Special Article

Executive Summary: Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children

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In 2001, the Surviving Sepsis Campaign (SSC) began to develop evidence-based guidelines and recommendations for the resuscitation and management of patients with sepsis. With the 2016 edition, the Society of Critical Care Medicine and European Society of Intensive Care Medicine recommended a separate task force be dedicated to guideline formulation for children.

The objective of the "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children" is to provide guidance for the care of infants, children, and adolescents with septic shock and other sepsis-associated organ dysfunction. Recommendations are intended to guide "best practice" rather than to establish a treatment algorithm or to define standard of care and cannot replace the clinician's decision-making capability when presented with a patient's unique set of clinical variables.

METHODS

This executive summary briefly reviews the methodology, with additional details provided in the complete guidelines document published in *Pediatric Critical Care Medicine* and *Intensive Care Medicine.*

Definitions

For these guidelines, we defined "septic shock" in children as severe infection leading to cardiovascular dysfunction (including hypotension, need for treatment with a vasoactive medication, or impaired perfusion) and "sepsis-associated organ dysfunction" in children as severe infection leading to cardiovascular and/or noncardiovascular organ dysfunction. These definitions include the criteria set forth by the 2005 International Pediatric Sepsis Consensus Conference (1), as the majority of studies used to establish evidence for these guidelines referred to this nomenclature. However, studies that defined sepsis in children as severe infection leading to life-threatening organ dysfunction were included even if criteria used to define sepsis deviated from the 2005 consensus definitions. Because several methods to identify acute organ dysfunction in children are currently available, we did not to require a specific definition or scheme for this purpose.

Scope of Patients

The panel intended these guidelines to apply to all patients from greater than or equal to 37 weeks gestation at birth to 18 years with septic shock or other sepsis-associated acute organ

dysfunction. Practically, all infants, children, and adolescents with septic shock or other sepsis-associated organ dysfunction are included in this scope. For simplicity, we used the term "children" to refer to infants, school-aged children, and adolescents in these guidelines.

All recommendations apply to children with septic shock and other sepsis-associated acute organ dysfunction unless specific qualifications, such as the subset with immune compromise, are included in the recommendation. Even though these guidelines are not intended to address the management of infection with or without systemic inflammatory response syndrome *when there is not associated acute organ dysfunction*, we recognize that sepsis exists as a spectrum and some children without known acute organ dysfunction may still benefit from similar therapies as those with known organ dysfunction. Finally, acknowledging that neonatal sepsis, especially in premature babies, may have distinct pathology, biology, and therapeutic considerations, newborns less than 37 weeks gestation are excluded from the scope of these guidelines. The panel sought to include term neonates (0–28 d) born at greater than or equal to 37 weeks gestation within the scope of these guidelines because these infants may be recognized and resuscitated outside of a newborn nursery or neonatal ICU. However, because the panel did not specifically address studies of neonates with perinatal infection or all conditions that can be associated with neonatal sepsis (e.g., persistent pulmonary hypertension of the newborn), these guidelines do not address all management considerations for neonatal sepsis.

Application of Guidelines by Local Resource Availability

The intended users of these guidelines are health professionals caring for children in a hospital, emergency, or other acute care setting. However, many of the recommendations are likely to apply to the care of children in other settings and will need to be adapted to specific environments and resource availability. In addition, these guidelines were largely developed without consideration of the availability of healthcare services, although we realize that medical care is necessarily carried out within the confines of locally available resources. The panel supports that these guidelines should constitute a general scheme of "best practice," but that translation of these guidelines to treatment algorithms or bundles and standards of care will need to account for variation in the availability of local healthcare resources, particularly in resource-limited settings.

Selection and Organization of Panel Members

The selection of panel members was based on their expertise in specific aspects of pediatric sepsis, with broad international and multi-professional representation from diverse geographic settings and healthcare systems. Three members from the lay public were also included.

Panelists were divided into the following subgroups: 1) recognition and management of infection, 2) hemodynamics and resuscitation, 3) ventilation, 4) endocrine and metabolic therapies, and 5) adjunctive therapies. A sixth subgroup reviewed research priorities. Each subgroup was supported by a trained methodologist.

