Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children

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American Academy of Pediatrics; Australia and New Zealand Intensive Care Society, Canadian Critical Care Society; European Society of Intensive Care Medicine; European Society of Paediatric and Neonatal Intensive Care; Pediatric Infectious Disease Society; Scandinavian Society of Anaesthesiology and Intensive Care Medicine; Society of Critical Care Medicine; UK Sepsis Trust; World Federation of Pediatric Intensive and Critical Care Societies

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ABSTRACT

Objective: To develop evidence-based recommendations for clinicians caring for children (including infants, school-aged children, and adolescents) with septic shock and other sepsis-associated organ dysfunction.

Design: A panel of 49 international experts, representing 12 international organizations, as well as 3 methodologists and 3 public members was convened. Panel members assembled at key international meetings (for those panel members attending the conference), and a stand-alone meeting was held for all panel members in November 2018. A formal conflict-of-interest (COI) policy was developed at the onset of the process and enforced throughout. Teleconferences and electronic-based discussion among the chairs, co-chairs, methodologists, and group heads, as well as within subgroups, served as an integral part of the guideline development process.

Methods: The panel consisted of 6 subgroups: recognition and management of infection, hemodynamics and resuscitation, ventilation, endocrine and metabolic therapies, adjunctive therapies, and research priorities. We conducted a systematic review for each Population, Intervention, Control, and Outcomes (PICO) question to identify the best available evidence, statistically summarized the evidence, and then assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We used the evidence-to-decision framework to formulate recommendations as strong or weak, or as a best practice statement. In addition, “in our practice” statements were included when evidence was inconclusive to issue a recommendation, but the panel felt that some guidance based on practice patterns may be appropriate.

Results: The panel provided 77 statements on the management and resuscitation of children with septic shock and other sepsis-associated organ dysfunction. Overall, 6 were strong recommendations, 49 were weak recommendations, and 9 were best-practice statements. For 13 questions, no recommendations could be made; but, for 10 of these, “in our practice” statements were provided. In addition, 49 research priorities were identified.

Conclusions: A large cohort of international experts was able to achieve consensus regarding many recommendations for the best care of children with sepsis, acknowledging that most aspects of care had relatively low quality of evidence resulting in the frequent issuance of weak recommendations. Despite this challenge, these recommendations regarding the management of children with septic shock and other sepsis-associated organ dysfunction provide a foundation for consistent care to improve outcomes and inform future research.

Key Words: evidence-based medicine; Grading of Recommendations Assessment, Development, and Evaluation criteria; guidelines; infection; pediatrics; sepsis; septic shock; Surviving Sepsis Campaign.

INTRODUCTION

Sepsis is a leading cause of morbidity, mortality, and health care utilization for children worldwide. Globally, an estimated 22 cases of childhood sepsis per 100,000 person-years and 2,202 cases of neonatal sepsis per 100,000 live births occur, translating into 1.2 million cases of childhood sepsis per year (1). More than 4% of all hospitalized patients <18 years and ~8% of patients admitted to pediatric intensive care units (PICUs) in high-income countries have sepsis (2-6). Mortality for children with sepsis ranges from 4% to as high as 50%, depending on illness severity, risk factors, and geographic location (2, 3, 7-9). The majority of children who die from sepsis suffer from refractory shock and/or multiple organ dysfunction syndrome, with many deaths occurring within the initial 48 to 72 hours of treatment (10-13). Early identification and appropriate resuscitation and management are therefore critical to optimizing outcomes for children with sepsis.

In 2001, the Surviving Sepsis Campaign (SSC) was formed by the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum. A primary aim of the SSC was to develop evidenced-based guidelines and recommendations for the resuscitation and management of patients with sepsis. The initial guidelines were published in 2004 and have been reviewed and updated every four years thereafter. Following the 2016 edition, SCCM and ESICM reaffirmed their commitment to evidence-based guidelines for all patients by forming separate task forces dedicated to guidelines for adults and children.

The objective of the SCCM/ESICM *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children* is to provide guidance for clinicians caring for children (including infants, school-aged children, and adolescents) with septic shock and other sepsis-associated organ dysfunction. We sought to leverage the expertise of a clinical and methodology team to create comprehensive evidence-based recommendations for the recognition and management of children with septic shock or other sepsis-associated acute organ dysfunction. Recommendations from these guidelines are based on the best current evidence but cannot replace the clinician's decision-making capability when presented with a patient's unique set of clinical variables. Recommendations are intended to guide "best practice" rather than to establish a treatment algorithm or to define standard of care. These guidelines are appropriate for treating septic shock and other sepsis-associated organ dysfunction in a hospital, emergency, or acute care setting, though some may be applicable elsewhere. Although recommendations were developed without consideration to availability of resources, we acknowledge that variation within and across health care systems and geographic regions will determine the practical application of these guidelines.

Although several recommendations for the care of children with sepsis and septic shock have been previously published (14-16), these new guidelines are not intended to update or iterate on these prior documents. Instead, it was the aim of SCCM/ESICM *Surviving Sepsis Campaign* to provide an evidence-based approach to the management of septic shock and other sepsis-associated organ dysfunction in children using a

comprehensive and transparent methodologic approach by a panel with geographic and professional diversity.

METHODOLOGY

Definitions

In 2005, the International Pediatric Sepsis Consensus Conference published definitions and criteria for sepsis, severe sepsis, and septic shock in children based on prevailing views of adult sepsis at the time with modifications for physiology based on age and maturational considerations (17). In 2016, new adult definitions and criteria were published (Sepsis-3) with *sepsis* defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and *septic shock* the subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (18). The term “severe sepsis” was replaced by this new definition of sepsis. Although application of Sepsis-3 to children has been attempted (19, 20), formal revisions to the 2005 pediatric sepsis definitions remain pending (21). Therefore, the majority of studies used to establish evidence for these guidelines referred to the 2005 nomenclature in which severe sepsis was defined as a) ≥2 age-based systemic inflammatory response syndrome (SIRS) criteria, b) confirmed or suspected invasive infection, and c) cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or ≥2 non-cardiovascular organ system dysfunctions; and septic shock was defined as the subset with cardiovascular dysfunction, which included hypotension, treatment with a vasoactive medication, or impaired perfusion. However, studies that defined sepsis as severe infection leading to life-threatening organ dysfunction were

included even if criteria used to define sepsis deviated from the 2005 consensus definitions.

For the purposes of these guidelines, we define *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 non-cardiovascular organ dysfunction. Because several methods to identify acute organ dysfunction in children are currently available (17, 19, 20, 22, 23), we chose 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 ≥37 weeks gestation at birth to 18 years-of-age with severe sepsis or septic shock as defined by the 2005 International Pediatric Sepsis Consensus Conference or inclusive of severe infection leading to life-threatening organ dysfunction. Practically, all infants, children, and adolescents with septic shock or other sepsis-associated acute organ dysfunction are included in this scope. For simplicity, we will henceforth use 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 SIRS *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 <37 weeks gestation are excluded from the scope of these guidelines. The panel sought to include term neonates (0-28 days) born at ≥37 weeks gestation within the scope of these guidelines because these infants may be recognized and resuscitated outside of a newborn nursery or neonatal intensive care unit. However, because the panel did not specifically address studies of neonates with perinatal infection or 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 target users of these guidelines are health professionals caring for children with septic shock or other sepsis-associated organ dysfunction in a hospital, emergency, or other acute care setting. However, we acknowledge that many of the recommendations are likely to apply to the care of children with septic shock and other sepsis-associated organ dysfunction across a broad array of settings with adaptation to specific environments and resource availability.

These guidelines were largely developed without consideration of health care resources (with some specific exceptions, e.g., fluid resuscitation), though we realize that medical care for children with septic shock and other sepsis-associated organ dysfunction 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 to treatment algorithms or bundles and standards of care will need to account for variation in the availability of local health care resources. The panel acknowledges as well the need for future research to test the adaptation of interventions to locally available resources.

Funding and Sponsorship

All funding for the development of these guidelines was provided by SCCM and ESICM. In addition, sponsoring organizations provided support for their members' involvement.

Selection and Organization of Panel Members

The selection of panel members was based on their expertise in specific aspects of pediatric sepsis. Co-chairs and co-vice chairs were appointed by the SCCM and ESICM governing bodies; panel members were then recommended by the co-chairs and co-vice chairs. Each panel member was required to be a practicing healthcare professional with a focus on the acute and/or emergent care of critically ill children with septic shock or other sepsis-associated acute organ dysfunction. Broad international and multi-professional representation from critical and intensive care medicine, emergency medicine, anesthesiology, neonatology, and infectious disease with inclusion of physicians, nurses, pharmacists, and advanced practice providers as part of the working group was ensured. Three members from the lay public were also included with a role to ensure that patient, family, and caregivers' opinions were considered in

prioritizing outcomes and finalizing recommendations that the clinicians proposed during the development process. Panelists were recruited from a wide number of countries and health care systems, including representation from resource-limited geographic areas. A demographically diverse panel with regard to sex, race, and geography was assembled. Members were then allocated to specific groups based on their expertise.

The methodology team included trained methodologists from McMaster University in Canada (WA, KC) and New York University in the United States (MN). The team included methodologists with a health research methodology degree (MSc or PhD) and/or advanced methodology training, all of whom are also practicing intensivists. The methodology team provided methodological guidance and leadership throughout the guideline development process.

Question Development and Outcome Prioritization

The panel was divided into groups: 1) recognition and management of infection, 2) hemodynamics and resuscitation, 3) ventilation, 4) endocrine and metabolic therapies, and 5) adjunctive therapies. A sixth subgroup was added to review research priorities in pediatric sepsis.

The co-chairs, co-vice chairs, and group heads made initial selections of the topics. We included topics addressed in the 2016 SSC adult guidelines that were relevant to children, as well as other key pediatric topics discussed in previously published guidelines (14-16). The PICO format, which describes the population (P), intervention (I), control (C), and outcomes (O), was used for all guideline questions. Group heads, panel members, and methodologists reviewed and selected PICO

questions considered important to guide care for children with septic shock or other sepsis-associated organ dysfunction. Panel members proposed additional PICO questions of high priority and clinical relevance. 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 [PALICC]) (24). 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 decision regarding PICO question inclusion was reached by discussion and consensus among the guideline panel leaders with input from panel members and the methodology team in each group.

In adherence with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, panel members compiled a list of potential outcomes for each PICO question. Subsequently, we electronically surveyed panel members and asked them to rate each outcome on a scale of 1 (not important) to 9 (critically important). We selected only outcomes that were critical (mean of 7 or more) for decision making, taking a patient's perspective. In addition, we presented all selected outcomes to public members to ask for their input and feedback. The final list of PICO questions is provided in **Supplemental Table 1**.

Search Strategy and Evidence Summation

For each PICO question, a professional medical librarian formulated the search strategy with input from the group heads, panel members, and methodologists. Searches utilized a combination of controlled vocabulary (e.g., “sepsis,” “bacterial infections,” “critical illness,” “intensive care units,” “pediatrics,” “NICU,” “PICU,” “emergency service”) and key words (e.g., “toxic shock,” “blood poisoning,” “acute infection,” “child”) in the core search. Additional controlled vocabulary and key words were incorporated to create separate strategies specific to the question posed. Research design filters (e.g., systematic reviews/meta-analyses, randomized controlled trials, observational studies) were also applied as appropriate. Only English language studies were included. No date restrictions were imposed on the searches, but we removed animal-only and opinion pieces from the results. The medical librarian searched a minimum of two major databases (e.g., Cochrane Library, PubMed/MEDLINE, or Embase) to identify relevant systematic reviews, clinical trials, and observational studies published through May 1, 2017. As this was the inaugural version of these guidelines for children, all publications up through May 1, 2017 were considered. Key studies published after the conclusion of the initial literature search on May 1, 2017 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. We excluded articles published in abstract form, in a language other than English, and those focused solely on pre-clinical data. Panel members, with input from methodologists, used the Cochrane risk of bias tool to assess the risk of bias of randomized trials (25) and Newcastle-Ottawa Scale to assess risk of bias of non-randomized studies (26).

When applicable, the methodologists used meta-analytic techniques to generate pooled estimates across two or more studies. For meta-analysis of randomized clinical trials (RCTs), we used random-effects model and inverse variance method to pool estimates across relevant studies. We reported relative risks (RR) and 95% confidence interval (CI) for binary outcomes, and mean difference (MD) and 95% CI for continuous outcomes. For observational data, we conducted meta-analyses if all individual studies provided adjusted estimates and included both an intervention and a control arm using a random-effects model and inverse variance method to pool adjusted odds ratio (OR) across relevant studies All analyses were conducted using RevMan software (Review Manager, version 5.3, Copenhagen).

Formulation of Recommendations

The GRADE approach principles guided the assessment of quality of evidence from high to very low based on 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 (27). Methodologists performed initial assessments of quality of evidence and incorporated feedback from panel members to generate final evidence profiles using GRADEpro GDT (28).

The panel initially considered only research focused on pediatric patients using a hierarchy of evidence **(Table 1).** Studies focusing on children with septic shock and other sepsis-associated organ dysfunction were prioritized, though 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 no studies or insufficient data in children with sepsis or general pediatric illness, evidence from studies of adult patients was considered using an *a priori* framework to determine appropriateness of indirect evidence (**Figure 1**). Evidence from adult studies was generally down-graded due to the indirectness of the evidence.

In a series of webinars, methodologists reviewed the relevant data for each PICO question with panel members to formulate initial recommendations. Each of the groups used the Evidence-to-Decision (EtD) framework to facilitate transition from evidence to the final recommendation. 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 (28).

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. 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. The implications of calling a recommendation strong or weak are shown in **Table 2**. A strong recommendation does not necessarily 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 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 (29).

Best practice statements (BPS) were developed as ungraded strong recommendations within strict conditions suggested by the GRADE Working Group (**Table 3**) (30). BPS were issued when the evidence could not be summarized or assessed 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 based on current practice patterns 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. As such, "in our practice" statements are intended only to describe current variation in care and are not meant to be construed as recommendations.

As new data are continuously generated, the Surviving Sepsis Campaign is committed to ensuring that these guidelines are updated or affirmed every four years or sooner if breaking and relevant evidence becomes available.

Voting Process

Panel members convened to review evidence and discuss recommendations in-person and through web conferences. Following the formulation of initial recommendations through discussion within subgroups, all panelists received links to

evidence profiles and polls created using SurveyMonkey, Inc (Palo Alto, CA) to indicate agreement, disagreement, or abstention. Only panel members without relevant conflicts of interest could vote. Voters could provide feedback for consideration in revising statements. Panelists also deliberated during face-to-face meetings, during which subgroups presented their draft statements for discussion. Up to three rounds of voting were conducted throughout this process of deliberation in an attempt to achieve final consensus. Acceptance of a statement required votes from 75% of the panel members with an 80% agreement threshold.

A summary of all statements determined by the panel is shown in **Appendix 1**. Evidence summaries and evidence profiles that informed the recommendations are included in the online supplementary content. Links to specific tables and figures appear within the relevant text.

Conflict of Interest Policy

Conflict-of-interest (COI) disclosures were sought through the Society of Critical Care Medicine from all panelists and support personnel prior to commencing activities, with updates annually and as needed. The process relied solely on personal disclosure, with clarifications sought when necessary, and centered primarily around potential financial conflicts. The co-vice chairs reviewed all COI disclosures in accordance with SCCM's standard operating procedures, sought clarification when necessary, and worked with the co-chairs to recommend appropriate recusals. There was no industry input into or support of the guideline development process. No panelists received

honoraria for any role in the guidelines process. Only librarians and a supporting project manager received compensation for their work.

Seven individuals were identified with potential COIs, but only 3 were deemed relevant to the final list of questions included in the scope of this guideline. These individuals were asked to abstain from voting on the final recommendations involving the potential COI. In addition, panel members were asked to voluntarily abstain from voting on final recommendations if they had a potential academic COI (e.g., grant application that could benefit from wording of a particular recommendation), though all panel members were welcome to participate in the group discussions leading up to the final recommendation to ensure that input was available from relevant experts.

A. 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.

Rationale: Systematic screening for sepsis in children is driven by the premise that earlier recognition will lead to more timely initiation of therapy, which will translate to improved morbidity and/or mortality. Screening tools are designed to increase reliability

of sepsis recognition and empower health-care professionals to seek rapid medical review. Rapid recognition of sepsis through standardized screening and procedures to guide management of patients identified as at-risk for sepsis should be an essential component of sepsis quality improvement (QI) programs. While the optimal method or tool for screening is unclear, we suggest that screening tools be adapted to the type of patients, resources, and processes within each institution.

Several studies demonstrating that institutional sepsis QI efforts improve outcomes have successfully incorporated screening tools (31-37). Most reported sepsis screens were designed to prompt clinicians to prioritize review of patients that had triggered the screen, hence the ultimate decision to treat or not remains with the clinician. Although RCTs have evaluated the role of systematic screening algorithms to recognize clinical deterioration in children more generally (38), high-quality trials on pediatric sepsis recognition are lacking (39), and data are not sufficient to suggest any particular screening tool, though several have been published (40-42) or shared on-line (http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx). Single-institution studies demonstrate that an electronic health record (EHR)-based screening tool can yield high sensitivity and, when coupled with sequential clinician assessment, improved specificity (43). For facilities that use an EHR, a step-wise approach combining EHR-triggered alerts followed by clinician assessment has the potential to shorten the time to sepsis recognition (41). Notably, no study was found on systematic sepsis screening in low- and middle-income countries meeting the PICO criteria.

Institutions should monitor and evaluate their practice following implementation of sepsis screening (44). Robust QI balancing measures that should be assessed include clinician response, anchoring bias, increased and/or inappropriate antimicrobial prescriptions, fluid overload, increased PICU admissions and transfers to higher levels of care, and health care utilization costs (45). Application of a screening tool requires ongoing optimization of sensitivity and specificity, continuous improvement efforts to maintain provider education and familiarity with the tool, and continual data acquisition to monitor implementation and increase utilization (42). Finally, screening tools must work well with existing or planned other early warning and rapid response systems (46, 47) that may also have inherent limitations (38, 48).

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- versus high-risk of having septic shock or sepsis. However, in our practice, if lactate levels can be rapidly obtained, we often measure blood lactate in children when evaluating for septic shock and other sepsis-associated organ dysfunction.**

Rationale: Blood lactate levels provide a valuable indirect marker of tissue hypoperfusion (49). While increased lactate levels are not specific, they provide a quantifiable surrogate for tissue hypoxia and can be rapidly obtained by point-of-care tests available in many settings. In adults, blood lactate >2 mmol/L is now included within the operational definition of septic shock as an indication of cellular/metabolic dysfunction, and measurement of lactate is included in the Hour-1 Sepsis Bundle, with

recommendations to repeat lactate measurement if the initial value exceeds 2 mmol/L(18, 50, 51). In children, several observational studies have demonstrated an association of elevated blood lactate levels with adverse outcomes in septic shock (11, 52-54). However, the optimal threshold to define *hyperlactatemia* remains unclear. In a PICU study, the mortality rate for children with hypotension requiring vasopressors with lactate >2 mmol/l was 32.0% compared to 16.1% if lactate was ≤2 mmol/l (11). Other studies have shown that lactate levels >4 mmol/L are consistently associated with mortality (52). Although blood lactate may be affected by the conditions of the blood draw (e.g., use of a tourniquet), both venous and arterial lactate measurements obtained have been shown to be independently associated with mortality in children (55). In one prospective study in children, normalization of lactate within 2-4 hours of presentation was associated with decreased risk of persistent organ dysfunction (adjusted relative risk [RR] 0.47, 95% confidence interval [CI] 0.29, 0.78) (56). However, no RCTs have tested whether initial or serial measurement of blood lactate directly informs evaluation and/or management in children. Lactate levels should therefore be interpreted as part of a more comprehensive assessment of clinical status and perfusion.

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

Rationale: Institutional protocols have been shown to improve the speed and reliability of care for children with septic shock or other sepsis-associated organ dysfunction.

Studies reported improvements in mortality, length of stay, duration of organ dysfunction, and development of new or progressive multiple organ dysfunction syndrome (8, 32-34, 36, 57-61). Most of these studies have focused on timely delivery of a “bundle of therapies” (e.g., blood culture, fluid bolus, and antibiotics). For example, an analysis of 1179 children with sepsis across 54 hospitals in New York State found that completion of a sepsis bundle within 1 hour was associated with lower risk-adjusted odds ratio (aOR) of in-hospital mortality (0.59, 95% CI 0.38, 0.93, p=0.02) (8). In a recent single institution study, bundle-compliant care in 1380 children with septic shock was associated with a five-times lower mortality (OR 0.20, 95%-CI 0.07, 0.53) (33). In another study, implementation of a sepsis protocol led to a substantial reduction in the proportion of children who no longer had organ dysfunction on day 2 after presentation (aOR 4.2, 95% CI 1.7, 10.4) (34). However, it should be noted that protocols studied to date have variable components, many studies do not report adherence to specific items within protocols, and only a few studies have attempted to adjust for initial illness severity or other patient factors, making it difficult to summarize studies using the GRADE approach. Therefore, because available evidence shows a strong and consistent association that adherence to protocols reduces variability in care and improves outcomes, we recommend implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction as a best practice.

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

Rationale: Blood cultures remain the most commonly used method to identify bacteremia. Identification of a blood-borne pathogen can have significant clinical implications on the type and duration of antimicrobial therapy and is an important mechanism to recognize multidrug resistant pathogens (62). Thus, whenever possible, blood cultures should be obtained prior to initiation of antimicrobial therapy in children with severe sepsis or septic shock. Although no studies have directly measured the effect of blood cultures alone on outcome in pediatric sepsis, several observational studies have demonstrated that a bundled approach to initial resuscitation that includes early blood cultures is associated with improved outcomes (8, 31, 33). If collection of the blood cultures is likely to delay administration of antimicrobial therapy to the patient, then administration of antimicrobials should take precedence, in view of the impact of delayed antimicrobial administration on patient outcomes (63). However, because blood cultures may be the only source of information identifying bacterial antibiotic susceptibility, it is important to make all reasonable efforts to collect blood cultures before timely antimicrobial administration. The collection of other biological specimens to identify pathogens from non-blood sites (e.g. urine, cerebrospinal fluid, tracheal aspirate, broncho-alveolar lavage, drainage from collections, etc.) should also happen as soon as possible, and depending on the suspected site of infection, such specimens may have a higher yield of pathogen identification than blood cultures. Clinicians should also consider the epidemiology of pediatric infections in relation to age, sex, and host

factors, such as comorbidities (64, 65). Specific patterns of pediatric bloodstream infections relating to age and comorbidities are well known, and approximatively one out of three bacteremia episodes are associated with organ dysfunction in a recent large population-based study (65).

Limitations of standard blood cultures include the time needed to grow and then identify pathogens and their antibiotic sensitivities, as well as the effect of previous therapy on diagnostic yield. New molecular technologies are becoming available to facilitate earlier and faster microbiological diagnoses. Such techniques may be able to identify a range of pathogens well before blood cultures are positive (66), and may potentially identify pathogens even after the administration of antimicrobial therapy. However, new molecular diagnostics are currently relatively expensive, are not sufficient for all pathogens and antibiotic sensitivities, and are not universally available.

B. ANTIMICROBIAL THERAPY

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

Rationale: Antimicrobials are the primary medical therapy that directly targets the underlying cause of sepsis, and there is strong biologic rationale for rapid delivery of

antimicrobials in patients with sepsis (67). Many QI initiatives have shown improved pediatric sepsis outcomes with implementation of a bundle that includes rapid delivery of intravenous antimicrobials (8, 32-34, 36, 57-61). Two retrospective observational studies have also demonstrated an association of faster time to antimicrobial therapy with reduced mortality for children with sepsis. The first study was an analysis of 130 children with sepsis (mortality of 12%), including 103 (79%) with septic shock, in which the unadjusted OR for mortality among children with antimicrobials delivered within versus after 60 minutes of sepsis recognition was 0.60 (95% CI 0.13 - 2.86) (63). The second study was an analysis of 1179 children, including 69% with septic shock, where completion of a sepsis bundle within 1 hour of sepsis recognition was associated with decreased mortality (OR 0.59, 95% CI 0.38, 0.93, p=0.02); however, initiation of antimicrobials alone by 1 hour of recognition was not associated with significant mortality reduction (OR 0.78, 95% CI 0.55, 1.12, p=0.18) (8). When the adjusted OR of these 2 studies were pooled, there was a possible reduction in mortality (OR 0.77, 95% CI 0.55, 1.08) **(Supplemental Table 2, Supplemental Figure 1.**) Other secondary end-points reported in the literature have also been associated with shorter time to initiation of antimicrobial therapy, including reduced length of stay, shorter duration of organ dysfunction, and reduced development of new or progressive multiple organ dysfunction syndrome (8, 32-34, 36, 57-61). Moreover, indirect evidence from adult sepsis generally supports a benefit to starting antimicrobial therapy as soon as possible after recognition of septic shock (68-73). Thus, timely antimicrobial therapy—ideally administered as part of a more comprehensive bundle of initial care—should be the goal for children with septic shock.

The definition of “timely” in this context represents an area of controversy relating to challenges in the accurate recognition of patients with sepsis and septic shock and the need to consider balancing QI metrics such as unnecessary antimicrobial usage (67, 74, 75). One pediatric study (63) indicated a dose-response gradient such that the longer time to antimicrobial therapy, the higher the mortality. Yet the mortality increase reached significance only when antimicrobials were administered >3 hours in comparison to <3 hours, whereas the mortality of patients receiving antimicrobials within <1 hour was not different from those receiving antimicrobials within <3 hours in that relatively small study. The second, larger pediatric study demonstrated a significant decrease in mortality if antimicrobials were administered within 1 hour, but only in the context of a bundle that included a blood culture and fluid bolus. (8) Thus, available pediatric studies do not provide a clear time cut-off after which the risk of mortality or other adverse outcomes increases, but rather support that there is likely to be an incremental risk for harm as time to antimicrobial initiation increases, in particular beyond 3 hours. Notably, the benefit of antimicrobial therapy within 1 hour of recognition has been most prominent in cohorts with a predominance of septic shock (as compared to sepsis without shock) patients (8, 63).

Based on limited pediatric evidence and indirect evidence from adult studies, the panel supported that, in children *with septic shock*, antimicrobial therapy should be initiated as soon as possible and ideally within 1 hour of recognition. Suspicion of septic shock can usually be guided by clinical findings rapidly ascertained through history and physical examination. While our recommendation to ideally administer antimicrobial administration within 1 hour of recognition of septic shock establishes a tangible goal

that emphasizes the importance of early antimicrobial therapy and assists clinicians in prioritizing bedside care, this cut-point should not be misconstrued as a known biological truth. Thus, dichotomous time-based metrics of the quality of care for children with sepsis, while pragmatic and potentially useful to trend, may be of less value than use of continuous variables such as median time to antimicrobials. Despite a very low quality of evidence on this topic, we provide a strong recommendation because the panel concluded that most patients would accept and most clinicians should seek to initiate antimicrobial therapy as soon as possible after recognition of septic shock in most situations.

For children *without clinical signs of shock*, the panel acknowledged that the diagnosis of sepsis-associated organ dysfunction has additional challenges related to the need to discriminate those with true sepsis from among a large number presenting with suspected infection (67). In view of the available evidence, we suggest starting antimicrobial therapy *as soon as possible* after sepsis recognition, while allowing up to 3 hours for appropriate diagnostic investigation for patients *without clinical signs of shock* and for those with an uncertain diagnosis. However, the diagnostic evaluation should be performed expeditiously and, if and when the evaluation supports a likely infection or evidence of septic shock or other sepsis-associated organ dysfunction becomes manifest, antimicrobial therapy should be immediately administered.

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).**

Rationale: Sepsis mortality is associated with delays to *appropriate* antimicrobial therapy, and hence optimal treatment for sepsis relies on accurate selection of antimicrobials to ensure activity against the major pathogens (50, 63, 71, 76). *Empiric therapy* refers to the initial choice of antimicrobials pending microbiological results (**Table 4**) and is based on the predicted likelihood of bacterial pathogens. Empiric therapy should cover a broad range of pathogens that are likely to cause the infection, acknowledging that, in rare circumstances, this may not fully cover very unusual pathogens. *Broad-spectrum therapy* refers to the use of *single- or multi-drug* antimicrobial therapy with activity against multiple groups of bacteria/pathogens. Broad-spectrum therapy is recommended for initial empiric therapy of children with septic shock or sepsis-associated organ dysfunction to increase the likelihood that the initial empirical therapy is effective against the causative pathogens.

The initial choice of empiric antimicrobials should take into account the specific clinical history (e.g., age, site of infection, concomitant disease states, comorbid conditions, indwelling devices). Patients with recent or current hospital exposure should receive empiric therapy that considers known infection or colonization, as well as any recent antimicrobial exposure. Institutions or regions should identify the most

appropriate first-line single-agent antimicrobial, taking into account anatomic site of infection, age, local epidemiology, and host comorbidity and risk factors (e.g., ceftriaxone is recommended for community-acquired sepsis by the National Institute for Health and Care Excellence (NICE) in the United Kingdom) (16). For complex patients or those recently or currently in hospital, the choice of empiric antimicrobials should also take into account concomitant underlying diseases, chronic organ failure, indwelling devices, the presence of immunosuppression or other form of immunocompromise, recent known infection or colonization with specific pathogens, and recent receipt of antimicrobials (65, 77, 78). When available, an infectious diseases clinician should be consulted. Other non-bacterial pathogens that are suspected as a cause of infection should also be targeted as part of initial antimicrobial therapy on a case-by-case basis.

Sepsis in children is most commonly due to gram-negative or gram-positive bacteria, although the relative prevalence of these pathogens varies by age, geographic region, location (community versus hospital) of sepsis onset, and other patient factors. Invasive fungal infections are largely restricted to immunocompromised patients and pre-term infants. Certain specific conditions put patients at risk for atypical or resistant pathogens, thus requiring specific empiric regimens. For example, neutropenic patients are at risk for an especially wide range of potential pathogens, including resistant gram-negative bacilli and *Candida* species, and neonates are at risk of sepsis caused by *listeria monocytogenes* and disseminated herpes simplex virus (HSV). Children with chronic conditions treated in hospital settings are prone to sepsis with resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). For children at risk for multidrug-resistant bacterial infections,

empiric broad-spectrum antimicrobial regimens may require more than one agent to broadly cover such potential pathogens.

For specific empiric broad-spectrum antimicrobial therapy, the reader is directed to published resources (77, 79) and the need to consider patient history, allergies, local epidemiology, and suspected site/source of infection. However, general suggestions can be provided here. For previously healthy children with community-acquired sepsis, a third-generation cephalosporin (e.g., ceftriaxone) may be sufficient. Vancomycin should be added in settings where MRSA or ceftriaxone-resistant pneumococci are prevalent, and addition of an aminoglycoside or substitution of a carbapenem is appropriate in settings where ceftriaxone resistance is common in gram-negative bacteria (80). For immunocompromised patients or hospital-acquired sepsis, antimicrobial therapy should begin with an anti-pseudomonal third- or higher-generation cephalosporin (e.g., cefepime), a broad-spectrum carbapenem (e.g., meropenem, imipenem/cilastatin), or an extended-range penicilin/β-lactamase inhibitor combination (e.g., piperacillin/tazobactam) (79). For neonates, therapy should also include ampicillin for listeria and consideration for empiric acyclovir if there is a clinical concern for HSV (77). For patients with a suspected or documented intra-abdominal source of infection, therapy should include broad coverage for gastrointestinal pathogens, including anaerobic bacteria, with either an extended-range pencillin/β-lactamase inhibitor combination or carbapenem, or addition of clindamycin or metronidazole. For patients who present with sepsis complicating an influenza-like illness during the local influenza season, empiric antiviral therapy should be started while awaiting the respiratory virus testing (81, 82). Patients at higher risk of antibiotic-resistant infection because of past

infection or colonization, local epidemiology, or recent broad-spectrum antibiotic use should receive an individually tailored empiric therapeutic regimen (83). In cases of suspected toxic shock syndrome or necrotizing fasciitis, empiric treatment should include clindamycin or lincomycin to limit toxin production and enhance bacterial clearance (84). Finally, for sepsis treated in regions endemic for rickettsial or parasitic pathogens (e.g., malaria), clinicians should consider adding relevant empiric coverage.

Targeted or definitive therapy refers to the antimicrobial regimen targeted to a specific pathogen(s) after microbiologic identification. As with empiric therapy, targeted/definitive therapy may be single- or multi-drug therapy, but should not be broader than required to treat the specific pathogen(s) after microbiologic identification (85, 86). Risks of unnecessary continuation of broad-spectrum antibiotic and other antimicrobial therapy include direct side effects and toxicities (such as the nephrotoxicity or ototoxicity of aminoglycosides), infection with *Clostridioides difficile* (formerly *Clostridium)* or fungal pathogens, and promotion of antimicrobial resistance in the patient and in the community. In addition, unnecessary exposure to antibiotics may lead to alteration of the human microbiome early in life, the impact of which is poorly understood but has been associated with worse outcomes such as necrotizing enterocolitis in newborns.

Because most microbiological cultures show significant growth within 24 to 36 hours of collection when a pathogen is present (87), empiric treatment should be re-evaluated after no more than 48 hours following initiation. If no pathogen is identified *and* bacterial/fungal infection is deemed unlikely, clinicians should stop empiric antimicrobial therapy to reduce unnecessary exposure to antibiotics/antifungals.

However, many children with a clinical diagnosis of septic shock do not have a pathogen isolated (5, 6). Patients with negative bacterial microbiological results may have false-negative tests due to antibiotic pre-treatment, absence of bacteremia (e.g., bacterial pneumonia despite true bacterial infection), or sepsis related to viral infections (88). Thus, the decision to continue, narrow, or stop antimicrobial therapy must often be made on the basis of clinician judgment and indirect clinical information, taking into account the clinical presentation, site and type of infection, host risk factors, and adequacy of clinical improvement. Complex patients should be discussed with pediatric infectious diseases and/or microbiology specialists to ensure likely pathogens are treated and that antibiotics and other antimicrobials are stopped when they are no longer necessary.

