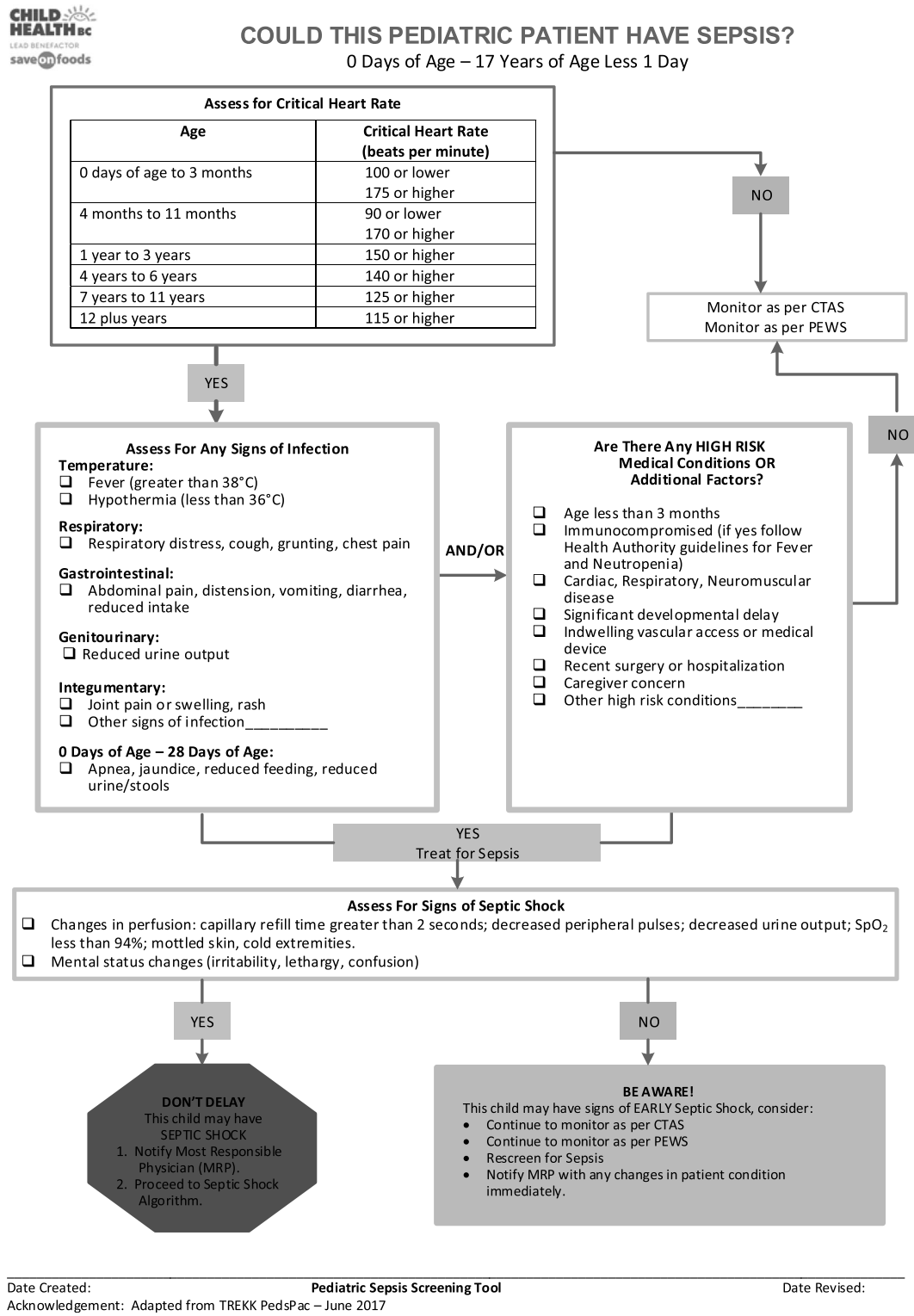

FIGURE 1. The early recognition tool for sepsis developed by BC Child Health. CTAS indicates Canadian Triage and Acuity Scale; PEWS, Pediatric Early Warning Score. Printed with permission of BC Child Health, Yasmin Tuff, October 2019.

antigen tests in urine should not be routinely ordered but may be helpful in supporting the diagnosis when invasive pneumococcal infection is suspected.

