# Surviving Sepsis Campaign Guidelines for the Management of Pediatric Sepsis in the Era of COVID19

Authors
Affiliations

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**Corresponding Author:**
Scott L. Weiss, MD MSCE FCCM
Associate Professor of Critical Care and Pediatrics
Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine
3401 Civic Center Blvd, Wood Building 6th Floor, Room 6037
Philadelphia, PA 19104
Phone: (215) 590-5505 Fax: (215) 590-4735
Email: WeissS@email.chop.edu

SARS-CoV-2 has presented new challenges for the delivery of health care. Since December 2019, there have been more than 4 million confirmed cases of COVID19 worldwide with over 300,000 death (JHU). Although children have been relatively spared against severe or critical COVID19-related illness, thousands of cases have still been reported across X countries (JHU). Many of these children have presented with or evolved to COVID19-induced septic shock or other sepsis-associated organ dysfunction (REF). More recently, hundreds of children have presented with a novel Pediatric Inflammatory Multisystem Syndrome-Toxic Shock (PIMS-TS) across Europe, the United States, and other regions (REF). This syndrome, although seemingly more of a post-infectious host response, also shares features with pediatric sepsis.

While the outbreak of acute COVID19 illness and subacute PIMS-TS has appropriately dominated media coverage, the incidence of *non*-COVID19 sepsis still greatly exceeds that of these novel cases. For example, using population-level data on the prevalence of sepsis among children, an estimated 27,444 children would have been hospitalized for sepsis in the US over the last five months (Hartman PCCM 2013). Even if social distancing had reduced the incidence of sepsis by up to 50 percent through limiting transmission of more typical pathogens, the number of children hospitalized for sepsis would have been at least 10-fold higher than for COVID19. Moreover, either because of fear of seeking medical attention, lack of accessible transportation, or an overwhelming of local resources, children are missing out on preventive care, essential vaccinations, and proper nutrition that could swell cases of sepsis worldwide (Lancet Glob Health 2020).

With a background incidence of sepsis now superimposed upon by acute COVID19 illness and PIMS-TS—both of which overlap with non-COVID19 sepsis—clinicians face new challenges to recognition and resuscitation of sepsis in children. Here, we examine the

application of the *2020 Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children* (REF) in the era of COVID19. We emphasize that these guidelines are applicable to children with septic shock or other sepsis-associated organ dysfunction caused by all pathogens, including the SARS-CoV-2 virus.

*Recognition of Sepsis:* The Surviving Sepsis Campaign suggests that, in children who present as acutely unwell, systematic screening should be implemented for timely recognition of septic shock and other sepsis-associated organ dysfunction. The underlying rationale for this guideline is grounded in the often subtle and non-specific manner in which sepsis and septic shock may present in children. This is critical at the current time when there is an high risk of diagnostic fixation or anchoring bias that a child with cardiopulmonary dysfunction must have acute COVID19 illness or PIMS-TS. Applying a systemic process to clinical assessment that includes non-COVID19 sepsis will ensure that all possible diagnoses are considered. This assessment should include elements that may help to reveal if the acute illness is attributable to acute COVID19, PIMS-TS, or a more typical sepsis syndrome (Table 1).

*Initial Resuscitation:* The approach to the initial resuscitation of children with clinical features concerning for septic shock or suspected sepsis should be similar regardless of a COVID19-related or alternative etiology. A consistent approach will ensure that all possible etiologies are addressed during the early phases of treatment. Although not specifically addressed by the Surviving Sepsis Campaign, all acutely ill children should be given oxygen for hypoxia and glucose/dextrose if hypoglycemia is present. More specifically for septic shock and suspected sepsis, the six key management steps are: 1) obtain intravenous (or, if necessary, intraosseous) access rapidly, 2) collect blood culture, 3) start broad-spectrum antibiotics, 4)

measure lactate, 5) administer fluid boluses if shock is present, and 6) start inotrope/vasoactive agents if shock persists (Figure 1A). These six steps are relevant for both COVID19 and non-COVID19 related illness.

Even if SARS-CoV-2 is the most likely pathogen or confirmatory viral testing is known, children with severe or critical illness are at risk for bacteremia or other secondary bacterial co-infections (e.g., pneumonia). Thus, it is appropriate to collect a blood culture and start broad-spectrum antibiotics. For children with clinical evidence of shock, antimicrobial therapy for all likely pathogens should be administered within one hour of initial recognition of shock. For children without shock in whom non-cardiovascular organ dysfunction is suspected, an expedited diagnostic evaluation should commence to confirm or exclude the presence of sepsis and likelihood of acute infection. If acute infection is deemed likely based on clinical and laboratory features or rapid microbiological testing, or sepsis-associated organ dysfunction is identified, appropriate antimicrobial therapy should be administered as soon as possible, but no later than three hours from initial suspicion of sepsis. If the SARS-CoV-2 virus is only likely causative pathogen or the child's symptoms are most consistent with PIMS-TS, then it may be appropriate to forego empiric antimicrobial therapy. However, we would caution against premature exclusion of alternative or concurrent pathogens that could benefit from initial empirical antimicrobial therapy. If antimicrobial therapy is started, the Surviving Sepsis Campaign guidelines to narrow or stop such therapy according to site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice are appropriate children with and without COVID19.