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).**

Rationale: The selection of an empiric antimicrobial regimen requires consideration of a patient's underlying disease state, potential history of prior infections and colonization with multidrug-resistant organisms (MDROs), presence of immunosuppression, and possible recent antimicrobial use, as well as local pathogen prevalence and susceptibility profile(50, 89, 90). Empiric therapy may be single- or multi-drug, but should be broad spectrum in nature as defined in Table 4. For select patients or with concern for particular types of infection, this may necessitate adding a glycopeptide (i.e., vancomycin) to ensure empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) or a second gram-negative agent (e.g., aminoglycoside in addition to a beta-lactam or second/third-generation cephalosporin) when antibiotic resistance is a concern. However, routinely including an aminoglycoside or a glycopeptide for synergy or "double-coverage" as part of an empiric regimen is not supported by the available data (90-101).

A recent Cochrane review evaluated beta-lactam monotherapy versus beta-lactam and aminoglycoside combination regimens for sepsis and included 69 trials accounting for 7863 participants, including neonatal and pediatric patients(89). In trials where the mono- and multidrug arm used the same beta-lactam, no difference in clinical outcomes was observed between study groups. In studies where the monotherapy arm contained a beta-lactam of broader spectrum than the multidrug arm, monotherapy showed a possible benefit for all-cause mortality (OR 0.85, 95% CI 0.71, 1.01) and a significant advantage for clinical failure (OR 0.75, 95% CI 0.67, 0.84) (89). Additionally, indirect evidence from adults with sepsis including 13 RCTs comparing empirical mono- versus combination antibiotic therapy suggests mortality and other outcomes are not

improved by empiric combination therapy (91). Therefore, many children with septic shock and other sepsis-associated organ dysfunction do not require empiric multi-drug therapy. Clinicians should continually re-evaluate the local epidemiology and resistance rates to ensure monotherapy remains appropriate (89).

Certain clinical scenarios, however, may necessitate multi-drug antimicrobial therapy. For example, in patients at high risk for resistant gram-negative infections with sepsis, combining a beta- lactam/beta-lactamase inhibitor agent (i.e., piperacillin/tazobactam combination) with an aminoglycoside (i.e., gentamicin) can be considered, not for synergy, but for expanded coverage to treat both susceptible and resistant pathogens until final identification and susceptibilities are known (102-104). Additionally, a synergistic multi-drug regimen may be appropriate in select settings, even for targeted/definitive therapy, such as device-associated infections, enterococcal endocarditis, staphylococcal endocarditis, group B streptococcal sepsis, and carbapenem-resistant Enterobacteriaceae infections (105, 106).

Pediatric patients with cancer and transplant recipients have a substantial degree of immunosuppression and represent a population at higher risk for colonization and infection with multi-drug resistant organisms (107, 108). The 2017 guidelines for the management of fever and neutropenia (FN) in children with cancer and hematopoietic stem-cell transplantation recommended monotherapy with an anti-pseudomonas beta-lactam, a fourth-generation cephalosporin, or a carbapenem as empiric therapy in high-risk pediatric patients with FN (79). The three RCTs in high-risk pediatric FN comparing monotherapy with aminoglycoside-containing combination therapy found no significant differences in failure rates, infection-related mortality, or overall mortality (79, 109, 110).

The meta-analysis also confirmed the efficacy and safety of monotherapy without the addition of an aminoglycoside. However, the 2017 guidelines on the management of children with FN did recommend addition of a second gram-negative agent and/or a glycopeptide when resistant organisms were suspected for patients who are clinically unstable (i.e., septic shock) and in centers with a high rate of resistant pathogens (79). Therefore, for children with septic shock or other sepsis-associated organ dysfunction who have immune compromise and/or are at high risk for multidrug-resistant pathogens, we suggest empiric multi-drug therapy.

Currently, specific resistance rate thresholds do not exist to help clinicians decide when the addition of a glycopeptide or second gram-negative agent for sepsis or septic shock is necessary. The US guidelines for the management of community-acquired pneumonia in adults suggest a 25% rate of high-level macrolide resistance in the community as the threshold beyond which macrolides should not be used (111, 112). Additionally, current guidelines from the Infectious Diseases Society of America recommend an alternative antibiotic for skin and soft tissue infections if the local clindamycin resistance rate is greater than 10% (113). Considering the current rates of morbidity and mortality for patients with sepsis or septic shock, a local or regional antimicrobial resistance rate exceeding 10% is probably a prudent threshold for the addition of a second agent if that pathogen is suspected(5, 63).

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).

Rationale: Sepsis may alter the pharmacokinetics and pharmacodynamics of antimicrobials. Therefore, antimicrobial dosing should be individualized to deliver effective and timely treatment of life-threatening infection, while at the same time limiting adverse medication effects. Sub-therapeutic dosing can lead to failure to clear the infection, prolong organ dysfunction, and can lead to the development of antimicrobial resistance. A substantial proportion of sepsis patients are at risk for altered drug metabolism and/or clearance, including those with kidney and hepatic dysfunction and those treated with extracorporeal therapies (114). In particular, continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) both lead to profound alteration of antimicrobial clearance, requiring individual dose adaptation (115). Therapeutic drug monitoring (TDM), where available, can permit individualized antimicrobial dosing to achieve maximal effect while minimizing toxicity (116).

Examples of sepsis and septic shock-related altered pharmacokinetics include increased volume of distribution as a result of fluid therapy and capillary leak (*Vd*) (117), decreased antimicrobial clearance as a result of altered renal and hepatic organ perfusion and organ dysfunction (118), and higher unbound drug levels due to hypoalbuminemia leading to increased clearance(119). Hepatic dysfunction impairs the metabolism of lipophilic and highly albumin bound antibiotics, leading to drug accumulation and toxicity. In renal dysfunction, time-dependent antibiotics cleared by the kidneys, such as the beta-lactams, require reduced dosing frequency.

The 3 main determinants of antimicrobial efficacy are: a) the time during which the concentration of the drug remains above the minimum inhibitory concentration (MIC)

of the causative pathogen (T>MIC) (time-dependent antibiotics); b) the peak concentration to MIC ratio (C_{max}/MIC) (concentration-dependent antibiotics); and c) the ratio of the 24-hour area under the concentration-time curve divided by the MIC (AUC24/MIC) (concentration-dependent with time-dependence antibiotics). The main classes of time-dependent antibiotics include beta-lactams (penicillins, cephalosporins, carbapenems, monobactams) and lincosamides (clindamycin and lincomycin). For amoxicillin-clavulanic acid, current published dosing regimens in critically ill children can result in sub-therapeutic concentrations in the early period of sepsis due to augmented renal clearance (120, 121). In sepsis, the use of continuous or extended infusions with loading doses, as opposed to intermittent dosing, may lead to improved outcomes in patients treated with beta-lactam antibiotics (122).

The main classes of concentration-dependent antibiotics include aminoglycosides and metronidazole. In some centers, drug concentrations measured within 60 minutes before or after administration of aminoglycosides are used to estimate the C_{min} and C_{max}, respectively, and together with the MIC of the pathogen, can help to guide appropriate antimicrobial dosing (119). Concentration-dependent antibiotics may require an altered dosing frequency to maximize bacterial killing by preserving the C_{max}/MIC.

Glycopeptides, oxazolidinones, fluoroquinolones, polymixins, daptomycin, azithromycin, and tigecycline are examples of concentration-dependent with time-dependent antibiotics. For vancomycin, this can mean higher doses, but that comes with an increased risk of toxicity. For this reason, continuous vancomycin infusions may be considered to achieve optimal concentrations in some patients (123). For

concentration-dependent with time-dependent antibiotics, dose optimization involves adjusting the dosing interval rather than administered dose (119).

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 hours 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.

Rationale: The misuse and overuse of broad-spectrum antimicrobials in health care, the community, veterinary medicine, and the environment have contributed to a global public health emergency (124). De-escalation of antimicrobials, where appropriate, is warranted to minimize adverse effects of unnecessarily prolonged administration. To date, quality improvement efforts in adults have shown that safe and effective antimicrobial de-escalation can be achieved by daily assessment and discussion (125, 126).

Several host biomarkers have also been proposed to aid in the safe de-escalation of antimicrobial therapy. In adults with severe infections and sepsis, procalcitonin has been shown to successfully guide de-escalation (127-131) with an associated improved mortality (132). Similar reductions in length of antimicrobial therapy have also been safely achieved in neonatal populations (133) using

procalcitonin as a guide. In the United Kingdom, the NICE committee concluded that in emergency room and critical care settings, procalcitonin testing shows promise but currently insufficient evidence is available to recommend the routine adoption of procalcitonin-guided antimicrobial de-escalation (www.nice.org.uk/guidance/dg18).

Although a relationship between antimicrobial stewardship programs (ASP) and a decrease in antimicrobial resistance has not yet been shown, studies suggest that inpatient pediatric ASPs may reduce antimicrobial usage without contributing to adverse patient outcomes (124). The “Start Smart - Then Focus” work from Public Health England suggests a pragmatic approach of the 5 “antimicrobial prescribing decision” options to include: 1) stop antimicrobials if there is no evidence of infection, 2) switch antimicrobials from intravenous to oral, 3) change antimicrobials – ideally to a narrower spectrum – or broader if required, 4) continue and document next review date or stop date, and 5) outpatient parenteral antimicrobial therapy (134). De-escalating antimicrobial therapy must be based in sound clinical judgment and needs to be adapted to local epidemiology and identified resistance patterns.

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).

Rationale: The main purposes of antimicrobial therapy in patients with sepsis are to reduce the pathogen load rapidly and to prevent recurrence. Important determinants of the required duration of antimicrobial therapy include site of infection, ability to drain or remove fixed infectious foci, choice of antimicrobial therapy, time to clearance of

positive cultures, the nature of the causative pathogen, and the integrity of the host immune response. There is no evidence that severity of sepsis is an important determinant of optimal duration of therapy because illness severity is not expected to affect clearance of infection.

The optimal duration of antimicrobial therapy can differ by site of infection because of a high pathogen burden, poor antimicrobial penetration, or presence of difficult-to-eradicate microbial biofilms at the site. For example, longer duration of therapy is typically required for treatment of endocarditis, undrained abscesses, and prosthetic joint infection without device removal (135-137). Characteristics of the causative organism that may affect optimal duration of therapy include resistance or decreased susceptibility to front-line antimicrobials and propensity to cause deep-seated or difficult-to-eradicate infection. For example, optimal duration of treatment for endocarditis caused by methicillin-susceptible *Staphylococcus aureus* may be shorter than for that caused by methicillin-resistant *Staphylococcus aureus* (137). Similarly, although 7-10 days of therapy is appropriate for treatment of uncomplicated gram negative bacteremia in immunocompetent hosts (138, 139), uncomplicated *S. aureus* bacteremia requires a longer course of therapy to effect cure (140-142), likely because of unrecognized seeding (143). Integrity of host immunity may also affect clearance of infection, so antimicrobial therapy for infection in neutropenic pediatric patients with cancer is often continued until resolution of neutropenia (79).

A systematic review evaluated studies describing duration of treatment for clinically and microbiologically-documented infections in children and provides evidence-based clinical guidelines for optimal duration of antimicrobial therapy for

specific conditions(144). Given the lack of studies on the duration of antimicrobial therapy for pediatric patients with sepsis specifically, we refer to this previously published guideline as best evidence. Importantly, there are no data to support that the presence of organ dysfunction or a higher initial illness severity necessitates longer therapy for specific infection types (other than attention to how such organ dysfunction may affect antimicrobial pharmacokinetics and pharmacodynamics).

Observational studies suggest that longer exposure to antibiotics is associated with risk of potential adverse events including necrotizing enterocolitis in very low birthweight infants (145), candidemia in hospitalized children (146, 147), development of antimicrobial resistance (148) and *Clostridioides difficile* (formerly *Clostridium*) infection (149). Several meta-analyses, RCTs, and observational studies have compared long- versus short-duration antibiotic therapy for serious infections (141, 145, 150-168). Most studies suggest that shorter courses were associated with similar clinical outcomes compared to longer durations; these include neonatal bacteremia (159, 164), pyelonephritis (169), uncomplicated bacterial meningitis (155, 156, 160-162, 165, 166), and pneumonia (170, 171). In contrast to these infections, some studies have identified scenarios where longer durations of antimicrobial therapy is superior. For example, an RCT suggested that 14 days of antibiotic therapy was superior to 7 days for treatment of neonates with *Staphylococcus aureus* bacteremia (141), and an observational study suggested that >10 days was superior to ≤10 days of antibiotic therapy in children treated for gram-negative bacteremia without removal of a pre-existing CVC (163).

C. 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).**

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).**

Rationale: Source control is defined as physical modalities taken to control or remove the source of infection or to prevent spread of the infection systemically or to adjacent tissues (172). Source control may include percutaneous or deep abscess drainage, drainage of an empyema, septic joint, or subperiosteal abscess, removal of infected hardware or central venous catheters (CVCs), or debridement of necrotizing soft-tissue infection. The adult SSC guidelines recommend source control as soon as is reasonably feasible after resuscitation, ideally within 6-12 hours of diagnosis (50). Waiting for patients to clinically stabilize prior to intervention is not recommended, as delaying adequate source control may lead to further clinical deterioration (6). While source control as an adjunct to antimicrobial and other medical therapy has been best described for abdominal infections in adults and has been associated with reduction in

mortality (173), the role of source control for pediatric sepsis has been less well elucidated (174).

The importance of source control in children has been shown for skin and deep tissue abscesses and necrotizing fasciitis (174-176). Despite the relative paucity of pediatric data, source control is an important facet of treatment of sepsis, and should not be delayed. Larger collections containing infected material often are poorly penetrated by intravenous antimicrobials and contribute to direct and hematogenous spread, ongoing inflammation, and organ dysfunction.

A common, but potentially preventable, source of infection is central line-associated bloodstream infections (CLABSI). Delayed removal of a CVC in neonates and in patients with fungemia or Enterobacteriaceae bacteremia increases the risk of death or slows recovery (177-180). Removal of a CVC that is the source of infection is therefore generally warranted unless extenuating circumstances exist. Fungal infection dictates immediate removal, while in case of coagulase negative *Staphylococcus spp* or clinically stable patients with infection caused by gram-negative rods, infections can often be initially treated through the CVC as a temporizing measure. The decision to remove the CVC, or not, should ultimately be made based on the pathogen suspected/recovered and host factors, such as immune status. (**Supplemental Table 3.)**

D. 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.

Rationale:

Effective fluid resuscitation in septic shock can correct hypovolemia caused by capillary leak, vasodilation, and fluid losses. Without maintenance of adequate atrial filling pressures, cardiac output will fall and organ perfusion will be compromised.

Three RCTs of different volume resuscitation strategies in children with septic shock in settings in which advanced supportive care (e.g., intubation, mechanical ventilation, and intensive care) was accessible have been published (181-183). These studies have a combined total of only 316 children and showed no difference in mortality between the restrictive and liberal fluid resuscitation groups (**Supplemental Table 4, Supplemental Figure 2**).

In geographic settings in which advanced supportive care, including mechanical ventilation, is limited and/or intensive care is not routinely accessible, the only large-scale RCT of different bolus fluid volume resuscitation strategies in severe infection in children was the Fluid Expansion as Supportive Therapy (FEAST) study (**Supplemental Table 4, Supplemental Figure 2**) (184). The FEAST study was conducted in Africa in a low-resource setting without access to PICU admission. Children between 60 days and 12 years of age with a severe febrile illness and abnormal perfusion were randomized to either rapid volume expansion with 20 mL/kg of intravenous 0.9% saline or 5% albumin or no bolus with maintenance fluid only (control group). Among the 3141 study participants, malaria and anemia were highly prevalent. Overall, the RCT demonstrated a lower mortality after 48 hours in children receiving conservative fluid therapy (i.e., no bolus fluid, maintenance fluid only) than among those given liberal initial fluid therapy (i.e., 20 mL/kg fluid bolus with maintenance fluid) with a RR of 0.72 (95% CI 0.57, 0.9). Notably, 29 additional children enrolled with severe hypotension (systolic blood

pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age) were treated with 40 mL/kg fluid bolus per the planned protocol without randomization to the control group. One additional child who was randomized to the control group also received a 40 mL/kg fluid bolus due to severe hypotension.

For children with septic shock diagnosed by abnormal perfusion or hypotension in healthcare systems with availability of advanced supportive and intensive care, and in the absence of signs of fluid overload, the panel suggests administering up to 40-60 mL/kg fluid bolus therapy in the first hour of resuscitation. Fluid resuscitation should be titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop. Clinical markers of cardiac output can include heart rate, capillary refill, and urine output. Although no high-quality RCTs demonstrate clear superiority of this practice, numerous observational studies have reported improved patient outcomes with routine administration of up to 40-60 mL/kg fluid bolus therapy in the first hour of resuscitation (8, 32, 33, 36, 185-188). The panel provides only a weak recommendation for this resuscitation strategy in healthcare systems with availability of intensive care because a more restrictive fluid resuscitation strategy has not been shown to be inferior in this setting and indirect data (184) indicate harm from rapid fluid boluses in other settings. For this recommendation, the panel judged the balance of observational data supporting initial fluid bolus therapy to outweigh an indirect suggestion of harm because the generalizability of the FEAST trial to healthcare systems with availability of advanced supportive and intensive care is not clear.

For children with septic shock without signs of fluid overload in low-resource settings where advanced supportive and intensive care is not available, the panel recommends against bolus fluid administration, while starting maintenance fluids, in the first hour *if hypotension is not present*, and suggests administering up to 40 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour *if hypotension is present*. The strong recommendation against bolus fluid *if hypotension is not present* was based on the FEAST trial, in which rapid bolus fluid in the first hour of resuscitation increased mortality compared to maintenance fluids only.

For the subset of children with septic shock *and hypotension*, we suggest cautious administration of fluid bolus therapy in low-resource settings because there are insufficient data to conclude that fluid resuscitation is not beneficial in children with septic shock *and hypotension*. In the FEAST study, all children with *severe* hypotension were treated with 40 mL/kg of bolus fluid (184) and so it is not known if fluid bolus therapy was beneficial or harmful in this subgroup of children. It should also be noted that children with gastroenteritis were excluded from FEAST, as ongoing fluid losses should be replaced with intravenous or oral rehydration as indicated. A recent analysis of children with *moderate* hypotension who were randomized to either fluid bolus or maintenance fluid in the FEAST trial was published after completion of our initial systematic review but considered by the panel to be potentially influential (189). In this analysis, only children with moderate hypotension were included because children with severe hypotension were not allocated to the control (no bolus) arm. Fluid bolus therapy in children with moderate hypotension was not beneficial or harmful compared to maintenance fluid only (RR of death = 1.48, 95% CI 0.61–3.66, p=0.41). Although

children who were reclassified as meeting all three WHO shock criteria of cold extremities, prolonged capillary refill >3 seconds, and weak, fast pulse (14) had 48% mortality in the bolus groups versus 20% mortality in the control group, this difference was not statistically significant (p=0.07). These cases were a very small proportion of the total FEAST trial participants (only 72 [2.3%] had moderate hypotension and 65 [2%] met the full WHO shock criteria), and no data were provided about differential patient characteristics between these very small *post hoc* subgroups to assess for potential confounding. Therefore, until further data are available, the panel suggests cautious administration of fluid bolus therapy for the subset of children with septic shock *and hypotension* in low-resource settings as a weak recommendation based on low quality of evidence.

Although a suggestion of *up to* 40 mL/kg was included for hypotensive shock in low-resource settings because this volume was administered to children with severe hypotension in the FEAST study, fluid administration should always be titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop. For purposes of this weak recommendation, hypotension can be defined as a) systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age (184) or b) by the WHO criteria of cold extremities *with* prolonged capillary refill >3 seconds *and* weak, fast pulse (14). Although the panel did not review different approaches to fluid bolus therapy in hypotensive children in low-resource settings, WHO recommends 10-20 mL/kg of isotonic crystalloid over 30-60 minutes, followed by an additional 10

mL/kg over 30 minutes if condition has not improved and signs of fluid overload, cardiac failure, or neurological deterioration have not developed (14).

Fluid boluses may be administered as 10 or 20 mL/kg, according to clinician preference. To facilitate rapid intravenous fluid administration (as well as other intravenous therapies, such as antimicrobials and vasoactive medications), clinicians should consider alternative methods of vascular access if initial attempts at peripheral vein cannulation are not immediately successful. Intraosseous access is rapid and effective and recommended by Pediatric Advanced Life Support (PALS), Advanced Pediatric Life Support (APLS), and the International Liaison Committee on Resuscitation (ILCOR). Ultrasound-guided peripheral intravenous catheter placement, CVCs, and umbilical venous catheter access are alternatives if the skills are immediately available (190, 191). In all healthcare systems, repeat boluses should only be administered after reassessment of hemodynamic status if shock has not resolved and signs of fluid overload are not present.

Although fluid bolus therapy should be discontinued if signs of fluid overload are present or develop, early recognition of fluid overload by clinical examination is a challenge in children. Identifying fluid overload is especially difficult in young children, in whom crackles (rales) are often absent even in the context of gross pulmonary edema. Worsening respiratory status, particularly increasing respiratory rate, radiographic evidence of pulmonary edema in an intubated patient, or new or expanding hepatomegaly may be the only clues of evolving fluid overload. Bedside ultrasound may also be helpful to assess fluid overload, as there is emerging evidence to suggest that a

"full" inferior vena cava with minimal variation across the respiratory cycle demonstrated on ultrasound indicates a fluid-replete circulation (192).

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 to crystalloids.**

Rationale: The FEAST trial investigated 3141 African children with infection and impaired perfusion, who were randomly assigned to resuscitation with 5% human albumin solution or 0.9% saline boluses or no boluses on admission to the hospital. Although both the albumin and 0.9% saline arms exhibited higher mortality than the no bolus arm, comparing human albumin solution to 0.9% saline (RR 1.02, 95% CI 0.8, 1.28) showed no difference in mortality (184). In the absence of any clear benefit of albumin administration in children with sepsis, and in view of the additional costs in comparison to crystalloids, problems of availability, and the potential risk of blood-borne infection, we suggest against the routine use of albumin for initial fluid resuscitation in children with sepsis.

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).

Rationale: Increasing evidence from observational studies and RCTs in adults suggests that resuscitation with crystalloid fluids containing high chloride concentrations (e.g., 0.9% saline) is associated with hyperchloremic acidosis, systemic inflammation, acute kidney injury, coagulopathy, and mortality when compared to resuscitation with more balanced/buffered crystalloids (e.g., lactated Ringer's, PlasmaLyte) (193). Although no pediatric RCTs compare balanced/buffered crystalloids to 0.9% saline, there are 2 large observational studies in children with sepsis (194, 195). They included a total of 30,532 children with sepsis, 2100 of whom received only balanced/buffered crystalloids for the first 72 hours of hospital admission, and 28,432 who received 0.9% saline (**Supplemental Table 5**). These studies showed that use of balanced/buffered crystalloids was associated with lower mortality (OR 0.79, 95% CI 0.65, 0.95) but not AKI (OR 0.98, 95% CI 0.94-1.02) (194, 195). Indirect evidence from adult patients, including two large RCTs, also demonstrates benefit with balanced/buffered crystalloids over 0.9% saline, with adult patients who received larger volumes of fluid and those with sepsis exhibiting the greatest benefit (193, 196). Taken together, these data support that the desirable consequences of balanced/buffered crystalloids probably outweigh the undesirable consequences (including cost), especially in those who require large volume of fluid resuscitation. Therefore, pending further high-quality pediatric data, we suggest that balanced/buffered crystalloids should generally be preferred over 0.9% saline for resuscitation of children with septic shock or other sepsis-associated organ dysfunction without a specific indication for an alternative fluid type (e.g., 0.9% saline

may be preferred in patients with hyponatremia or concern for increased intracranial pressure).

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).

Rationale: No studies compare starches with other fluids in children. However, in adults with severe sepsis and septic shock (**Supplemental Table 6**), two large RCTs showed increased risk of mortality, coagulopathy, and AKI in patients receiving hydroxyethyl starch (HES) (197, 198). A meta-analysis further confirmed the risk of harm with HES (199). In the US, the Food and Drug Administration (FDA) has restricted the use of HES (200) and the European Medicines Agency has recommended complete suspension of its use (201). Therefore, we strongly recommend against the use of HES in children with sepsis.

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).

Rationale: One RCT of gelatin-derived fluid in pediatric septic shock compared it to 0.9% saline in 60 patients. The estimates were imprecise, and showed no difference in mortality, days of using vasoactive medications, or AKI between the two groups (202) (**Supplemental Table 7).** In the absence of any data indicating benefit of gelatin in children, we suggest against its use in pediatric sepsis.

E. HEMODYNAMIC MONITORING

24. We were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5th or 50th percentile for age in children with septic shock and other sepsis-associated organ dysfunction. However, in our practice, we target MAP to between the 5th and 50th percentile or >50th percentile for age.

Rationale: While no data from RCTs support specific hemodynamic targets in children, evidence suggests that targeting MAP of approximately 65 mmHg (5th percentile) in adults with septic shock may be beneficial (203). In the absence of evidence from RCTs, we were unable to reach consensus to recommend a specific MAP target for children. However, in our practice, 37% of panel members reported targeting MAP between the 5th and 50th percentile for age and 45% reported targeting MAP >50th percentile for age. Many panelists also commented that lower blood pressures are acceptable if other hemodynamic parameters (e.g., mental status, perfusion, urine output, lactate) are improving. RCTs to define optimal hemodynamic targets, including MAP, are urgently required to inform practice in pediatric sepsis. In settings where direct measurement of MAP is less reliable, systolic blood pressure provides a reasonable alternative.

A previous recommendation to target perfusion pressure (MAP minus central venous pressure [CVP]) lacks supporting data (204). Prioritizing CVP measurement is also impractical during early resuscitation (such as in most pediatric emergency departments); CVP also provides an unreliable assessment of left ventricular preload.

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 ($ScvO_2$).

Rationale: The ACCM previously recommended clinical assessment of children in septic shock to differentiate "warm" versus "cold" shock based on extremity temperature, capillary refill, pulse strength, diastolic blood pressure, and pulse pressure. Depending on "warm" or "cold" classification, different resuscitation strategies were suggested (e.g., fluid and vasopressors for "warm" shock and inotropes for "cold" shock). However, a number of observational studies have demonstrated very poor correlation of clinical assessments with cardiac index and systemic vascular resistance as measured by advanced monitoring (205-210). Indeed, many children who appeared to have "warm" shock by clinical examination had evidence of myocardial dysfunction, thus demonstrating the challenge of using clinical signs alone to direct therapy. Hence, we suggest not attempting to make this distinction using clinical assessments alone, though this categorical distinction may be helpful if advanced hemodynamic monitoring

is available to assess patient physiology more accurately. Examples of advanced monitoring include invasive arterial blood pressure monitoring with pulse contour analysis, ultrasound Doppler of the ascending or descending thoracic aorta (suprasternal or esophageal Doppler), cardiac ultrasound/echocardiography (211), or measurement of $ScvO_2$ (212). All of these parameters (other than $ScvO_2$) will provide additional assessment of cardiac index and/or systemic vascular resistance index beyond clinical signs, which may then be used to direct and titrate treatment. There is also emerging evidence that fluid responsiveness may be predicted by aortic blood flow peak velocity variation (ΔV_{peak}) in mechanically ventilated children (213). In an RCT of 90 children admitted to a PICU in Egypt, addition of serial echocardiography provided early recognition of septic myocardial dysfunction and hypovolemia that was not apparent on clinical assessment and resulted in faster shock reversal, less fluid overload, shorter LOS, and lower mortality compared with the group without serial echocardiography (211). When advanced hemodynamic monitoring is available, it is appropriate to target the normal range for parameters such as cardiac index, systemic vascular resistance index, stroke index, and $ScvO_2$ (**Table 5**). No evidence supports targeting a supranormal range of cardiac index.

Until recently, adult guidelines have recommended early goal-directed therapy (EGDT) based on the protocol published by Rivers et al in 2001(214). This recommendation described the use of a series of "goals" that included CVP and $ScvO_2$. This approach is no longer recommended following a failure to show reduction in mortality in 3 subsequent large multicenter RCTs (215-217). In children, there has only been one small RCT supporting the use of a protocolized approach including targeting

$ScvO_2$ > 70%. This study included 102 children with fluid-refractory septic shock and showed a reduced risk of death (RR 0.3, 95% CI 0.13, 0.68) from a very high baseline mortality of 39% (26). No high-quality RCTs have investigated other hemodynamic variables to guide therapy in children **(Supplemental Table 8, Supplemental Figure 3**).

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.

Rationale: Although blood lactate is not a direct measure of tissue perfusion, increased lactate is associated with worse outcomes in children (11). Only one pediatric observational study of lactate-guided resuscitation, which included 77 children with sepsis in the ED, was available (**Supplemental Table 9**). This study showed that lactate normalization was associated with a decreased risk of persistent organ dysfunction (RR 0.46, 95% CI 0.29, 0.73; adjusted RR 0.47, 95% CI 0.29, 0.78) (56). There is also indirect evidence from adult sepsis, with six RCTs (total of 1007 patients) evaluating lactate-guided resuscitation of patients with septic shock (218-223). The pooled estimates across all RCTs showed significant reduction in mortality compared to

resuscitation without lactate monitoring (RR 0.66, 95% CI 0.55, 0.81) (**Supplemental Table 9**). Therefore, while there was not sufficient evidence to propose a recommendation to measure lactate to differentiate low- versus high-risk of sepsis among children with infection or suspected infection (see Recommendation 2), we do suggest that blood lactate levels be used to help guide resuscitation of children with established septic shock or other sepsis-associated organ dysfunction.

F. 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. However, in our practice, we select either epinephrine or norepinephrine as the first-line vasoactive infusion guided by clinician preference, individual patient physiology, and local system factors.**
31. **We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock. However, in our practice, we often or sometimes administer a dilute concentration of the initial vasoactive medication through a peripheral vein if central venous access is not readily accessible.**

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, or sooner if fluid overload develops or other concerns for fluid administration are present. 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.

Rationale: Epinephrine and norepinephrine both have vasopressor and inotropic effects, are widely used, and are effective in treating children with fluid-refractory septic shock. No studies directly compare epinephrine with norepinephrine. However, epinephrine has been compared to dopamine in two RCTs in children with fluid-refractory septic shock (224, 225). Across both studies, epinephrine was associated with a lower risk of mortality (RR 0.63, 95% CI 0.40, 0.99) and more organ failure-free days among survivors by day 28 (MD 4 more days, 95% CI 2.0 to 6.0) (**Supplemental Table 10, Supplemental Figure 4**).

Norepinephrine has not been studied in children with septic shock, but in a randomized trial of norepinephrine versus saline in sedated, mechanically ventilated children, mortality was not different between groups (RR 0.50 95% CI 0.10-2.43, **Supplemental Table 11a**) but the norepinephrine group showed higher urine output (p=0.016) and improved blood pressure (p=0.04) suggesting improved perfusion relative to saline (226). Evidence from adult trials (**Supplemental Table 11b**) shows a lower mortality rate (RR, 0.93 95% CI 0.86-1.00) and lower incidence of arrhythmias (RR 0.48

95% CI 0.40-0.58]) with norepinephrine than with dopamine, and no difference in mortality with epinephrine than with norepinephrine (RR, 0.96 95% CI 0.77-1.21) (227).

Evidence is insufficient to recommend either epinephrine or norepinephrine as the initial vasoactive agent for children with fluid-refractory septic shock. In a survey of our panel members, an equal number used epinephrine and norepinephrine as the first-line vasoactive medication with a general preference for epinephrine to treat myocardial dysfunction and low cardiac output and for norepinephrine to increase systemic vascular resistance. It therefore seems reasonable to use either epinephrine or norepinephrine as the initial vasoactive agent, with the choice made based on individual patient physiology, clinician preference, and local system factors. Once cardiac ultrasound/echocardiography or other advanced monitoring is available, selection of vasoactive therapy should be driven by individual patient physiology.

No pediatric data identify when shock becomes “fluid-refractory” and, thus, to guide when to start vasoactive infusions. However, excessive fluid resuscitation can lead to fluid overload, which has been associated with increased mortality in critically ill children (228). A trial comparing a fluid-sparing strategy with early initiation of vasoactive medications compared to a fluid-liberal resuscitation strategy is currently ongoing (SQUEEZE trial, Clinical Trials.gov NCT03080038). Until further data are available, we consider it reasonable to begin vasoactive infusions after 40-60 mL/kg of fluid resuscitation if the patient continues to have evidence of abnormal perfusion. Additional fluid resuscitation may be concurrently administered if the patient demonstrates physiologic improvement following each fluid bolus and without signs of fluid overload.

All vasoactive agents, including norepinephrine, may be initiated through peripheral venous (or intraosseous, if in place) access if central venous access is not readily available to avoid delays in therapy (229, 230). However, central venous access should be obtained as soon as reasonably practicable. In our practice, 82% of panel members reported at least sometimes administering the initial vasoactive infusion peripherally if central venous or intraosseous access was not readily available, particularly in the emergency department or other non-PICU settings. Most panelists preferred epinephrine or dopamine to norepinephrine if peripheral infusion was needed. Although epinephrine or norepinephrine is the preferred first-line medication, dopamine may be substituted as the first-line vasoactive infusion, administered either peripherally or centrally, if neither epinephrine nor norepinephrine is 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.

Rationale: Vasopressin-receptor agonists (vasopressin or terlipressin) have been studied in three RCTs in children (**Supplemental Table 12**). Vasopressin was compared with saline in one study in children with vasodilatory shock (231) and in one study of children with severe lung disease (232). Terlipressin was compared with usual care in children with septic shock (233). The mortality rate (RR, 1.14 [0.80-1.62]) and

ischemic events (RR, 1.56; 95% CI, 0.41-5.91) were higher vasopressin/terlipressin. There were fewer vasoactive-free days with vasopressin (median 25.2d in AVP (IQR 0.0-28.3), median 27.5d in control (IQR 23.1-28.9). In six RCTs in adults, renal replacement therapy was required less often with vasopressin (RR, 0.74 95% CI 0.51-1.08) (234). Weighing the benefit of avoiding renal replacement therapy against the potential harm from ischemic events and the non-significant difference in mortality, we suggest that vasopressin may be added or catecholamines may be further titrated in children on high doses of catecholamines.