Procalcitonin is an early marker of infectious disease; however, there is no evidence showing that procalcitonin can be used to diagnose sepsis and/or the need for antibiotics, but it may be

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used in follow-up to stop antibiotics. Hence, it is of no use to the emergency physicians in this regard.[20]

Lactate measurements are readily available with point-of-care blood gas sampling, and are helpful to alert the clinician to perfusion abnormalities and may indicate septic shock. Pediatric studies supporting lactate guided resuscitation in children are lacking, but one prospective study by Scott et al[21] showed that patients who cleared their lactate within 2 to 4 hours had a significantly lower risk of persistent organ dysfunction for 48 hours.

Sepsis has a complex pathophysiology, and one biomarker is unlikely to enable early recognition of sepsis. Future developments may consist of panels of biomarkers with significance for sepsis recognition or prognostication unique for different patient categories.[20]

TREATMENT OF SEPSIS OR SEPTIC SHOCK IN CHILDREN

Treatment for sepsis or septic shock should include infection treatment and source control, reversal of hemodynamic abnormalities, and preservation of end-organ perfusion.[22] These tasks are best achieved by the use of a "resuscitation and stabilization" bundle. Implementing the complete bundle avoids missing crucial steps. An example of a resuscitation bundle, developed by Translating Emergency Medicine for Kids (TREKK), is given in Figure 2.

Initial treatment in all cases should be dictated by the clinical presentation. For those who present in extremis and significant cardiorespiratory compromise or failure, resuscitation should follow the Pediatric Advanced Life Support (PALS) guidelines.[23] For children with sepsis without cardiovascular compromise suggesting septic shock, vital signs should be obtained and either frequently reassessed and electrocardiogram, blood pressure, and saturation monitoring applied. Oxygen should be given by facemask if needed, and intravenous access established. If intravenous access is not obtained within the first 5 to 10 minutes, intraosseous access should be considered. Intravenous or intraosseous access can be used for obtaining blood tests and for access to the circulation for drugs and fluid administration. For children in septic shock, continuous