Question Development and Outcome Prioritization

The panel selected topics addressed in the 2016 adult SSC guidelines that were relevant to children, as well as other key topics important to children with sepsis. The PICO format, which describes the population (P), intervention (I), control (C), and outcomes (O), was used for all guideline questions. For practical reasons, we excluded several issues pertaining to general acute or critical illness that were not specific for sepsis (e.g., head-of-bed positioning during invasive mechanical ventilation) and have been addressed in other guidelines (e.g., Pediatric Acute Lung Injury Consensus Conference) (2). However, topics with particular relevance to children with septic shock or other sepsis-associated acute organ dysfunction were included in this guideline, even if there was evaluation of similar or overlapping topics in previous publications. The final list of PICO questions is provided as **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/B139) in the complete guidelines.

Search Strategy and Evidence Summation

Professional medical librarians assisted with the literature searches and utilized a combination of controlled vocabulary (e.g., "sepsis," "bacterial infections," "critical illness," "intensive care units," "pediatrics," "NICU," "PICU," "emergency service"), key words (e.g., "toxic shock," "blood poisoning," "acute infection," "child"), and qualifiers specific to each PICO question. Only English language studies were included. As this was the inaugural version of these guidelines for children, all publications through May 1, 2017, were considered. Key studies published after the conclusion of the initial literature search were incorporated into the evidence synthesis if identified by panel members as important and relevant even if they were not part of the initial literature review.

Formulation of Recommendations

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) principles guided the assessment of quality of evidence from high to very low and were used to determine the strength of recommendations. The GRADE approach to assess the quality of evidence is based on the evaluation of six domains: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, 5) publication bias, and 6) assessment of the balance between benefit and harm, patients' values and preferences, cost and resources, and feasibility and acceptability of the intervention (3).

The panel initially considered research focused on pediatric patients using the following hierarchy of evidence: systematic reviews, randomized controlled trials, prospective observational studies, retrospective observational studies, case-control studies, and large case series. Research focusing on children with septic shock and other sepsis-associated organ dysfunction was prioritized, although studies inclusive of more general pediatric populations (e.g., all PICU patients) were considered

for some questions on a case-by-case basis. If there were insufficient data in children with sepsis or general pediatric illness, data from adult studies were considered using a pre-specified framework to guide appropriateness of indirect evidence.

Each of the subgroups used the Evidence-to-Decision (EtD) framework to facilitate transition from evidence to recommendations. The EtD framework ensured that panel members took into consideration not only the quality of evidence and magnitude of effect, but also balance between benefits and harms, patients' values and preferences, resources, cost, acceptability, and feasibility (4).

We classified recommendations as strong or weak using the language "We recommend…" or "We suggest…," respectively. We judged a strong recommendation in favor of an intervention to have desirable effects of adherence that will clearly outweigh the undesirable effects. The implications of calling a recommendation strong are that most patients would accept that intervention and that most clinicians should use it in most situations. However, a strong recommendation does not imply a standard of care, and circumstances may exist in which a strong recommendation cannot or should not be followed for an individual patient. We judged a weak recommendation in favor of an intervention to have desirable consequences of adherence that will probably outweigh the undesirable consequences, but confidence is diminished either because the quality of evidence was low or the benefits and risks were closely balanced. We anticipate that a weak recommendation, while still relevant for most patients in most settings, will be more heavily influenced by clinical circumstances and patients' values than a strong recommendation. We permitted strong recommendations "for" an intervention based on low or very low quality of evidence when the intervention had the potential to improve survival and there was low risk for immediate harm. We permitted strong recommendations "against" an intervention based on low or very low quality of evidence when there was uncertain benefit but very likely or certain harm, including high costs (5).

Best practice statements (BPSs) were offered when the evidence could not be summarized using GRADE methodology but the benefit or harm was deemed unequivocal. In addition, when evidence was insufficient to make a recommendation, but the panel felt that some guidance may be appropriate, we issued an "in our practice" statement. The "in our practice" statements were developed through a survey of panelists to ascertain their state of current practice in an attempt to describe current variation in care. "In our practice" statements, therefore, should not be construed as recommendations.

Voting Process

Panel members convened to review evidence and discuss recommendations in-person and through web conferences. Panelists then indicated agreement or disagreement (or abstention if conflict of interest present) with each recommendation. Up to three rounds of voting were conducted in an attempt to achieve consensus. Acceptance of a statement required votes from 75% of panel members with an 80% agreement threshold.

Conflict of Interest Policy

Conflict-of-interest disclosures were sought from all panelists prior to commencing activities, with updates annually and as needed. There was no industry input into or support of the guideline development process. Only librarians and a supporting project manager received compensation for their work.