33. We were unable to issue a recommendation about adding an inodilator in children with septic shock and cardiac dysfunction despite other vasoactive agents. However, in our practice, we sometimes use inodilators in children with septic shock and evidence of persistent hypoperfusion and cardiac dysfunction despite other vasoactive agents.

Rationale: There are no RCTs of inodilators (including milrinone, dobutamine, or levosimendan) in children with septic shock with persistent hypoperfusion and cardiac dysfunction. A report of two children described improvement in cardiac output with addition of inodilators (235). A case series of 10 children with meningococcal septic shock treated with milrinone described improved core-to-peripheral temperature gradient, with stable blood pressure and no change in acidosis (236). These data were not sufficient to formulate a recommendation. However, in our practice, 77% of panel members reported at least sometimes using inodilators in children with septic shock who had evidence of persistent hypoperfusion and cardiac dysfunction despite other

vasoactive agents, typically in a PICU with advanced hemodynamic monitoring available.

G. VENTILATION

34. We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock. However, in our practice, we commonly intubate children with fluid-refractory, catecholamine-resistant septic shock without respiratory failure.

Rationale: There are no RCTs and/or observational studies of children receiving early intubation for refractory shock without respiratory failure compared to delayed or no intubation for the same condition, nor is there suitable indirect evidence to substantiate a formal recommendation. However, it is well understood that a high metabolic demand from refractory shock typically indicated by progressive lactic acidemia and end-organ dysfunction can be, at least in part, mitigated by early invasive mechanical ventilation even without clinical symptoms of acute pulmonary edema or respiratory failure (237-239). Moreover, chest radiograph findings can "lag" behind clinical deterioration (240, 241) such that patients with refractory shock and a "negative" chest radiograph may still progress toward more overt acute respiratory distress syndrome (ARDS). Lung ultrasound may provide an alternative tool to chest radiograph in detecting lung pathology, but its utility to identify which sepsis patients may benefit from early mechanical ventilation is not yet clear(242-245). For these reasons, 48% of panel members often or always and 35% sometimes intubate children with fluid-refractory, catecholamine-resistant septic shock even in the absence of clear respiratory failure, while 17% rarely or never do so. Of note, when intubating, caution should be exercised

to avoid worsening hypotension or precipitating cardiac arrest as medications used for inducing anesthesia at the time of tracheal intubation, along with conversion from spontaneous breathing to use of positive pressure ventilation, may result in a transient deterioration in patient hemodynamics. The panel does recognize that in some settings, invasive mechanical ventilation may not be available or feasible—or may even be detrimental. In these instances, transport of the patient to a higher level of care can be life-saving.

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).

Rationale: Etomidate is a short-acting intravenous anesthetic agent that has been used for inducing anesthesia and sedation for tracheal intubation in patients with unstable hemodynamics. However, concerns regarding the drug's effect on adrenal function have been raised in adult studies. No RCTs exist in critically ill children with or without sepsis comparing etomidate to another anesthesia/sedative regimen. Two observational studies included children. One study from 1984 (246) enrolled acutely injured adults and children (44 intubated with etomidate versus 90 intubated with a benzodiazepine and opioid). A more recent study (247) enrolled children with meningococcal sepsis or septic shock with 23 intubated with etomidate as compared to 37 intubated with any other combination of sedatives. While caution must be taken given the small sample size, each of these studies reported higher mortality after use of etomidate (pooled OR 4.51, 95% CI 1.82, 11.16) **(Supplemental Table 13).** In addition,

den Brinker et al (247) reported a significant association of etomidate with adrenal insufficiency, with cortisol to adrenocorticotropin hormone (ACTH) ratios decreasing by 83% after etomidate exposure. Indirect evidence is available from 4 RCTs in adults (248-251). In the largest of these trials, Jabre et al (251) compared 234 critically ill adults intubated with etomidate to 235 intubated with an alternative medication regimen and found higher adrenal insufficiency in the etomidate group (OR 1.79, 95% CI 1.37, 2.36). Pooled odds of all 4 adult studies was 1.89 (95% CI 1.47, 2.44) with all studies suggesting significantly increased risk of adrenal insufficiency after etomidate administration. Importantly, this effect was seen even after 1 dose of etomidate. Unfortunately, there is no conclusive evidence to recommend an optimal alternative induction agent to etomidate, though ketamine and fentanyl are routinely available and can offer favorable hemodynamic profiles in the setting of shock.

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

Remarks: When non-invasive mechanical ventilation is initiated, clinicians should carefully and frequently re-evaluate the patient's condition.

Rationale: Non-invasive mechanical ventilation with continuous positive airway pressure ventilation (CPAP) or bi-level positive airway pressure ventilation (BiPAP) may allow for decreased work of breathing and improved oxygenation in the face of sepsis-induced PARDS. Therefore, it is possible to avoid intubation in sepsis patients who are

identified early with mild PARDS physiology and no evidence of advancing end-organ dysfunction. However, no RCTs in either critically ill children or children with sepsis-induced PARDS compare the effect of non-invasive ventilation to invasive mechanical ventilation on clinical outcomes. Observational studies have tested whether non-invasive mechanical ventilation could mitigate the need for invasive mechanical ventilation but none specifically focused on children with sepsis (252-258). We undertook a meta-analysis of 3 observational studies that evaluated the association of non-invasive mechanical ventilation with mortality in a general PICU population (254, 256, 259). Using unadjusted estimates pooled from the data across all 3 studies, we found non-invasive ventilation to be associated with a decreased risk of death (RR 0.21, 95% CI 0.09, 0.47) (**Supplemental Figure 5).** One additional RCT in immunocompromised children with acute respiratory dysfunction did not find that early non-invasive ventilation reduced intubation compared to standard care, but the trial was small (42 participants) due to low consent and overall slow recruitment and the direct relevance to children with sepsis-induced PARDS without a clear indication for intubation and who are responding to initial resuscitation was not clear (260). Thus, it is reasonable to try non-invasive mechanical ventilation in children with sepsis-induced PARDS who do not have a clear indication for intubation. However, non-invasive ventilation should be reserved for children with sepsis who are responding to initial resuscitation, do not have evidence for ongoing or worsening end-organ dysfunction, and in whom close monitoring and frequent re-evaluation can be ensured (255, 257, 261). This recommendation for children with sepsis-induced PARDS aligns with the

2015 PALICC (262) and 2017 Pediatric Mechanical Ventilation Consensus Conference (PEMVECC)(263) guidelines.

37. We suggest using high positive end-expiratory pressure (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 fractional inspired oxygen (FiO_2) grid though adverse hemodynamic effects of high PEEP may be more prominent in children with septic shock.

Rationale: PEEP helps to prevent alveolar collapse, restore end-expiratory lung volume, and improve mean airway pressures, all of which help to improve adequate oxygenation in PARDS patients and minimize unnecessary use of high FiO_2. Adult ARDS patients have been successfully managed with judicious and strict application of a PEEP/FiO_2 grid, initially implemented in the ARDS-network ARMA trial (264). This grid has been applied in children with PARDS enrolled in RCTs (265), but a pediatric-specific PEEP/FiO_2 grid has not been determined or validated. In 2017, a multi-center observational study by the Collaborative Pediatric Critical Care Research Network reported that pediatric critical care clinicians almost uniformly limit PEEP to 10 cm H_2O irrespective of oxygenation and FiO_2 (266). This is in contrast to the PEMVECC (263) and PALICC (24) recommendations for use of PEEP in excess of 15 cm H_2O for severe PARDS patients. Our panel reviewed several observational studies of PARDS patients,

all published since 2007, each including 12-30% sepsis-induced PARDS (266-278). The largest, a multicenter study by Khemani et al (278), evaluated 1,134 PARDS patients of whom 26% were managed with lower PEEP relative to ARDSnet protocol and experienced greater mortality than those managed in accordance with a higher PEEP strategy as recommended by the ARDSnet PEEP/FiO_2 grid (**Supplemental Table 14**). After adjustment for relevant co-morbidities, pediatric patients managed with a PEEP strategy at or above that recommended by the ARDSnet low PEEP/FiO2 grid had a decreased odds of death compared to children managed with PEEP lower than that recommended by the ARDSnet low PEEP/FiO2 grid (adjusted OR 0.50, 95% CI 0.31-0.81).

The panel concluded that PEEP levels >10 cm H_20 may be necessary with progressive hypoxemia, with the precise amount of "high" PEEP carefully titrated for each individual while attending to the potential adverse hemodynamic effects of increasing intrathoracic pressure in children with septic shock. Therefore, although the optimal approach to setting PEEP has not yet been determined in children with PARDS, carefully increasing PEEP for children with sepsis-induced PARDS who require FiO2 exceeding 60% and/or exhibit ongoing hypoxemia is reasonable, rather than continuing to manage such children with a low- or moderate- PEEP strategy of ≤10 cm H_2O.

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.

Rationale: ARDS is characterized by decreased lung compliance, risk for atelectasis, and increased intrapulmonary shunt. Recruitment maneuvers have been used in both children and adults temporarily to increase transpulmonary pressure to recruit lung units with the goal of improving both oxygenation and ventilation. Most recruitment maneuvers include either sustained inflation or a step-wise incremental or decremental PEEP titration methodology. However, many clinicians and researchers remain concerned that the optimal strategy for lung recruitment has not been determined and injudicious implementation of recruitment maneuvers can result in hemodynamic compromise (279), hypercarbia (280), and/or ventilator-induced lung injury (281). PEMVECC did not recommend use of recruitment maneuvers in children, citing an overall lack of evidence in this area (263). In contrast, the 2015 PALICC provided a weak recommendation in favor of recruitment maneuvers with prioritization of a slow stepwise incremental and decremental PEEP method (24).

Two observational studies are potentially informative about use of recruitment maneuvers in children with sepsis-induced PARDS (269, 270). (**Supplemental Table 15.)** First, Boriosi et al (282) enrolled 21 children with lung injury, of whom 66% had sepsis, and used incremental PEEP recruitment maneuvers. Patients experienced improved oxygenation as measured by both the partial pressure of oxygen in arterial blood to FiO_2 ratio (PaO_2/FiO_2 or P/F) and alveolar-to-arterial oxygen (A-a O_2) gradient for the 4 hours after recruitment. Second, Duff et al (283) enrolled 32 children and used

the sustained inflation technique, which also resulted in improved oxygenation for the ensuing 6 hours. However, neither study tested the association of recruitment maneuvers with clinical outcomes, such as ventilator days or mortality. Consequently, despite the potential for benefit for some patients coupled with the possibility of harm (284, 285), insufficient data do not allow us to recommend either for or against recruitment maneuvers in sepsis-induced PARDS patients at this time.

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 hours per day, as tolerated.

Rationale: Prone positioning almost uniformly improves oxygenation in adults with ARDS and children with PARDS. While the exact mechanisms continue to be elucidated, prone position has been shown to recruit areas of collapsed, de-recruited lung with resultant improved elastance, decreased lung stress and strain, and improved functional residual capacity (286). Given that pulmonary perfusion is thought to be consistent both dorsally and ventrally, an improvement in lung aeration can be met with continued perfusion, thereby reducing ventilation-perfusion mismatching (287). Most recent RCTs in adults support use of prone positioning as a potentially life-saving management strategy (**Supplemental Table 16**), especially in those meeting severe ARDS criteria (i.e., P/F <150 mmHg) (288). This benefit is seen particularly in patients who are positioned for prolonged periods of time, most commonly reported as 12-20 hours per day. Two pediatric RCTs tested the use of prone positioning in PARDS

patients (265, 289). Pooled analyses of these two studies yielded a RR of 0.99 (95% CI 0.36, 2.69) for mortality in prone positioning as compared to supine positioning for this patient population (**Supplemental Table 16, Figure 6**). Importantly, no serious adverse events were reported in these trials, although the prone positioning methodology was protocolized in each with particular attention to avoid accidental endotracheal extubation and pressure injury. PALICC (24) did not recommend routine use of prone positioning in PARDS patients but suggested its consideration in severe PARDS. The panel noted that the National Institutes of Health (NIH) has approved and funded an international RCT of prone positioning in severe PARDS (ClinicalTrials.gov identifier NCT02902055).

40. We recommend against the routine use of inhaled nitric oxide (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)

Rationale: The presumptive mechanism of sepsis-induced PARDS involves alveolar epithelial injury, vascular endothelial injury, and activation of inflammatory, fibrosis, and coagulation cascades. As such, PARDS is not a disease process primarily of pulmonary arterial hypertension, the therapeutic target of iNO therapy, and so is not recommended for routine use in children with sepsis-associated PARDS. Nonetheless, many PARDS patients have co-morbidities that include risk for pulmonary hypertension (e.g., chronic lung disease after prematurity, congenital heart disease after repair or palliation) or

clinical features, such as acidemia and hypoxemia, that increase pulmonary arterial pressures. Thus, inhaled nitric oxide therapy may be considered in children with documented pulmonary hypertension or severe right ventricular dysfunction (241, 290)(REF). Such use of iNO in sepsis must be balanced against its lack of availability or high cost in many areas of the world and, that once in place, iNO use carries a potential patient safety consideration as inadvertent and abrupt discontinuation of the therapy can result in a rapid and potentially life-threatening rebound pulmonary hypertensive crisis.

Several small RCTs (291-293) and observational studies have described significant improvement in oxygenation after iNO therapy (294). Many, but not all, of these studies include patients with sepsis (292, 293, 295-298), and few analyze longer term, clinically relevant outcomes such as mortality. A 2016 Cochrane review indicated no mortality benefit from iNO administration (RR 0.78, 95% CI 0.51, 1.18) in 3RCTs (299). Our analysis of two recent observational studies, one conducted in children on ECMO and another in children with severe PARDS, respectively, suggest possible increased mortality risk (296, 298), whereas one RCT of 55 PARDS patients indicated improved duration of mechanical ventilation in PARDS survivors (293) **(Supplemental Table 17, Supplemental Figure 7)** Taken together, these data do not support *routine* use of iNO in all children with sepsis-induced PARDS but do raise the potential for benefit as an emergency rescue therapy for severe, sepsis-induced PARDS with refractory hypoxemia after other oxygenation strategies have been optimized. Emergency rescue use of iNO may allow time to realize benefit from other therapies, such as lung recruitment, or provide a bridge to ECMO or another intervention.

However, when iNO is used, we agree with the PALICC recommendation that "assessment of benefit must be undertaken promptly and serially to minimize toxicity and to eliminate continued use without established effect" (24). These recommendations align with the 2004 guidelines for use of iNO therapy in neonates and children issued by the European Society for Pediatric and Neonatal Intensive Care (300), PALICC guidelines (24), and a 2017 Cochrane review (294) as no relevant change in evidence has become available.

42. We were unable to issue a recommendation to use high-frequency oscillatory ventilation (HFOV) versus conventional ventilation in children with sepsis-induced PARDS. However, in our practice, there is no preference to use or not use HFOV in patients with severe PARDS and refractory hypoxia.

Rationale: HFOV provides a sustained mean airway pressure with superimposed high frequency, pendelluft-type, oscillatory breaths that may improve oxygenation in patients with moderate-to-severe lung disease while minimizing barotrauma, volutrauma, and atelectrauma. However, the most efficacious timing of application, optimal settings, and ideal population of patients likely to benefit have not been well established. HFOV may be difficult to apply effectively in centers with little experience, and is not universally available. Despite these practical limitations, both PALICC (24) and PEMVECC (263) endorsed cautionary use of HFOV as an alternative type therapy in patients with severe PARDS. In our panel, clinicians who use versus those who do not use HFOV in patients with severe PARDS and refractory hypoxia were nearly evenly distributed.

Application of HFOV in adult ARDS patients has yielded concerning results due to a potentially increased mortality observed in the adult OSCILLATE RCT (301) and a neutral result in the adult OSCAR RCT (302). Pediatric data include 2 observational studies with a non-HFOV control group and 3 randomized trials. In the two observational studies, oxygenation improved with HFOV relative to conventional ventilation but there was a non-significant trend toward increased mortality (Guo et al: 34.6% versus 22.7%, adjusted OR 2.74, 95% CI 0.52, 14.6; Bateman et al: 25% versus 17%, adjusted OR 1.28, 95% CI 0.92, 1.79)(303, 304). Among three small RCTs, however, a trend toward reduced mortality in those managed with HFOV was observed (pooled RR 0.77, 95% CI 0.43, 1.36)(305-307). A large, multi-center, international RCT of HFOV compared to conventional mechanical ventilation in severe PARDS patients, including children with and without sepsis, is underway and will seek to address many of these issues (www.clinicaltrials.gov/ NCT02902055).

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 to 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 hours after ARDS onset.

Rationale: Indirect evidence from 3 adult RCTs (308-310) found that early use of neuromuscular blocking agents (NMBAs) for up to 48 hours in adults with severe ARDS, defined as PaO_2/FiO_2 ratio <150 mmHg, improved 90-day survival and shortened duration of mechanical ventilation without increasing muscle weakness. In a multi-

center double-blind RCT (310), 340 patients with early severe ARDS, meeting criteria within 48 hours, were randomized to receive either cisatracurium besylate or placebo once adequately sedated. After adjustment for baseline PaO_2/FiO_2, plateau pressure, and the Simplified Acute Physiology Score, the cisatracurium group had a hazard ratio for death at 90 days of 0.68 (95% CI 0.48, 0.98) compared to the placebo group. Early use of NMBAs was also associated with decreased organ system dysfunction, less air leak, and a decreased pro-inflammatory response (311). These findings remained consistent when combined with earlier smaller studies from the same group of investigators in a meta-analysis. However, a more recent adult trial of early neuromuscular blockade in those with moderate to severe ARDS was stopped for futility at the second interim analysis (enrollment of 1006 patients) with a 90-day mortality difference of 42.5% in the intervention limb versus 42.8% in the control limb. In this study, the intervention group received continuous cisatracurium and deep sedation for 48 hours compared to the control arm that received lighter sedation targets (Richmond Agitation Scale of 0 to -1). Both limbs received low tidal volume ventilation with high PEEP strategy. Notably, only 13.8% of patients enrolled in ROSE had non-pulmonary sepsis as a primary diagnosis.

In pediatrics, there are no prospective data regarding the use of NMBAs in PARDS (with or without sepsis), although there is an ongoing pediatric trial in the Netherlands (Clinical Trials.Gov NCT02902055). In one large retrospective study of 317 children with PARDS, of whom 23% experienced sepsis-induced PARDS (312), mortality was lower in those children treated with neuromuscular blockade (8.8% versus 17.7%). However, duration of mechanical ventilation was longer in the treatment group

and proportion with neuromuscular weakness was not assessed **(Supplemental Table 18).**

H. CORTICOSTEROIDS

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

45. We suggest that either intravenous 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).

Rationale: A potential role for intravenous hydrocortisone as adjunctive therapy for septic shock is supported by various roles of cortisol in homeostasis and the stress response. For example, cortisol directly decreases reuptake of norepinephrine (313), augments beta-adrenergic receptor sensitivity in the heart, and enhances calcium availability in myocardial and vascular smooth muscle cells (314) promoting myocardial contractility and vasoconstriction, respectively. Cortisol helps to inhibit prostacyclin and endogenous nitric oxide production, resulting in increased vascular tone (315), modulation of capillary leak (316), and augmentation of the beta-adrenergic receptor in the heart (315). However, potential adverse side effects of corticosteroid therapy include hyperglycemia (317, 318), catabolism-related diffuse neuromuscular weakness (including the diaphragm) (319, 320), and hospital-acquired infections (321). These

effects may be under-appreciated in critically ill patients, but can contribute to worse outcomes (322).

At least one pediatric (323) and several adult (324) interventional trials examining adjunctive corticosteroids for septic shock have concluded that this drug class hastens resolution of shock. Of the four adult, high-quality contemporary RCTs, two reported a mortality reduction and two did not (325-329). A recent meta-analysis of 42 RCTs including 9,969 adults and 225 children with sepsis found that corticosteroids possibly result in a small reduction in short-term mortality (RR 0.93, 95% CI 0.84, 1.03), long-term mortality (0.94, 95% CI 0.89, 1.00), faster resolution of shock, and shorter LOS, while also possibly increasing the risk of neuromuscular weakness (RR 1.21, 95% CI 1.01, 1.52) (330). Despite a weak recommendation to treat sepsis with hydrocortisone based on the findings noted in the overall meta-analysis (331), the pediatric studies enrolled a combined small number of subjects, reported inconsistent conclusions, had methodologic limitations, and did not demonstrate an overall mortality reduction (323, 332-334). **(Supplemental Table 19)**.

Observational cohort studies have reported either harm or no benefit with hydrocortisone in children with septic shock (5, 335-339). For example, a retrospective analysis of the REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE (RESOLVE) trial of activated protein C in pediatric sepsis found no differences in mortality, duration of mechanical ventilation and vasoactive-inotropic support, or PICU stay among 193 children who received and 284 who did not receive open-labeled corticosteroids (336). Despite the *post hoc* analysis, age, sex, PRISM-III scores, baseline number of dysfunctional organs, and baseline Pediatric Overall

Performance Category scores did not differ between corticosteroid-treated and corticosteroid non–treated groups.

Several pediatric and adult studies have attempted to use random cortisol and/or cosyntropin-stimulated cortisol serum concentrations to identify which patients with septic shock may benefit from hydrocortisone therapy, but reliable cutoffs have not been clearly identified. Challenges relate to variability in 1) the cortisol assay itself; 2) cortisol metabolism (11-beta-hydroxysteroid dehydrogenase) during sepsis; 3) corticosteroid-binding globulin concentrations; and 4) multiple tissue (e.g., elastase, anti-glucocorticoid compounds) and cellular (e.g., glucocorticoid receptor) factors. Therefore, use of random cortisol or stimulation tests to guide corticosteroid prescription in children with septic shock cannot be recommended as this time. However, for any patient with a clinical concern for primary adrenal insufficiency (e.g., a patient with significant and unexplained hypoglycemia, hyponatremia, and/or hyperkalemia), a high-dose cosyntropin-stimulation test should be performed. Interpretation should focus on the baseline serum ACTH concentration (above normal indicating primary adrenal insufficiency) and the 60-minute stimulated serum cortisol concentration (<18 µg/dL indicating primary adrenal insufficiency) (340).

In summary, no high-quality investigations currently support or refute the routine use of adjunctive corticosteroids for pediatric septic shock or other sepsis-associated organ dysfunction. At the time of this publication, an RCT is in progress to examine the potential risks and benefits of adjunctive hydrocortisone for fluid and vasoactive-inotropic recalcitrant septic shock in children. However, this uncertainty does not apply to children presenting with septic shock or other sepsis-associated organ dysfunction

who also have acute or chronic corticosteroid exposure, hypothalamic-pituitary-adrenal axis disorders, congenital adrenal hyperplasia or other corticosteroid-related endocrinopathies, or have recently been treated with ketoconazole or etomidate, for whom prescription of stress-dose hydrocortisone is indicated, with or without evaluation of the adrenal axis (341).

I. ENDOCRINE AND METABOLIC

46. We recommend against insulin therapy to maintain a blood 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 or other sepsis-associated organ dysfunction. However, in our practice, there was consensus to target blood glucose levels below 180 mg/dL (10 mmol/L) but there was not consensus about the lower limit of the target range.

Rationale: While hyperglycemia has been associated with poor outcomes in numerous studies of critically ill children and adults, three prospective multicenter randomized clinical trials of glucose control to a low target range (including 50-80, 70-100, 72-126, 80-110 mg/dL or 2.8-4.4, 3.9-5.6, 4.0-7.0, 4.4-6.1 mmol/L) have not demonstrated clinical benefit in children (342-344) (**Supplemental Table 20**). One single-center RCT did show substantial mortality benefit, but there was a high rate of severe hypoglycemia and the higher target range cohort had substantially higher blood glucose levels than those used in the other multicenter RCTs (345). A trial involving children with burn

injuries, a unique PICU population, demonstrated no mortality benefit, but did find a significant reduction in morbidity (346). Notably, all trials included sepsis patients but none targeted them exclusively. Meta-analyses of all published prospective trials in children have shown no clinical benefits overall, but showed a substantially higher risk of hypoglycemia when using insulin therapy to maintain a glucose target below 140 mg/dL (7.8mmol/L) (347, 348). Even brief episodes of severe hypoglycemia during septic shock in children may be a risk factor for poor long-term developmental outcomes (349-352).

Treating hyperglycemia ≥180 mg/dL (≥10 mmol/L) may be desirable as incidence of insulin-induced hypoglycemia in the studied pediatric cohorts with targets of 140-180 mg/dL (7.8-10.0 mmol/L) is extremely low. There are, however, no direct comparisons between treatment to <180 mg/dL (10.0 mmol/L) and no treatment. Therefore, evidence cannot definitively guide this therapeutic target. However, given that the guidelines for adults recommend an upper limit of 180 mg/dL (10 mmol/L) and given the lack of harm demonstrated in the pediatric trials with those targets, treating children with septic shock or other sepsis-associated organ dysfunction with intravenous insulin with a goal upper blood glucose target of 180 mg/dL (10 mmol/L) is reasonable. The lower target, i.e., the glucose concentration below which insulin infusion should be discontinued, has also not been specifically studied, but is reasonable to set at 140-150 mg/dL (7.8-8.3 mmol/L), based on similar principles. In a survey of our panel members, 32.5% always or often and 17.5% sometimes target glucose levels between 140 and 180 mg/dL. Regardless of the glucose target, the overriding goal during insulin therapy should be avoidance of hypoglycemia.

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. However, in our practice, we often target normal calcium levels for children with septic shock requiring vasoactive infusion support.

Rationale: Calcium has an essential role in nearly all cellular processes, including myocardial contractility and vasomotor tone. As such, intracellular and circulating levels of calcium are tightly regulated. During septic shock, derangements in calcium regulation frequently occur in critically ill adults and children. However, a systematic review of adult literature found no evidence to support treating hypocalcemia of critical illness (353). Calcium supplementation may actually worsen organ dysfunction and is correlated with adverse outcomes in critically ill adult patients receiving PN (354). Although the prevalence of hypocalcemia in critically ill children has been reported to be up to 75% and is associated with organ dysfunction (355), no studies in children with septic shock have investigated the effect of calcium supplementation to treat hypocalcemia. However, in our practice, 65% of panel members always or often and 20% sometimes target normal calcium levels with parenteral calcium administration in children with septic shock requiring vasoactive infusion support. Only 15% of panel members rarely or never target normal calcium levels.

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).

Rationale: Critically ill children, similar to adults, develop low tri-iodothyronine (T3) and low normal thyroxine (T4) concentrations without the compensatory rise in thyroid stimulating hormone (TSH) that is typical of the "sick euthyroid" state or hypothyroxinemia of non-thyroidal illness (356). The decrease in T3 is due both to increased thyroid hormone turnover and to decreased de-iodination of T4 to T3, with redirection of T4 metabolism toward higher levels of biologically inactive reverse T3. The magnitude of the drop in T3 within the first 24 hours of illness reflects the severity of illness (357). Although of theoretical benefit, few trials of thyroid hormone replacement have been conducted in critically ill children and none in children with sepsis. Two prospective RCTs in children undergoing cardiac surgery (without sepsis) showed no difference in mortality, vasoactive days, or PICU LOS (358, 359). One open-label study in premature neonates also showed no difference in clinical outcomes (360). Taken together, there are no direct data to inform a recommendation for children with sepsis, and no indirect data from other critically ill children to support a recommendation for the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state.

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).

Rationale: Fever is a complex physiologic response associated with sepsis, and it remains unclear whether fever is a beneficial (361) or a harmful (362) response to infection. Potential benefits include inhibiting the growth of some pathogens and increased neutrophil production and lymphocyte proliferation. Conversely, fever is associated with an increased metabolic rate (which may or may not have detrimental effects in patients with sepsis) and may impair some components of immune function. Fever can also make patients uncomfortable (363). Thus, the putative benefits of maintaining normothermia by treating fever are unclear.

No direct evidence for or against the use of antipyretics in febrile children with sepsis-associated organ dysfunction exists. Rather, the panel had to consider indirect data extrapolated from studies in adults. One systematic review of adult patients studied the use of antipyretics and physical cooling methods included 8 RCTs (1507 patients) and 8 observational studies (17,432 patients) (364). This study had 28-day mortality as the primary outcome, with additional outcomes of early mortality (i.e., death on or prior to day 14), frequency of acquisition of hospital-acquired infection, frequency of shock reversal, and mean changes in body temperature, heart rate, and minute ventilation. No difference was noted in 28-day mortality. Effects on early mortality differed between the randomized (favored reduced mortality with antipyretic therapy) and observational (favored increased mortality with antipyretic therapy) studies. While antipyretic therapy successfully decreased body temperature, there was no effect on heart rate, minute ventilation, shock reversal, or acquisition of nosocomial infections. This study did not assess outcome measures of patient comfort. Based on available data, we are not able to recommend the optimal approach to fever in children with sepsis. However, it is

reasonable to provide antipyretic therapy to optimize patient comfort, to reduce metabolic demand under certain clinical scenarios (e.g., refractory shock, pulmonary hypertension), and to reduce extreme body temperatures.

J. NUTRITION

51. We were unable to issue a recommendation regarding early hypocaloric/trophic enteral feeding followed by slow increase to full enteral feeding versus early full enteral feeding in children with septic shock or sepsis-associated organ dysfunction without contraindications to enteral feeding. However, in our practice, there is a preference to commence early enteral nutrition within 48 hours of admission in children with septic shock or sepsis-associated organ dysfunction who have no contraindications to enteral nutrition and to increase enteral nutrition in a stepwise fashion until nutritional goals are met.

Rationale: No studies examine the enteral nutrition advancement strategy in children with septic shock or other sepsis-associated organ dysfunction. Indirect evidence from a small RCT in critically ill children examines early (6-24 hour) versus late enteral nutrition (>24 hour) in, respectively, 57 and 52 children (365). Early enteral feeding had no effect on duration of PICU stay, but a trend toward better survival in the early feeding group (30% in early feeding versus 48% in late feeding, p=0.07) was shown. There is also indirect evidence from the EDEN trial in adults (366) in which 200 patients were randomized to receive either trophic or full enteral feeding for the first 6 days. This study

demonstrated no difference in number of ventilator-free days, mortality at 60 days, or infectious complications, but trophic enteral feeding was associated with less gastrointestinal intolerance. Because neither of these studies was conclusive nor directly studied children with septic shock or other sepsis-associated organ dysfunction, no evidence-based recommendation could be made by the panel. However, in critically ill children, a stepwise approach to increasing enteral feeds has been shown to reduce time needed to reach nutritional goals (367-370). In our practice, 60% of panel members always or often and 20% sometimes commence early enteral feeding within 48 hours of admission in children with septic shock or sepsis-associated organ dysfunction who have no contraindications to enteral nutrition, while 20% of panel members rarely or never pursue this practice.

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.

Rationale: We reviewed indirect evidence from three observational studies (two retrospective and one prospective) in post-operative/cardiac pediatric populations. These studies reported that enteral feeding was tolerated in patients on non-escalating/weaning doses of vasoactive agents without increased adverse effects or gastrointestinal complications (371-373). In another study of 339 critically ill children,

there was no association between enteral feeding and the development of severe gastrointestinal outcomes such as vomiting, diarrhea, abdominal distension, bleeding, necrotizing enterocolitis, or perforation (371). However, in the report, the decision to start enteral nutrition may have been biased by the clinical condition of the patient. In a retrospective study of 52 critically ill children, the use of vasoactive medications was not associated with an increase in feeding intolerance or gastrointestinal complications (372). In a prospective observational study of critically ill children who received post-pyloric feeding, 44/65 (67.7%) of patients with shock and 284/461 (61.6%) of patients without shock received enteral nutrition within 48 hours. Although gastrointestinal complications were more common in children admitted with shock, no association between the incidence of digestive tract complications and early (first 48 hours) or late administration of post-pyloric enteral nutrition was reported (373). Based on these studies which, while providing indirect evidence, all consistently found that enteral feeding was not associated with harm, we recommend not to withhold enteral nutrition solely because vasoactive-inotropic medications are being used. Current evidence supports starting enteral nutrition in hemodynamically stable patients who are no longer requiring fluid resuscitation or escalating doses of vasoactive agents.

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

Rationale: No studies have been published on this specific issue of nutrition in children with septic shock or other sepsis-associated organ dysfunction. However, in a general cohort of 1440 critically ill children enrolled in the international multicenter RCT of pediatric early versus late PN in critical illness (374), withholding parenteral nutrition during the first week in PICU when enteral nutrition was less than 80% of prescribed goal was clinically superior to providing supplemental parental nutrition within 24 hours of admission (375). Secondary analyses of the PEPaNIC trial showed that withholding PN was also beneficial in term neonates and children who were undernourished at admission (376, 377), though withholding parenteral nutrition in term neonates was also associated with increased risk of severe hypoglycemia (376). A long-term follow-up 2 years after PICU admission showed that withholding parenteral nutrition for 1 week did not affect survival, anthropometrics, or health status, but did improve certain domains of neurocognitive development (378). Although the results of the PEPaNIC trial corroborated the findings from adult RCTs, the optimal timing of parenteral nutrition in the critically ill child with sepsis is still not clear (374, 379-381). Our recommendation is based on one trial and therefore, the evidence to withhold PN in the first 7 days of PICU admission is of moderate certainty and must be explored further using pragmatic timing for PN in the first week, particularly in severely malnourished patients and neonates.

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).

Rationale: In two RCTs evaluating immunomodulatory formulas, including lipid emulsions, in critically ill children, outcomes were not significantly different (382, 383). One RCT was terminated during interim analysis because of unlikely benefit in the intervention arm (383). In another small RCT, use of enteral feeding supplemented with or without omega-3 fatty acids in 120 critically ill children with sepsis was investigated (384). Univariate analyses showed a significant difference in inflammatory mediators and reduction in PICU LOS, but these outcome benefits were not evident in the multivariable analyses. Taken together, although promising, insufficient evidence is available to support routine supplementation in pediatric sepsis with specialized lipid emulsions.