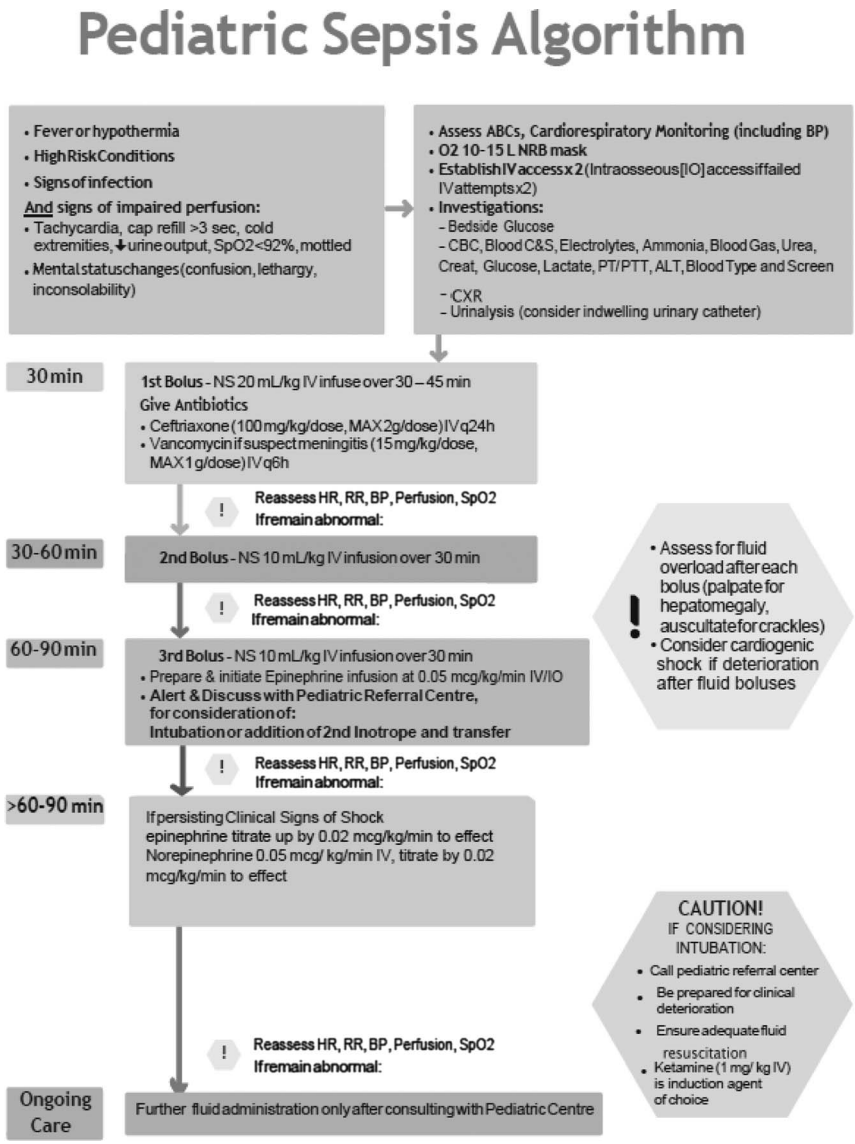

FIGURE 2. The sepsis treatment protocol as developed by TREKK. BP indicates blood pressure; HR, heart rate; RR, respiratory rate; SpO_2, oxygen saturation. Printed with permission of TREKK, Dr Garth Meckler, October 2019.

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monitoring and early treatment offer the best chance of a good outcome. In all cases, the PALS guideline should be adhered to in addition to the American College of Critical Care Medicine guidelines modified to local context.

Glucose estimation, complete blood cell count, coagulation screen, electrolytes, liver enzymes, and creatinine should be sent for investigation. Cultures should be obtained, and antibiotics, adjusted to local bacterial resistance patterns, should be given. The initial antibiotic administered should cover most common pathogens. Broad-spectrum coverage usually includes a third-generation cephalosporin and vancomycin to cover for multiresistant organisms. For neonates and infants, ampicillin combined with a third-generation cephalosporine or gentamicin offers coverage for perinatal infections including group B streptococci and listeria. Acyclovir should be added for neonates younger than 28 days as an antiviral agent against herpes simplex infections, because bacterial sepsis (thrombocytopenia, respiratory collapse, elevated transaminases) may mimic meningitis and encephalitis and treating early will limit the devastating late consequences. Because cerebrospinal fluid not always can be obtained within a couple of hours because of clinical instability, thrombocytopenia, or ongoing resuscitation, cerebrospinal fluid pleocytosis cannot always guide therapy. It is therefore recommended to give acyclovir early, pending cultures. Immunocompromised children, those with health care–associated infections, or those who are known to have previous infections with certain organisms usually need individualized treatment, which should be guided by local guidelines and an infectious disease specialist.

For children in shock, intravascular volume expansion with fluid boluses should be undertaken. The volume, rate, and type of fluid have been vigorously debated. In resource-rich areas with contemporary ED and critical care facilities, administering up to 40 to 60 mL/kg in bolus fluid (10–20 mL/kg per bolus) during the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction is recommended. However, in resource-poor settings with no critical care services, administering up to 20 mL/kg in bolus fluid (10–20 mL/kg per bolus) during the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction is recommended.[24] If the patient does not respond to the recommended fluid regime, the patient is in fluid refractory shock and needs to be started on inotrope/vasopressor therapy. Epinephrine or norepinephrine infusions are now being recommended as first choices, although dopamine has traditionally occupied that role. Maintenance of mean arterial pressure to maintain end-organ perfusion in combination with clinical monitoring of perfusion should guide fluid and vasopressor therapy.

After each fluid bolus, patients should be reassessed for signs of clinical improvement and the need for further boluses. Fluid overload will present as liver enlargement, increasing tachypnea, pulmonary rales, and or crepitations. Patients with failing hemodynamics due to myocardial dysfunction will not respond to repeated fluid boluses. Repeated fluid loading in this clinical situation simply results in elevated venous and capillary pressures with capillary leak. The goal is rapid restoration of organ perfusion, clinically shown by normalization of capillary refill, central and peripheral pulses, perfusion, and mental status.

