Perspective of the Surviving Sepsis Campaign on the Management of Pediatric Sepsis in the Era of Coronavirus Disease 2019*

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Abstract: Severe acute respiratory syndrome coronavirus 2 is a novel cause of organ dysfunction in children, presenting as either coronavirus disease 2019 with sepsis and/or respiratory failure or a hyperinflammatory shock syndrome. Clinicians must now consider these diagnoses when evaluating children for septic shock and sepsis-associated organ dysfunction. The Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children provide an appropriate framework for the early recognition and initial resuscitation of children with sepsis or septic shock caused by all pathogens, including severe acute respiratory syndrome coronavirus 2. However, the potential benefits of select adjunctive therapies may differ from non-coronavirus disease 2019 sepsis. (Pediatr Crit Care Med 2020; 21:e1031–e1037)

Key Words: children; coronavirus disease 2019; sepsis; septic shock; severe acute respiratory syndrome coronavirus 2

More than 5 million cases of coronavirus disease 2019 (COVID-19) have been confirmed worldwide, with over 320,000 deaths (1). Studies from China, Italy, and the United States found that 1.7–2.0% of these cases occurred in those less than 19 years old, translating to ~90,000 known COVID-19 illnesses in children (2–4). Approximately 5–7% of these children have presented with or developed severe/critical COVID-19 with myocardial dysfunction, shock, pediatric acute respiratory distress syndrome (PARDS), altered mental status, and/or multiple organ dysfunction syndrome (2, 4, 5). Organ dysfunctions triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be considered a phenotype of pediatric sepsis or septic shock. More recently, there has been a surge in children presenting with hyperinflammatory shock resembling atypical Kawasaki disease, Kawasaki-shock, and/or toxic shock syndrome, alternatively termed Pediatric Inflammatory Multisystem Syndrome Temporally associated with Severe acute respiratory syndrome coronavirus 2 infection (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C) (6–9). Although this syndrome may represent a postinfectious host response, it also shares features with pediatric sepsis.

While COVID-19 and PIMS-TS/MIS-C have justifiably dominated attention, we cannot overlook that the incidence of non-COVID-19 sepsis continues to exceed these novel cases in...
children. 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 United States over the last 5 months (10). Even if social distancing reduced the incidence of sepsis by up to 50% by limiting transmission of more typical pathogens, the number of children hospitalized for sepsis in the United States would have remained at least 10-fold higher than for COVID-19. Furthermore, fear to seek medical attention, lack of accessible transportation, overwhelmed local resources, and disrupted supply chains risk delaying sepsis recognition and exacerbating inequities in health. For example, reduced access to preventive care, vaccinations, and proper nutrition are predicted to increase the number of sepsis cases in children worldwide (11).

With the background incidence of sepsis now superimposed upon by COVID-19 and PIMS-TS/MIS-C—both of which overlap with non-COVID-19 sepsis—clinicians face new challenges to recognition and resuscitation of sepsis in children. Here, we examine the application of the “Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children” (12, 13) in the era of COVID-19.

**APPLICATION OF SURVIVING SEPSIS CAMPAIGN GUIDELINES**

**Recognition**

The Surviving Sepsis Campaign suggests that systematic screening should be implemented for timely recognition of septic shock and other sepsis-associated organ dysfunction (12, 13). The underlying rationale for this guideline is grounded in the often subtle and nonspecific manner in which sepsis and septic shock may present in children. This is critical at the current time when there is a high risk of diagnostic fixation or anchoring bias that a child with cardiopulmonary dysfunction must have acute COVID-19 illness or PIMS-TS/MIS-C (14). Applying a systematic process to clinical assessment that includes