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

Rationale: Although routine measurement of GRV is a relatively common practice in PICUs, there is no direct evidence in pediatric sepsis. In a two-center observational cohort study of critically ill children admitted with a variety of diagnoses, one center reported routine use of GRV monitoring while the other center did not practice GRV measurements (385). The center that advanced enteral nutrition without routine measurements of GRV did not have an increase in the incidence of vomiting, ventilator acquired pneumonia, or necrotizing enterocolitis in comparison with the other PICU (**Supplemental Table 21**). Although there are likely some children for whom measuring GRV would likely be useful (e.g., gastroparesis, omphalocele, gastroschisis), no

evidence supports routine measurements in all patients at this time and, if measured, GRV is not sufficient to diagnose EN intolerance.

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)

Rationale: In 3 small RCTs, gastric versus post-pyloric enteral feeding were compared in mechanically-ventilated children with a variety of diagnoses (386-388). The outcomes reported included lower caloric achievement with gastric feeding and delayed start of enteral feeding with post-pyloric feeding (386, 387). No significant difference was found in the incidence of ventilator-associated pneumonia between gastric and post-pyloric feeding (388). On the basis of these studies, there is no clear evidence that post-pyloric feeding is beneficial and there is concern for potential harm through delayed optimization of enteral nutrition. Therefore, we suggest that feeding with a gastric tube is physiologic and, based on current evidence, the preferred method for enteral nutrition. Post-pyloric feeding may be considered in patients in whom gastric feeding is either contraindicated (e.g., high-risk for aspiration) or was not tolerated/advanced, and as a result, nutritional goals were unable to be met.

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).

Rationale: Prokinetic agents, such as metoclopramide and erythromycin, are often used in the PICU in an effort to reduce feeding intolerance (389). Indirect evidence for this question was provided from the only pediatric randomized control trial, which was a combined intervention of enteral zinc, selenium, glutamine, and intravenous metoclopramide. In critically ill children, this combined intervention failed to reduce the development of sepsis or incidence of hospital-acquired infection in immunocompetent children, although the intervention including metoclopramide did reduce the rate of hospital-acquired infection and sepsis in immunocompromised children. However, the application of this study to children who already have sepsis is not clear. Prokinetic agents are also not without risk as they have been associated with prolongation of the QT interval and ventricular arrhythmias (390-392). Further investigation is needed to determine if prokinetic agents are beneficial in patients with sepsis, particularly in immunocompromised children.

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).

Rationale: Although clinical research examining the use of selenium among critically ill neonates and adults has been done (**Supplemental Table 22**), there no data regarding selenium supplementation as potential adjunctive therapy for pediatric sepsis. Selenium plays a key role as a cofactor for glutathione peroxidase, iodothyronine deiodinase, and

thioredoxin (393); accordingly, selenium deficiency could affect thyroid metabolism and the response to oxidative stress during critical illness. Moreover, low serum selenium concentrations are common in critical illness (394, 395) and infection (396), and have been associated with measures of oxidative stress in neonates (397) and adults (398).

A systematic review of investigations examining selenium supplementation in preterm neonates reported improved outcomes, including reduction in occurrence of sepsis (399). Similarly, a published systematic review and meta-analysis of the effect of parenteral selenium supplementation in critically ill adult sepsis patients concluded that this intervention reduced risk of mortality (400), but when the meta-analysis was updated to include the results of a more recent RCT, there was no difference in mortality in those treated with or without selenium supplementation (50). In an interventional trial examining the potential benefit of zinc, selenium, glutamine, and metoclopramide administration to critically ill children, there was no reduction in the primary outcome measure, namely, time until the first episode of nosocomial infection/sepsis (383). Based on lack of interventional trials examining selenium supplementation in the setting of pediatric sepsis and sepsis-associated organ dysfunction, we suggest against its use as a weak recommendation.

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).

Rationale: During catabolic stress, the human body is unable to produce adequate quantities of glutamine and, therefore, its essential role as a fuel source for enterocytes

and immune cells is diminished. Over the past two decades, several investigations of glutamine administration alone and in various combinations with other nutritional supplements have been conducted in critically ill populations (383, 401-407), including those with sepsis(402, 408-410). Contemporary studies have not found glutamine in any form (enteral or parenteral) and/or in combination with other nutritional elements to significantly improve morbidity or mortality in critically ill infants, children, and adults, including those with sepsis (411-413) (**Supplemental Table 23**). However, single element studies administering only glutamine to children with sepsis and septic shock are scarce. An RCT by Jordan et al (404) randomized children (49 control; 49 interventional) with sepsis and septic shock for the purpose of examining oxidative stress and inflammatory response. This investigation supports earlier studies in broader populations finding no differences in PICU (p=0.062) or hospital LOS (p= 0.09) or hospital mortality (p=0.31). Two other studies of glutamine administration in combination with other elements to children with septic shock and critical illness are available (383, 402). The RCT by Briassoulis et al (402) examined children with septic shock receiving glutamine in combination with arginine, antioxidants, and omega-3 fatty acids. Although the main outcome of change in cytokines showed some promise, no difference was noted between groups for hospital survival (80% versus 87%) or LOS (10.4 ±2.2 versus 11.4 ±2.5 days) (15). Carcillo et al (383) randomized 283 subjects from 8 PICUs to a control group receiving whey protein formula or an intervention group receiving formula with zinc, selenium, glutamine and IV metoclopramide supplementation. There was no difference between hospital-acquired infections and clinical sepsis per 100 days (p=0.81), PICU LOS (p= 0.16), or 28-day mortality (8/139 [5.8%] versus 15/145

[10.3%]). Subjects from this trial were also categorized by immune status with the suggestion that immune status may play a role in the effectiveness of nutritional supplemental, including glutamine (414). However, no direct evidence regarding glutamine supplementation in children with sepsis exists; hence, we suggest against the use of glutamine therapy in children with septic shock or other sepsis-associated organ dysfunction until further data become available.

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).

Rationale: Reduced availability of arginine in sepsis may lead to decreased endogenous nitric oxide synthesis, loss of microcirculatory regulation, and altered immune response (415-417). In the only pediatric RCT of arginine supplementation in children with sepsis (418), ten children received infusions of arginine and had enhanced arginine oxidation and increased nitric oxide levels, but no clinical outcomes were reported. In indirect data from adult studies, RCTs of L-arginine supplementation have been small and have reported both positive and negative effects on mortality (419-423). One trial in septic adults found decreased mortality(421), but other studies found no benefit or increased mortality in adults with sepsis(419, 422, 423). Some authors found improvement in secondary outcomes in patients with sepsis, such as reduced infectious complications and shorter LOS, but the relevance of these findings and their applicability to children with sepsis in the face of potential harm is unclear. Hence, in the absence of evidence of demonstrated benefit, we suggest against the use of arginine

therapy in children with sepsis-associated organ dysfunction until further data become available.

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).

Rationale: Alterations in zinc homeostasis and associations between zinc levels and outcomes have been reported in the critically ill. Benefits of zinc supplementation have been shown in some forms of infectious illnesses. However, no trials of zinc supplementation in children with sepsis have been conducted. One RCT in critically ill children comparing daily supplementation with zinc, selenium, glutamine, and metoclopramide versus whey protein was stopped during interim analysis due to futility (383). Based on conflicting studies in the adult literature, routine supplementation of zinc is not recommended in nutritional guidelines for critically ill adults (424). Future RCTs examining the optimal timing and dose of zinc in children with sepsis and septic shock and its impact on immune response and clinical outcomes might help answer this question.

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).

Rationale: Ascorbic acid (vitamin C) has multiple physiologic functions. Most importantly in the setting of sepsis, vitamin C is an antioxidant and neutralizes reactive

oxygen and nitrogen radicals, inhibits activation of pro-inflammatory cytokines, increases endogenous vasopressor synthesis, and inhibits bacterial replication (425-427). Adults with sepsis frequently have very low levels of vitamin C. In one study, 88% of adults with septic shock had hypovitaminosis C (428). Small studies in adults suggest that treatment of septic patients with vitamin C may improve organ dysfunction (429) and reduce mortality (430). Vitamin C has also been used as a component of combination therapy, typically with thiamine and corticosteroids, in adults with sepsis (431). One study compared such treatment in 47 adult patients with sepsis to historical control patients (432). Treatment was associated with decreased hospital mortality (OR 0.13, 95% CI 0.04, 0.48), shorter duration of vasopressor therapy, and improved organ dysfunction scores **(Supplemental Table 24).**

Currently, there are no data on the use of vitamin C in critically ill children or in pediatric sepsis. The prevalence of low vitamin C levels in septic children is unknown, and no studies have investigated the effect of vitamin C supplementation, either alone or in combination with other agents, in the treatment of pediatric sepsis.

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

Rationale: Thiamine is a crucial factor in cellular metabolism. In its active form, thiamine pyrophosphate (TPP) is an essential coenzyme used to generate energy (ATP) from glucose. The human body does not produce thiamine and, with a short half-life and small body stores, thiamine deficiency can develop within days of critical illness

and inadequate nutrition, resulting in impaired oxidative and carbohydrate metabolism. Low blood concentrations of thiamine have been reported on admission of critically ill children and adults with sepsis and septic shock (433-435). A study examining thiamine deficiency in children admitted to the PICU showed that low blood thiamine concentration in those with severe sepsis or septic shock was associated with mortality (OR 8.40, 95% CI 1.38, 51.0)(434). In an RCT of 88 adults with septic shock (**Supplemental Table 25**), there were no differences between treatment with thiamine versus placebo for the primary outcome of change in lactate levels or the secondary outcomes of mortality, shock reversal, and LOS (433). However, on *post hoc* analysis, thiamine treatment in the subgroup with thiamine deficiency on admission was associated with lower lactate level within 24 hours and lower mortality (p=0.047). However, more evidence is needed to recommend whether thiamine supplementation should be used to treat children with septic shock or other sepsis-associated organ dysfunction. Also, it may be important for this evidence to be considered in the context of thiamine status at PICU admission.

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

Rationale: A systematic review and meta-analysis of 17 studies including 2,783 patients showed that approximately half of critically ill children have VDD (25-hydroxy vitamin D [25(OH)D] level < 50 nmol/L or <20 ng/mL) at PICU admission (190). Further, VDD was associated with higher illness severity, multiple organ dysfunction, and mortality across these studies. Six of these studies focused on or separately analyzed

children with sepsis (436-440). Three studies reported a greater need for vasoactive agents in VDD children (436-438), although mortality across these six studies was not associated with VDD (436-440) **(Supplemental Table 26).**

Vitamin D levels are lowered by fluid resuscitation, which can confound the association with illness severity and disease complications (437). In addition, free or bioavailable 1,25$(OH)_2$D is the active form which is influenced by the level of vitamin D binding protein (VDBP) and a patient's VDBP genotype, which was not estimated or measured in prior studies (441). Although vitamin D levels are a potentially modifiable risk factor via supplementation, a meta-analysis of rapid normalization of vitamin D levels concluded that it is best achieved using loading therapy that takes into account disease status, determines baseline vitamin D level, and considers patient weight (442-444). A loading dose >300,000 IU should be avoided outside of RCTs evaluating risk and benefit.

Hypervitaminosis D is associated with hypercalcemia and other severe complications (445) and vitamin D overdoses can be fatal (446). No current data support that rapid acute correction of VDD is an effective treatment in septic shock or improves outcomes of septic children. Further, measurement of 25$(OH)_2$D levels is not currently a standard component of sepsis care and methods of accurately measuring bioavailable vitamin D are not yet widely validated. However, if VDD is diagnosed, repletion should occur as a usual part of general holistic pediatric care according to recommended guidelines independently of the presence of sepsis (447).

K. BLOOD PRODUCTS

65. We suggest against transfusion of red blood cells 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 (TAXI) guidelines, for the purposes of red blood cell transfusion, "hemodynamically stabilized" is defined as a mean arterial blood pressure higher than 2 standard deviations below normal for age and no increase in vasoactive medications for at least 2 hours.

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

Rationale: The only study evaluating specific red blood cell (RBC) transfusion thresholds in children with sepsis is a *post hoc* subgroup analysis of the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study (448) (**Supplemental Table 27**). This study included 137 stabilized critically ill children (MAP >2 standard deviations below normal for age and cardiovascular support not increased for at least 2 hours before enrollment) with sepsis, with a hemoglobin ≤ 9.5 g/dL within 7 days after PICU admission. Patients were randomized to receive RBCs if hemoglobin decreased to either <7.0 g/dL (restrictive group) or 9.5 g/dL (liberal group). No differences were found between the restrictive versus liberal group in the primary endpoint of new or progressive multiple organ dysfunction syndrome (18.8% versus 19.1%) or mortality (p=0.44). These results are similar to those from primary analysis of the TRIPICU study (449), as well as in adults (450). Our suggestion against transfusion

if hemoglobin is >7 g/dL in hemodynamically-stable children with sepsis parallels the TAXI recommendations (451).

Insufficient data are available to guide red blood cell transfusion therapy in children with unstable septic shock. Two pediatric RCTs did demonstrate decreased mortality when red blood transfusion to goal hemoglobin ≥10 (hematocrit >30%) was included as part of an early goal-directed therapy algorithm targeting $ScvO_2$, but the impact of each individual component, including red blood transfusion, is unclear (212, 452). In critically ill adults, the Transfusion Requirements in Septic Shock (TRISS) trial randomized 998 subjects with septic shock to either a transfusion threshold hemoglobin of 7 g/dL or 9 g/dL (453). At randomization, all patients had hypotension (mean arterial pressure <70 mmHg) and/or were being treated with vasopressors. Ninety-day mortality showed no differences (relative risk, 0.94; 95%CI 0.78-1.09), suggesting that a restrictive transfusion strategy in hemodynamically unstable septic adults was safe. **(Supplemental Table 27.)** The SSC recommends that RBC transfusion in adults occur only when hemoglobin concentration decreases to <7.0 g/dL in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence)(50). This adult recommendation is also valid for hemodynamically unstable patients.

However, in the absence of pediatric data, we are not able to provide a recommendation for critically ill children with unstable septic shock.

67. We suggest against prophylactic platelet transfusion based solely on platelet levels in non-bleeding children with septic shock or other sepsis-

associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence).

Rationale: One observational study demonstrated an association between the administration of platelet transfusions to critically ill children and worse clinical outcomes (**Supplemental Table 28**), including longer ICU LOS, progressive organ dysfunction, and increased mortality (454). Indirect evidence can be found in an RCT of 660 infants born at less than 34 weeks gestational age, the majority of whom were treated for sepsis, that compared a platelet transfusion threshold of 50,000 /mm^3 (high threshold) with 25,000 /mm^3 (low threshold)(455). More infants in the high- versus low-threshold group received at least one platelet transfusion (90% vs 53%). More adverse events, including new major bleeding or death, were also seen in the high threshold group (OR 1.57, 95% CI 1.06, 2.32).

Although existing evidence does not support a platelet threshold at which transfusion is absolutely indicated, the risk of spontaneous bleeding may be greater at lower platelet counts, e.g., <10-20,000 /mm^3. In addition, some populations of thrombocytopenic critically ill children may have a relatively high risk of bleeding, such as those with oncological diagnoses or those receiving ECMO. Because the threshold at which the benefits of platelet transfusion outweigh the risks is unknown, clinical judgment based on patient risk factors for bleeding in addition to the measured platelet level must be exercised carefully.

68. We suggest against prophylactic plasma transfusion in non-bleeding 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.

***Rationale*:** No direct data exist to inform a recommendation about plasma transfusion in pediatric sepsis. One RCT evaluates prophylactic plasma transfusion in critically ill children without sepsis. Pieters et al randomized 81 children <2 years of age requiring primary repair of craniosynostosis to receive plasma using either a prophylactic (in absence of bleeding) or reactive (when the patient was bleeding) strategy (456). The prophylactic plasma transfusion group received a significantly higher volume of plasma compared to the reactive group (29.7 mL/kg versus 16.1 mL/kg, $p < 0.001$). Despite an improvement in coagulation values in the prophylactic group, there was no difference in PRBC transfusion requirements or blood loss between the two groups. **(Supplemental Table 29)** Additionally, a meta-analysis published in 2012 that included 80 RCTs (mostly in adults) concluded that there was no consistent evidence for benefit of prophylactic plasma transfusion across a range of indications that were evaluated (457). Observational studies in critically ill children have shown that plasma transfusions are associated with worse clinical outcomes (458, 459). Furthermore, plasma transfusion frequently fails to correct abnormal coagulation tests in critically ill adults and children (459, 460). We therefore suggest against prophylactic plasma transfusions for children with septic shock and other sepsis-associated organ dysfunction who are not bleeding.

However, some specific patient populations might benefit from prophylactic plasma transfusions, such as patients with worsening coagulation tests at high risk for

disseminated intravascular coagulopathy (DIC), children with comorbid cancer, or children with sepsis on extracorporeal life support (ECLS).

L. 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 thrombocytopenia-associated multiple organ failure (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.**

Rationale: Therapeutic plasma exchange (PLEX) for septic shock or sepsis-associated organ dysfunction aims to normalize the plasma milieu of a systemically inflamed septic patient. Currently, no large RCTs have evaluated PLEX in pediatric septic shock or sepsis-associated organ dysfunction. Rimmer et al. performed a meta-analysis that included 4 small RCTs evaluating PLEX in adults (n=128) and pediatric (n=66) patients with sepsis and septic shock. PLEX was associated with reduced mortality in adults (RR 0.63, 95% CI 0.42, 0.96), but not in children (RR 0.96, 95% CI 0.28, 3.38) (461). However, because of the heterogeneity of the patient population, inclusion criteria, technical modalities of PLEX (filtration versus centrifugation), and types of replacement fluid (plasma versus albumin) in these 4 studies as well as the costs and potential risks, it PLEX cannot be routinely recommended as this time **(Supplemental Table 30)**.

Similarly, the American Society for Apheresis recommended that the "optimum role of apheresis therapy is not established" in sepsis with multi-organ failure (462).

TAMOF is an inflammatory phenotype of sepsis-induced multiple organ dysfunction in children that can be identified clinically by new-onset thrombocytopenia and evolving multiple organ dysfunction (463, 464). Autopsies performed on patients who died with TAMOF revealed disseminated microvascular thromboses in various organs (463). These patients had deficient activity of a disintegrin and metalloproteinase with thrombospondin type 1 motif (ADAMTS-13), elevated von Willebrand factor (VWF) activity, and the presence of ultra-large plasma VWF (463, 465). Decreased activity of ADAMTS-13 leads to high circulating levels of ultra-large VWF that induce widespread platelet activation and thrombotic microangiopathy. A number of inflammatory mediators are elevated in sepsis that can inhibit or inactivate ADAMTS-13 including interleukin (IL)-6, granulocyte elastase, plasmin, thrombin, plasma free hemoglobin, shigatoxins, and immunoglobulin G auto-antibody (466-471).

Three studies have examined the utility of PLEX in children with sepsis and TAMOF (463, 472, 473). In the most recent and largest study (n=81), Fortenberry et al. reported that PLEX was associated with lower 28-day mortality by multivariate analysis (aRR 0.45, 95% CI 0.23, 0.90) and by propensity score weighting (aRR, 0.46, 95% CI 0.22, 0.97) (472). In a retrospective cohort study from the Turkish TAMOF Network (n=42), PLEX was associated with lower 28-day mortality compared to the no PLEX group (27% versus 70%; p=0.004) (473)). In the third study, Nguyen et al randomized 10 children to either PLEX or standard therapy (463). The 5 patients who received PLEX had restoration of ADAMTS-13 activity and greater survival (5/5) compared to

standard therapy (1/5, p<0.05). Taken together, these data support a biologic rationale for the use of PLEX in TAMOF, i.e., the removal of pathologic ultra-large VWF and ADAMTS-13 inhibitors and restoration of ADAMTS-13 activity. This approach of using PLEX is similar to the rationale for using PLEX in thrombotic thrombocytopenic purpura (474). While the panel acknowledges a potential benefit for PLEX and encourages an RCT to better define the utility of PLEX in children with sepsis and TAMOF, a recommendation could not be made based on existing data.

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).**

Rationale: Renal replacement therapy is increasingly being used in PICUs for renal and non-renal conditions. The rationale for renal replacement therapy in septic shock includes impending or established fluid overload following initial resuscitation or for cytokine removal, reversal of coagulopathy, to buffer lactic acidosis, to address AKI, or a combination of these factors. Continuous renal replacement therapy (CRRT) may be useful for treating established fluid overload or to prevent further fluid overload while allowing liberal volume administration for nutrition, antimicrobials, and other medications, sedation, and transfusions. In addition, certain techniques of continuous blood purification may help to regulate systemic inflammation and promote kidney recovery (475). Fluid overload has been shown to cause increased morbidity and mortality in various intensive care settings and there is documented favorable association of CRRT in fluid overload (476).

However, no high-quality studies in critically ill children with sepsis exist to directly determine whether RRT is definitively beneficial compared to diuretics and/or fluid restriction. Most of the data come from adult studies where outcomes have varied from mortality to ICU length of stay and ventilator- and vasoactive-free days. One study addressed the timing of CRRT initiation in 27 children with sepsis and multiple organ dysfunction, demonstrating that CRRT was associated with survival when started within 48 hours of admission compared to those started on CRRT after 48 hours of admission (61% versus 33%, p<0.001). However, timing of CRRT initiation was at the discretion of the treating team, raising concern for confounding between groups, and all patients in both groups experienced normalization of kidney function (477) **(Supplemental Table 31).**

The possible benefits of CRRT must also be weighed against potential risks, including the need for an invasive catheter, costs, limited availability in some centers, the need for clinician and nursing-specialist expertise, and the challenge of optimal timing (e.g., following resuscitation for fluid removal or earlier for acute cytokine clearance). Therefore, as the initial treatment strategy, we judge that fluid restriction and use of diuretics are reasonable in the presence of impending or established fluid overload with CRRT reserved as a second-line option 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.

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).

Rationale: High-volume hemofiltration (HVHF) for critically ill patients with septic shock and AKI is an appealing strategy for maintaining acid–base and fluid homeostasis, or for having a potential immunomodulatory effect in sepsis by removal of toxins and other inflammatory mediators, especially cytokines that contribute to organ injury and dysfunction.

In adults, use of higher CRRT flux rates (>35 mL/kg/hr filtration-dialysis), while initially encouraging, has not shown overall mortality benefit in subsequent RCTs and meta-analysis. A 2017 Cochrane review found no significant benefit in mortality, severity of organ dysfunction, LOS, or adverse effects with HVHF versus standard hemofiltration rates in critically ill adults (478). Notably, the results of this meta-analysis show that very few studies have been conducted to investigate the use of HVHF in critically ill patients with septic shock (four studies totaling 201 participants).

In a study involving 155 pediatric patients with severe sepsis, HVHF treatment did not significantly reduce 28-day mortality compared to standard volume CRRT. Moreover, there were no significant reductions in plasma levels of inflammatory mediators or in improving hemodynamic variables for HVHF. However, the incidence of hyperglycemia was significantly higher in HVHF group than in CVVH group (479) (**Supplemental Table 32**).

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

Rationale: ECMO was introduced more than 40 years ago to support patients with reversible but severe cardiovascular and/or respiratory failure refractory to conventional medical therapy. As such, children with life-threatening sepsis-induced ARDS are often considered as candidates for ECMO rescue (480), and PALICC endorsed ECMO for the treatment of refractory hypoxia (24). The use of ECMO in pediatric sepsis has increased over the past decade (481, 482); whether this has improved survival remains to be determined (483). To date, no RCT examining the effect of ECMO on outcome in pediatric sepsis has been published. In the absence of such data, using propensity score matching, Barbaro et al (484) reported that children with severe PARDS enrolled in the RESTORE trial had similar mortality rates when supported with ECMO (15/61, 25%) as compared with those who were not (18/61, 30%)(485) **(Supplemental Table 33).** Research is underway to determine optimal pre-ECMO candidacy (486) as measures of renal, hepatic, neurologic, and hematologic dysfunction, and particularly the presence of blood stream infections, seem to discriminate mortality risk better than traditional pediatric severity of illness scores such as Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM), and Pediatric Logistic Organ Dysfunction (PELOD). Clearly, ECMO is not available worldwide, and transfer of highly unstable patients to higher levels of care that offer the therapy can carry substantial risk. However, adult and pediatric data suggest a potential association with improved mortality, particularly if transfer is to high volume ECMO centers (487, 488).

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

Rationale: Several anecdotal reports of use of VA ECMO in the management of refractory septic shock in children exist. (The role of veno-venous [VV] ECMO for oxygenation/ventilation failure is addressed in the Ventilation section.) More recent reports suggest that VA ECMO may be associated with better survival than conventional therapy, and strategies to maximize flow rates to reverse shock and multiple organ dysfunction may play an important role (489, 490). However, considerable concern surrounds the risks of this highly invasive therapy, such as hemorrhage and thromboembolic events.

The most recent and largest report of VA-ECMO in 44 pediatric patients with refractory septic shock secondary to bacterial, viral, or fungal infection admitted to 7 tertiary PICUs across 5 different countries compared their outcome to 120 children with refractory septic shock managed by conventional therapy (491). Inclusion in the study required children to meet 3 of 4 criteria for severe septic shock in the first 24 hours of their ICU stay: arterial pH ≤7.15, arterial lactate ≥4.0 mmol/L, base excess ≤ -10 mmol/L, and in-hospital cardiac arrest. Patients were excluded if they had cyanotic congenital heart disease, myocarditis, or an out-of-hospital cardiac arrest. The results showed no significant difference in survival to hospital discharge (50% in the VA ECMO cohort versus 40% in the conventional therapy cohort). Survival was significantly higher in patients who received high ECMO flows (>150 mL/kg/min at 4 hours after institution

of ECMO) compared with children who received standard ECMO flows or no ECMO (**Supplemental Table 34.)**

The potential use of VA ECMO for refractory septic shock suggests that the definition of refractory septic shock (RSS) should be standardized across institutions. As yet, no universal definition of refractory septic shock in children exists. One published definition that could be applied is from the European Society of Paediatric and Neonatal Intensive Care (492). The suggested definition for RSS was blood lactate >8 mmol/L or a 1 mmol/L lactate increase after 6 hours of resuscitation and high vasoactive dependency (vasopressor-inotrope score >200), or myocardial dysfunction defined as the occurrence of a resuscitation-responsive cardiac arrest in PICU or cardiac ultrasound findings with left ventricle ejection fraction <25% or a cardiac index <2.2 L/min/m^2.

M. IMMUNOGLOBULINS

75. We suggest against the routine use of intravenous immune globulin (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.

Rationale: The proposed rationale for IVIG in severe infections is to boost passive immunity through neutralization of bacterial toxins, promoting opsonization of bacteria, and inhibition of immune cell proliferation and inflammatory mediators. However, IVIG has considerable batch-to-batch variability and its true biologic activity is not clear.

There are no high-quality studies of IVIG in critically ill children with sepsis, and small observational studies have reported conflicting results (493). An RCT of polyclonal IVIG in 100 children with sepsis demonstrated a reduction in mortality (28% versus 44%), LOS (6 versus 9 days), and less progression to complications (8% versus 32%)(494). However, a more recent multicenter trial of polyclonal IVIG in 3,493 neonates with suspected or proven serious infection found no significant differences in mortality or major disability (495). Other studies have been carried out with specific monoclonal antibodies (e.g., monoclonal antibody against endotoxin in children with meningococcal septic shock), but there are no definitive data to support general benefit of polyclonal immunoglobulin in neonates or children with septic shock at this time. Data from adult patients with septic shock also do not support a routine benefit of IVIG (496), though administration of IgM- and IgA-enriched polyclonal IVIG has shown possible efficacy (497). **(Supplemental Table 35.)**

For patients with toxic shock syndrome, especially those with streptococcal etiology, polyclonal IVIG may have clinical utility (498). Other potential pediatric populations that may benefit from IVIG in sepsis are those with necrotizing fasciitis (though evidence in adults does not support use (499, 500)), and those with primary humoral immunodeficiencies or immunocompromised with documented low immunoglobulin levels.

N. 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%.

Rationale: Stress ulcer prophylaxis should not be routinely administered to children with septic shock or other sepsis-associated organ dysfunction, as evidence for benefit is lacking (501) and may increase risk of adverse effects, such as pneumonia or *Clostridioides difficile* (formerly *Clostridium)* infection (502). Rather than routine, universal administration of stress-ulcer prophylaxis, individual patients should be assessed for the presence of risk factors of clinically important gastrointestinal bleeding. These include multiple organ dysfunction(503), prolonged mechanical ventilation (>48 hours), coagulopathy, persistent shock, and treatment with corticosteroids and non-steroidal anti-inflammatory agents(504).

The risk of GI bleeding is also reduced by mucosal protection introduced by gastric feeding. Early enteral nutrition could therefore be a viable alternative to pharmacological stress-ulcer prophylaxis. A meta-analysis of 1836 adult patients reported that, in the presence of enteral nutrition, pharmacological stress ulcer prophylaxis did not significantly change the risk of GI bleeding. Notably, in those patients who received enteral nutrition and were treated with stress ulcer prophylaxis, the risk of pneumonia was increased compared to patients on parenteral nutrition (OR 2.81, 95% CI 1.2, 6.6)(505) **(Supplemental Table 36).**

77. We suggest against routine deep vein thrombosis (DVT) 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).

Rationale: An open-label RCT of low molecular weight heparin to prevent CVC-associated thrombosis in the PICU was terminated early because of poor recruitment (506). Eleven (14.1%) of 78 patients randomized to reviparin had DVT proven on venogram versus 10 (12.5%) of 80 controls (OR 1.15, 95% CI 0.42, 3.23). Three adverse events (major bleed or death) all occurred in the control group and no deaths occurred because of venous thromboembolism (**Supplemental Table 37**). A subsequent systematic review found the quality of evidence to be low and that the efficacy of low molecular weight heparin in preventing CVC-associated thrombosis is unknown (507). It is important to highlight that these studies were specific to children with CVCs who may or may not have had sepsis and that they may not apply to the general thromboembolic risk in children with sepsis.

While CVCs represent the principal risk factor for DVT in infants (508), older children may have other risk factors. For example, the risk of DVT increases in adolescence, obesity, cancer, and in those with multiple medical conditions, especially renal and cardiac disease (509, 510). At present, it is unknown whether certain high-risk populations of children with sepsis may benefit from DVT prophylaxis.

KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES

This report from the SSC pediatric guidelines panel covers 5 main topic areas (i.e., early recognition and infection, hemodynamics, ventilation, endocrine and metabolic therapies, and adjunctive therapies) with a total of 76 recommendations arising from 67 PICO questions. On review of these evidence-based analyses, it is clear that, for many PICO questions, the literature review failed to identify sufficient data to develop strong (or even weak in some instances) recommendations for critically ill children with septic shock or other sepsis-associated organ dysfunction. These SSC pediatric guidelines, at the same time, also identified gaps that can inform future research opportunities. As new research populates the evidence-base, it can then be used to develop future iterations of the SSC pediatric guidelines, creating a cycle designed to grow the evidence and increase the number of strong recommendations in the future. Further clarity is needed from both informative pathophysiology studies as well as well-designed RCTs, and the panelists have listed these in the text. The design of meaningful and effective future research should be informed by the needs identified by the collective clinical expertise within the panel.

Overall, the process of developing the SSC-pediatric guidelines generated at least 29 pathophysiology questions warranting further study and 23 RCTs (i.e., total of 52 studies). We presented these questions as research opportunities, but have not yet prioritized these opportunities into a formal research agenda (**Table 6**). We envision that many of the pathophysiology questions can be taken up by individual research groups and we hope that the SSC children's guidelines document will serve as a template of current evidence and how best to fill the gaps in our knowledge. In contrast, the necessary RCTs will need a coordinated national/international effort and our community

will need to prioritize the most appropriate studies at different phases of management (i.e., recognition, fluid resuscitation, first 48 hours, etc.).

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Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children

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The following sponsoring organizations with formal liaison appointees endorse this guideline:

American Academy of Pediatrics; Australia and New Zealand Intensive Care Society, Canadian Critical Care Society; European Society of Intensive Care Medicine; European Society of Paediatric and Neonatal Intensive Care; Pediatric Infectious Disease Society; Scandinavian Society of Anaesthesiology and Intensive Care Medicine; Society of Critical Care Medicine; UK Sepsis Trust; World Federation of Pediatric Intensive and Critical Care Societies

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ABSTRACT

Objective: To develop evidence-based recommendations for clinicians caring for children (including infants, school-aged children, and adolescents) with septic shock and other sepsis-associated organ dysfunction.

Design: A panel of 49 international experts, representing 12 international organizations, as well as 3 methodologists and 3 public members was convened. Panel members assembled at key international meetings (for those panel members attending the conference), and a stand-alone meeting was held for all panel members in November 2018. A formal conflict-of-interest (COI) policy was developed at the onset of the process and enforced throughout. Teleconferences and electronic-based discussion among the chairs, co-chairs, methodologists, and group heads, as well as within subgroups, served as an integral part of the guideline development process.

Methods: The panel consisted of 6 subgroups: recognition and management of infection, hemodynamics and resuscitation, ventilation, endocrine and metabolic therapies, adjunctive therapies, and research priorities. We conducted a systematic review for each Population, Intervention, Control, and Outcomes (PICO) question to identify the best available evidence, statistically summarized the evidence, and then assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We used the evidence-to-decision framework to formulate recommendations as strong or weak, or as a best practice statement. In addition, “in our practice” statements were included when evidence was inconclusive to issue a recommendation, but the panel felt that some guidance based on practice patterns may be appropriate.

Results: The panel provided 776 statements on the management and resuscitation of children with septic shock and other sepsis-associated organ dysfunction. Overall, 65 were strong recommendations, 49 were weak recommendations, and 9 were best-practice statements. For 13 questions, no recommendations could be made; but, for 10 of these, “in our practice” statements were provided. In addition, 49 research priorities were identified.

Conclusions: A large cohort of international experts was able to achieve consensus regarding many recommendations for the best care of children with sepsis, acknowledging that most aspects of care had relatively low quality of evidence resulting in the frequent issuance of weak recommendations. Despite this challenge, these recommendations regarding the management of children with septic shock and other sepsis-associated organ dysfunction provide a foundation for consistent care to improve outcomes and inform future research.

Key Words: evidence-based medicine; Grading of Recommendations Assessment, Development, and Evaluation criteria; guidelines; infection; pediatrics; sepsis; septic shock; Surviving Sepsis Campaign.