Intubation should always be considered in patients with decreased consciousness, those with inability to protect their airway, or those with severely compromised cardiovascular or respiratory systems and may be done at any time in the treatment sequence depending on the child's clinical status.

MONITORING

Besides clinical surveillance, children should be monitored with electrocardiogram, saturation, and (non)invasive blood pressure monitoring. With ongoing acute resuscitation, there is no place for more invasive (cardiac output) monitoring, like central line placement for central venous oxygen saturation determination, in the ED. Emergency central lines may be needed for intravenous access, when the intraosseous needle needs to be replaced, and no peripheral intravenous access could be obtained. Clinical response will show as normalization of heart rate and peripheral perfusion, return of urine output, normalization of consciousness, and if previously hypotensive, normalization of blood pressure. As mentioned previously, the effect of fluid boluses needs to be evaluated, and if signs of fluid overload develop in combination with cardiovascular compromise, an urgent cardiologic consultation is required to rule out heart disease.

Increasingly, emergency physicians are trained to use ultrasound, and this gives a new range of monitoring possibilities. Both monitoring fluid status and even cardiac echocardiography to assess myocardial dysfunction can be done with ultrasound. Differentiating between hypovolemia and cardiac dysfunction can help determine the right treatment modality for an individual patient, diminishing excessive fluid administration, and evaluate given treatment.[25] Standardization of measurements and determination of their impact on outcome have to be studied in larger populations.

GLUCOCORTICOIDS

Cortisone should be given to patients suspected or known to have adrenal failure, either primary or secondary. In septic patients presenting with bacterial meningitis, dexamethasone given before or at the time of the first antibiotic dose has been shown to reduce hearing loss as a consequence of *Haemophilus influenzae* meningitis.[26] There is no evidence that cortisone treatment will reduce mortality of catecholamine-resistant septic shock, either in adult or in pediatrics, although many pediatric intensive care unit clinicians prescribe steroids, as it has been shown to reduce the duration of vasopressor refractory septic shock.[27]

EVALUATION OF CARE PROCESSES AND OUTCOMES OF CARE

The largest study evaluating the implementation of a 1-hour treatment bundle was done in New York. The "New York Sepsis Care Mandate" was implemented after the tragic death of a pediatric septic patient, and consisted of a treatment bundle that was implemented and endorsed in EDs in and around New York. Adherence to a bundle of 3 elements (blood culture, antibiotic treatment, and a fluid bolus), which were completed within 1 hour after the suspicion of sepsis, resulted in improved survival.[12] Completion of each individual element of the bundle within 1 hour was not associated with lower mortality, signaling the significance of completing all elements.

There have been several studies reporting quality improvement initiatives aimed at improving adherence to guidelines, and improved outcomes can result. The area where most gain can be achieved is that of early recognition of sepsis and septic shock.[28]

Cruz and colleagues[29] reported that shorter time from triage to first fluid bolus and antibiotic administration in their ED decreased the need for mechanical ventilation, vasoactive agents, and improved survival. Larsen and colleagues[30] reported that increased compliance with fluid goals and checking lactate within 1 hour, and administering antibiotics within 3 hours resulted in decreased hospital length of stay and mortality. Similarly, adherence to 5 bundled components of PALS for septic shock (early recognition,

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obtaining vascular access, administering intravenous fluids, delivering vasopressors for fluid refractory shock, and antibiotic administration) resulted in shorter intensive care and hospital length of stay.[31]

Given these positive experiences, we recommend the implementation of a recognition bundle with a sepsis screening tool, to identify children with sepsis early, as well as a treatment bundle and algorithm that is context specific. Moreover, periodic evaluation and reinforcement are necessary to sustain gains.[32]

CONCLUSIONS

Sepsis and septic shock are a continuum of acute, life-threatening infectious disease. Recommendations for successful sepsis outcomes may include adherence to 3 bundles: a "recognition," a "resuscitation and stabilization," and a "performance" bundle. The recognition bundle should include a screening tool, increasing chances of early identification of children with sepsis.