| Characteristic                      | Non-COVID-19 Sepsis | Acute COVID-19 Illness | Pediatric Inflammatory Multisystem Syndrome Temporarily Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/Multisystem Inflammatory Syndrome in Children |
|------------------------------------|---------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial symptoms                   |                     |                        |                                                                                                                                                                                                 |
| Fever                              | Common              | Common                 | Common (typically persistent for days)                                                                                                                                                            |
| Cough                              | Possible            | Common                 | Uncommon                                                                                                                                                                                          |
| Shortness of breath                | Common              | Common                 | Uncommon                                                                                                                                                                                          |
| Rhinorrhea                         | Possible            | Possible               | Uncommon                                                                                                                                                                                          |
| Gastrointestinal^                   | Possible           | Possible               | Common                                                                                                                                                                                            |
| Tachypnea                          | Common              | Common                 | Possible                                                                                                                                                                                          |
| Tachycardia                        | Common              | Common                 | Common                                                                                                                                                                                            |
| Myalgia                            | Possible            | Common                 | Uncommon                                                                                                                                                                                          |
| Sore throat                        | Possible            | Possible               | Uncommon                                                                                                                                                                                          |
| Fatigue                            | Common              | Common                 | Common                                                                                                                                                                                            |
| Headache                           | Possible            | Common                 | Uncommon                                                                                                                                                                                          |
| Conjunctival erythema              | Uncommon            | Uncommon               | Common                                                                                                                                                                                            |
| Cervical lymphadenopathy           | Possible            | Not reported           | Possible                                                                                                                                                                                           |
| Dried, cracked lips, or "strawberry tongue" | Uncommon        | Uncommon               | Common                                                                                                                                                                                            |
| Rash                               | Possible            | Uncommon               | Common                                                                                                                                                                                            |
| Anosmia                            | Uncommon            | Possible               | Not reported                                                                                                                                                                                       |
| Dysgeusia                          | Uncommon            | Possible               | Not reported                                                                                                                                                                                       |

(Continued)
non-COVID-19 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 COVID-19 illness, PIMS-TS/MIS-C, or a more typical sepsis syndrome (Table 1). In addition, increased attention to infection control measures and personal protective equipment during screening and through resuscitation is needed to protect healthcare workers and limit transmission of SARS-CoV-2, along with other contagious pathogens (15, 16).

**Initial Resuscitation**

The approach to the initial resuscitation of children with clinical features of sepsis or septic shock should be similar regardless of a COVID-19-related or alternative etiology. A consistent approach will ensure that all possible etiologies are addressed in a timely fashion. Specifically, the six key management steps are as follows: 1) obtain IV (or, if necessary, intraosseous) access; 2) collect blood culture; 3) start broad-spectrum antimicrobials; 4) measure lactate; 5) administer fluid boluses if shock is present; and 6) start

| Characteristic                                      | Non-COVID-19 Sepsis       | Acute COVID-19 Illness | Pediatric Inflammatory Multisystem Syndrome Temporarily Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/Multisystem Inflammatory Syndrome in Children |
|-----------------------------------------------------|---------------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **Laboratory results**                              |                           |                        |                                                                                                                                  |
| WBCs                                                | Low, normal, or high     | Low, normal, or high  | Low, normal, or high                                                                                                               |
| Absolute lymphocytes                                | Low to normal            | Very low               | Very low                                                                                                                          |
| Platelets                                           | Low to normal            | Normal to high         | Normal to high                                                                                                                     |
| Sodium                                              | Low, normal, or high     | Normal                 | Low                                                                                                                              |
| Alanine aminotransferase, aspartate aminotransferase| Normal to high           | Normal to high         | High                                                                                                                              |
| Creatinine                                          | Normal to high           | Normal to high         | Normal to high                                                                                                                     |
| C-reactive protein                                  | High                     | High                   | High                                                                                                                              |
| Procalcitonin                                       | High                     | Normal to high         | Normal to high                                                                                                                     |
| Erythrocyte sedimentation rate                      | High                     | Low to normal          | Low to normal                                                                                                                      |
| Ferritin                                            | Normal to high           | High                   | Very high                                                                                                                          |
| Fibrinogen                                          | Low (with disseminated intravascular coagulation or macrophage activation syndrome), normal, or high | High | Usually high (but can be low)                                                                                                        |
| d-dimer                                             | Normal to high           | Very high              | Very high                                                                                                                          |
| Troponin                                            | Often normal             | Often high             | High                                                                                                                              |
| Brain natriuretic peptide                           | Normal to high           | Normal to high         | Very high                                                                                                                          |
| Triglyceride                                        | Normal                   | High                   | High                                                                                                                              |
| Microbiology                                        |                           |                        |                                                                                                                                  |
| Blood culture                                       | ± Positive               | Negative \(^b\)         | Negative \(^b\)                                                                                                                    |
| SARS-CoV-2 polymerase chain reaction                | Negative                 | Positive               | ± Positive (often with high cycle time)\(^c\)                                                                                      |
| SARS-CoV-2 immunoglobulin G                         | Negative                 | Unknown                | Positive                                                                                                                          |

COVID-19 = coronavirus disease 2019, SARS-CoV-2 = severe acute respiratory distress syndrome coronavirus.

