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

Scott L. Weiss, MD, MSCE, FCCM[1]; Mark J. Peters, MD, PhD[2]; Michael S. D. Agus, MD, FCCM, FAAP[3]; Waleed Alhazzani, MD, MSc, FRCPC[4]; Karen Choong, MB, BCh, MSc, FRCP(C)[4]; Heidi R. Flori, MD, FAAP[5]; David P. Inwald, MB, BChir, FRCPCH, FFICM, PhD[6]; Simon Nadel, MBBS, MRCP, FRCP[6]; Mark E. Nunnally, MD, FCCM[7]; Luregn J. Schlapbach, MD, PhD, FCICM[8]; Robert C. Tasker, MB BS, MA, AM, MD, FRCPHC, FRCP[3]; Pierre Tissieres, MD, DSc (Co-Chair)[9]; Niranjan Kissoon, MB BS, MCCM, FRCP(C), FAAP, FACPE (Co-Chair)[10]; for the Children's Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children Taskforce

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

*See also p. 1020.

[1]Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.
[2]UCL Great Ormond Street Institute of Child Health, Great Ormond Street Hospital and NIHR Biomedical Research Centre London, London, United Kingdom.
[3]Boston Children's Hospital and Harvard Medical School, Boston, MA.
[4]McMaster University, Hamilton, ON, Canada.
[5]C.S. Mott Children's Hospital, Ann Arbor, MI.
[6]Addenbrooke's Hospital, Cambridge, London, United Kingdom.
[7]New York University Langone Medical Center, New York, NY.
[8]The University of Queensland and Queensland Children's Hospital, Brisbane, QLD, Australia.
[9]Paris Saclay University Hospitals, Assistance Publique Hopitaux de Paris, Paris, France.
[10]British Columbia Children's Hospital, Vancouver, BC, Canada.

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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

TABLE 1. Characteristics of Non-Coronavirus Disease 2019 Sepsis, Acute Coronavirus Disease 2019 Illness, and Pediatric Inflammatory Multisystem Syndrome Temporally Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/ Multisystem Inflammatory Syndrome in Children

Characteristic	Non-COVID-19 Sepsis	Acute COVID-19 Illness	Pediatric Inflammatory Multisystem Syndrome Temporally 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[a]	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*)

TABLE 1. (*Continued*). Characteristics of Non-Coronavirus Disease 2019 Sepsis, Acute Coronavirus Disease 2019 Illness, and Pediatric Inflammatory Multisystem Syndrome Temporally Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/Multisystem Inflammatory Syndrome in Children

Characteristic	Non-COVID-19 Sepsis	Acute COVID-19 Illness	Pediatric Inflammatory Multisystem Syndrome Temporally 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
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.