Signs and symptoms of sepsis may change rapidly over time and in response to therapy; thus, patients should be monitored constantly and always be evaluated for effect of therapies.

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CME EXAMINATION
February 2020

Please mark your answers on the ANSWER SHEET.

"Early recognition and Emergency Treatment of Sepsis and Septic Shock in Children"

1. Sepsis is defined as:
   a. Life-threatening infection
   b. Life-threatening organ dysfunction caused by a severe infection
   c. Life-threatening infection with organ dysfunction
   d. Life-threatening organ dysfunction caused by a dysregulated host response

2. Septic shock:
   a. Presents with signs of cardiovascular dysfunction
   b. Can only be diagnosed if the patient is hypotensive
   c. Will not increase mortality odds when compared with sepsis if treated correctly
   d. Is easier to recognize in a neonate than an older child

3. In the treatment of septic shock, the following is true:
   a. Inotropes should be started as soon as IV access is obtained.
   b. Three fluid boluses of 20 mL/kg need to be given as soon as possible.
   c. A fluid bolus should be given as soon as possible, and if the patient is not responding, inotropes should be started before further fluid is given.
   d. Each given fluid bolus should be evaluated for effect, and the adequate amount of fluid for each patient may differ.

4. To diagnose septic shock in a pediatric patient
   a. Lactate needs to be >2 mmol/L
   b. The patient needs to belong to a risk group for sepsis
   c. A bundled approach including a sepsis screening tool can be used
   d. Blood cultures need to show growth of at least one type of bacteria

5. Bundled sepsis treatment:
   a. Has not been shown to give improvement in outcomes
   b. Needs to contain a strict number of measures to be effective
   c. Is recommended to be institute specific to increase adherence
   d. Is similar to following the existing guidelines

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ANSWER SHEET FOR THE *PEDIATRIC EMERGENCY CARE* CME PROGRAM EXAM
February 2020

Please answer the questions on page 107 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____
Street Address _____
City/State/Zip _____
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Specialty _____

1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)
4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)

Your completion of this activity includes evaluating them. Please respond to the following questions below.

Please rate this activity (1 - minimally, 5 - completely)	1	2	3	4	5
Was effective in meeting the educational objectives	○	○	○	○	○
Was appropriately evidence-based	○	○	○	○	○
Was relevant to my practice	○	○	○	○	○

Please rate your ability to achieve the following objectives, both before this activity and after it::
1 (minimally) to 5 (completely)

	Pre					Post				
	1	2	3	4	5	1	2	3	4	5
1. Discuss sepsis and septic shock in children,	○	○	○	○	○	○	○	○	○	○
2. treat sepsis or septic shock in children,	○	○	○	○	○	○	○	○	○	○
3. evaluate care processes and outcomes of care in sepsis.	○	○	○	○	○	○	○	○	○	○

How many of your patients are likely to be impacted by what you learned from these activities?

○ <20% ○ 20%–40% ○ 40%–60% ○ 60%–80% ○ >80%

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 - definitely will not change, 5 - definitely will change)	1	2	3	4	5
	○	○	○	○	○

How will you apply what you learned from these activities (mark all that apply):

- In diagnosing patients ○
- In monitoring patients ○
- In educating students and colleagues ○
- As part of a quality or peformance improvement project ○
- For maintenance of board certification ○
- To consider enrolling patients in clinical trials ○
- In making treatment decisions ○
- As a foundation to learn more ○
- In educating patients and their caregivers ○
- To confirm current practice ○
- For maintenance of licensure ○

Other _____

Please list at least one strategy you learned from this activity that you will apply in practice:
Please list at least one (1) change you will make to your practice as a result of this activity:

Did you perceive any bias for or against any commercial products or devices?	Yes	No
	○	○

If yes, please explain:
How long did it take you to complete these activities? _____ hours _____ minutes
What are your biggest clinical challenges related to pediatric emergency care?
[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

Mail by January 31, 2022 to
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