INTRODUCTION

Sepsis is a leading cause of morbidity, mortality, and health care utilization for children worldwide. Globally, an estimated 22 cases of childhood sepsis per 100,000 person-years and 2,202 cases of neonatal sepsis per 100,000 live births occur, translating into 1.2 million cases of childhood ~~and 3 million cases of neonatal~~ sepsis per year (1). More than 4% of all hospitalized patients <18 years and ~8% of patients admitted to pediatric intensive care units (PICUs) in high-income countries have sepsis (2-6). Mortality for children with sepsis ranges from 4% to as high as 50%, depending on illness severity, risk factors, and geographic location (2, 3, 7-9). The majority of children who die from sepsis suffer from refractory shock and/or multiple organ dysfunction syndrome, with many deaths occurring within the initial 48 to 72 hours of treatment (10-13). Early identification and appropriate resuscitation and management are therefore critical to optimizing outcomes for children with sepsis.

In 2001, the Surviving Sepsis Campaign (SSC) was formed by the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum. A primary aim of the SSC was to develop evidenced-based guidelines and recommendations for the resuscitation and management of patients with sepsis. The initial guidelines were published in 2004 and have been reviewed and updated every four years thereafter. Following the 2016 ~~iteration~~edition, SCCM and ESICM reaffirmed their commitment to evidence-based guidelines for all patients by forming separate task forces dedicated to guidelines for adults and children.

The objective of the SCCM/ESICM *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-~~Associated~~ associated Organ Dysfunction in Children* is to provide guidance for clinicians caring for children (including infants, school-aged children, and adolescents) with septic shock and other sepsis-associated organ dysfunction. We sought to leverage the expertise of a clinical and methodology team to create comprehensive evidence-based recommendations for the recognition and management of children with septic shock or other sepsis-associated acute organ dysfunction. Recommendations from these guidelines are based on the best current evidence but cannot replace the clinician's decision-making capability when presented with a patient's unique set of clinical variables. Recommendations are intended to guide "best practice" rather than to establish a treatment algorithm or to define standard of care. These guidelines are appropriate for treating septic shock and other sepsis-associated organ dysfunction in a hospital, emergency, or acute care setting, though some may be applicable elsewhere. Although recommendations were developed without consideration to availability of resources, we acknowledge that variation within and across health care systems and geographic regions will determine the practical application of these guidelines.

Although several recommendations for the care of children with sepsis and septic shock have been previously published (14-16), these new guidelines are not intended to update or iterate on these prior documents. Instead, it was the aim of SCCM/ESICM *Surviving Sepsis Campaign* to provide an evidence-based approach to the management of septic shock and other sepsis-associated organ dysfunction in children using a

comprehensive and transparent methodologic approach by a panel with geographic and professional diversity.

METHODOLOGY

Definitions ~~and Scope~~

In 2005, the International Pediatric Sepsis Consensus Conference published definitions and criteria for sepsis, severe sepsis, and septic shock in children based on prevailing views of adult sepsis at the time with modifications for physiology based on age and maturational considerations (17). ~~Of note, by these criteria, septic shock in children is defined as cardiovascular dysfunction (i.e., abnormal perfusion) with or without hypotension.~~ In 2016, new adult definitions and criteria were published (Sepsis-3) with *sepsis* defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and *septic shock* the subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (18). The term "severe sepsis" was replaced by this new definition of sepsis. Although application of Sepsis-3 to children has been attempted (19, 20), formal revisions to the 2005 pediatric sepsis definitions remain pending (21). Therefore, the majority of studies used to establish evidence for these guidelines ~~in the literature was expected to~~ refer~~red~~ to the 2005 nomenclature in which severe sepsis ~~in children~~ was defined as a) ≥2 age-based systemic inflammatory response syndrome (SIRS) criteria, b) confirmed or suspected invasive infection, and c) cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or ≥2 non-cardiovascular organ system dysfunctions~~.~~; and ~~. S~~septic shock ~~in children~~ was defined as the subset with cardiovascular dysfunction, which

included hypotension, treatment with a vasoactive medication, or impaired perfusion. However, studies that defined sepsis as severe infection leading to life-threatening organ dysfunction were included even if criteria used to define sepsis deviated from the 2005 consensus definitions.

For the purposes of these guidelines, we define *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 non-cardiovascular organ dysfunction. Because several methods to identify acute organ dysfunction in children are currently available (17, 19, 20, 22, 23), we chose not to require a specific definition or scheme for this purpose.

Scope of Patients

~~Given that the definition of sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" is generally applicable to children and in anticipation of an update to pediatric sepsis definitions, t~~The panel ~~identified the scope of these~~ intended these guidelines to ~~include~~ apply to all patients from ≥37 ~~weeks~~weeks gestation at birth to 18 years-of-age with severe sepsis or septic shock as defined by the 2005 International Pediatric Sepsis Consensus Conference or inclusive of severe infection leading to life-threatening organ dysfunction. Practically, all infants, children, and adolescents with septic shock or other sepsis-associated acute organ dysfunction are included in this scope. For simplicity, we will henceforth use the term "children" to refer to infants, school-aged children, and adolescents in these guidelines.

~~Thus, a~~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 SIRS *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. ~~Because several methods to identify acute organ dysfunction in children are currently available, (17, 19, 20, 22, 23) we chose not to require a specific definition or scheme for this purpose.~~ Finally, acknowledging that neonatal sepsis, especially in premature babies, may have distinct pathology, biology, and therapeutic considerations, ~~studies that focused exclusively on~~ newborns <37 weeks gestation ~~were~~are excluded from the scope of these guidelines. The panel sought to include term neonates (0-28 days) born at ≥37 weeks gestation within the scope of these guidelines because these infants may be recognized and resuscitated outside of a newborn nursery or neonatal intensive care unit. However, because the panel did not specifically address studies of neonates with perinatal infection or 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 target users of these guidelines are health professionals caring for children with septic shock or other sepsis-associated organ dysfunction in a hospital,

emergency, or other acute care setting. However, we acknowledge that many of the recommendations are likely to apply to the care of children with septic shock and other sepsis-associated organ dysfunction across a broad array of settings with adaptation to specific environments and resource availability.

~~In addition, t~~These guidelines were largely ~~considered~~ developed without consideration of health care resources (with some specific exceptions, e.g., fluid resuscitation), though we realize that medical care for children with septic shock and other sepsis-associated organ dysfunction 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 to treatment algorithms or bundles and standards of care will need to account for variation in the availability of local health care resources. The panel acknowledges as well the need for future research to test the adaptation of interventions to locally available resources.

Funding and Sponsorship

All funding for the development of these guidelines was provided by SCCM and ESICM. In addition, sponsoring organizations provided support for their members' involvement.

Selection and Organization of Panel Members

The selection of panel members was based on their expertise in specific aspects of pediatric sepsis. Co-chairs and co-vice chairs were appointed by the SCCM and ESICM governing bodies; panel members were then recommended by the co-chairs

and co-vice chairs. Each panel member was required to be a practicing healthcare professional with a focus on the acute and/or emergent care of critically ill children with septic shock or other sepsis-associated acute organ dysfunction. Broad international and multi-professional representation from critical and intensive care medicine, emergency medicine, anesthesiology, neonatology, and infectious disease with inclusion of physicians, nurses, pharmacists, and advanced practice providers as part of the working group was ensured. Three members from the lay public were also included with a role to ensure that patient, family, and caregivers' opinions were considered in prioritizing outcomes and finalizing recommendations that the clinicians proposed during the development process. Panelists were recruited from a wide number of countries and health care systems, including representation from resource-limited geographic areas. A demographically diverse panel with regard to sex, race, and geography was assembled. Members were then allocated to specific groups based on their expertise.

The methodology team included trained methodologists from McMaster University in Canada (WA, KC) and New York University in the United States (MN). The team included methodologists with a health research methodology degree (MSc or PhD) and/or advanced methodology training, all of whom are also practicing intensivists. The methodology team provided methodological guidance and leadership throughout the guideline development process.

Question Development and Outcome Prioritization

The panel was divided into groups: 1) recognition and management of infection, 2) hemodynamics and resuscitation, 3) ventilation, 4) endocrine and metabolic

therapies, and 5) adjunctive therapies. A sixth subgroup was added to review research priorities in pediatric sepsis.

The co-chairs, co-vice chairs, and group heads made initial selections of the topics. We included topics addressed in the 2016 SSC adult guidelines that were relevant to children, as well as other key pediatric topics discussed in previously published guidelines (14-16). The PICO format, which describes the population (P), intervention (I), control (C), and outcomes (O), was used for all guideline questions. Group heads, panel members, and methodologists reviewed and selected PICO questions considered important to guide care for children with septic shock or other sepsis-associated organ dysfunction. Panel members proposed additional PICO questions of high priority and clinical relevance. 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 [PALICC]) (24). 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 decision regarding PICO question inclusion was reached by discussion and consensus among the guideline panel leaders with input from panel members and the methodology team in each group.

In adherence with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, panel members compiled a list of potential outcomes for each PICO question. Subsequently, we electronically surveyed panel

members and asked them to rate each outcome on a scale of 1 (not important) to 9 (critically important). We selected only outcomes that were critical (mean of 7 or more) for decision making, taking a patient's perspective. In addition, we presented all selected outcomes to public members to ask for their input and feedback. The final list of PICO questions is provided in **Supplemental Table 1**.

Search Strategy and Evidence Summation

For each PICO question, a professional medical librarian formulated the search strategy with input from the group heads, panel members, and methodologists. Searches utilized a combination of controlled vocabulary (e.g., "sepsis," "bacterial infections," "critical illness," "intensive care units," "pediatrics," "NICU," "PICU," "emergency service") and key words (e.g., "toxic shock," "blood poisoning," "acute infection," ~~"PICU,"~~ "child") in the core search. Additional controlled vocabulary and key words were incorporated to create separate strategies specific to the question posed. Research design filters (e.g., systematic reviews/meta-analyses, randomized controlled trials, observational studies) were also applied as appropriate. Only English language studies were included. No date restrictions were imposed on the searches, but we removed animal-only and opinion pieces from the results. The medical librarian searched a minimum of two major databases (e.g., Cochrane Library, PubMed/MEDLINE, or Embase) to identify relevant systematic reviews, clinical trials, and observational studies published through May 1, 2017. As this was the inaugural version of these guidelines for children, all publications up through May 1, 2017 were considered. Key studies published after the conclusion of the initial literature search on

May 1, 2017 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. We excluded articles published in abstract form, in a language other than English, and those focused solely on pre-clinical data. ~~After finalizing the searches for each PICO question, panel members screened the titles and abstracts, reviewed full text of potentially relevant articles, and abstracted relevant data using a standardized form.~~ Panel members, with input from methodologists, used the Cochrane risk of bias tool to assess the risk of bias of randomized trials (25) and Newcastle-Ottawa Scale to assess risk of bias of non-randomized studies (26).

When applicable, the methodologists used meta-analytic techniques to generate pooled estimates across two or more studies. For meta-analysis of randomized clinical trials (RCTs), we used random-effects model and inverse variance method to pool estimates across relevant studies. We reported relative risks (RR) and 95% confidence interval (CI) for binary outcomes, and mean difference (MD) and 95% CI for continuous outcomes. For observational data, we conducted meta-analyses if all individual studies provided adjusted estimates and included both an intervention and a control arm using a random-effects model and inverse variance method to pool adjusted odds ratio (OR) across relevant studies All analyses were conducted using RevMan software (Review Manager, version 5.3, Copenhagen).

Formulation of Recommendations

The GRADE approach 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) ~~other criteria, followed by~~ assessment of the balance between benefit and harm, patients' values and preferences, cost and resources, and feasibility and acceptability of the intervention (27). Methodologists performed initial assessments of quality of evidence and incorporated feedback from panel members to generate final evidence profiles using GRADEpro GDT (28).

The panel initially considered only research focused on pediatric patients using ~~the following~~a hierarchy of evidence~~: systematic reviews of randomized trials, individual RCTs, systematic reviews of observational studies, and prospective observational studies~~ **(Table 1).** ~~Evidence from RCTs started as high-quality but could be downgraded due to concerns within the above-6 GRADE criteria. Evidence from observational studies began as low-quality that could be upgraded on the basis of a large magnitude of effect or other factors. If none of these study designs were available, the panel considered retrospective observational studies, case-control studies, and large case series.~~ Studies focusing on children with septic shock and other sepsis-associated organ dysfunction were prioritized, though 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 no studies or insufficient data in children with sepsis or general pediatric illness, evidence ~~of~~ from studies of adult patients was considered using an *a priori* framework to determine appropriateness of indirect evidence (**Figure 1**). ~~For PICO questions in which adult data were deemed appropriate to consider, the same hierarchy of evidence was applied, though the quality of e~~Evidence from adult

studies was generally down-graded due to the indirectness of the evidence. ~~To streamline this process across the groups, we developed and used a framework to help guide whether indirect evidence was appropriate to use (**Figure 1**).~~

In a series of webinars, methodologists reviewed the relevant data for each PICO question with panel members to formulate initial recommendations. Each of the groups used the Evidence-to-Decision (EtD) framework to facilitate transition from evidence to the final recommendation. 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 (28).

We classified recommendations as strong or weak using the language "We recommend…" or "We suggest…," respectively. ~~We used the strength of a recommendation to reflect our confidence about whether the desirable consequences of the adherence to the intervention would outweigh the undesirable consequences. Thus, w~~We judged a strong recommendation in favor of an intervention to have desirable effects of adherence that will clearly outweigh the undesirable effects. 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. The implications of calling a recommendation strong or weak are shown in **Table 2**. ~~are that most patients would accept that intervention and that most clinicians should use it in most situations (**Table 2**). However, a~~A strong recommendation does not necessarily 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 ~~We permitted strong recommendations based on low or very low quality of evidence for life-threatening scenarios or when there was uncertain benefit but very likely or certain harm~~ (29).

Best practice statements (BPS) were developed as ungraded strong recommendations within strict conditions suggested by the GRADE Working Group (**Table 3**) (30). BPS were issued when the evidence could not be summarized or assessed using GRADE methodology but the benefit or harm was deemed unequivocal. In addition, when ~~the~~ evidence ~~was lacking or~~ was insufficient to make a recommendation, but the panel felt that some guidance based on current practice patterns may be appropriate, we issued ~~a number of~~an "in our practice" statement~~s~~. The "in our practice statements" were developed through a survey of panelists to ascertain

their state of current practice ~~for PICO questions without sufficient evidence to formulate a recommendation, but identified as common enough scenarios to ascertain the extent of agreement among panelists' clinical practice~~. As such, "in our practice" statements are intended only to describe current variation in care and are not meant to be construed as recommendations. ~~We summarize the implication of statements or recommendations in Table 2.~~

As new data are continuously generated, the Surviving Sepsis Campaign is committed to ensuring that these guidelines are updated or affirmed every four years or sooner if breaking and relevant evidence becomes available.

Voting Process

Panel members convened to review evidence and discuss recommendations ~~at key international meetings (for those panel members attending the conference), and a stand-alone meeting was held for all panel members in Hamilton, Ontario, Canada in November 2018~~in-person and through web conferences. Following the formulation of initial recommendations through discussion within subgroups, all panelists received links to evidence profiles and polls created using SurveyMonkey, Inc (Palo Alto, CA) to indicate agreement, disagreement, or abstention. Only panel members without relevant conflicts of interest could vote. Voters could provide feedback for consideration in revising statements. Panelists also deliberated during face-to-face meetings, during which subgroups presented their draft statements for discussion. Up to three rounds of voting were conducted throughout this process of deliberation in an attempt to achieve

final consensus. Acceptance of a statement required votes from 75% of the panel members with an 80% agreement threshold.

A summary of all statements determined by the panel is shown in **Appendix 1**. Evidence summaries and evidence profiles that informed the recommendations are included in the online ~~Supplementary~~ supplementary ~~Content~~content. Links to specific tables and figures appear within the relevant text.

Conflict of Interest Policy

Conflict-of-interest (COI) disclosures were sought through the Society of Critical Care Medicine from all panelists and support personnel prior to commencing activities, with updates annually and as needed. The process relied solely on personal disclosure, with clarifications sought when necessary, and centered primarily around potential financial conflicts. The co-vice chairs reviewed all COI disclosures in accordance with SCCM's standard operating procedures, sought clarification when necessary, and worked with the co-chairs to recommend appropriate recusals. There was no industry input into or support of the guideline development process. No panelists received honoraria for any role in the guidelines process. Only librarians and a supporting project manager received compensation for their work.

Seven individuals were identified with potential COIs, but only 3 were deemed relevant to the final list of questions included in the scope of this guideline. These individuals were asked to abstain from voting on the final recommendations involving the potential COI. In addition, panel members were asked to voluntarily abstain from voting on final recommendations if they had a potential academic COI (e.g., grant

application that could benefit from wording of a particular recommendation), though all panel members were welcome to participate in the group discussions leading up to the final recommendation to ensure that input was available from relevant experts.

A. SCREENING, DIAGNOSIS, AND SYSTEMATIC MANAGEMENT OF SEPSIS~~RECOGNITION AND MANAGEMENT~~

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.

Rationale: Systematic screening for sepsis in children is driven by the premise that earlier recognition will lead to more timely initiation of therapy, which will translate to improved morbidity and/or mortality. Screening tools are designed to increase reliability of sepsis recognition and empower health-care professionals to seek rapid medical review. Rapid recognition of sepsis through standardized screening and procedures to guide management of patients identified as at-risk for sepsis should be an essential component of sepsis quality improvement (QI) programs. While the optimal method or tool for screening is unclear, we suggest that screening tools be adapted to the type of patients, resources, and processes within each institution.

Several studies demonstrating that institutional sepsis QI efforts improve outcomes have successfully incorporated screening tools (31-37). Most reported sepsis screens were designed to prompt clinicians to prioritize review of patients that had triggered the screen, hence the ultimate decision to treat or not remains with the clinician. Although RCTs have evaluated the role of systematic screening algorithms to recognize clinical deterioration in children more generally (38), high-quality trials on pediatric sepsis recognition are lacking (39), and data are not sufficient ~~data~~ to suggest any particular screening tool, though several have been published (40-42) or shared on-line (http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx). Single-institution studies demonstrate that an electronic health record (EHR)-based screening tool can yield~~ed~~ high sensitivity and, when coupled with sequential clinician assessment, improved specificity (43). For facilities that use an EHR, a step-wise approach combining EHR-triggered alerts followed by clinician assessment ~~thus~~ has the potential to shorten the time to sepsis recognition (41). Notably, no study was found on systematic sepsis screening in low- and middle--income countries meeting the PICO criteria.

Institutions should monitor and evaluate their practice following implementation of sepsis screening (44). Robust QI balancing measures that should be assessed include clinician response, anchoring bias, increased and/or inappropriate antimicrobial prescriptions, fluid overload, increased PICU admissions and transfers to higher levels of care, and health care utilization costs (45). Application of a screening tool requires ongoing optimization of sensitivity and specificity, continuous improvement efforts to maintain provider education and familiarity with the tool, and continual data acquisition

to monitor implementation and increase utilization (42). Finally, screening tools must work well with existing or planned other early warning and rapid response systems (46, 47) that may also have inherent limitations (38, 48).

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- versus high-risk of having septic shock or sepsis. However, in our practice, if lactate levels can be rapidly obtained, we often measure blood lactate in children when evaluating for septic shock and other sepsis-associated organ dysfunction.**

Rationale: Blood lactate levels provide a valuable indirect marker of tissue hypoperfusion (49) ~~and can contribute to the early recognition, diagnosis, and management of pediatric septic shock (17)~~. While increased lactate levels are not specific, they provide a quantifiable surrogate for tissue hypoxia and can be rapidly obtained by point-of-care tests available in many settings. In adults, blood lactate >2 mmol/L is now included within the operational definition of septic shock as an indication of cellular/metabolic dysfunction, and measurement of lactate is included in the Hour-1 Sepsis Bundle, with recommendations to repeat lactate measurement if the initial value exceeds 2 mmol/L(18, 50, 51). In children, several observational studies have demonstrated an association of elevated blood lactate levels with adverse outcomes in septic shock (11, 52-54). However, the optimal threshold to define *hyperlactatemia* remains unclear. In a PICU study, the mortality rate for children with hypotension requiring vasopressors with lactate >2 mmol/l was 32.0% compared to 16.1% if lactate

was ≤2 mmol/l (11). Other studies have shown that lactate levels >4 mmol/L are consistently associated with mortality (52). Although blood lactate may be affected by the conditions of the blood draw (e.g., use of a tourniquet), both venous and arterial lactate measurements obtained have been shown to be independently associated with mortality in children (55). In ~~a retrospective~~one prospective ~~pediatric~~ study in children, normalization of lactate within 2-4 hours of presentation was associated with decreased risk of persistent organ dysfunction (adjusted relative risk [RR] 0.47, 95% confidence interval [CI] 0.29, 0.78) (56). However, no ~~pediatric~~ RCTs have tested whether initial or serial measurement of blood lactate directly informs evaluation and/or management in children. Lactate levels should therefore be interpreted as part of a more comprehensive assessment of clinical status and perfusion.

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

Rationale: Institutional protocols have been shown to improve the speed and reliability of care for children with septic shock or other sepsis-associated organ dysfunction. Studies reported improvements in mortality, length of stay, duration of organ dysfunction, and development of new or progressive multiple organ dysfunction syndrome (8, 32-34, 36, 57-61). Most of these studies have focused on timely delivery of a "bundle of therapies" (e.g., blood culture, fluid bolus, and antibiotics). For example, an analysis of 1179 children with sepsis across 54 hospitals in New York State found that completion of a sepsis bundle within 1 hour was associated with lower risk-adjusted

odds ratio (aOR) of in-hospital mortality (0.59, 95% CI 0.38, 0.93, p=0.02) (8). In a recent single institution study, bundle-compliant care in 1380 children with septic shock was associated with a five-times lower mortality (OR 0.20, 95%-CI 0.07, 0.53) (33). In another study, implementation of a sepsis protocol led to a substantial reduction in the proportion of children who no longer had organ dysfunction on day 2 after presentation (aOR 4.2, 95% CI 1.7, 10.4) (34). However, it should be noted that protocols studied to date have variable components, many studies do not report adherence to specific items within protocols, and only a few studies have attempted to adjust for initial illness severity or other patient factors, making it difficult to summarize studies using the GRADE approach. Therefore, because available evidence shows a strong and consistent association that adherence to protocols reduces variability in care and improves outcomes, we recommend implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction as a best practice.

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

Rationale: Blood cultures remain the most commonly used method to identify bacteremia. Identification of a blood-borne pathogen can have significant clinical implications on the type and duration of antimicrobial therapy and is an important mechanism to recognize multidrug resistant pathogens (62). Thus, whenever possible, blood cultures should be obtained prior to initiation of antimicrobial therapy in children

with severe sepsis or septic shock. Although no studies have directly measured the effect of blood cultures alone on outcome in pediatric sepsis, several observational studies have demonstrated that a bundled approach to initial resuscitation that includes early blood cultures is associated with improved outcomes (8, 31, 33). If collection of the blood cultures is likely to delay administration of antimicrobial therapy to the patient, then administration of antimicrobials should take precedence, in view of the impact of delayed antimicrobial administration on patient outcomes (63). However, ~~increased mortality is associated with increased time to initiation of *appropriate* antimicrobial therapy (63), and in many settings,~~ because blood cultures may be the only source of information identifying bacterial antibiotic susceptibility, it is important to make all reasonable efforts to collect blood cultures before timely antimicrobial administration. The collection of other biological specimens to identify pathogens from non-blood sites (e.g. urine, cerebrospinal fluid, tracheal aspirate, broncho-alveolar lavage, drainage from collections, etc.) should also happen as soon as possible, and depending on the suspected site of infection, such specimens may have a higher yield of pathogen identification than blood cultures. Clinicians should also consider the epidemiology of pediatric infections in relation to age, sex, and host factors, such as comorbidities (64, 65). Specific patterns of pediatric bloodstream infections relating to age and comorbidities are well known, and approximatively one out of three bacteremia episodes are associated with organ dysfunction in a recent large population-based study (65).

Limitations of standard blood cultures include the time needed to grow and then identify pathogens and their antibiotic sensitivities, as well as the effect of previous

therapy on diagnostic yield. New molecular technologies are becoming available to facilitate earlier and faster microbiological diagnoses. Such techniques may be able to identify a range of pathogens well before blood cultures are positive (66), and may potentially identify pathogens even after the administration of antimicrobial therapy. However, new molecular diagnostics are currently relatively expensive, are not sufficient for all pathogens and antibiotic sensitivities, and are not universally available.

B. ANTIMICROBIAL THERAPY

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

Rationale: Antimicrobials are the primary medical therapy that directly targets the underlying cause of sepsis, and there is strong biologic rationale for rapid delivery of antimicrobials in patients with sepsis (67). Many QI initiatives have shown improved pediatric sepsis outcomes with implementation of a bundle that includes rapid delivery of intravenous antimicrobials (8, 32-34, 36, 57-61). Two retrospective observational studies have also demonstrated an association of faster time to antimicrobial therapy with reduced mortality for children with sepsis. The first study was an analysis of 130 children with sepsis (mortality of 12%), including 103 (79%) with septic shock, in which

the unadjusted OR for mortality ~~for~~among children ~~where~~ with antimicrobials ~~were~~ delivered within versus after 60 minutes of sepsis recognition was ~~reduced with an unadjusted OR of~~ 0.60 (95% CI 0.13 - 2.86) (63). The second study was an analysis of 1179 children, including 69% with septic shock, where completion of a sepsis bundle within 1 hour of sepsis recognition was associated with decreased mortality (OR 0.59, 95% CI 0.38, 0.93, p=0.02); however, initiation of antimicrobials alone by 1 hour of recognition was not associated with significant mortality reduction (OR 0.78, 95% CI 0.55, 1.12, p=0.18) (8). When the adjusted OR of these 2 studies were pooled, there was a possible reduction in mortality (OR 0.77, 95% CI 0.55, 1.08) **(Supplemental Table 2, Supplemental Figure 1.~~, Table 2~~)**~~.~~ Other secondary end-points reported in the literature have also been associated with shorter time to initiation of antimicrobial therapy, including reduced length of stay, shorter duration of organ dysfunction, and reduced development of new or progressive multiple organ dysfunction syndrome (8, 32-34, 36, 57-61). Moreover, indirect evidence from adult sepsis generally supports a benefit to starting antimicrobial therapy as soon as possible after recognition of septic shock (68-73). Thus, timely antimicrobial therapy—ideally administered as part of a more comprehensive bundle of initial care—should be the goal for children with septic shock.

The definition of “timely” in this context represents an area of controversy relating to challenges in the accurate recognition of patients with sepsis and septic shock and the need to consider balancing QI metrics such as unnecessary antimicrobial usage (67, 74, 75). One pediatric study (63) indicated a dose-response gradient such that the longer time to antimicrobial therapy, the higher the mortality. Yet the mortality increase

reached significance only when antimicrobials were administered >3 hours in comparison to <3 hours, whereas the mortality of patients receiving antimicrobials within <1 hour was not different from those receiving antimicrobials within <3 hours in that relatively small study. The second, larger pediatric study demonstrated a significant decrease in mortality if antimicrobials were administered within 1 hour, but only in the context of a bundle that included a blood culture and fluid bolus. (8) Thus, available pediatric studies do not provide a clear time cut-off after which the risk of mortality or other adverse outcomes increases, but rather support that there is likely to be an incremental risk for harm as time to antimicrobial initiation increases, in particular beyond 3 hours. Notably, the benefit of antimicrobial therapy within 1 hour of recognition has been most prominent in cohorts with a predominance of septic shock (as compared to sepsis without shock) patients (8, 63).

Based on limited pediatric evidence and indirect evidence from adult studies, the panel supported that, in children *with septic shock*, antimicrobial therapy should be initiated as soon as possible and ideally within 1 hour of recognition. Suspicion of septic shock can usually be guided by clinical findings rapidly ascertained through history and physical examination. While our recommendation to ideally administer antimicrobial administration within 1 hour of recognition of septic shock establishes a tangible goal that emphasizes the importance of early antimicrobial therapy and assists clinicians in prioritizing bedside care, this cut-point should not be misconstrued as a known biological truth. Thus, dichotomous time-based metrics of the quality of care for children with sepsis, while pragmatic and potentially useful to trend, may be of less value than use of continuous variables such as median time to antimicrobials. Despite a very low

quality of evidence on this topic, we provide a strong recommendation because the panel concluded that most patients would accept and most clinicians should seek to initiate antimicrobial therapy as soon as possible after recognition of septic shock in most situations.

For children *without clinical signs of shock*, the panel acknowledged that the diagnosis of sepsis-associated organ dysfunction has additional challenges related to the need to discriminate those with true sepsis from among a large number presenting with suspected infection (67). In view of the available evidence, we suggest starting antimicrobial therapy *as soon as possible* after sepsis recognition, while allowing up to 3 hours for appropriate diagnostic investigation for patients *without clinical signs of shock* and for those with an uncertain diagnosis. However, the diagnostic evaluation should be performed expeditiously and, if and when the evaluation supports a likely infection or evidence of septic shock or other sepsis-associated organ dysfunction becomes manifest, antimicrobial therapy should be immediately administered.

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).**

Rationale: Sepsis mortality is associated with delays to *appropriate* antimicrobial therapy, and hence optimal treatment for sepsis relies on accurate selection of antimicrobials to ensure activity against the major pathogens (50, 63, 71, 76). *Empiric therapy* refers to the initial choice of antimicrobials pending microbiological results (**Table 4**) and is based on the predicted likelihood of bacterial pathogens. Empiric therapy should cover a broad range of pathogens that are likely to cause the infection, acknowledging that, in rare circumstances, this may not fully cover very unusual pathogens. *Broad-spectrum therapy* refers to the use of *single- or multi-drug* antimicrobial therapy with activity against multiple groups of bacteria/pathogens. Broad-spectrum therapy is recommended for initial empiric therapy of children with septic shock or sepsis-associated organ dysfunction to increase the likelihood that the initial empirical therapy is effective against the causative pathogens.

The initial choice of empiric antimicrobials should take into account the specific clinical history (e.g., age, site of infection, concomitant disease states, comorbid conditions, indwelling devices). Patients with recent or current hospital exposure should receive empiric therapy that considers known infection or colonization, as well as any recent antimicrobial exposure. Institutions or regions should identify the most appropriate first-line single-agent antimicrobial, taking into account anatomic site of infection, age, local epidemiology, and host comorbidity and risk factors (e.g., ceftriaxone is recommended for community-acquired sepsis by the National Institute for Health and Care Excellence (NICE) in the United Kingdom) (16). For complex patients or those recently or currently in hospital, the choice of empiric antimicrobials should also take into account ~~the specific clinical history such as the clinical syndrome/site of~~

~~infection,~~ concomitant underlying diseases, chronic organ failure, indwelling devices, the presence of immunosuppression or other form of immunocompromise, recent known infection or colonization with specific pathogens, and recent receipt of antimicrobials (65, 77, 78). When available, an infectious diseases clinician should be consulted. Other non-bacterial pathogens that are suspected as a cause of infection should also be targeted as part of initial antimicrobial therapy on a case-by-case basis.

Sepsis in children is most commonly due to gram-negative or gram-positive bacteria, although the relative prevalence of these pathogens varies by age, geographic region, location (community versus hospital) of sepsis onset, and other patient factors. Invasive fungal infections are largely restricted to immunocompromised patients and pre-term infants. Certain specific conditions put patients at risk for atypical or resistant pathogens, thus requiring specific empiric regimens. For example, neutropenic patients are at risk for an especially wide range of potential pathogens, including resistant gram-negative bacilli and *Candida* species, and neonates are at risk of sepsis caused by *listeria monocytogenes* and disseminated herpes simplex virus (HSV). Children with chronic conditions treated in hospital settings are prone to sepsis with resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). For children at risk for multidrug-resistant bacterial infections, empiric broad-spectrum antimicrobial regimens may require more than one agent to broadly cover such potential pathogens.

For specific empiric broad-spectrum antimicrobial therapy, the reader is directed to published resources (77, 79) and the need to consider patient history, allergies, local epidemiology, and suspected site/source of infection. However, general suggestions

can be provided here. For previously healthy children with community-acquired sepsis, a third-generation cephalosporin (e.g., ceftriaxone) may be sufficient. Vancomycin should be added in settings where MRSA or ceftriaxone-resistant pneumococci are prevalent, and addition of an aminoglycoside or substitution of a carbapenem is appropriate in settings where ceftriaxone resistance is common in gram-negative bacteria (80). For immunocompromised patients or hospital-acquired sepsis, antimicrobial therapy should begin with an anti-pseudomonal third- or higher-generation cephalosporin (e.g., cefepime), a broad-spectrum carbapenem (e.g., meropenem, imipenem/cilastatin), or an extended-range penicilin/β-lactamase inhibitor combination (e.g., piperacillin/tazobactam) (79). For neonates, therapy should also include ampicillin for listeria and consideration for empiric acyclovir if there is a clinical concern for HSV (77). For patients with a suspected or documented intra-abdominal source of infection, therapy should include broad coverage for gastrointestinal pathogens, including anaerobic bacteria, with either an extended-range pencillin/β-lactamase inhibitor combination or carbapenem, or addition of clindamycin or metronidazole. For patients who present with sepsis complicating an influenza-like illness during the local influenza season, empiric antiviral therapy should be started while awaiting the respiratory virus testing (81, 82). Patients at higher risk of antibiotic-resistant infection because of past infection or colonization, local epidemiology, or recent broad-spectrum antibiotic use, should receive an individually tailored empiric therapeutic regimen (83). In cases of suspected toxic shock syndrome or necrotizing fasciitis, empiric treatment should include clindamycin or lincomycin to limit toxin production and enhance bacterial

clearance (84). Finally, for sepsis treated in regions endemic for rickettsial or parasitic pathogens (e.g., malaria), clinicians should consider adding relevant empiric coverage.