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

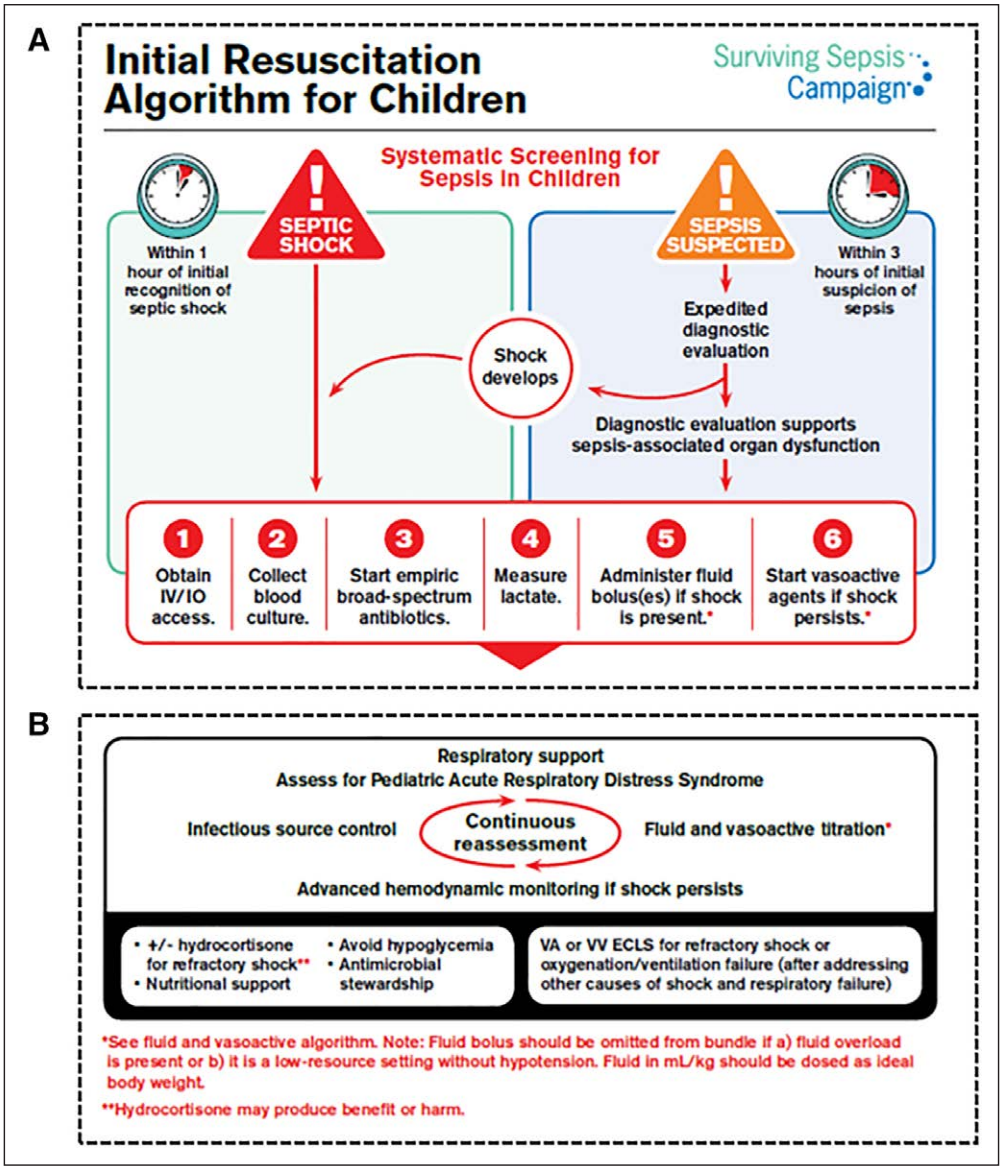

Figure 1. Initial resuscitation algorithm for children with septic shock or suspected sepsis. **A**, Initial resuscitation. **B**, Ongoing management. Reproduced with permission from https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients. ECLS = extracorporeal life support, IO = intraosseous, VA = venoarterial, VV = venovenous.

inotrope/vasoactive agents if shock persists (**Fig. 1*A***). 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. 1*B***) 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.

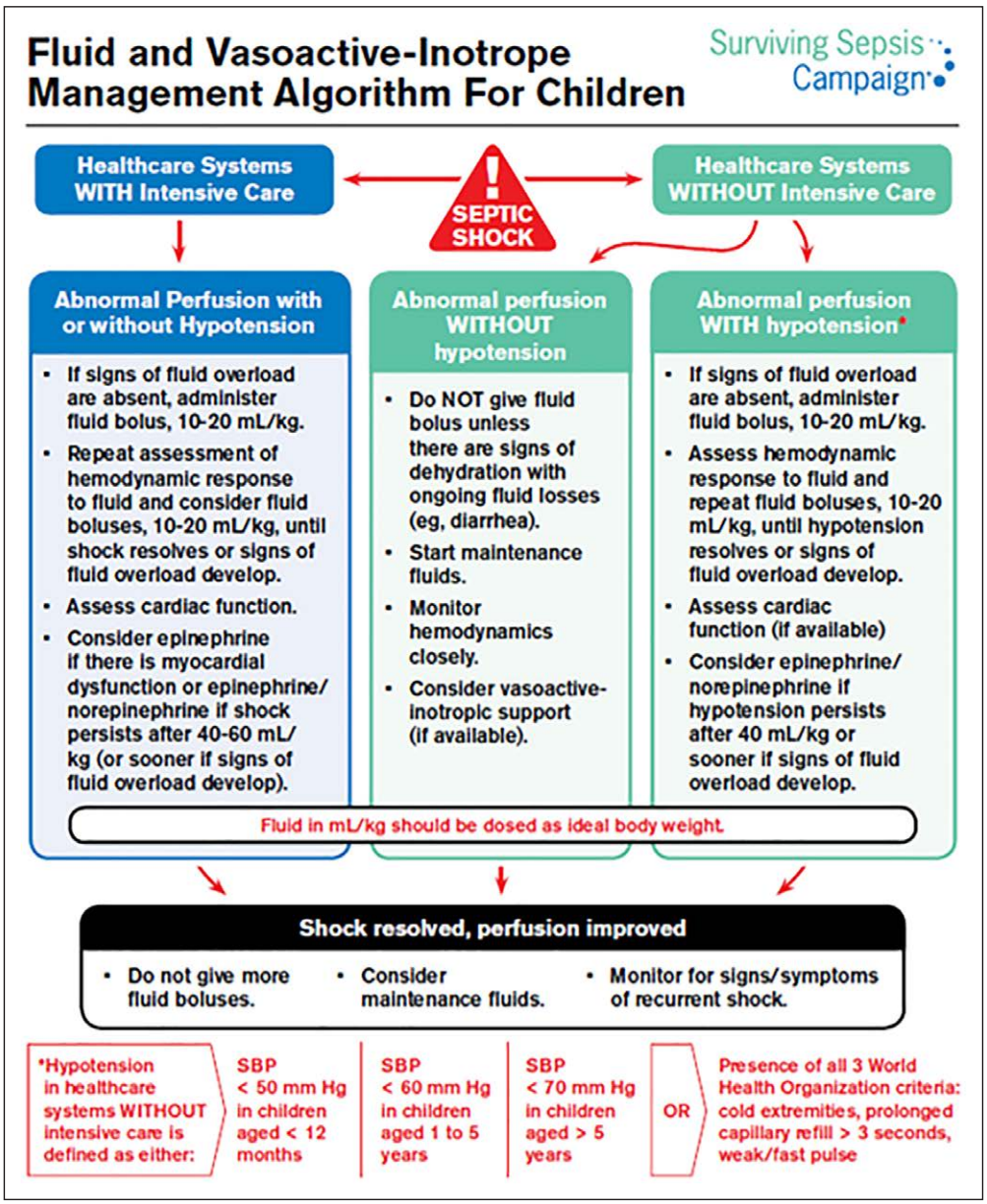

Figure 2. Fluid and vasoactive-inotrope management algorithm for children with septic shock. Reproduced with permission from https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients. SBP = systolic blood pressure.

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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For information regarding this article, E-mail: WeissS@email.chop.edu

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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 Brierly, 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, Pittsburg, PA); Christopher L. Carroll, MD, MD, MS, FCCM, FAAP (Connecticut Children's Medical Center, Hartford, CT); Enitan D. Carrol, 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, FRCPC, 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).