RECOMMENDATIONS

The consensus recommendations of the "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children" are summarized in **Table 1** of this executive summary. The rationale and evidence profiles supporting each recommendations are presented in the complete guidelines (6). The panel issued 77 statements on the management and resuscitation of children with septic shock and other sepsis-associated organ dysfunction, including six strong recommendations, 49 weak recommendations, and nine BPSs. For 13 questions, no recommendations could be made, but, for 10 of these, "in our practice" statements were provided. In addition, 52 knowledge gaps and research opportunities were identified (see complete guidelines).

CONCLUSIONS

Although most aspects of care had relatively low quality of evidence resulting in the frequent issuance of weak recommendations, these guidelines regarding the management of children with septic shock and other sepsis-associated organ dysfunction should provide a foundation for consistent care to improve outcomes and inform future research.

TABLE 1. Executive Summary of Guidelines

SCREENING, DIAGNOSIS, AND SYSTEMATIC MANAGEMENT OF SEPSIS

1) In children who present as acutely unwell, we suggest implementing systematic screening for timely recognition of septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

   Remarks: Systematic screening needs to be tailored to the type of patients, resources, and procedures within each institution. Evaluation for the effectiveness and sustainability of screening should be incorporated as part of this process.

2) We were unable to issue a recommendation about using blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction into low-vs high-risk of having septic shock or sepsis.

3) We recommend implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction (BPS).

4) We recommend obtaining blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (BPS).

ANTIMICROBIAL THERAPY

5) In children with septic shock, we recommend starting antimicrobial therapy *as soon as possible*, within 1 hr of recognition (strong recommendation, very low quality of evidence).

6) In children with sepsis-associated organ dysfunction but without shock, we suggest starting antimicrobial therapy *as soon as possible* after appropriate evaluation, within 3 hr of recognition (weak recommendation, very low quality of evidence).

7) We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (BPS).

8) Once the pathogen(s) and sensitivities are available, we recommend narrowing empiric antimicrobial therapy coverage (BPS).

9) If no pathogen is identified, we recommend narrowing or stopping empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice (BPS).

10) In children without immune compromise and without high risk for multidrug-resistant pathogens, we suggest against the routine use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy (weak recommendation, very low quality of evidence).

    Remarks: In certain situations, such as confirmed or strongly suspected group B streptococcal sepsis, use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy may be indicated.

11) In children with immune compromise and/or at high risk for multidrug-resistant pathogens, we suggest using empiric multi-drug therapy when septic shock or other sepsis-associated organ dysfunction is present/suspected (weak recommendation, very low quality of evidence).

12) We recommend using antimicrobial dosing strategies that have been optimized based on published pharmacokinetic/pharmacodynamic principles and with consideration of specific drug properties (BPS).

13) In children with septic shock or sepsis-associated organ dysfunction who are receiving antimicrobials, we recommend daily assessment (e.g., clinical, laboratory assessment) for de-escalation of antimicrobial therapy (BPS).

    Remarks: This assessment should include a review of the ongoing indication for empiric antimicrobial therapy after the first 48 hr that is guided by microbiologic results and in response to clinical improvement and/or evidence of infection resolution. This recommendation applies to patients being treated with empiric, targeted, and combination therapy.

14) We recommend determining the duration of antimicrobial therapy according to the site of infection, microbial etiology, response to treatment, and ability to achieve source control (BPS).

SOURCE CONTROL

15) We recommend that emergent source control intervention be implemented as soon possible after a diagnosis of an infection amenable to a source control procedure is made (BPS). Population, Intervention, Control, and Outcomes (PICO) 12.

    Remarks: Appropriate diagnostic testing to identify the site of infection and microbial etiology should be performed, and advice from specialist teams (e.g., infectious diseases, surgery) should be sought, as appropriate, in order to prioritize interventions needed to achieve source control.

16) We recommend removal of intravascular access devices that are confirmed to be the source of sepsis or septic shock after other vascular access has been established and depending on the pathogen and the risks/benefits of a surgical procedure (strong recommendation, low quality of evidence).

(*Continued*)

TABLE 1. (*Continued*). Executive Summary of Guidelines

FLUID THERAPY

17) In healthcare systems with availability of intensive care, we suggest 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 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 (weak recommendation, low quality of evidence).