Targeted or definitive therapy refers to the antimicrobial regimen targeted to a specific pathogen(s) after microbiologic identification. As with empiric therapy, targeted/definitive therapy may be single- or multi-drug therapy, but should not be broader than required to treat the specific pathogen(s) after microbiologic identification (85, 86)~~(79, 80)~~. Risks of unnecessary continuation of broad-spectrum antibiotic and other antimicrobial therapy include direct side effects and toxicities (such as the nephrotoxicity or ototoxicity of aminoglycosides), infection with *Clostridioides difficile* (formerly *Clostridium)* or fungal pathogens, and promotion of antimicrobial resistance in the patient and in the community. In addition, unnecessary exposure to antibiotics may lead to alteration of the human microbiome early in life, the impact of which is poorly understood but has been associated with worse outcomes such as necrotizing enterocolitis in newborns.

Because most microbiological cultures show significant growth within 24 to 36 hours of collection when a pathogen is present (87)~~(81)~~, empiric treatment should be re-evaluated after no more than 48 hours following initiation. If no pathogen is identified *and* bacterial/fungal infection is deemed unlikely, clinicians should stop empiric antimicrobial therapy to reduce unnecessary exposure to antibiotics/antifungals. However, many children with a clinical diagnosis of septic shock do not have a pathogen isolated (5, 6). Patients with negative bacterial microbiological results may have false-negative tests due to antibiotic pre-treatment, absence of bacteremia (e.g., bacterial pneumonia despite true bacterial infection), or sepsis related to viral infections

(88)~~(82)~~. Thus, the decision to continue, narrow, or stop antimicrobial therapy must often be made on the basis of clinician judgment and indirect clinical information, taking into account the clinical presentation, site and type of infection, host risk factors, and adequacy of clinical improvement. Complex patients should be discussed with pediatric infectious diseases and/or microbiology specialists to ensure likely pathogens are treated and that antibiotics and other antimicrobials are stopped when they are no longer necessary.

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).**

Rationale: The selection of an empiric antimicrobial regimen requires consideration of a patient's underlying disease state, potential history of prior infections and colonization with multidrug-resistant organisms (MDROs), presence of immunosuppression, and possible recent antimicrobial use, as well as local pathogen prevalence and

susceptibility profile(50, 89, 90)~~(50, 83, 84)~~. Empiric therapy may be single- or multi-drug, but should be broad spectrum in nature as defined in Table 4. For select patients or with concern for particular types of infection, this may necessitate adding a glycopeptide (i.e., vancomycin) to ensure empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) or a second gram-negative agent (e.g., aminoglycoside in addition to a beta-lactam or second/third-generation cephalosporin) when antibiotic resistance is a concern. However, routinely including an aminoglycoside or a glycopeptide for synergy or "double-coverage" as part of an empiric regimen is not supported by the available data (90-101)~~(84-95)~~.

A recent Cochrane review evaluated beta-lactam monotherapy versus beta-lactam and aminoglycoside combination regimens for sepsis and included 69 trials accounting for 7863 participants, including neonatal and pediatric patients(89)~~(83)~~. In trials where the mono- and multidrug arm used the same beta-lactam, no difference in clinical outcomes was observed between study groups. In studies where the monotherapy arm contained a beta-lactam of broader spectrum than the multidrug arm, monotherapy ~~suggested~~ showed a possible benefit for all-cause mortality (OR 0.85, 95% CI 0.71, 1.01) and a significant advantage for clinical failure (OR 0.75, 95% CI 0.67, 0.84) (89)~~(83)~~. Additionally, indirect evidence from adults with sepsis including 13 RCTs comparing empirical mono- versus combination antibiotic therapy suggests mortality and other outcomes are not improved by empiric combination therapy (91)~~(85)~~. Therefore, many children with septic shock and other sepsis-associated organ dysfunction do not require empiric multi-drug therapy. Clinicians should continually re-

evaluate the local epidemiology and resistance rates to ensure monotherapy remains appropriate (89)~~(83)~~.

Certain clinical scenarios, however, may necessitate multi-drug antimicrobial therapy. For example, in patients at high risk for resistant gram-negative infections with sepsis, combining a beta- lactam/beta-lactamase inhibitor agent (i.e., piperacillin/tazobactam combination) with an aminoglycoside (i.e., gentamicin) can be considered, not for synergy, but for expanded coverage to treat both susceptible and resistant pathogens until final identification and susceptibilities are known (102-104)~~(96-98)~~. Additionally, a synergistic multi-drug regimen may be appropriate in select settings, even for targeted/definitive therapy, such as device-associated infections, enterococcal endocarditis, staphylococcal endocarditis, group B streptococcal sepsis, and carbapenem-resistant Enterobacteriaceae infections (105, 106)~~(99, 100)~~.

Pediatric patients with cancer and transplant recipients have a substantial degree of immunosuppression and represent a population at higher risk for colonization and infection with multi-drug resistant organisms (107, 108)~~(101, 102)~~. The 2017 guidelines for the management of fever and neutropenia (FN) in children with cancer and hematopoietic stem-cell transplantation recommended monotherapy with an anti-pseudomonas beta-lactam, a fourth-generation cephalosporin, or a carbapenem as empiric therapy in high-risk pediatric patients with FN (79)~~(103)~~. The three RCTs in high-risk pediatric FN comparing monotherapy with aminoglycoside-containing combination therapy found no significant differences in failure rates, infection-related mortality, or overall mortality (79, 109, 110)~~(103-105)~~. The meta-analysis also confirmed the efficacy and safety of monotherapy without the addition of an aminoglycoside.

However, the 2017 guidelines on the management of children with FN did recommend addition of a second gram-negative agent and/or a glycopeptide when resistant organisms were suspected for patients who are clinically unstable (i.e., septic shock) and in centers with a high rate of resistant pathogens (79)~~(103)~~. Therefore, for children with septic shock or other sepsis-associated organ dysfunction who have immune compromise and/or are at high risk for multidrug-resistant pathogens, we suggest empiric multi-drug therapy.

Currently, specific resistance rate thresholds do not exist to help clinicians decide when the addition of a glycopeptide or second gram-negative agent for sepsis or septic shock is necessary. The US guidelines for the management of community-acquired pneumonia in adults suggest a 25% rate of high-level macrolide resistance in the community as the threshold beyond which macrolides should not be used (111, 112)~~(106, 107)~~. Additionally, current guidelines from the Infectious Diseases Society of America recommend an alternative antibiotic for skin and soft tissue infections if the local clindamycin resistance rate is greater than 10% (113)~~(108)~~. Considering the current rates of morbidity and mortality for patients with sepsis or septic shock, a local or regional antimicrobial resistance rate exceeding 10% is probably a prudent threshold for the addition of a second agent if that pathogen is suspected(5, 63).

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).

Rationale: Sepsis may alter the pharmacokinetics and pharmacodynamics of antimicrobials. Therefore, antimicrobial dosing should be individualized to deliver effective and timely treatment of life-threatening infection, while at the same time limiting adverse medication effects. Sub-therapeutic dosing can lead to failure to clear the infection, prolong organ dysfunction, and can lead to the development of antimicrobial resistance. A substantial proportion of sepsis patients are at risk for altered drug metabolism and/or clearance, including those with kidney and hepatic dysfunction and those treated with extracorporeal therapies (114)~~(109)~~. In particular, continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) both lead to profound alteration of antimicrobial clearance, requiring individual dose adaptation (115)~~(110)~~. Therapeutic drug monitoring (TDM), where available, can permit individualized antimicrobial dosing to achieve maximal effect while minimizing toxicity (116)~~(111)~~.

Examples of sepsis and septic shock-related altered pharmacokinetics include increased volume of distribution as a result of fluid therapy and capillary leak (*Vd*) (117)~~(112)~~, decreased antimicrobial clearance as a result of altered renal and hepatic organ perfusion and organ dysfunction (118)~~(113)~~, and higher unbound drug levels due to hypoalbuminemia leading to increased clearance(119)~~(114)~~. Hepatic dysfunction impairs the metabolism of lipophilic and highly albumin bound antibiotics, leading to drug accumulation and toxicity. In renal dysfunction, time-dependent antibiotics cleared by the kidneys, such as the beta-lactams, require reduced dosing frequency.

The 3 main determinants of antimicrobial efficacy are: a) the time during which the concentration of the drug remains above the minimum inhibitory concentration (MIC)

of the causative pathogen (T>MIC) (time-dependent antibiotics); b) the peak concentration to MIC ratio (C_{max}/MIC) (concentration-dependent antibiotics); and c) the ratio of the 24-hour area under the concentration-time curve divided by the MIC (AUC24/MIC) (concentration-dependent with time-dependence antibiotics). The main classes of time-dependent antibiotics include beta-lactams (penicillins, cephalosporins, carbapenems, monobactams) and lincosamides (clindamycin and lincomycin). For amoxicillin-clavulanic acid, current published dosing regimens in critically ill children can result in sub-therapeutic concentrations in the early period of sepsis due to augmented renal clearance (120, 121)~~(115, 116)~~. In sepsis, the use of continuous or extended infusions with loading doses, as opposed to intermittent dosing, may lead to improved outcomes in patients treated with beta-lactam antibiotics (122)~~(117)~~.

The main classes of concentration-dependent antibiotics include aminoglycosides and metronidazole. In some centers, drug concentrations measured within 60 minutes before or after administration of aminoglycosides are used to estimate the C_{min} and C_{max}, respectively, and together with the MIC of the pathogen, can help to guide appropriate antimicrobial dosing (119)~~(114)~~. Concentration-dependent antibiotics may require an altered dosing frequency to maximize bacterial killing by preserving the C_{max}/MIC.

Glycopeptides, oxazolidinones, fluoroquinolones, polymixins, daptomycin, azithromycin, and tigecycline are examples of concentration-dependent with time-dependent antibiotics. For vancomycin, this can mean higher doses, but that comes with an increased risk of toxicity. For this reason, continuous vancomycin infusions may be considered to achieve optimal concentrations in some patients (123)~~(118)~~. For

concentration-dependent with time-dependent antibiotics, dose optimization involves adjusting the dosing interval rather than administered dose (119)~~(114)~~.

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 hours 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.

Rationale: The misuse and overuse of broad-spectrum antimicrobials in health care, the community, veterinary medicine, and the environment have contributed to a global public health emergency (124)~~(128)~~. De-escalation of antimicrobials, where appropriate, is warranted to minimize adverse effects of unnecessarily prolonged administration. To date, quality improvement efforts in adults have shown that safe and effective antimicrobial de-escalation can be achieved by daily assessment and discussion (125, 126)~~(129, 130)~~.

Several host biomarkers have also been proposed to aid in the safe de-escalation of antimicrobial therapy. In adults with severe infections and sepsis, procalcitonin has been shown to successfully guide de-escalation (127-131)~~(131-135)~~ with an associated improved mortality (132)~~(136)~~. Similar reductions in length of antimicrobial therapy have also been safely achieved in neonatal populations (133)~~(137)~~

using procalcitonin as a guide. In the United Kingdom, the NICE committee concluded that in emergency room and critical care settings, procalcitonin testing shows promise but currently insufficient evidence is available to recommend the routine adoption of procalcitonin-guided antimicrobial de-escalation (www.nice.org.uk/guidance/dg18).

Although a relationship between antimicrobial stewardship programs (ASP) and a decrease in antimicrobial resistance has not yet been shown, studies suggest that inpatient pediatric ASPs may reduce antimicrobial usage without contributing to adverse patient outcomes (124)~~(128)~~. The "Start Smart - Then Focus" work from Public Health England suggests a pragmatic approach of the 5 "antimicrobial prescribing decision" options to include: 1) stop antimicrobials if there is no evidence of infection, 2) switch antimicrobials from intravenous to oral, 3) change antimicrobials – ideally to a narrower spectrum – or broader if required, 4) continue and document next review date or stop date, and 5) outpatient parenteral antimicrobial therapy (134)~~(138)~~. De-escalating antimicrobial therapy must be based in sound clinical judgment and needs to be adapted to local epidemiology and identified resistance patterns.

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).

Rationale: The main purposes of antimicrobial therapy in patients with sepsis are to reduce the pathogen load rapidly and to prevent recurrence. Important determinants of the required duration of antimicrobial therapy include site of infection, ability to drain or remove fixed infectious foci, choice of antimicrobial therapy, time to clearance of

positive cultures, the nature of the causative pathogen, and the integrity of the host immune response. There is no evidence that severity of sepsis is an important determinant of optimal duration of therapy because illness severity is not expected to affect clearance of infection.

The optimal duration of antimicrobial therapy can differ by site of infection because of a high pathogen burden, poor antimicrobial penetration, or presence of difficult-to-eradicate microbial biofilms at the site. For example, longer duration of therapy is typically required for treatment of endocarditis, undrained abscesses, and prosthetic joint infection without device removal (135-137)~~(139-141)~~. Characteristics of the causative organism that may affect optimal duration of therapy include resistance or decreased susceptibility to front-line antimicrobials and propensity to cause deep-seated or difficult-to-eradicate infection. For example, optimal duration of treatment for endocarditis caused by methicillin-susceptible *Staphylococcus aureus* may be shorter than for that caused by methicillin-resistant *Staphylococcus aureus* (137)~~(141)~~. Similarly, although 7-10 days of therapy is appropriate for treatment of uncomplicated gram negative bacteremia in immunocompetent hosts (138, 139)~~(142, 143)~~, uncomplicated *S. aureus* bacteremia requires a longer course of therapy to effect cure (140-142)~~(144-146)~~, likely because of unrecognized seeding (143)~~(147)~~. Integrity of host immunity may also affect clearance of infection, so antimicrobial therapy for infection in neutropenic pediatric patients with cancer is often continued until resolution of neutropenia (79)~~(103)~~.

A systematic review evaluated studies describing duration of treatment for clinically and microbiologically-documented infections in children and provides

evidence-based clinical guidelines for optimal duration of antimicrobial therapy for specific conditions(144)~~(148)~~. Given the lack of studies on the duration of antimicrobial therapy for pediatric patients with sepsis specifically, we refer to this previously published guideline as best evidence. Importantly, there are no data to support that the presence of organ dysfunction or a higher initial illness severity necessitates longer therapy for specific infection types (other than attention to how such organ dysfunction may affect antimicrobial pharmacokinetics and pharmacodynamics).

Observational studies suggest that longer exposure to antibiotics is associated with risk of potential adverse events including necrotizing enterocolitis in very low birthweight infants (145)~~(149)~~, candidemia in hospitalized children (146, 147)~~(150, 151)~~, development of antimicrobial resistance (148)~~(152)~~ and *Clostridioides difficile* (formerly *Clostridium*) infection (149)~~(153)~~. Several meta-analyses, RCTs, and observational studies have compared long- versus short-duration antibiotic therapy for serious infections (141, 145, 150-168)~~(145, 149, 154-172)~~. Most studies suggest that shorter courses were associated with similar clinical outcomes compared to longer durations; these include neonatal bacteremia (159, 164)~~(163, 168)~~, pyelonephritis (169)~~(173)~~, uncomplicated bacterial meningitis (155, 156, 160-162, 165, 166)~~(159, 160, 164-166, 169, 170)~~, and pneumonia (170, 171)~~(174, 175)~~. In contrast to these infections, some studies have identified scenarios where longer durations of antimicrobial therapy is superior. For example, an RCT suggested that 14 days of antibiotic therapy was superior to 7 days for treatment of neonates with *Staphylococcus aureus* bacteremia (141)~~(145)~~, and an observational study suggested that >10 days was superior to ≤10

days of antibiotic therapy in children treated for gram-negative bacteremia without removal of a pre-existing CVC (163)~~(167)~~.

C. 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).

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).

Rationale: Source control is defined as physical modalities taken to control or remove the source of infection or to prevent spread of the infection systemically or to adjacent tissues (172)~~(119)~~. Source control may include percutaneous or deep abscess drainage, drainage of an empyema, septic joint, or subperiosteal abscess, removal of infected hardware or central venous catheters (CVCs), or debridement of necrotizing soft-tissue infection. The adult SSC guidelines recommend source control as soon as is reasonably feasible after resuscitation, ideally within 6-12 hours of diagnosis (50).

Waiting for patients to clinically stabilize prior to intervention is not recommended, as delaying adequate source control may lead to further clinical deterioration (6). While source control as an adjunct to antimicrobial and other medical therapy has been best described for abdominal infections in adults and has been associated with reduction in mortality (173)~~(120)~~, the role of source control for pediatric sepsis has been less well elucidated (174)~~(121)~~.

The importance of source control in children has been shown for skin and deep tissue abscesses and necrotizing fasciitis (174-176)~~(121-123)~~. Despite the relative paucity of pediatric data, source control is an important facet of treatment of sepsis, and should not be delayed. Larger collections containing infected material often are poorly penetrated by intravenous antimicrobials and contribute to direct and hematogenous spread, ongoing inflammation, and organ dysfunction.

A common, but potentially preventable, source of infection is central line-associated bloodstream infections (CLABSI). Delayed removal of a CVC in neonates and in patients with fungemia or Enterobacteriaceae bacteremia increases the risk of death or slows recovery (177-180)~~(124-127)~~. Removal of a CVC that is the source of infection is therefore generally warranted unless extenuating circumstances exist. Fungal infection dictates immediate removal, while in case of coagulase negative *Staphylococcus spp* or clinically stable patients with infection caused by gram-negative rods, infections can often be initially treated through the CVC as a temporizing measure. The decision to remove the CVC, or not, should ultimately be made based on the pathogen suspected/recovered and host factors, such as immune status. (**Supplemental Table 3.**)

D. ~~HEMODYNAMICS AND RESUSCITATION~~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, we suggest administering up to 20 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, moderate quality of evidence).**~~ **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, ~~T~~the need for ~~bolus~~ fluid administration should be guided by frequent reassessment of clinical markers of cardiac output, serial blood lactate measurement and advanced monitoring, when available. ~~Even in low-resource settings, the subset of children with septic shock *and hypotension* should receive cautious fluid bolus therapy.~~ Signs of fluid overload that should limit further fluid bolus therapy may include clinical signs of pulmonary edema or new or worsening hepatomegaly.~~Clinical markers of cardiac output may include heart rate, blood pressure, capillary refill time, level of consciousness, and urine output. The need for bolus fluid administration should be guided by frequent reassessment of clinical markers of cardiac output, serial blood lactate measurement and advanced monitoring, when available. Even in low-resource settings, the subset of children with septic shock *and hypotension* should receive cautious fluid bolus therapy. Signs of fluid overload may include clinical signs of pulmonary edema or new or worsening hepatomegaly.~~

Rationale:

~~Septic shock is characterized by abnormal perfusion, including tachycardia, decreased blood pressure, prolonged capillary refill, organ dysfunction and increased serum lactate (17).~~ Effective fluid resuscitation in septic shock can correct ~~relative~~ hypovolemia~~,~~ caused by capillary leak, ~~and~~ vasodilation, and fluid losses. Without maintenance of adequate atrial filling pressures, cardiac output will fall and organ perfusion will be compromised. ~~However, the cardiovascular physiology in childhood septic shock is~~

~~variable. In older children, particularly those with healthcare-acquired infections (e.g., CLABSI), a vasodilatory picture may dominate with tachycardia, hypotension, bounding pulses, warm peripheries, and flash capillary refill. In younger children with community-acquired infection (e.g., meningococcal sepsis), the phenotype is more likely to be one of impaired cardiac output due to the direct effects of bacterial toxins and inflammatory mediators on myocardial cell function and profound vasoconstriction (176). In this latter case the presentation may be with tachycardia, hypotension, cold peripheries, and prolonged capillary refill. Although observational studies have generally supported a role for fluid resuscitation in children with septic shock (8, 32, 33, 35, 177-180), the optimal rate, volume, and timing of fluid resuscitation across such variable physiologic presentations has not been conclusively demonstrated.~~

Three RCTs of different volume resuscitation strategies in children with septic shock in settings in which advanced supportive care (e.g., intubation, mechanical ventilation, and intensive care) was accessible have been published ~~(181-183)~~ (181-183). These studies have a combined total of only 316 children and showed no difference in mortality between the restrictive and liberal fluid resuscitation groups (**Supplemental Table 4, Supplemental Figure 2**).

In geographic settings in which advanced supportive care, including mechanical ventilation, is limited and/or intensive care is not routinely accessible, the only large-scale RCT of different bolus fluid volume resuscitation strategies in severe infection in children was the Fluid Expansion as Supportive Therapy (FEAST) study (**Supplemental Table 4, Supplemental Figure 2**) ~~(184)~~(184). The FEAST study was conducted in Africa~~,~~ in a low-resource setting without access to PICU admission. Children between

60 days and 12 years of age with a severe febrile illness and abnormal perfusion were randomized to either rapid volume expansion with 20 mL/kg of intravenous 0.9% saline or 5% albumin or no bolus with maintenance fluid only (control group). Among the 3141 study participants, malaria and anemia were highly prevalent. Overall, the RCT demonstrated a lower mortality after 48 hours in children receiving conservative fluid therapy (i.e., no bolus fluid, maintenance fluid only) than among those given liberal initial fluid therapy (i.e., 20 mL/kg fluid bolus with maintenance fluid) with a RR of 0.72 (95% CI 0.57, 0.9). Notably, 29 additional children enrolled with severe hypotension (systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age) were treated with 40 mL/kg fluid bolus per the planned protocol without randomization to the control group. One additional child who was randomized to the control group also received a 40 mL/kg fluid bolus due to severe hypotension. ~~The FEAST study has resulted in some reluctance to use a high-volume fluid resuscitation strategy in critically ill children, even in settings in which intensive care is available.~~

For children with septic shock diagnosed by abnormal perfusion or hypotension in healthcare systems with availability of advanced supportive and intensive care, and in the absence of signs of fluid overload, ~~T~~the panel suggests administering up to 40-60 mL/kg fluid bolus therapy in the first hour of resuscitation. Fluid resuscitation should be ~~in health care systems with availability of advanced supportive and intensive care,~~ titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop. Clinical markers of cardiac output can include heart rate, capillary refill, and urine output. Although no high-quality RCTs ~~support~~ demonstrate clear superiority of

this practice, ~~several~~ numerous observational studies ~~investigating this approach to resuscitation~~ have reported improved patient outcomes with routine administration of up to 40-60 mL~~l~~/kg fluid bolus therapy in the first hour of resuscitation ~~(8, 32, 33, 36, 177-179, 185)~~(8, 32, 33, 36, 185-188). ~~Notably,~~ ~~t~~The panel provides only a weak recommendation for this resuscitation strategy in healthcare systems with availability of intensive care ~~given that~~because a more restrictive fluid resuscitation strategy has not been shown to be inferior in this setting ~~and~~and indirect data ~~(184)~~(184) indicate harm from rapid fluid boluses in other settings. ~~, indeed, may be superior in health care systems with limited availability of advanced supportive and intensive care, as seen in the FEAST trial.~~ For this recommendation, the panel judged the balance of observational data supporting initial fluid bolus therapy to outweigh an indirect suggestion of harm because the generalizability of the FEAST trial to healthcare systems with availability of advanced supportive and intensive care is not clear. ~~A weak recommendation (i.e., suggestion) to administer up to 40-60 mL/kg in bolus fluid therapy over the first hour indicates the panel's judgment that the majority of individuals in this situation would want this course of action, but different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient's circumstances.~~

For children with septic shock without signs of fluid overload in low-resource settings where advanced supportive and intensive care is not available, the panel recommends against bolus fluid administration, while starting maintenance fluids, in the first hour *if hypotension is not present*, and suggests administering up to 40 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour *if hypotension is present* ~~The~~

~~suggestion to limit initial fluid bolus resuscitation to 20 mL/kg in the first hour for children in low-resource settings where advanced supportive and intensive care is not available~~. The strong recommendation against bolus fluid *if hypotension is not present* was based on the FEAST trial, in which rapid bolus fluid in the first hour of resuscitation increased mortality compared to maintenance fluids only. ~~aligns with the World Health Organization (WHO) recommendations for treatment of circulatory impairment in low-resource settings (14). A weak recommendation (i.e., suggestion) to administer *up to* 20 mL/kg in bolus fluid in healthcare systems with limited availability of advanced supportive and intensive care indicates the panel's uncertainty of whether this amount of fluid may cause harm in some patients without severe hypotension. Notably,~~

For the subset of children with septic shock *and hypotension*, we suggest cautious administration of fluid bolus therapy in low-resource settings because there are insufficient data to conclude that fluid resuscitation is not beneficial in children with septic shock *and hypotension*.

In the FEAST study, all children with *severe* hypotension were treated with 40 mL/kg of bolus fluid ~~(184)~~(184) and so it is not known if fluid bolus therapy was beneficial or harmful in this subgroup of children. It should also be noted that children with gastroenteritis were excluded from FEAST, as ongoing fluid losses should be replaced with intravenous or oral rehydration as indicated. A recent analysis of children with *moderate* hypotension who were randomized to either fluid bolus or maintenance fluid in the FEAST trial was published after completion of our initial systematic review but considered by the panel to be potentially influential (189)~~(REF)~~. In this analysis, only children with moderate hypotension were included because children with severe

hypotension were not allocated to the control (no bolus) arm. Fluid bolus therapy in children with moderate hypotension was not beneficial or harmful compared to maintenance fluid only (RR of death = 1.48, 95% CI 0.61–3.66, p=0.41). Although children who were reclassified as meeting all three WHO shock criteria of cold extremities, prolonged capillary refill >3 seconds, and weak, fast pulse ~~(14)~~(14) had 48% mortality in the bolus groups versus 20% mortality in the control group, this difference was not statistically significant (p=0.07). These cases were a very small proportion of the total FEAST trial participants (only 72 [2.3%] had moderate hypotension and 65 [2%] met the full WHO shock criteria), and no data were provided about differential patient characteristics between these very small *post hoc* subgroups to assess for potential confounding. Therefore, until further data are available, the panel suggests cautious administration of fluid bolus therapy for the subset of children with septic shock *and hypotension* in low-resource settings as a weak recommendation based on low quality of evidence.

Although a suggestion of *up to* 40 mL/kg was included for hypotensive shock in low-resource settings because this volume was administered to children with severe hypotension in the FEAST study, fluid administration should always be titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop. For purposes of this weak recommendation, hypotension can be defined as a) systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age ~~(184)~~(184) or b) by the WHO criteria of cold extremities *with* prolonged capillary refill >3 seconds *and* weak, fast pulse ~~(14)~~(14). Although the panel did not review different

approaches to fluid bolus therapy in hypotensive children in low-resource settings, ~~T~~the WHO recommends 10-20 mL/kg of isotonic crystalloid over 30-60 minutes, followed by an additional 10 mL/kg over 30 minutes if condition has not improved and signs of fluid overload, cardiac failure, or neurological deterioration have not developed ~~(14)~~(14). Fluid boluses may be administered as 10 or 20 mL/kg, according to clinician preference. To facilitate rapid intravenous fluid administration (as well as other intravenous therapies, such as antimicrobials and vasoactive medications), clinicians should consider alternative methods of vascular access if initial attempts at peripheral vein cannulation are not immediately successful. Intraosseous access is rapid and effective and recommended by Pediatric Advanced Life Support (PALS), Advanced Pediatric Life Support (APLS), and the International Liaison Committee on Resuscitation (ILCOR). Ultrasound-guided peripheral intravenous catheter placement, CVCs, and umbilical venous catheter access are alternatives if the skills are immediately available ~~(186, 187)~~(190, 191). In all healthcare systems, repeat boluses should only be administered after reassessment of hemodynamic status ~~and~~ if shock has not resolved and signs of fluid overload are not present.~~Septic shock is characterized by abnormal perfusion, including tachycardia, decreased blood pressure, prolonged capillary refill, organ dysfunction and increased serum lactate (17). Effective fluid resuscitation in septic shock can correct relative hypovolemia, caused by capillary leak and vasodilation. Without maintenance of adequate atrial filling pressures, cardiac output will fall. However, the cardiovascular physiology in childhood septic shock is variable. In older children, particularly those with healthcare-acquired infections (e.g., CLABSI), a vasodilatory picture may dominate with tachycardia, hypotension, bounding pulses,~~

warm peripheries, and flash capillary refill. In younger children with community-acquired infection (e.g., meningococcal sepsis), the phenotype is more likely to be one of impaired cardiac output due to the direct effects of bacterial toxins and inflammatory mediators on myocardial cell function and profound vasoconstriction (176). In this latter case the presentation may be with tachycardia, hypotension, cold peripheries, and prolonged capillary refill. Although observational studies have generally supported a role for fluid resuscitation in children with septic shock (8, 32, 33, 35, 177-180), the optimal rate, volume, and timing of fluid resuscitation across such variable physiologic presentations has not been conclusively demonstrated.

Three RCTs of different volume resuscitation strategies in children with septic shock in settings in which advanced supportive care (e.g., intubation, mechanical ventilation, and intensive care) was accessible have been published (181-183). These studies have a combined total of only 316 children and showed no difference in mortality between the restrictive and liberal fluid resuscitation groups.

In geographic settings in which advanced supportive care is limited and/or intensive care is not routinely accessible, the only large-scale RCT of different bolus fluid volume resuscitation strategies in severe infection in children was the Fluid Expansion as Supportive Therapy (FEAST) study (184). The FEAST study was conducted in Africa, in a low-resource setting without access to PICU admission. Among the 3141 study participants, malaria and anemia were highly prevalent. Overall, the RCT demonstrated a lower mortality after 48 hours in children receiving conservative fluid therapy (i.e., no bolus fluid, maintenance fluid only) than among those given liberal initial fluid therapy

(i.e., 20 mL/kg fluid bolus with maintenance fluid) with a RR of 0.72 (95% CI 0.57, 0.9). The FEAST study has resulted in some reluctance to use a high-volume fluid resuscitation strategy in critically ill children, even in settings in which intensive care is available.

The panel suggests administering up to 40-60 mL/kg fluid bolus therapy in the first hour of resuscitation in health care systems with availability of advanced supportive and intensive care, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop. Clinical markers of cardiac output can include heart rate, capillary refill, and urine output. Although no high-quality RCTs support this practice, several observational studies investigating this approach to resuscitation have reported improved patient outcomes with routine administration of up 40-60 mLl/kg fluid bolus therapy in the first hour of resuscitation (8, 32, 33, 36, 177-179, 185). Notably, the panel provides only a weak recommendation given that a more restrictive fluid resuscitation strategy has not been shown to be inferior and, indeed, may be superior in health care systems with limited availability of advanced supportive and intensive care, as seen in the FEAST trial. A weak recommendation (i.e., suggestion) to administer up to 40-60 mL/kg in bolus fluid therapy over the first hour indicates the panel's judgment that the majority of individuals in this situation would want this course of action, but different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient's circumstances.

The suggestion to limit initial fluid bolus resuscitation to 20 mL/kg in the first hour for children in low-resource settings where advanced supportive and intensive care is not available aligns with the World Health Organization (WHO) recommendations for

~~treatment of circulatory impairment in low-resource settings (14). A weak recommendation (i.e., suggestion) to administer *up to* 20 mL/kg in bolus fluid in healthcare systems with limited availability of advanced supportive and intensive care indicates the panel's uncertainty of whether this amount of fluid may cause harm in some patients without severe hypotension. Notably, no data support that such a restrictive approach to fluid resuscitation is beneficial in children with septic shock *and hypotension*, as even the subset of children in the FEAST study with severe febrile illness *and hypotension* were treated with 40 mL/kg of bolus fluid. (184) Therefore, cautious administration of fluid bolus therapy should be considered for the subset of children with septic shock *and hypotension* in low-resource settings. The WHO recommends 10-20 mL/kg of isotonic crystalloid over 30-60 minutes, followed by an additional 10 mL/kg over 30 minutes if condition has not improved (14).~~

~~Fluid boluses may be administered as 10 or 20 mL/kg, according to clinician preference. To facilitate rapid intravenous fluid administration (as well as other intravenous therapies, such as antimicrobials and vasoactive medications), clinicians should consider alternative methods of vascular access if initial attempts at peripheral vein cannulation are not immediately successful. Intraosseous access is rapid and effective and recommended by Pediatric Advanced Life Support (PALS), Advanced Pediatric Life Support (APLS), and the International Liaison Committee on Resuscitation (ILCOR). Ultrasound-guided peripheral intravenous catheter placement, CVCs, and umbilical venous catheter access are alternatives if the skills are immediately available (186, 187). In all healthcare systems, repeat boluses should only be administered after reassessment of hemodynamic status and if shock has not resolved.~~

Although fluid bolus therapy should be discontinued if signs of fluid overload are present or develop, early recognition of fluid overload by clinical examination is a challenge in children. Identifying fluid overload is especially difficult in young children, in whom crackles (rales) are often absent even in the context of gross pulmonary edema. Worsening respiratory status, particularly increasing respiratory rate, radiographic evidence of pulmonary edema in an intubated patient, or new or expanding hepatomegaly may be the only clues of evolving fluid overload. Bedside ultrasound may also be helpful to assess fluid overload, as there is emerging evidence to suggest that a "full" inferior vena cava with minimal variation across the respiratory cycle demonstrated on ultrasound indicates a fluid-replete circulation (192)~~(188)~~.

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 to crystalloids.**

Rationale: The FEAST trial investigated 3141 African children with infection and impaired perfusion, who were randomly assigned to resuscitation with 5% human albumin solution or 0.9% saline boluses or no boluses on admission to the hospital. Although both the albumin and 0.9% saline arms exhibited higher mortality than the no bolus arm, comparing human albumin solution to 0.9% saline (RR 1.02, 95% CI 0.8, 1.28) showed no difference in mortality (184)~~(184)~~. In the absence of any clear benefit

of albumin administration in children with sepsis, and in view of the additional costs in comparison to crystalloids, problems of availability, and the potential risk of blood-borne infection, we suggest against the routine use of albumin for initial fluid resuscitation in children with sepsis.

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).