\(^a\) Gastrointestinal symptoms include nausea, vomiting, diarrhea, or abdominal pain.

\(^b\) Blood culture may be positive in setting of concurrent bacterial infection.

\(^c\) Higher cycle time can suggest lower viral load, which may support longer time from initial infection.
inotrope/vasoactive agents if shock persists (Fig. 1A). These six steps are relevant for both COVID-19 and non-COVID-19-related illness. Although not specifically addressed by the Surviving Sepsis Campaign, all acutely ill children should also be given oxygen for hypoxia and dextrose if hypoglycemia is present.

Even in cases where SARS-CoV-2 is the most likely pathogen or has already been confirmed, patients with COVID-19 are at risk for bacteremia or other secondary bacterial or viral coinfections (e.g., pneumonia) (17, 18). Thus, it is appropriate to collect a blood culture and start empiric broad-spectrum antimicrobials. For children with clinical evidence of shock, antimicrobial therapy for all likely pathogens should be administered within 1 hour of initial recognition of shock. For children without shock in whom organ dysfunction is suspected, an expedited diagnostic evaluation should commence to confirm or exclude the presence of sepsis and seek evidence of acute infection. If acute bacterial (or fungal) infection is deemed likely based on clinical or laboratory findings 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 SARS-CoV-2 is the only likely pathogen or the child’s symptoms are most consistent with PIMS-TS/MIS-C, then it may be appropriate to forego empiric antimicrobial therapy. However, we caution against premature exclusion of alternative or concurrent pathogens that could benefit from early antimicrobial therapy. For example, antibiotics targeting *Staphylococcus* and *Streptococcus* are indicated if symptoms overlap with toxic shock syndrome. If antimicrobial therapy is started, the Surviving Sepsis Campaign guidelines recommendations to narrow or stop such therapy according to microbial results, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice are appropriate in children with and without COVID-19.

Regardless of etiology, shock should be treated with judicious fluid administration guided by frequent reassessment of clinical markers of organ perfusion, blood lactate measurement, and advanced hemodynamic monitoring, when available. In healthcare systems with the ability to provide intensive care (either locally or via interhospital transport), 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. In healthcare systems without capacity to locally administer or transfer to access ventilator and hemodynamic support, fluid bolus therapy should be avoided unless hypotension is present. Early assessment of myocardial contractility is also necessary to assess for sepsis-induced cardiac dysfunction that may benefit from early initiation of inotropic support (see below). Either epinephrine or norepinephrine may be administered through a peripheral vein or intraosseous access...
if central venous access is not readily accessible. This framework of deliberate—rather than reflexive—fluid resuscitation and vasoactive support is appropriate for children with and without COVID-19 or PIMS-TS/MIS-C (Fig. 2).

**Myocardial Dysfunction**

Decreased cardiac output is common in pediatric sepsis (19, 20). 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 requiring inotropic support. This seems to be especially prevalent in COVID-19 and PIMS-TS/MIS-C, where reports indicate acute myocardial injury with higher levels of troponin and brain natriuretic peptide than are typically seen in non-COVID-19 sepsis (6, 21, 22). Thus, early echocardiography, electrocardiogram, and cardiac-specific biomarkers is especially important when treating a child for septic shock or suspected sepsis in the era of COVID-19. In addition, because hyperlactatemia can suggest impaired cardiac output, early measurement of blood lactate, when available, is recommended for all children. In children with signs of PIMS-TS/MIS-C, cardiology expertise will be required to assess for coronary artery aneurysms.