18) In healthcare systems with no availability of intensive care and *in the absence of hypotension*, we recommend against bolus fluid administration while starting maintenance fluids (strong recommendation, high quality of evidence).

19) In healthcare systems with no availability of intensive care, *if hypotension is present*, we suggest administering up to 40 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour with titration to clinical markers of cardiac output and discontinued if signs of fluid overload develop (weak recommendation, low quality of evidence).

Remarks: Clinical markers of cardiac output may include heart rate, blood pressure, capillary refill time, level of consciousness, and urine output. In all settings, the need for fluid administration should be guided by frequent reassessment of clinical markers of cardiac output, serial blood lactate measurement, and advanced monitoring, when available. Signs of fluid overload that should limit further fluid bolus therapy may include clinical signs of pulmonary edema or new or worsening hepatomegaly.

20) We suggest using crystalloids, rather than albumin, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).

Remarks: Although there is no difference in outcomes, this recommendation takes into consideration cost and other barriers of administering albumin compared with crystalloids.

21) We suggest using balanced/buffered crystalloids, rather than 0.9% saline, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

22) We recommend against using starches in the acute resuscitation of children with septic shock or other sepsis-associated organ dysfunction (strong recommendation, moderate quality of evidence).

23) We suggest against using gelatin in the resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

HEMODYNAMIC MONITORING

24) We were unable to issue a recommendation about whether to target MAP at the 5th or 50th percentile for age in children with septic shock and other sepsis-associated organ dysfunction.

25) We suggest not using bedside clinical signs in isolation to categorize septic shock in children as “warm” or “cold” (weak recommendation, very low quality of evidence).

26) We suggest using advanced hemodynamic variables, when available, in addition to bedside clinical variables to guide the resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

Remarks: Advanced hemodynamic monitoring may include cardiac output/cardiac index, systemic vascular resistance, or central venous oxygen saturation.

27) We suggest using trends in blood lactate levels, in addition to clinical assessment, to guide resuscitation of children with septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

Remarks: In children with an elevated blood lactate, repeat testing that reveals a persistent elevation in blood lactate may indicate incomplete hemodynamic resuscitation and should prompt efforts, as needed, to further promote hemodynamic stability.

VASOACTIVE MEDICATIONS

28) We suggest using epinephrine, rather than dopamine, in children with septic shock (weak recommendation, low quality of evidence).

29) We suggest using norepinephrine, rather than dopamine, in children with septic shock (weak recommendation, very low quality of evidence).

30) We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock.

31) We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock.

Remarks: It is reasonable to begin vasoactive infusions after 40–60 mL/kg of fluid resuscitation if the patient continues to have evidence of abnormal perfusion. Either epinephrine or norepinephrine may be administered through a peripheral vein (or intraosseous, if in place) if central venous access is not readily accessible. Dopamine may be substituted as the first-line vasoactive infusion, administered either peripherally or centrally, if epinephrine or norepinephrine is not readily available.

32) We suggest either adding vasopressin or further titrating catecholamines in children with septic shock who require high-dose catecholamines (weak recommendation, low quality of evidence).

Remarks: No consensus was achieved on the optimal threshold for initiating vasopressin. Therefore, this decision should be made according to individual clinician preference.

33) We were unable to issue a recommendation about adding an inodilator in children with septic shock and cardiac dysfunction despite other vasoactive agents.

(*Continued*)

TABLE 1. (*Continued*). Executive Summary of Guidelines

VENTILATION

34) We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock.

35) We suggest not to use etomidate when intubating children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

36) We suggest a trial of noninvasive mechanical ventilation (over invasive mechanical ventilation) in children with sepsis-induced PARDS without a clear indication for intubation and who are responding to initial resuscitation (weak recommendation, very low quality of evidence).

Remarks: When noninvasive mechanical ventilation is initiated, clinicians should carefully and frequently reevaluate the patient's condition.

37) We suggest using high PEEP in children with sepsis-induced PARDS (weak recommendation, very low quality of evidence).

Remarks: The exact level of high PEEP has not been tested or determined in PARDS patients. Some RCTs and observational studies in PARDS have used and advocated for use of the ARDS-network PEEP to F_{IO_2} grid though adverse hemodynamic effects of high PEEP may be more prominent in children with septic shock.

38) We cannot suggest for or against the use of recruitment maneuvers in children with sepsis-induced PARDS and refractory hypoxemia.