Rationale: Increasing evidence from observational studies and RCTs in adults suggests that resuscitation with crystalloid fluids containing high chloride concentrations (e.g., 0.9% saline) is associated with hyperchloremic acidosis, systemic inflammation, acute kidney injury, coagulopathy, and mortality when compared to resuscitation with more balanced/buffered crystalloids (e.g., lactated Ringer's, PlasmaLyte) (193)~~(209)~~. Although no pediatric RCTs compare ~~balanced~~balanced/buffered crystalloids to 0.9% saline, there are 2 large observational studies in children with sepsis (194, 195)~~(210, 211)~~. They included a total of 30,532 children with sepsis, 2100 of whom received only ~~balanced~~balanced/buffered crystalloids for the first 72 hours of hospital admission, and 28,432 who received 0.9% saline (**Supplemental Table 5**). These studies showed that use of ~~balanced~~balanced/buffered crystalloids was associated with lower mortality (OR 0.79, 95% CI 0.65, 0.95) but not AKI (OR 0.98, 95% CI 0.94-1.02) (194, 195)~~(210, 211)~~. Indirect evidence from adult patients, including two large RCTs, also demonstrates benefit with ~~balanced~~balanced/buffered crystalloids over 0.9% saline, with adult patients

who received larger volumes of fluid and those with sepsis exhibiting the greatest benefit (193, 196)~~(209, 212)~~. Taken together, these data support that the desirable consequences of ~~balanced~~balanced/buffered crystalloids probably outweigh the undesirable consequences (including cost), especially in those who require large volume of fluid resuscitation. Therefore, pending further high-quality pediatric data, we suggest that ~~balanced~~balanced/buffered crystalloids should generally be preferred over 0.9% saline for resuscitation of children with septic shock or other sepsis-associated organ dysfunction without a specific indication for an alternative fluid type (e.g., 0.9% saline may be preferred in patients with hyponatremia or concern for increased intracranial pressure).

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).

Rationale: No studies compare starches with other fluids in children. However, in adults with severe sepsis and septic shock **(Supplemental Table 6)**, two large RCTs showed increased risk of mortality, coagulopathy, and AKI in patients receiving hydroxyethyl starch (HES) (197, 198)~~(213, 214)~~. A meta-analysis further confirmed the risk of harm with HES (199)~~(215)~~. In the US, the Food and Drug Administration (FDA) has restricted the use of HES (200)~~(216)~~ and the European Medicines Agency has recommended complete suspension of its use (201)~~(217)~~. Therefore, we strongly recommend against the use of HES in children with sepsis.

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).

Rationale: One RCT of gelatin-derived fluid in pediatric septic shock compared it to 0.9% saline in 60 patients. The estimates were imprecise, and showed no difference in mortality, days of using vasoactive medications, or AKI between the two groups (202)~~(218)~~ (**Supplemental Table ~~5~~7).** In the absence of any data indicating benefit of gelatin in children, we suggest against its use in pediatric sepsis.

E. HEMODYNAMIC MONITORING

24. We were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5th or 50th percentile for age in children with septic shock and other sepsis-associated organ dysfunction. However, in our practice, we target MAP to between the 5th and 50th percentile or >50th percentile for age.

Rationale: While no data from RCTs support specific hemodynamic targets in children, evidence suggests that targeting MAP of approximately 65 mmHg (5th percentile) in adults with septic shock may be beneficial (203)~~(189)~~. In the absence of evidence from RCTs, we were unable to reach consensus to recommend a specific MAP target for children. However, in our practice, 37% of panel members reported targeting MAP between the 5th and 50th percentile for age and 45% reported targeting MAP >50th percentile for age. Many panelists also commented that lower blood pressures are acceptable if other hemodynamic parameters (e.g., mental status, perfusion, urine

output, lactate) are improving. RCTs to define optimal hemodynamic targets, including MAP, are urgently required to inform practice in pediatric sepsis. In settings where direct measurement of MAP is less reliable, systolic blood pressure provides a reasonable alternative.

A previous recommendation to target perfusion pressure (MAP minus central venous pressure [CVP]) lacks supporting data (204)~~(190)~~. Prioritizing CVP measurement is also impractical during early resuscitation (such as in most pediatric emergency departments); CVP also provides an unreliable assessment of left ventricular preload.

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 ($ScvO_2$).

Rationale: The ACCM previously recommended clinical assessment of children in septic shock to differentiate "warm" versus "cold" shock based on extremity temperature, capillary refill, pulse strength, diastolic blood pressure, and pulse pressure.

Depending on “warm” or “cold” classification, different resuscitation strategies were suggested (e.g., fluid and vasopressors for “warm” shock and inotropes for “cold” shock). However, a number of observational studies have demonstrated very poor correlation of clinical assessments with cardiac index and systemic vascular resistance as measured by advanced monitoring (205-210)~~(191-196)~~. Indeed, many children who appeared to have “warm” shock by clinical examination had evidence of myocardial dysfunction, thus demonstrating the challenge of using clinical signs alone to direct therapy. Hence, we suggest not attempting to make this distinction using clinical assessments alone, though this categorical distinction may be helpful if advanced hemodynamic monitoring is available to assess patient physiology more accurately. Examples of advanced monitoring include invasive arterial blood pressure monitoring with pulse contour analysis, ultrasound Doppler of the ascending or descending thoracic aorta (suprasternal or esophageal Doppler), cardiac ultrasound/echocardiography (211)~~(197)~~, or measurement of $ScvO_2$ (212)~~(187)~~. All of these parameters (other than $ScvO_2$) will provide additional assessment of cardiac index and/or systemic vascular resistance index beyond clinical signs, which may then be used to direct and titrate treatment. There is also emerging evidence that fluid responsiveness may be predicted by aortic blood flow peak velocity variation (ΔV_{peak}) in mechanically ventilated children (213)~~(198)~~. In an RCT of 90 children admitted to a PICU in Egypt, addition of serial echocardiography provided early recognition of septic myocardial dysfunction and hypovolemia that was not apparent on clinical assessment and resulted in faster shock reversal, less fluid overload, shorter LOS, and lower mortality compared with the group without serial echocardiography (211)~~(197)~~. When advanced hemodynamic monitoring

is available, it is appropriate to target the normal range for parameters such as cardiac index, systemic vascular resistance index, stroke index, and $ScvO_2$ (**Table 5**). No evidence supports targeting a supranormal range of cardiac index.

Until recently, adult guidelines have recommended early goal-directed therapy (EGDT) based on the protocol published by Rivers et al in 2001(214)~~(199)~~. This recommendation described the use of a series of "goals" that included CVP and $ScvO_2$. This approach is no longer recommended following a failure to show reduction in mortality in 3 subsequent large multicenter RCTs (215-217)~~(200-202)~~. ~~These findings may reflect important improvements in sepsis resuscitation protocols in general, meaning EGDT (as described by Rivers et al.) no longer offers a significant advantage.~~ In children, there has only been one small RCT supporting the use of a protocolized approach including targeting $ScvO_2 > 70\%$. This study included 102 children with fluid-refractory septic shock and showed a reduced risk of death (RR 0.3, 95% CI 0.13, 0.68) from a very high baseline mortality of 39% ~~(26)~~(26). No high-quality RCTs have investigated other hemodynamic variables to guide therapy in children **(Supplemental Table 8, Supplemental Figure 3)**.

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.

Rationale: Although blood lactate is not a direct measure of tissue perfusion, increased lactate is associated with worse outcomes in children (11). Only one pediatric observational study of lactate-guided resuscitation, which included 77 children with sepsis in the ED, was available **(Supplemental Table 9)**. This study showed that lactate normalization was associated with a decreased risk of persistent organ dysfunction (RR 0.46, 95% CI 0.29, 0.73; adjusted RR 0.47, 95% CI 0.29, 0.78) (56). There is also indirect evidence from adult sepsis, with six RCTs (total of 1007 patients) evaluating lactate-guided resuscitation of patients with septic shock (218-223)~~(203-208)~~. The pooled estimates across all RCTs showed significant reduction in mortality compared to resuscitation without lactate monitoring (RR 0.66, 95% CI 0.55, 0.81) **(Supplemental Table 9)**. Therefore, while there was not sufficient evidence to propose a recommendation to measure lactate to differentiate low- versus high-risk of sepsis among children with infection or suspected infection (see ~~recommendation~~ Recommendation #2), we do suggest that blood lactate levels be used to help guide resuscitation of children with established septic shock or other sepsis-associated organ dysfunction.

F. 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. However, in our practice, we select either epinephrine or norepinephrine as the first-line vasoactive infusion guided by clinician preference, individual patient physiology, and local system factors.**

31. **We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock. However, in our practice, we often or sometimes administer a dilute concentration of the initial vasoactive medication through a peripheral vein if central venous access is not readily accessible.**

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, or sooner if fluid overload develops or other concerns for fluid administration are present. 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.

Rationale: Epinephrine and norepinephrine both have vasopressor and inotropic effects, are widely used, and are effective in treating children with fluid-refractory septic shock. No studies directly compare epinephrine with norepinephrine. However,

epinephrine has been compared to dopamine in two RCTs in children with fluid-refractory septic shock (224, 225)~~(219, 220)~~. Across both studies, epinephrine was associated with a lower risk of mortality (RR 0.63, 95% CI 0.40, 0.99) and more organ failure-free days among survivors by day 28 (MD 4 more days, 95% CI 2.0 to 6.0) (**Supplemental Table 10, Supplemental Figure 4**).

Norepinephrine has not been studied in children with septic shock, but in a randomized trial of norepinephrine versus saline in sedated, mechanically ventilated children, mortality was not different between groups~~lower with norepinephrine~~ (RR 0.50 95% CI 0.10-2.43, **Supplemental Table 11a**) but the norepinephrine group showed higher urine output (p=0.016) and improved blood pressure (p=0.04) suggesting improved perfusion relative to saline (226)~~(221)~~. Evidence from adult trials (**Supplemental Table 11b**) shows a lower mortality rate (RR, 0.93 95% CI 0.86-1.00) and lower incidence of arrhythmias (RR 0.48 95% CI 0.40-0.58]) with norepinephrine than with dopamine, and no difference in mortality with epinephrine than with norepinephrine (RR, 0.96 95% CI 0.77-1.21) (227)~~(222)~~.

Evidence is insufficient to recommend either epinephrine or norepinephrine as the initial vasoactive agent for children with fluid-refractory septic shock. In a survey of our panel members, an equal number used epinephrine and norepinephrine as the first-line vasoactive medication with a general preference for epinephrine to treat myocardial dysfunction and low cardiac output and for norepinephrine to increase systemic vascular resistance. It therefore seems reasonable to use either epinephrine or norepinephrine as the initial vasoactive agent, with the choice made based on individual patient physiology, clinician preference, and local system factors. Once cardiac

ultrasound/echocardiography or other advanced monitoring is available, selection of vasoactive therapy should be driven by individual patient physiology.

No pediatric data identify when shock becomes “fluid-refractory” and, thus, to guide when to start vasoactive infusions. However, excessive fluid resuscitation can lead to fluid overload, which has been associated with increased mortality in critically ill children (228)~~(223)~~. A trial comparing a fluid-sparing strategy with early initiation of vasoactive medications compared to a fluid-liberal resuscitation strategy is currently ongoing (SQUEEZE trial, Clinical Trials.gov NCT03080038). Until further data are available, we consider it reasonable to begin vasoactive infusions after 40-60 mL/kg of fluid resuscitation if the patient continues to have evidence of abnormal perfusion. Additional fluid resuscitation may be concurrently administered if the patient demonstrates physiologic improvement following each fluid bolus and without signs of fluid overload.

All vasoactive agents, including norepinephrine, may be initiated through peripheral venous (or intraosseous, if in place) access if central venous access is not readily available to avoid delays in therapy (229, 230)~~(224, 225)~~. However, central venous access should be obtained as soon as reasonably practicable. In our practice, 82% of panel members reported at least sometimes administering the initial vasoactive infusion peripherally if central venous or intraosseous access was not readily available, particularly in the emergency department or other non-PICU settings. Most panelists preferred epinephrine or dopamine to norepinephrine if peripheral infusion was needed. Although epinephrine or norepinephrine is the preferred first-line medication, dopamine

may be substituted as the first-line vasoactive infusion, administered either peripherally or centrally, if neither epinephrine nor norepinephrine is 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.

Rationale: Vasopressin-receptor agonists (vasopressin or terlipressin) have been studied in three RCTs in children **(Supplemental Table 12)**. Vasopressin was compared with saline in one study in children with vasodilatory shock (231)~~(226)~~ and in one study of children with severe lung disease (232)~~(227)~~. Terlipressin was compared with usual care in children with septic shock (233)~~(228)~~. The mortality rate (RR, 1.14 [0.80-1.62]) and ischemic events (RR, 1.56; 95% CI, 0.41-5.91) were higher vasopressin/terlipressin. There were fewer vasoactive-free days with vasopressin (median 25.2d in AVP (IQR 0.0-28.3), median 27.5d in control (IQR 23.1-28.9). In six RCTs in adults, renal replacement therapy was required less often with vasopressin (RR, 0.74 95% CI 0.51-1.08) (234)~~(229)~~. Weighing the benefit of avoiding renal replacement therapy against the potential harm from ischemic events and the non-significant difference in mortality, we suggest that vasopressin may be added or catecholamines may be further titrated in children on high doses of catecholamines.

33. We were unable to issue a recommendation about adding an inodilator in children with septic shock and cardiac dysfunction despite other vasoactive agents. However, in our practice, we sometimes use inodilators in children with septic shock and evidence of persistent hypoperfusion and cardiac dysfunction despite other vasoactive agents.

Rationale: There are no RCTs of inodilators (including milrinone, dobutamine, or levosimendan) in children with septic shock with persistent hypoperfusion and cardiac dysfunction. A report of two children described improvement in cardiac output with addition of inodilators (235)~~(230)~~. A case series of 10 children with meningococcal septic shock treated with milrinone described improved core-to-peripheral temperature gradient, with stable blood pressure and no change in acidosis (236)~~(231)~~. These data were not sufficient to formulate a recommendation. However, in our practice, 77% of panel members reported at least sometimes using inodilators in children with septic shock who had evidence of persistent hypoperfusion and cardiac dysfunction despite other vasoactive agents, typically in a PICU with advanced hemodynamic monitoring available.

G. VENTILATION

34. We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock. However, in our practice, we commonly intubate children with fluid-refractory, catecholamine-resistant septic shock without respiratory failure.

Rationale: There are no RCTs and/or observational studies of children receiving early intubation for refractory shock without respiratory failure compared to delayed or no

intubation for the same condition, nor is there suitable indirect evidence to substantiate a formal recommendation. However, it is well understood that a high metabolic demand from refractory shock typically indicated by progressive lactic acidemia and end-organ dysfunction can be, at least in part, mitigated by early invasive mechanical ventilation even without clinical symptoms of acute pulmonary edema or respiratory failure (237-239)~~(236-238)~~. Moreover, chest radiograph findings can "lag" behind clinical deterioration (240, 241)~~(239, 240)~~ such that patients with refractory shock and a "negative" chest radiograph may still progress toward more overt acute respiratory distress syndrome (ARDS). Lung ultrasound may provide an alternative tool to chest radiograph in detecting lung pathology, but its utility to identify which sepsis patients may benefit from early mechanical ventilation is not yet clear(242-245)~~(241-244)~~. For these reasons, 48% of panel members often or always and 35% sometimes intubate children with fluid-refractory, catecholamine-resistant septic shock even in the absence of clear respiratory failure, while 17% rarely or never do so. Of note, when intubating, caution should be exercised to avoid worsening hypotension or precipitating cardiac arrest as medications used for inducing anesthesia at the time of tracheal intubation, along with conversion from spontaneous breathing to use of positive pressure ventilation, may result in a transient deterioration in patient hemodynamics. The panel does recognize that in some settings, invasive mechanical ventilation may not be available or feasible—or may even be detrimental. In these instances, transport of the patient to a higher level of care can be life-saving.

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).

Rationale: Etomidate is a short-acting intravenous anesthetic agent that has been used for inducing anesthesia and sedation for tracheal intubation in patients with unstable hemodynamics. However, concerns regarding the drug's effect on adrenal function have been raised in adult studies. No RCTs exist in critically ill children with or without sepsis comparing etomidate to another anesthesia/sedative regimen. Two observational studies included children. One study from 1984 (246)~~(245)~~ enrolled acutely injured adults and children (44 intubated with etomidate versus 90 intubated with a benzodiazepine and opioid). A more recent study (247)~~(246)~~ enrolled children with meningococcal sepsis or septic shock with 23 intubated with etomidate as compared to 37 intubated with any other combination of sedatives. While caution must be taken given the small sample size, each of these studies reported higher mortality after use of etomidate (pooled OR 4.51, 95% CI 1.82, 11.16) **(Supplemental Table ~~8~~13).** In addition, den Brinker et al (247)~~(246)~~ reported a significant association of etomidate with adrenal insufficiency, with cortisol to adrenocorticotropin hormone (ACTH) ratios decreasing by 83% after etomidate exposure. Indirect evidence is available from 4 RCTs in adults (248-251)~~(247-250)~~. In the largest of these trials, Jabre et al (251)~~(250)~~ compared 234 critically ill adults intubated with etomidate to 235 intubated with an alternative medication regimen and found higher adrenal insufficiency in the etomidate group (OR 1.79, 95% CI 1.37, 2.36). Pooled odds of all 4 adult studies was 1.89 (95% CI 1.47, 2.44) with all studies suggesting significantly increased risk of

adrenal insufficiency after etomidate administration. Importantly, this effect was seen even after 1 dose of etomidate. Unfortunately, there is no conclusive evidence to recommend an optimal alternative induction agent to etomidate, though ketamine and fentanyl are routinely available and can offer favorable hemodynamic profiles in the setting of shock.

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

Remarks: When non-invasive mechanical ventilation is initiated, clinicians should carefully and frequently re-evaluate the patient's condition.

Rationale: Non-invasive mechanical ventilation with continuous positive airway pressure ventilation (CPAP) or bi-level positive airway pressure ventilation (BiPAP) may allow for decreased work of breathing and improved oxygenation in the face of sepsis-induced PARDS. Therefore, it is possible to avoid intubation in sepsis patients who are identified early with mild PARDS physiology and no evidence of advancing end-organ dysfunction. However, no RCTs in either critically ill children or children with sepsis-induced PARDS compare the effect of non-invasive ventilation to invasive mechanical ventilation on clinical outcomes. Observational studies have tested whether non-invasive mechanical ventilation could mitigate the need for invasive mechanical ventilation but none specifically focused on children with sepsis (252-258)~~(251-257)~~. We undertook a meta-analysis of 3 observational studies that evaluated the association of

non-invasive mechanical ventilation with mortality in a general PICU population (254, 256, 259)~~(253, 255, 258)~~. Using unadjusted estimates pooled from the data across all 3 studies, we found non-invasive ventilation to be associated with a decreased risk of death (RR 0.21, 95% CI 0.09, 0.47) (**Supplemental Figure ~~3~~5).** One additional RCT in immunocompromised children with acute respiratory dysfunction did not find that early non-invasive ventilation reduced intubation compared to standard care, but the trial was small (42 participants) due to low consent and overall slow recruitment and the direct relevance to children with sepsis-induced PARDS without a clear indication for intubation and who are responding to initial resuscitation was not clear (260)~~(259)~~. Thus, it is reasonable to try non-invasive mechanical ventilation in children with sepsis-induced PARDS who do not have a clear indication for intubation. However, non-invasive ventilation should be reserved for children with sepsis who are responding to initial resuscitation, do not have evidence for ongoing or worsening end-organ dysfunction, and in whom close monitoring and frequent re-evaluation can be ensured (255, 257, 261)~~(254, 256, 260)~~. This recommendation for children with sepsis-induced PARDS aligns with the 2015 PALICC (262)~~(261)~~ and 2017 Pediatric Mechanical Ventilation Consensus Conference (PEMVECC)(263)~~(262)~~ guidelines.

37. **We suggest using high positive end-expiratory pressure (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 fractional inspired oxygen (FiO_2) grid though adverse hemodynamic effects of high PEEP may be more prominent in children with septic shock.

Rationale: PEEP helps to prevent alveolar collapse, restore end-expiratory lung volume, and improve mean airway pressures, all of which help to improve adequate oxygenation in PARDS patients and minimize unnecessary use of high FiO_2. Adult ARDS patients have been successfully managed with judicious and strict application of a PEEP/FiO_2 grid, initially implemented in the ARDS-network ARMA trial (264)~~(263)~~. This grid has been applied in children with PARDS enrolled in RCTs (265)~~(264)~~, but a pediatric-specific PEEP/FiO_2 grid has not been determined or validated. In 2017, a multi-center observational study by the Collaborative Pediatric Critical Care Research Network reported that pediatric critical care clinicians almost uniformly limit PEEP to 10 cm H_2O irrespective of oxygenation and FiO_2 (266)~~(265)~~. This is in contrast to the PEMVECC (263)~~(262)~~ and PALICC (24) recommendations for use of PEEP in excess of 15 cm H_2O for severe PARDS patients. Our panel reviewed several observational studies of PARDS patients, all published since 2007, each including 12-30% sepsis-induced PARDS (266-278)~~(265-277)~~. The largest, a multicenter study by Khemani et al (278)~~(277)~~, evaluated 1,134 PARDS patients of whom 26% were managed with lower PEEP relative to ARDSnet protocol and experienced greater mortality than those managed in accordance with a higher PEEP strategy as recommended by the ARDSnet PEEP/FiO_2 grid **(Supplemental Table 14)**. After adjustment for relevant co-morbidities, pediatric patients managed with a PEEP strategy at or above that recommended by the ARDSnet low PEEP/FiO2 grid had a decreased odds of death compared to children

managed with PEEP lower than that recommended by the ARDSnet low PEEP/FiO2 grid (adjusted OR 0.50, 95% CI 0.31-0.81).

The panel concluded that PEEP levels >10 cm H_20 may be necessary with progressive hypoxemia, with the precise amount of "high" PEEP carefully titrated for each individual while attending to the potential adverse hemodynamic effects of increasing intrathoracic pressure in children with septic shock. Therefore, although the optimal approach to setting PEEP has not yet been determined in children with PARDS, carefully increasing PEEP for children with sepsis-induced PARDS who require FiO2 exceeding 60% and/or exhibit ongoing hypoxemia is reasonable, rather than continuing to manage such children with a low- or moderate- PEEP strategy of ≤10 cm H_2O.

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.

Rationale: ARDS is characterized by decreased lung compliance, risk for atelectasis, and increased intrapulmonary shunt. Recruitment maneuvers have been used in both children and adults temporarily to increase transpulmonary pressure to recruit lung units with the goal of improving both oxygenation and ventilation. Most recruitment maneuvers include either sustained inflation or a step-wise incremental or decremental

PEEP titration methodology. However, many clinicians and researchers remain concerned that the optimal strategy for lung recruitment has not been determined and injudicious implementation of recruitment maneuvers can result in hemodynamic compromise (279)~~(278)~~, hypercarbia (280)~~(279)~~, and/or ventilator-induced lung injury (281)~~(280)~~. PEMVECC did not recommend use of recruitment maneuvers in children, citing an overall lack of evidence in this area (263)~~(262)~~. In contrast, the 2015 PALICC provided a weak recommendation in favor of recruitment maneuvers with prioritization of a slow stepwise incremental and decremental PEEP method (24).

Two observational studies are potentially informative about use of recruitment maneuvers in children with sepsis-induced PARDS ~~(268, 269)~~(269, 270). (**Supplemental Table ~~10~~15.**) First, Boriosi et al (282)~~(281)~~ enrolled 21 children with lung injury, of whom 66% had sepsis, and used incremental PEEP recruitment maneuvers. Patients experienced improved oxygenation as measured by both the partial pressure of oxygen in arterial blood to FiO_2 ratio (PaO_2/FiO_2 or P/F) and alveolar-to-arterial oxygen (A-a O_2) gradient for the 4 hours after recruitment. Second, Duff et al (283)~~(282)~~ enrolled 32 children and used the sustained inflation technique, which also resulted in improved oxygenation for the ensuing 6 hours. However, neither study tested the association of recruitment maneuvers with clinical outcomes, such as ventilator days or mortality. Consequently, despite the potential for benefit for some patients coupled with the possibility of harm (284, 285)~~(283, 284)~~, insufficient data do not allow us to recommend either for or against recruitment maneuvers in sepsis-induced PARDS patients at this time.

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 hours per day, as tolerated.

Rationale: Prone positioning almost uniformly improves oxygenation in adults with ARDS and children with PARDS. While the exact mechanisms continue to be elucidated, prone position has been shown to recruit areas of collapsed, de-recruited lung with resultant improved elastance, decreased lung stress and strain, and improved functional residual capacity (286)~~(285)~~. Given that pulmonary perfusion is thought to be consistent both dorsally and ventrally, an improvement in lung aeration can be met with continued perfusion, thereby reducing ventilation-perfusion mismatching (287)~~(286)~~. Most recent RCTs in adults support use of prone positioning as a potentially life-saving management strategy (**Supplemental Table 16**), especially in those meeting severe ARDS criteria (i.e., P/F <150 mmHg) (288)~~(287)~~. This benefit is seen particularly in patients who are positioned for prolonged periods of time, most commonly reported as 12-20 hours per day. Two pediatric RCTs tested the use of prone positioning in PARDS patients (265, 289)~~(264, 288)~~. Pooled analyses of these two studies yielded a RR of 0.99 (95% CI 0.36, 2.69) for mortality in prone positioning as compared to supine positioning for this patient population (**Supplemental Table 16, Figure 6**). Importantly, no serious adverse events were reported in these trials, although the prone positioning methodology was protocolized in each with particular attention to avoid accidental endotracheal extubation and pressure injury. PALICC (24) did not recommend routine use of prone positioning in PARDS patients but suggested its consideration in severe

PARDS. The panel noted that the National Institutes of Health (NIH) has approved and funded an international RCT of prone positioning in severe PARDS (ClinicalTrials.gov identifier NCT02902055).

40. We recommend against the routine use of inhaled nitric oxide (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)

Rationale: The presumptive mechanism of sepsis-induced PARDS involves alveolar epithelial injury, vascular endothelial injury, and activation of inflammatory, fibrosis, and coagulation cascades. As such, PARDS is not a disease process primarily of pulmonary arterial hypertension, the therapeutic target of iNO therapy, and so is not recommended for routine use in children with sepsis-associated PARDS. Nonetheless, many PARDS patients have co-morbidities that include risk for pulmonary hypertension (e.g., chronic lung disease after prematurity, congenital heart disease after repair or palliation) or clinical features, such as acidemia and hypoxemia, that ~~. Further, many manifestations of PARDS, especially severe PARDS, will~~ increase ~~endogenous~~ pulmonary arterial pressures~~. including acidosis and hypoxemia, thus increasing shunt fraction.~~ Thus, inhaled nitric oxide therapy may be considered in children with documented pulmonary hypertension or severe right ventricular dysfunction (241, 290)~~Inhaled nitric oxide therapy~~ (REF). Such use of iNO in sepsis must be balanced against its lack of

availability or high cost in many areas of the world and, that ~~is not available in many parts of the world and, in others, is extremely costly. In the US, FDA approval for iNO treatment is restricted to use in patients with primary pulmonary hypertension. Finally,~~ once in place, iNO use carries a potential patient safety consideration as inadvertent and abrupt discontinuation of the therapy can result in a rapid and potentially life-threatening rebound pulmonary hypertensive crisis.

Several small RCTs (291-293)~~(289-291)~~ and observational studies have described significant improvement in oxygenation after iNO therapy (294)~~(292)~~. Many, but not all, of these studies include patients with sepsis (292, 293, 295-298)~~(290, 291, 293-296)~~, and few analyze longer term, clinically relevant outcomes such as mortality. A 2016 Cochrane review indicated no mortality benefit from iNO administration (RR 0.78, 95% CI 0.51, 1.18) in 3RCTs (299)~~(297)~~. Our analysis of two recent observational studies, one conducted in children on ECMO and another in children with severe PARDS, respectively, suggest possible increased mortality risk (296, 298)~~(294, 296)~~, whereas one RCT of 55 PARDS patients indicated improved duration of mechanical ventilation in PARDS survivors (293)~~(291)~~ **(Supplemental Table 17, Supplemental Figure ~~4~~ 7 ~~Table 12~~)**~~.~~ Taken together, these data do not support *routine* use of iNO in all children with sepsis-induced PARDS but do raise the potential for benefit as an emergency rescue therapy for severe, sepsis-induced PARDS with refractory hypoxemia after other oxygenation strategies have been optimized. Emergency rescue use of iNO may allow time to realize benefit from other therapies, such as lung recruitment, or provide a bridge to ECMO or another intervention. However, when iNO is used, we agree with the PALICC recommendation that “assessment of benefit must

be undertaken promptly and serially to minimize toxicity and to eliminate continued use without established effect" (24). These recommendations align with the 2004 guidelines for use of iNO therapy in neonates and children issued by the European Society for Pediatric and Neonatal Intensive Care (300)~~(298)~~, PALICC guidelines (24), and a 2017 Cochrane review (294)~~(292)~~ as no relevant change in evidence has become available.

42. We were unable to issue a recommendation to use high-frequency oscillatory ventilation (HFOV) versus conventional ventilation in children with sepsis-induced PARDS. However, in our practice, there is no preference to use or not use HFOV in patients with severe PARDS and refractory hypoxia.

Rationale: HFOV provides a sustained mean airway pressure with superimposed high frequency, pendelluft-type, oscillatory breaths that may improve oxygenation in patients with moderate-to-severe lung disease while minimizing barotrauma, volutrauma, and atelectrauma. However, the most efficacious timing of application, optimal settings, and ideal population of patients likely to benefit have not been well established. HFOV may be difficult to apply effectively in centers with little experience, and is not universally available. Despite these practical limitations, both PALICC (24) and PEMVECC (263)~~(262)~~ endorsed cautionary use of HFOV as an alternative type therapy in patients with severe PARDS. In our panel, clinicians who use versus those who do not use HFOV in patients with severe PARDS and refractory hypoxia were nearly evenly distributed.

Application of HFOV in adult ARDS patients has yielded concerning results due to a potentially increased mortality observed in the adult OSCILLATE RCT (301)~~(299)~~ and a

neutral result in the adult OSCAR RCT (302)~~(300)~~. Pediatric data include 2 observational studies with a non-HFOV control group and 3 randomized trials. In the two observational studies, oxygenation improved with HFOV relative to conventional ventilation but there was a non-significant trend toward increased mortality (Guo et al: 34.6% versus 22.7%, adjusted OR 2.74, 95% CI 0.52, 14.6; Bateman et al: 25% versus 17%, adjusted OR 1.28, 95% CI 0.92, 1.79)(303, 304)~~(301, 302)~~. Among three small RCTs, however, a trend toward reduced mortality in those managed with HFOV was observed (pooled RR 0.77, 95% CI 0.43, 1.36)(305-307)~~(303-305)~~. A large, multi-center, international RCT of HFOV compared to conventional mechanical ventilation in severe PARDS patients, including children with and without sepsis, is underway and will seek to address many of these issues (www.clinicaltrials.gov/ NCT02902055).

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 to 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 hours after ARDS onset.

Rationale: Indirect evidence from 3 adult RCTs (308-310)~~(306-308)~~ found that early use of neuromuscular blocking agents (NMBAs) for up to 48 hours in adults with severe ARDS, defined as PaO_2/FiO_2 ratio <150 mmHg, improved 90-day survival and shortened duration of mechanical ventilation without increasing muscle weakness. In a multi-center double-blind RCT (310)~~(308)~~, 340 patients with early severe ARDS, meeting criteria within 48 hours, were randomized to receive either cisatracurium

besylate or placebo once adequately sedated. After adjustment for baseline PaO_2/FiO_2, plateau pressure, and the Simplified Acute Physiology Score, the cisatracurium group had a hazard ratio for death at 90 days of 0.68 (95% CI 0.48, 0.98) compared to the placebo group. Early use of NMBAs was also associated with decreased organ system dysfunction, less air leak, and a decreased pro-inflammatory response (311)~~(309)~~. These findings remained consistent when combined with earlier smaller studies from the same group of investigators in a meta-analysis. However, a more recent adult trial of early neuromuscular blockade in those with moderate to severe ARDS was stopped for futility at the second interim analysis (enrollment of 1006 patients) with a 90-day mortality difference of 42.5% in the intervention limb versus 42.8% in the control limb. In this study, the intervention group received continuous cisatracurium and deep sedation for 48 hours compared to the control arm that received lighter sedation targets (Richmond Agitation Scale of 0 to -1). Both limbs received low tidal volume ventilation with high PEEP strategy. Notably, only 13.8% of patients enrolled in ROSE had non-pulmonary sepsis as a primary diagnosis.

In pediatrics, there are no prospective data regarding the use of NMBAs in PARDS (with or without sepsis), although there is an ongoing pediatric trial in the Netherlands (Clinical Trials.Gov NCT02902055). In one large retrospective study of 317 children with PARDS, of whom 23% experienced sepsis-induced PARDS (312)~~(310)~~, mortality was lower in those children treated with neuromuscular blockade (8.8% versus 17.7%). However, duration of mechanical ventilation was longer in the treatment group and proportion with neuromuscular weakness was not assessed **(Supplemental Table ~~13~~18).**

H. ~~ENDOCRINE AND METABOLIC THERAPIES~~CORTICOSTEROIDS

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

45. We suggest that either intravenous 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).

Rationale: A potential role for intravenous hydrocortisone as adjunctive therapy for septic shock is supported by various roles of cortisol in homeostasis and the stress response. For example, cortisol directly decreases reuptake of norepinephrine (313)~~(320)~~, augments beta-adrenergic receptor sensitivity in the heart, and enhances calcium availability in myocardial and vascular smooth muscle cells (314)~~(321)~~ promoting myocardial contractility and vasoconstriction, respectively. Cortisol helps to inhibit prostacyclin and endogenous nitric oxide production, resulting in increased vascular tone (315)~~(322)~~, modulation of capillary leak (316)~~(323)~~, and augmentation of the beta-adrenergic receptor in the heart ~~resulting in improved myocardial contractility~~ (315)~~(322)~~. However, potential adverse side effects of corticosteroid therapy ~~prescription must be considered, such as~~include hyperglycemia (317, 318)~~(324, 325)~~, catabolism-related diffuse neuromuscular weakness (including the diaphragm) (319, 320)~~(326, 327)~~, and hospital-acquired infections (321)~~(328)~~. These effects ~~that~~ may be

under-appreciated in critically ill patients, but can~~could~~ contribute to worse outcomes (322)~~(329)~~.