Vascular access is necessary to facilitate intravenous fluid administration and other therapies, such as antimicrobials and vasoactive medications. Regardless of etiology, shock

should be treated with judicious fluid administration that is guided by frequent reassessment of clinical markers of organ perfusion, serial blood lactate measurement, and advanced hemodynamic monitoring, when available. In healthcare systems with the ability to provide intensive care (either in a local emergency or formal intensive care unit or via transport to such a facility), the Surviving Sepsis Campaign suggests administering up to 40-60 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour, titrated to clinical markers of organ perfusion and discontinued if signs of fluid overload develop. Fluid bolus therapy should not be given—or at least the volume of each bolus should be reduced—if signs of fluid overload are present or there is no evidence of even transient hemodynamic improvement. Instead, early assessment of myocardial contractility may reveal sepsis-induced cardiac dysfunction that may be more appropriately treated with early initiation of inotropic support, such as epinephrine (see below). Either epinephrine or norepinephrine (or dopamine) may be administered through a peripheral vein if central venous access is not readily accessible. This general framework of deliberate—rather than reflexive—fluid resuscitation and vasoactive support is appropriate for children with and without COVID19 (Figure 2).

*Myocardial Dysfunction:* Decreased cardiac output is common in pediatric sepsis. In addition to absolute or relative hypovolemia from reduced intake, increased losses (fever, vomiting, diarrhea), and capillary leak, many children with sepsis experience myocardial dysfunction. This may be especially prevalent in acute COVID19 illness and PIMS-TS, where children have been reported to have higher levels of troponin and brain natriuretic peptide than is typically seen in non-COVID19 sepsis. Therefore, early assessment of cardiac function with point of care ultrasound or echocardiography and cardiac-specific biomarkers is especially important when treating a child for septic shock or suspected sepsis in the era of COVID19. In

addition, because hyperlactatemia can suggest impaired cardiac output, early measurement of blood lactate, when available, is recommended for all children.

*Ongoing Management and Adjunctive Therapies:* After (or even concurrent with) initial resuscitation, clinicians should titrate respiratory support, assess for and treat pediatric acute respiratory distress syndrome (PARDS), continue to titrate fluid and vasoactive therapy, and ensure adequate source control (Figure 1B). These guidelines are appropriate for children with and without COVID19. However, for children with acute COVID19 illness and, in particular, PIMS-TS, the potential benefits for more routine administration of select adjunctive therapies, such as corticosteroids, anticoagulation, intravenous immunoglobulins, and other immunomodulatory agents, may differ from non-COVID19 sepsis . Given the current uncertainly of such therapies, early consultation with subspecialists who may not otherwise commonly contribute to the acute management of pediatric sepsis, such as rheumatology, cardiology, and hematology, is appropriate. Finally, as with non-COVID19 sepsis, consideration to enrollment in relevant clinical trials, where and when available, is also encouraged for children COVID19-related illness.

In summary, the *2020 Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children* are applicable to children with septic shock or other sepsis-associated organ dysfunction caused by all pathogens, including the SARS-CoV-2 virus. As with the clinical heterogeneity inherent in non-COVID19 sepsis, clinicians should thoughtfully tailor and augment these guidelines rather than exclude the SARS-CoV-2 virus as one cause of sepsis in children.

## REFERENCES

**Table 1: Characteristics of Non-COVID19 Sepsis, Acute COVID19 Illness, and PIMS-TS**

| | **Non-COVID19 Sepsis** | **Acute COVID19 Illness** | **PIMS-TS** |
|---|---|---|---|
| Symptoms | | | |
| Fever | Common | Common | Common, typically prolonged for >4 days |
| Cough | | | |
| V/D/abd pain | | | |
| Rash | | | |
| Etc.. | | | |
| | | | |
| Laboratory | | | |
| WBC | | | |
| ALC | | | |
| Platelets | | | |
| CRP | | | |
| PCT | | | |
| Ferritin | | | |
| D-dimer | | | |
| Troponin | | | |
| BNP | | | |
| Triglyceride | | | |
| | | | |
| | | | |
| Others??? | | | |
| | | | |
| Microbiology | | | |
| Blood culture | | | |
| SARS-CoV-2 PCR | Negative | Positive | +/- Positive (often with high CT) |
| SARS-CoV-2 IgG | Negative | Unknown | Positive |