Remarks: If a recruitment maneuver is considered, the use of a stepwise, incremental and decremental PEEP titration maneuver is preferred over sustained inflation techniques that have not been optimized through direct testing in PARDS patients. All PARDS patients must be carefully monitored for tolerance of the maneuver.

39) We suggest a trial of prone positioning in children with sepsis and severe PARDS (weak recommendation, low quality of evidence).

Remarks: Research trials in adults with ARDS and children with PARDS have emphasized prone positioning for at least 12 hr per day, as tolerated.

40) We recommend against the routine use of iNO in all children with sepsis-induced PARDS (strong recommendation, low quality of evidence).

41) We suggest using iNO as a rescue therapy in children with sepsis-induced PARDS and refractory hypoxemia after other oxygenation strategies have been optimized (weak recommendation, moderate quality of evidence).

42) We were unable to issue a recommendation to use high-frequency oscillatory ventilation vs conventional ventilation in children with sepsis-induced PARDS.

43) We suggest using neuromuscular blockade in children with sepsis and severe PARDS (weak recommendation, very low quality of evidence).

Remarks: The exact duration of neuromuscular blockade use in severe PARDS patients has not been determined to date. Most of the adult RCT data and pediatric observational data support treatment for 24–48 hr after ARDS onset.

CORTICOSTEROIDS

44) We suggest against using IV hydrocortisone to treat children with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (weak recommendation, low quality of evidence).

45) We suggest that either IV hydrocortisone or no hydrocortisone may be used if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability (weak recommendation, low quality of evidence).

ENDOCRINE AND METABOLIC

46) We recommend against insulin therapy to maintain glucose target at or below 140 mg/dL (7.8 mmol/L) (strong recommendation, moderate quality of evidence).

47) We were unable to issue a recommendation regarding what blood glucose range to target for children with septic shock and other sepsis-associated organ dysfunction.

48) We were unable to issue a recommendation as to whether to target normal blood calcium levels in children with septic shock or sepsis-associated organ dysfunction.

49) We suggest against the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state (weak recommendation, low quality of evidence).

50) We suggest either antipyretic therapy or a permissive approach to fever in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).

(*Continued*)

TABLE 1. (*Continued*). Executive Summary of Guidelines

NUTRITION

51) We were unable to issue a recommendation regarding early hypocaloric/trophic enteral feeding followed by slow increase to full enteral feeding vs early full enteral feeding in children with septic shock or sepsis-associated organ dysfunction without contraindications to enteral feeding.

52) We suggest not withholding enteral feeding solely on the basis of vasoactive-inotropic medication administration (weak recommendation, low quality of evidence).

Remarks: Enteral feeding is not contraindicated in children with septic shock after adequate hemodynamic resuscitation who no longer require escalating doses of vasoactive agents or in whom weaning of vasoactive agents has started.

53) We suggest enteral nutrition as the preferred method of feeding and that parenteral nutrition may be withheld in the first 7 d of PICU admission in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).

54) We suggest against supplementation with specialized lipid emulsions in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

55) We suggest against the routine measurements of gastric residual volumes in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

56) We suggest administering enteral feeds through a gastric tube, rather than a post-pyloric feeding tube, to children with septic shock or other sepsis-associated organ dysfunction who have no contraindications to enteral feeding (weak recommendation, low quality of evidence).

57) We suggest against the routine use of prokinetic agents for the treatment of feeding intolerance in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

58) We suggest against the use of selenium in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

59) We suggest against the use of glutamine supplementation in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

60) We suggest against the use of arginine in the treatment of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

61) We suggest against using zinc supplementation in children with septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

62) We suggest against the use of ascorbic acid (vitamin C) in the treatment of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

63) We suggest against the use of thiamine to treat children with sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

64) We suggest against the acute repletion of vitamin D deficiency for treatment of septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

BLOOD PRODUCTS

65) We suggest against transfusion of RBCs if the blood hemoglobin concentration is ≥ 7 g/dL in hemodynamically stabilized children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

Remarks: According to the 2018 Transfusion and Anemia Expertise Initiative guidelines, for the purposes of RBC transfusion, "hemodynamically stabilized" is defined as a MAP higher than 2 SDs below normal for age and no increase in vasoactive medications for at least 2 hr.

66) We cannot make a recommendation regarding hemoglobin transfusion thresholds for critically ill children with unstable septic shock.