**Ongoing Management and Adjunctive Therapies**

Clinicians should titrate respiratory support, assess for and treat PARDS (12, 13, 23), continue to titrate fluid and vasoactive therapy, ensure adequate source control, and consider extracorporeal membrane oxygenation if shock is refractory (Fig. 1B) for children with and without SARS-CoV-2. However, for children with COVID-19 and PIMS-TS/MIS-C, the potential benefits of select adjunctive therapies, such as corticosteroids, anticoagulation, plasma exchange, IV immunoglobulins, convalescent plasma, and other immunotherapies, may differ from non-COVID-19 sepsis (6, 24–28). Given the current uncertainty of such therapies, early consultation with additional subspecialists, such as rheumatology, cardiology, and hematology, is appropriate in acute COVID-19 and PIMS-TS/MIS-C. Finally, as with non-COVID-19 sepsis, enrollment in clinical trials is also encouraged for children COVID-19-related illness.

**CONCLUSIONS**

The Surviving Sepsis Campaign provides an appropriate framework for the initial management of children with sepsis and septic shock caused by all pathogens, including SARS-CoV-2. However, clinicians should thoughtfully tailor and augment these guidelines as experience and knowledge develop about the unique ways in which SARS-CoV-2 leads
to sepsis, respiratory failure, and hyperinflammatory shock in children.

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APPENDIX

Listed are subject matter experts from the Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children Task Force have voted to affirm this work: Joe Briery, FRCPCH, FFICM (Great Ormond Street NIHR Biomedical Research Centre, London, London, United Kingdom); Jeffrey J. Cies, PharmD, MPH, BCPS-AQ ID, BCPPS, FCCP, FCCM, FPPA (St. Christopher’s Hospital for Children, Philadelphia, PA); Daniele De Luca, MD, PhD (Paris Saclay University, Paris, France); Akash Deep, MD (Kings College Hospital, London, London, United Kingdom); Joseph Carcillo, MD (University of Pittsburgh School of Medicine, Pittsburgh, PA); Christopher L. Carroll, MD, MD, MS, FCCM, FAAP (Connecticut Children’s Medical Center, Hartford, CT); Enitan D. Carroll, MBChB, DTMH, FRCPCH (University of Liverpool Institute of Infection, Veterinary and Ecological Sciences, Liverpool, London, United Kingdom); Saul Faust, FRCPCH, PhD (University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, London, United Kingdom); Mark W. Hall, MD (Nationwide Children’s Hospital, Columbus, OH); Koen F. M. Joosten, MD, PhD (Erasmus University Medical Center, Rotterdam, The Netherlands and Beatrix Children’s Hospital, University Medical Center Groningen, Groningen, The Netherlands); Poonam Joshi, PhD (All India Institute of Medical Sciences, New Delhi, India); Martin C. J. Kneyber, MD, PhD, FCCM (Beatrix Children’s Hospital, Groningen, The Netherlands); Oliver Karam, MD, PhD (Children’s Hospital of Richmond at VCU, Richmond, VA); Graeme MacLaren, MSc, MSCS (National University Health System, Singapore and Royal Children’s Hospital, Melbourne, VIC, Australia); Nilesh M. Mehta, MD (Boston Children’s Hospital and Harvard Medical School, Boston, MA); Morten Hylander Møller, MD, PhD (Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark); Christopher J. L. Newth, MD, ChB, FRCP, FRACP (Children’s Hospital of Los Angeles, Los Angeles, CA); Trung Nguyen, MD, FAAP (Texas Children’s Hospital, Houston, TX); Akira Nishisaki, MD, MSCE, FAAP (Children’s Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Margaret Parker, MD, MCCM, FAAP (Stony Brook University, Stony Brook, NY); Raina Paul, MD, FAAP (Advocate Children’s Hospital, Park Ridge, IL); Suchitra Ranjit, MD, FCCM (Apollo Hospitals, Chennai, India); Lewis H. Romer, MD (Johns Hopkins Children’s Center, Baltimore, MD); Halden Scott, MD, MSCS, FAAP, FACEP (Children’s Hospital Colorado, Aurora, CO); Eric A. Williams, MD, MS, MMM, FAAP, FCCM (Texas Children’s Hospital, Houston, TX); Joshua Wolf, MBBS, PhD, FRACP (St. Jude Children’s Hospital, Memphis, TN); and Jerry J. Zimmerman, MD, PhD, FCCM (Seattle Children’s Hospital, Seattle, WA).