67) We suggest against prophylactic platelet transfusion based solely on platelet levels in nonbleeding children with septic shock or other sepsis-associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence).

68) We suggest against prophylactic plasma transfusion in nonbleeding children with septic shock or other sepsis-associated organ dysfunction and coagulation abnormalities (weak recommendation, very low quality of evidence).

Remarks: Prophylactic plasma transfusion refers to situations in which there is an abnormality in laboratory coagulation testing but no active bleeding.

(*Continued*)

TABLE 1. (*Continued*). Executive Summary of Guidelines

PLASMA EXCHANGE, RENAL REPLACEMENT, AND EXTRACORPOREAL SUPPORT

69) We suggest against using plasma exchange in children with septic shock or other sepsis-associated organ dysfunction without TAMOF (weak recommendation, very low quality of evidence).

70) We cannot suggest for or against the use of plasma exchange in children with septic shock or other-sepsis-associated organ dysfunction with TAMOF.

71) We suggest using renal replacement therapy to prevent or treat fluid overload in children with septic shock or other sepsis-associated organ dysfunction who are unresponsive to fluid restriction and diuretic therapy (weak recommendation, very low quality of evidence).

72) We suggest against high-volume hemofiltration over standard hemofiltration in children with septic shock or other sepsis-associated organ dysfunction who are treated with renal replacement therapy (weak recommendation, low quality of evidence).

73) We suggest using venovenous ECMO in children with sepsis-induced PARDS and refractory hypoxia (weak recommendation, very low quality of evidence).

74) We suggest using venoarterial ECMO as a rescue therapy in children with septic shock only if refractory to all other treatments (weak recommendation, very low quality of evidence).

IMMUNOGLOBULINS

75) We suggest against the routine use of IVIG in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

Remarks: Although routine use of IVIG is not recommended, select patients may benefit from such treatment.

PROPHYLAXIS

76) We suggest against the routine use of stress ulcer prophylaxis in critically ill children with septic shock or other sepsis-associated organ dysfunction, except for high-risk patients (weak recommendation, very low quality of evidence).

Remarks: Although "routine" stress ulcer prophylaxis is not recommended, some high-risk patients may benefit from stress ulcer prophylaxis. Studies have supported benefit of stress ulcer prophylaxis when baseline rate of clinically important bleeding is approximately 13%.

77) We suggest against routine deep vein thrombosis prophylaxis (mechanical or pharmacologic) in critically ill children with septic shock or other sepsis-associated organ dysfunction, but potential benefits may outweigh risks and costs in specific populations (weak recommendation, low quality of evidence).

ARDS = acute respiratory distress syndrome, BPS = best practice statement, ECMO = extracorporeal membrane oxygenation, iNO = inhaled nitric oxide, IVIG = IV immune globulin, MAP = mean arterial blood pressure, PARDS = pediatric acute respiratory distress syndrome, PEEP = positive end-expiratory pressure, RCT = randomized controlled trial, TAMOF = thrombocytopenia-associated multiple organ failure.

Drs. Weiss and Peters served as arbiters for conflict interest management and adjudication throughout the guidelines process following standard operating procedures set forth by Society of Critical Care Medicine (SCCM) and endorsed by European Society of Intensive Care Medicine. Dr. Weiss participates in Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) and Shock Society. Dr. Peters participates in the UK PICS study group (vice-chair) and has testified as an expert witness in cases of clinical negligence, causation of injuries. Dr. Agus participates in the American Academy of Pediatrics, Pediatric Academic Societies, American Pediatric Society, Society for Pediatric Research, and The American Society for Clinical Investigation, and he has testified as an expert witness in cases related to ICU and/or endocrinology in children. Dr. Flori participates in American Thoracic Society (ATS) State Chapter (Executive Board Member–Michigan and California State Chapters) and PALISI Network (Steering committee member for various studies being implemented through the Network from intramural funding, governmental, or grant funding from Gerber Foundation). Dr. Nadel (past president) received funding from La Jolla Pharmaceutical (consulting), and he participates in the European Society of Pediatric and Neonatal Intensive Care Medicine (ESPNIC) (Medical President). Dr. Brierley (past president) participates in the ESPNIC. Dr. Carrol participates in NICE (Diagnostic Advisory Committee panel) and National Institutes for Health Research (two scientific panels, i4i and DTF). Dr. Cheifetz participates in American Association for Respiratory Care and ATS (volunteer activities) and has testified as an expert witness for medical malpractice cases, he is an advisor to Philips, and a contributor to Up-to-Date. Dr. Cies received funding from Allergan, Merck, Thermo Fisher Scientific, and Atlantic Diagnostic Laboratories (consultant), and he participates in Pediatric Pharmacy Advocacy Group (multiple positions), Society of Infectious Diseases Pharmacists (Vice-Chair of the Interorganizations Liaison Committee), and the American College of Clinical Pharmacists (member and fellow). Dr. Cruz has provided testimony for legal cases involving children with tuberculosis-related meningitis and is an associate editor for *Pediatrics*. Dr. De Luca serves as Medical President-elect on the Executive Committee of ESPNIC, he served as a consultant and lecturer on the external advisory board and received research and educational grants from Chiesi Farmaceutici S.p.A and AbbVie, and travel grants from AbbVie, he has been a lecturer for Philips, Radiometer, and Waire. Dr. Faust served as chair of the UK NICE Guideline Committee for Sepsis in Children and Adults published in 2016 and for Lyme disease published in 2018, serves as a regional representative to the UK NHS England Clinical Reference Group for commissioning pediatric specialist medicine care (immunology and infection). Dr. Hall receives funding from La Jolla Pharmaceuticals (consultant on the data safety monitoring board for a clinical trial of a sepsis therapeutic), and he participates in the ATS (online journal club editor) and the American Board of Pediatrics (Critical Care Medicine sub-board). Dr. Ishimine participates in SAEM (Consensus Conference Co-Chair), American Board of Pediatrics/American Board of Emergency Medicine (Immediate Past Chair of the Pediatric Emergency Medicine Subboard), and the American College of Emergency Physicians (Pediatric Emergency Medicine Committee member). Dr. Javouhey received funding from CSL Behring (trial on Intravenous Immunoglobulins in toxic shock syndrome in children). Dr. Karam participates

in BloodNet, PALISI, ISBT, AABB, and CCCTG. Dr. Kneyber participates in the ESPNIC. Dr. MacLaren participates in Extracorporeal Life Support Organization (Executive Committee). Dr. Mehta participates in the American Society for Parenteral and Enteral Nutrition (president). Dr. Møller participates in the Science Systems and Applications (board member). Dr. Newth received funding from Philips Research North America (consulting concerning monitoring in PICU), and he participates in the ATS. Dr. Nishisaki's institutional department receives an unrestricted grant from Nihon Kohden (involves an activity to develop a device to measure capillary refill time), and he participates in the Society for Simulation in Healthcare and International Society for Pediatric Simulation. Dr. Nunnally reports service on committees and board seats for the SCCM's American College of Critical Care Medicine (Regent), Society of Critical Care Anesthesiologists (director), the American Society of Anesthesiologists (committee), International Anesthesia Research Society, and NYSA. Dr. Randolph's institution received funding from Genentech (influenza biomarker study research support); she has received funding from Bristol Myers Squibb (consultant in 2017) and La Jolla Pharmaceuticals (design of pediatric septic shock trial of angiotensin II); and she participates in the ATS and the International Sepsis Forum. Dr. Ranjit participates as the Chancellor of College of Pediatric Critical Care, India. Dr. Tume participates in ESPNIC (Nursing President) and the UK PICS Scientific and Education Committee. Dr. Verger participates in the American Association of Critical-Care Nurses (Cert. Corp. Governance Committee) and the Academy of Nursing (Acute and Critical Care Special Interest Group). Dr. Williams participates in the Pediatric Cardiac Intensive Care Society. Dr. Wolf received funding support for participation in industry-sponsored research from Merck & Co, Astellas, and Cempra Pharmaceuticals, and he received other support from Karius, Empatica, and Bluespark Technologies. Dr. Zimmerman received funding from Immunexpress, Seattle and is Past President of SCCM (sepsis biomarker research), and he participates in the AAP and Pediatric Academic Society. Dr. Tissieres received funding from Baxter acute therapies, Bristol-Myers Squibb Company, Chiesi Farmaceutici S.p.A., Faron Pharmaceuticals (consulting, renal replacement therapy), and Biomerieux, funding from La Jolla Pharmaceuticals, Chiesi Farmaceutici S.p.A., and is President ESPNIC (research grant, biomarkers sepsis), and he participates in the Swiss Intensive Care Society, Swiss Pediatric Society, and the French Society of Intensive Care. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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