At least one pediatric (323)~~(330)~~ and several adult (324)~~(331)~~ interventional trials examining adjunctive corticosteroids for septic shock have concluded that this drug class hastens resolution of shock. Of the four adult, high-quality contemporary RCTs, two reported a ~~benefit in terms of~~ mortality reduction and two did not (325-329)~~(332-336)~~. A recent meta-analysis of 42 RCTs including 9,969 adults and 225 children ~~(overall mean age 49.5 years)~~ with sepsis found that corticosteroids possibly result in a small reduction in short-term mortality (RR 0.93, 95% CI 0.84, 1.03), long-term mortality (0.94, 95% CI 0.89, 1.00), faster resolution of shock, and shorter LOS, while also possibly increasing the risk of neuromuscular weakness (RR 1.21, 95% CI 1.01, 1.52) (330)~~(337)~~. Despite a weak recommendation to treat sepsis with hydrocortisone based on the findings noted in the overall meta-analysis (331)~~(338)~~, the ~~no improvements in mortality were reported in any of the published pediatric RCTs, and the~~ pediatric studies enrolled a combined small number~~s~~ of subjects, reported inconsistent conclusions, ~~and~~ had methodologic limitations, and did not demonstrate an overall mortality reduction (323, 332-334)~~(330, 339-341)~~ **(Supplemental Table ~~15~~19)**.

~~Several pediatric descriptive cohort investigations~~Observational cohort studies have reported either harm or no benefit with hydrocortisone in ~~pediatric~~ children with septic shock (5, 335-339)~~(5, 342-346)~~. For example, a retrospective analysis of the REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE (RESOLVE) trial of activated protein C in pediatric sepsis found no differences in mortality, duration of mechanical ventilation and vasoactive-inotropic support, or PICU

stay among 193 children who received and 284 who did not receive open-labeled corticosteroids ~~database facilitated examination of the role of adjunctive corticosteroids on outcomes in pediatric septic shock~~ (336)~~(343)~~. Despite the *post hoc* analysis, ~~A~~age, sex, PRISM-III scores, baseline number of dysfunctional organs, and baseline Pediatric Overall Performance Category scores did not differ between corticosteroid-treated and corticosteroid non–treated groups. ~~In this trial designed to examine the potential benefit of adjunctive activated protein C in pediatric sepsis, 193 subjects received adjunctive corticosteroids (mostly for septic shock) and 284 did not. Age, sex, PRISM-III scores, baseline number of dysfunctional organs, and baseline Pediatric Overall Performance Category scores did not differ between corticosteroid-treated and corticosteroid non–treated groups. Outcomes of mortality, duration of mechanical ventilation and vasoactive-inotropic support, and PICU stay did not differ between the two groups.~~

Several pediatric and adult ~~retrospective and prospective~~ studies have attempted to use random cortisol and/or cosyntropin-stimulated cortisol serum concentrations to identify which patients with septic shock ~~would~~may benefit from hydrocortisone therapy, but reliable cutoffs have not ~~yet to be~~ been clearly identified. ~~Many issues have been raised with regard to assessment of adrenal adequacy in this setting, including~~Challenges relate to variability in~~:~~ 1) the cortisol assay itself; 2) cortisol metabolism (11-beta-hydroxysteroid dehydrogenase) during sepsis; 3) corticosteroid-binding globulin concentrations; and 4) multiple tissue (e.g., elastase, anti-glucocorticoid compounds) and cellular (e.g., glucocorticoid receptor) factors. Therefore, use of random cortisol or stimulation tests to guide corticosteroid prescription in children with septic shock cannot be recommended as this time. However, for ~~In~~ any patient ~~where~~

~~the clinician is concerned about the presence of~~ with a clinical concern for primary adrenal insufficiency (e.g., a patient with significant and unexplained hypoglycemia, hyponatremia, and/or hyperkalemia), a high-dose cosyntropin-stimulation test should be performed. Interpretation should focus on the baseline serum ACTH concentration (above normal indicating primary adrenal insufficiency) and the 60-minute stimulated serum cortisol concentration (<18 µg/dL indicating primary adrenal insufficiency) (340)~~(347)~~.

In summary, no high-quality investigations currently support or refute the routine use of adjunctive corticosteroids for pediatric septic shock or other sepsis-associated organ dysfunction. At the time of this publication, an RCT is in progress to examine the potential risks and benefits of adjunctive hydrocortisone for fluid and vasoactive-inotropic recalcitrant septic shock in children. However, this uncertainty does not apply to ~~for~~ children presenting with septic shock or other sepsis-associated organ dysfunction who also have acute or chronic corticosteroid exposure, hypothalamic-pituitary-adrenal axis disorders, congenital adrenal hyperplasia or other corticosteroid-related endocrinopathies, ~~and~~ or have recently been treated ~~treatment~~ with ketoconazole or etomidate, ~~there is no disagreement that~~ for whom prescription of stress-dose hydrocortisone is indicated, with or without evaluation of the adrenal axis (341)~~(348)~~.

I. ENDOCRINE AND METABOLIC

46. We recommend against insulin therapy to maintain a blood 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 or other sepsis-associated organ dysfunction. However, in our practice, there was consensus to target blood glucose levels below 180 mg/dL (10 mmol/L) but there was not consensus about the lower limit of the target range.

Rationale: While hyperglycemia has been associated with poor outcomes in numerous studies of critically ill children and adults, three prospective multicenter randomized clinical trials of glucose control to a low target range (including 50-80, 70-100, 72-126, 80-110 mg/dL or 2.8-4.4, 3.9-5.6, 4.0-7.0, 4.4-6.1 mmol/L) have not demonstrated clinical benefit in children (342-344)~~(377-379)~~ (**Supplemental Table 20**). One single-center RCT did show substantial mortality benefit, but there was a high rate of severe hypoglycemia and the higher target range cohort had substantially higher blood glucose levels than those used in the other multicenter RCTs (345)~~(380)~~. A trial involving children with burn injuries, a unique PICU population, demonstrated no mortality benefit, but did find a significant reduction in morbidity (346)~~(381)~~. Notably, all trials included sepsis patients but none targeted them exclusively. Meta-analyses of all published prospective trials in children have shown no clinical benefits overall, but showed a substantially higher risk of hypoglycemia when using insulin therapy to maintain a glucose target below 140 mg/dL (7.8mmol/L) (347, 348)~~(382, 383)~~. Even brief episodes of severe hypoglycemia during septic shock in children may be a risk factor for poor long-term developmental outcomes (349-352)~~(384-387)~~.

Treating hyperglycemia ≥180 mg/dL (≥10 mmol/L) may be desirable as incidence of insulin-induced hypoglycemia in the studied pediatric cohorts with targets of 140-180

mg/dL (7.8-10.0 mmol/L) is extremely low. There are, however, no direct comparisons between treatment to <180 mg/dL (10.0 mmol/L) and no treatment. Therefore, evidence cannot definitively guide this therapeutic target. However, given that the guidelines for adults recommend an upper limit of 180 mg/dL (10 mmol/L) and given the lack of harm demonstrated in the pediatric trials with those targets, treating children with septic shock or other sepsis-associated organ dysfunction with intravenous insulin with a goal upper blood glucose target of 180 mg/dL (10 mmol/L) is reasonable. The lower target, i.e., the glucose concentration below which insulin infusion should be discontinued, has also not been specifically studied, but is reasonable to set at 140-150 mg/dL (7.8-8.3 mmol/L), based on similar principles. In a survey of our panel members, 32.5% always or often and 17.5% sometimes target glucose levels between 140 and 180 mg/dL. Regardless of the glucose target, the overriding goal during insulin therapy should be avoidance of hypoglycemia.

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. However, in our practice, we often target normal calcium levels for children with septic shock requiring vasoactive infusion support.

Rationale: Calcium has an essential role in nearly all cellular processes, including myocardial contractility and vasomotor tone. As such, intracellular and circulating levels of calcium are tightly regulated. During septic shock, derangements in calcium regulation frequently occur in critically ill adults and children. However, a systematic

review of adult literature found no evidence to support treating hypocalcemia of critical illness (353)~~(420)~~. Calcium supplementation may actually worsen organ dysfunction and is correlated with adverse outcomes in critically ill adult patients receiving PN (354)~~(421)~~. Although the prevalence of hypocalcemia in critically ill children has been reported to be up to 75% and is associated with organ dysfunction (355)~~(422)~~, no studies in children with septic shock have investigated the effect of calcium supplementation to treat hypocalcemia. However, in our practice, 65% of panel members always or often and 20% sometimes target normal calcium levels with parenteral calcium administration in children with septic shock requiring vasoactive infusion support. Only 15% of panel members rarely or never target normal calcium levels.

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).

Rationale: Critically ill children, similar to adults, develop low tri-iodothyronine (T3) and low normal thyroxine (T4) concentrations without the compensatory rise in thyroid stimulating hormone (TSH) that is typical of the "sick euthyroid" state or hypothyroxinemia of non-thyroidal illness (356)~~(423)~~. The decrease in T3 is due both to increased thyroid hormone turnover and to decreased de-iodination of T4 to T3, with redirection of T4 metabolism toward higher levels of biologically inactive reverse T3. The magnitude of the drop in T3 within the first 24 hours of illness reflects the severity of illness (357)~~(424)~~. Although of theoretical benefit, few trials of thyroid hormone

replacement have been conducted in critically ill children and none in children with sepsis. Two prospective RCTs in children undergoing cardiac surgery (without sepsis) showed no difference in mortality, vasoactive days, or PICU LOS (358, 359)~~(425, 426)~~. One open-label study in premature neonates also showed no difference in clinical outcomes (360)~~(427)~~. Taken together, there are no direct data to inform a recommendation for children with sepsis, and no indirect data from other critically ill children to support a recommendation for the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state.

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).

Rationale: Fever is a complex physiologic response associated with sepsis, and it remains unclear whether fever is a beneficial (361)~~(428)~~ or a harmful (362)~~(429)~~ response to infection. Potential benefits include inhibiting the growth of some pathogens and increased neutrophil production and lymphocyte proliferation. Conversely, fever is associated with an increased metabolic rate (which may or may not have detrimental effects in patients with sepsis) and may impair some components of immune function. Fever can also make patients uncomfortable (363)~~(430)~~. Thus, the putative benefits of maintaining normothermia by treating fever are unclear.

No direct evidence for or against the use of antipyretics in febrile children with sepsis-associated organ dysfunction exists. Rather, the panel had to consider indirect

data extrapolated from studies in adults. One systematic review of adult patients studied the use of antipyretics and physical cooling methods included 8 RCTs (1507 patients) and 8 observational studies (17,432 patients) (364)~~(431)~~. This study had 28-day mortality as the primary outcome, with additional outcomes of early mortality (i.e., death on or prior to day 14), frequency of acquisition of hospital-acquired infection, frequency of shock reversal, and mean changes in body temperature, heart rate, and minute ventilation. No difference was noted in 28-day mortality. Effects on early mortality differed between the randomized (favored reduced mortality with antipyretic therapy) and observational (favored increased mortality with antipyretic therapy) studies. While antipyretic therapy successfully decreased body temperature, there was no effect on heart rate, minute ventilation, shock reversal, or acquisition of nosocomial infections. This study did not assess outcome measures of patient comfort. Based on available data, we are not able to recommend the optimal approach to fever in children with sepsis. However, it is reasonable to provide antipyretic therapy to optimize patient comfort, to reduce metabolic demand under certain clinical scenarios (e.g., refractory shock, pulmonary hypertension), and to reduce extreme body temperatures.

J. NUTRITION

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

feeding. However, in our practice, there is a preference to commence early enteral nutrition within 48 hours of admission in children with septic shock or sepsis-associated organ dysfunction who have no contraindications to enteral nutrition and to increase enteral nutrition in a stepwise fashion until nutritional goals are met.

Rationale: No studies examine the enteral nutrition advancement strategy in children with septic shock or other sepsis-associated organ dysfunction. Indirect evidence from a small RCT in critically ill children examines early (6-24 hour) versus late enteral nutrition (>24 hour) in, respectively, 57 and 52 children (365)~~(349)~~. Early enteral feeding had no effect on duration of PICU stay, but a trend toward better survival in the early feeding group (30% in early feeding versus 48% in late feeding, p=0.07) was shown. There is also indirect evidence from the EDEN trial in adults (366)~~(350)~~ in which 200 patients were randomized to receive either trophic or full enteral feeding for the first 6 days. This study demonstrated no difference in number of ventilator-free days, mortality at 60 days, or infectious complications, but trophic enteral feeding was associated with less gastrointestinal intolerance. Because neither of these studies was conclusive nor directly studied children with septic shock or other sepsis-associated organ dysfunction, no evidence-based recommendation could be made by the panel. However, in critically ill children, a stepwise approach to increasing enteral feeds has been shown to reduce time needed to reach nutritional goals (367-370)~~(351-354)~~. In our practice, 60% of panel members always or often and 20% sometimes commence early enteral feeding within 48 hours of admission in children with septic shock or sepsis-associated organ

dysfunction who have no contraindications to enteral nutrition, while 20% of panel members rarely or never pursue this practice.

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.

Rationale: We reviewed indirect evidence from three observational studies (two retrospective and one prospective) in post-operative/cardiac pediatric populations. These studies reported that enteral feeding was tolerated in patients on non-escalating/weaning doses of vasoactive agents without increased adverse effects or gastrointestinal complications (371-373)~~(355-357)~~. In another study of 339 critically ill children, there was no association between enteral feeding and the development of severe gastrointestinal outcomes such as vomiting, diarrhea, abdominal distension, bleeding, necrotizing enterocolitis, or perforation (371)~~(355)~~. However, in the report, the decision to start enteral nutrition may have been biased by the clinical condition of the patient. In a retrospective study of 52 critically ill children, the use of vasoactive medications was not associated with an increase in feeding intolerance or gastrointestinal complications (372)~~(356)~~. In a prospective observational study of critically ill children who received post-pyloric feeding, 44/65 (67.7%) of patients with shock and 284/461 (61.6%) of patients without shock received enteral nutrition within 48

hours. Although gastrointestinal complications were more common in children admitted with shock, no association between the incidence of digestive tract complications and early (first 48 hours) or late administration of post-pyloric enteral nutrition was reported (373)~~(357)~~. Based on these studies which, while providing indirect evidence, all consistently found that enteral feeding was not associated with harm, we recommend not to withhold enteral nutrition solely because vasoactive-inotropic medications are being used. Current evidence supports starting enteral nutrition in hemodynamically stable patients who are no longer requiring fluid resuscitation or escalating doses of vasoactive agents.

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

Rationale: No studies have been published on this specific issue of nutrition in children with septic shock or other sepsis-associated organ dysfunction. However, in a general cohort of 1440 critically ill children enrolled in the international multicenter RCT of pediatric early versus late PN in critical illness (374)~~(358)~~, withholding parenteral nutrition during the first week in PICU when enteral nutrition was less than 80% of prescribed goal was clinically superior to providing supplemental parental nutrition within 24 hours of admission (375)~~(359)~~. Secondary analyses of the PEPaNIC trial showed that withholding PN was also beneficial in term neonates and children who were undernourished at admission (376, 377)~~(360, 361)~~, though withholding parenteral

nutrition in term neonates was also associated with increased risk of severe hypoglycemia (376)~~(360)~~. A long-term follow-up 2 years after PICU admission showed that withholding parenteral nutrition for 1 week did not affect survival, anthropometrics, or health status, but did improve certain domains of neurocognitive development (378)~~(362)~~. Although the results of the PEPaNIC trial corroborated the findings from adult RCTs, the optimal timing of parenteral nutrition in the critically ill child with sepsis is still not clear (374, 379-381)~~(358, 363-365)~~. Our recommendation is based on one trial and therefore, the evidence to withhold PN in the first 7 days of PICU admission is of moderate certainty and must be explored further using pragmatic timing for PN in the first week, particularly in severely malnourished patients and neonates.

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).

Rationale: In two RCTs evaluating immunomodulatory formulas, including lipid emulsions, in critically ill children, outcomes were not significantly different (382, 383)~~(366, 367)~~. One RCT was terminated during interim analysis because of unlikely benefit in the intervention arm (383)~~(367)~~. In another small RCT, use of enteral feeding supplemented with or without omega-3 fatty acids in 120 critically ill children with sepsis was investigated (384)~~(368)~~. Univariate analyses showed a significant difference in inflammatory mediators and reduction in PICU LOS, but these outcome benefits were not evident in the multivariable analyses. Taken together, although promising,

insufficient evidence is available to support routine supplementation in pediatric sepsis with specialized lipid emulsions.

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

Rationale: Although routine measurement of GRV is a relatively common practice in PICUs, there is no direct evidence in pediatric sepsis. In a two-center observational cohort study of critically ill children admitted with a variety of diagnoses, one center reported routine use of GRV monitoring while the other center did not practice GRV measurements (385)~~(369)~~. The center that advanced enteral nutrition without routine measurements of GRV did not have an increase in the incidence of vomiting, ventilator acquired pneumonia, or necrotizing enterocolitis in comparison with the other PICU (**Supplemental Table 21**). Although there are likely some children for whom measuring GRV would likely be useful (e.g., gastroparesis, omphalocele, gastroschisis), no evidence supports routine measurements in all patients at this time and, if measured, GRV is not sufficient to diagnose EN intolerance.

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)

Rationale: In 3 small RCTs, gastric versus post-pyloric enteral feeding were compared in mechanically-ventilated children with a variety of diagnoses (386-388)~~(370-372)~~. The outcomes reported included lower caloric achievement with gastric feeding and delayed start of enteral feeding with post-pyloric feeding (386, 387)~~(370, 371)~~. No significant difference was found in the incidence of ventilator-associated pneumonia between gastric and post-pyloric feeding (388)~~(372)~~. On the basis of these studies, there is no clear evidence that post-pyloric feeding is beneficial and there is concern for potential harm through delayed optimization of enteral nutrition. Therefore, we suggest that feeding with a gastric tube is physiologic and, based on current evidence, the preferred method for enteral nutrition. Post-pyloric feeding may be considered in patients in whom gastric feeding is either contraindicated (e.g., high-risk for aspiration) or was not tolerated/advanced, and as a result, nutritional goals were unable to be met.

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).

Rationale: Prokinetic agents, such as metoclopramide and erythromycin, are often used in the PICU in an effort to reduce feeding intolerance (389)~~(373)~~. Indirect evidence for this question was provided from the only pediatric randomized control trial, which was a combined intervention of enteral zinc, selenium, glutamine, and intravenous metoclopramide. In critically ill children, this combined intervention failed to reduce the development of sepsis or incidence of hospital-acquired infection in immunocompetent

children, although the intervention including metoclopramide did reduce the rate of hospital-acquired infection and sepsis in immunocompromised children. However, the application of this study to children who already have sepsis is not clear. Prokinetic agents are also not without risk as they have been associated with prolongation of the QT interval and ventricular arrhythmias (390-392)~~(374-376)~~. Further investigation is needed to determine if prokinetic agents are beneficial in patients with sepsis, particularly in immunocompromised children.

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).

Rationale: Although clinical research examining the use of selenium among critically ill neonates and adults has been done **(Supplemental Table 22)**, there no data regarding selenium supplementation as potential adjunctive therapy for pediatric sepsis. Selenium plays a key role as a cofactor for glutathione peroxidase, iodothyronine deiodinase, and thioredoxin (393)~~(388)~~; accordingly, selenium deficiency could affect thyroid metabolism and the response to oxidative stress during critical illness. Moreover, low serum selenium concentrations are common in critical illness (394, 395)~~(389, 390)~~ and infection (396)~~(391)~~, and have been associated with measures of oxidative stress in neonates (397)~~(392)~~ and adults (398)~~(393)~~.

A systematic review of investigations examining selenium supplementation in preterm neonates reported improved outcomes, including reduction in occurrence of sepsis (399)~~(394)~~. Similarly, a published systematic review and meta-analysis of the

effect of parenteral selenium supplementation in critically ill adult sepsis patients concluded that this intervention reduced risk of mortality (400)~~(395)~~, but when the meta-analysis was updated to include the results of a more recent RCT, there was no difference in mortality in those treated with or without selenium supplementation (50). In an interventional trial examining the potential benefit of zinc, selenium, glutamine, and metoclopramide administration to critically ill children, there was no reduction in the primary outcome measure, namely, time until the first episode of nosocomial infection/sepsis (383)~~(367)~~. Based on lack of interventional trials examining selenium supplementation in the setting of pediatric sepsis and sepsis-associated organ dysfunction, we suggest against its use as a weak recommendation.

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).

Rationale: During catabolic stress, the human body is unable to produce adequate quantities of glutamine and, therefore, its essential role as a fuel source for enterocytes and immune cells is diminished. Over the past two decades, several investigations of glutamine administration alone and in various combinations with other nutritional supplements have been conducted in critically ill populations (383, 401-407)~~(367, 396-402)~~, including those with sepsis(402, 408-410)~~(397, 403-405)~~. Contemporary studies have not found glutamine in any form (enteral or parenteral) and/or in combination with other nutritional elements to significantly improve morbidity or mortality in critically ill infants, children, and adults, including those with sepsis (411-413) **(Supplemental**

Table 23)~~(406-408)~~. However, single element studies administering only glutamine to children with sepsis and septic shock are scarce. An RCT by Jordan et al (404)~~(399)~~ randomized children (49 control; 49 interventional) with sepsis and septic shock for the purpose of examining oxidative stress and inflammatory response. This investigation supports earlier studies in broader populations finding no differences in PICU (p=0.062) or hospital LOS (p= 0.09) or hospital mortality (p=0.31). Two other studies of glutamine administration in combination with other elements to children with septic shock and critical illness are available (383, 402)~~(367, 397)~~. The RCT by Briassoulis et al (402)~~(397)~~ examined children with septic shock receiving glutamine in combination with arginine, antioxidants, and omega-3 fatty acids. Although the main outcome of change in cytokines showed some promise, no difference was noted between groups for hospital survival (80% versus 87%) or LOS (10.4 ±2.2 versus 11.4 ±2.5 days) ~~(15)~~(15). Carcillo et al (383)~~(367)~~ randomized 283 subjects from 8 PICUs to a control group receiving whey protein formula or an intervention group receiving formula with zinc, selenium, glutamine and IV metoclopramide supplementation. There was no difference between hospital-acquired infections and clinical sepsis per 100 days (p=0.81), PICU LOS (p= 0.16), or 28-day mortality (8/139 [5.8%] versus 15/145 [10.3%]). Subjects from this trial were also categorized by immune status with the suggestion that immune status may play a role in the effectiveness of nutritional supplemental, including glutamine (414)~~(409)~~. However, no direct evidence regarding glutamine supplementation in children with sepsis exists; hence, we suggest against the use of glutamine therapy in children with septic shock or other sepsis-associated organ dysfunction until further data become available.

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).

Rationale: Reduced availability of arginine in sepsis may lead to decreased endogenous nitric oxide synthesis, loss of microcirculatory regulation, and altered immune response (415-417)~~(410-412)~~. In the only pediatric RCT of arginine supplementation in children with sepsis (418)~~(413)~~, ten children received infusions of arginine and had enhanced arginine oxidation and increased nitric oxide levels, but no clinical outcomes were reported. In indirect data from adult studies, RCTs of L-arginine supplementation have been small and have reported both positive and negative effects on mortality (419-423)~~(414-418)~~. One trial in septic adults found decreased mortality(421)~~(416)~~, but other studies found no benefit or increased mortality in adults with sepsis(419, 422, 423)~~(414, 417, 418)~~. Some authors found improvement in secondary outcomes in patients with sepsis, such as reduced infectious complications and shorter LOS, but the relevance of these findings and their applicability to children with sepsis in the face of potential harm is unclear. Hence, in the absence of evidence of demonstrated benefit, we suggest against the use of arginine therapy in children with sepsis-associated organ dysfunction until further data become available.

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).

Rationale: Alterations in zinc homeostasis and associations between zinc levels and outcomes have been reported in the critically ill. Benefits of zinc supplementation have been shown in some forms of infectious illnesses. However, no trials of zinc supplementation in children with sepsis have been conducted. One RCT in critically ill children comparing daily supplementation with zinc, selenium, glutamine, and metoclopramide versus whey protein was stopped during interim analysis due to futility (383)~~(367)~~. Based on conflicting studies in the adult literature, routine supplementation of zinc is not recommended in nutritional guidelines for critically ill adults (424)~~(419)~~. Future RCTs examining the optimal timing and dose of zinc in children with sepsis and septic shock and its impact on immune response and clinical outcomes might help answer this question.

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).

Rationale: Ascorbic acid (vitamin C) has multiple physiologic functions. Most importantly in the setting of sepsis, vitamin C is an antioxidant and neutralizes reactive oxygen and nitrogen radicals, inhibits activation of pro-inflammatory cytokines, increases endogenous vasopressor synthesis, and inhibits bacterial replication (425-427)~~(432-434)~~. Adults with sepsis frequently have very low levels of vitamin C. In one study, 88% of adults with septic shock had hypovitaminosis C (428)~~(435)~~. Small studies in adults suggest that treatment of septic patients with vitamin C may improve organ dysfunction (429)~~(436)~~ and reduce mortality (430)~~(437)~~. Vitamin C has also been used

as a component of combination therapy, typically with thiamine and corticosteroids, in adults with sepsis (431)~~(438)~~. One study compared such treatment in 47 adult patients with sepsis to historical control patients (432)~~(439)~~. Treatment was associated with decreased hospital mortality (OR 0.13, 95% CI 0.04, 0.48), shorter duration of vasopressor therapy, and improved organ dysfunction scores **(Supplemental Table 24).**

Currently, there are no data on the use of vitamin C in critically ill children or in pediatric sepsis. The prevalence of low vitamin C levels in septic children is unknown, and no studies have investigated the effect of vitamin C supplementation, either alone or in combination with other agents, in the treatment of pediatric sepsis.

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

Rationale: Thiamine is a crucial factor in cellular metabolism. In its active form, thiamine pyrophosphate (TPP) is an essential coenzyme used to generate energy (ATP) from glucose. The human body does not produce thiamine and, with a short half-life and small body stores, thiamine deficiency can develop within days of critical illness and inadequate nutrition, resulting in impaired oxidative and carbohydrate metabolism. Low blood concentrations of thiamine have been reported on admission of critically ill children and adults with sepsis and septic shock (433-435)~~(440-442)~~. A study examining thiamine deficiency in children admitted to the PICU showed that low blood thiamine concentration in those with severe sepsis or septic shock was associated with mortality

(OR 8.40, 95% CI 1.38, 51.0)(434)(441). In an RCT of 88 adults with septic shock (**Supplemental Table 25**), there were no differences between treatment with thiamine versus placebo for the primary outcome of change in lactate levels or the secondary outcomes of mortality, shock reversal, and LOS (433)(440). However, on *post hoc* analysis, thiamine treatment in the subgroup with thiamine deficiency on admission was associated with lower lactate level within 24 hours and lower mortality (p=0.047). However, more evidence is needed to recommend whether thiamine supplementation should be used to treat children with septic shock or other sepsis-associated organ dysfunction. Also, it may be important for this evidence to be considered in the context of thiamine status at PICU admission.

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

Rationale: A systematic review and meta-analysis of 17 studies including 2,783 patients showed that approximately half of critically ill children have VDD (25-hydroxy vitamin D [25(OH)D] level < 50 nmol/L or <20 ng/mL) at PICU admission (190). Further, VDD was associated with higher illness severity, multiple organ dysfunction, and mortality across these studies. Six of these studies focused on or separately analyzed children with sepsis (436-440)(443-447). Three studies reported a greater need for vasoactive agents in VDD children (436-438)(443-445), although mortality across these six studies was not associated with VDD (436-440)(443-447) **(Supplemental Table 26)**.

Vitamin D levels are lowered by fluid resuscitation, which can confound the association with illness severity and disease complications (437)(444). In addition, free

or bioavailable 1,25(OH)$_2$D is the active form which is influenced by the level of vitamin D binding protein (VDBP) and a patient's VDBP genotype, which was not estimated or measured in prior studies (441)~~(448)~~. Although vitamin D levels are a potentially modifiable risk factor via supplementation, a meta-analysis of rapid normalization of vitamin D levels concluded that it is best achieved using loading therapy that takes into account disease status, determines baseline vitamin D level, and considers patient weight (442-444)~~(449-451)~~. A loading dose >300,000 IU should be avoided outside of RCTs evaluating risk and benefit.

Hypervitaminosis D is associated with hypercalcemia and other severe complications (445)~~(452)~~ and vitamin D overdoses can be fatal (446)~~(453)~~. No current data support that rapid acute correction of VDD is an effective treatment in septic shock or improves outcomes of septic children. Further, measurement of 25(OH)$_2$D levels is not currently a standard component of sepsis care and methods of accurately measuring bioavailable vitamin D are not yet widely validated. However, if VDD is diagnosed, repletion should occur as a usual part of general holistic pediatric care according to recommended guidelines independently of the presence of sepsis (447)~~(454)~~.

K. ~~ADJUNCTIVE THERAPIES~~BLOOD PRODUCTS

65. We suggest against transfusion of red blood cells 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 (TAXI) guidelines, for the purposes of red blood cell transfusion, "hemodynamically stabilized" is defined as a mean arterial blood pressure higher than 2 standard deviations below normal for age and no increase in vasoactive medications for at least 2 hours.

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

Rationale: The only study evaluating specific red blood cell (RBC) transfusion thresholds in children with sepsis is a *post hoc* subgroup analysis of the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study (448)~~(455)~~ **(Supplemental Table 27)**. This study included 137 stabilized critically ill children (MAP >2 standard deviations below normal for age and cardiovascular support not increased for at least 2 hours before enrollment) with sepsis, with a hemoglobin ≤ 9.5 g/dL within 7 days after PICU admission. Patients were randomized to receive RBCs if hemoglobin decreased to either <7.0 g/dL (restrictive group) or 9.5 g/dL (liberal group). No differences were found between the restrictive versus liberal group in the primary endpoint of new or progressive multiple organ dysfunction syndrome (18.8% versus 19.1%) or mortality (p=0.44). These results are similar to those from primary analysis of the TRIPICU study (449)~~(456)~~, as well as in adults (450)~~(457)~~. Our suggestion against transfusion if hemoglobin is >7 g/dL in hemodynamically-stable children with sepsis parallels the TAXI recommendations (451)~~(458)~~.

Insufficient data are available to guide red blood cell transfusion therapy in children with unstable septic shock. Two pediatric RCTs did demonstrate decreased

mortality when red blood transfusion to goal hemoglobin ≥10 (hematocrit >30%) was included as part of an early goal-directed therapy algorithm targeting $ScvO_2$, but the impact of each individual component, including red blood transfusion, is unclear (212, 452)~~(187, 459)~~. In critically ill adults, the Transfusion Requirements in Septic Shock (TRISS) trial randomized 998 subjects with septic shock to either a transfusion threshold hemoglobin of 7 g/dL or 9 g/dL (453)~~(460)~~. At randomization, all patients had hypotension (mean arterial pressure <70 mmHg) and/or were being treated with vasopressors. Ninety-day mortality showed no differences (relative risk, 0.94; 95%CI 0.78-1.09), suggesting that a restrictive transfusion strategy in hemodynamically unstable septic adults was safe. **(Supplemental Table ~~17~~27.)** The SSC recommends that RBC transfusion in adults occur only when hemoglobin concentration decreases to <7.0 g/dL in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence)(50). This adult recommendation is also valid for hemodynamically unstable patients.

However, in the absence of pediatric data, we are not able to provide a recommendation for critically ill children with unstable septic shock.

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

Rationale: One observational study demonstrated an association between the administration of platelet transfusions to critically ill children and worse clinical outcomes (**Supplemental Table 28**), including longer ICU LOS, progressive organ dysfunction, and increased mortality (454)~~(461)~~. Indirect evidence can be found in an RCT of 660 infants born at less than 34 weeks gestational age, the majority of whom were treated for sepsis, that compared a platelet transfusion threshold of 50,000 /mm^3 (high threshold) with 25,000 /mm^3 (low threshold)(455)~~(462)~~. More infants in the high- versus low-threshold group received at least one platelet transfusion (90% vs 53%). More adverse events, including new major bleeding or death, were also seen in the high threshold group (OR 1.57, 95% CI 1.06, 2.32).

Although existing evidence does not support a platelet threshold at which transfusion is absolutely indicated, the risk of spontaneous bleeding may be greater at lower platelet counts, e.g., <10-20,000 /mm^3. In addition, some populations of thrombocytopenic critically ill children may have a relatively high risk of bleeding, such as those with oncological diagnoses or those receiving ECMO. Because the threshold at which the benefits of platelet transfusion outweigh the risks is unknown, clinical judgment based on patient risk factors for bleeding in addition to the measured platelet level must be exercised carefully.

68. We suggest against prophylactic plasma transfusion in non-bleeding 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.

***Rationale*:** No direct data exist to inform a recommendation about plasma transfusion in pediatric sepsis. One RCT evaluates prophylactic plasma transfusion in critically ill children without sepsis. Pieters et al randomized 81 children <2 years of age requiring primary repair of craniosynostosis to receive plasma using either a prophylactic (in absence of bleeding) or reactive (when the patient was bleeding) strategy (456)~~(463)~~. The prophylactic plasma transfusion group received a significantly higher volume of plasma compared to the reactive group (29.7 mL/kg versus 16.1 mL/kg, $p < 0.001$). Despite an improvement in coagulation values in the prophylactic group, there was no difference in PRBC transfusion requirements or blood loss between the two groups. **(Supplemental Table ~~19~~29)** Additionally, a meta-analysis published in 2012 that included 80 RCTs (mostly in adults) concluded that there was no consistent evidence for benefit of prophylactic plasma transfusion across a range of indications that were evaluated (457)~~(464)~~. Observational studies in critically ill children have shown that plasma transfusions are associated with worse clinical outcomes (458, 459)~~(465, 466)~~. Furthermore, plasma transfusion frequently fails to correct abnormal coagulation tests in critically ill adults and children (459, 460)~~(466, 467)~~. We therefore suggest against prophylactic plasma transfusions for children with septic shock and other sepsis-associated organ dysfunction who are not bleeding.

However, some specific patient populations might benefit from prophylactic plasma transfusions, such as patients with worsening coagulation tests at high risk for

disseminated intravascular coagulopathy (DIC), children with comorbid cancer, or children with sepsis on extracorporeal life support (ECLS).

L. 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 thrombocytopenia-associated multiple organ failure (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.

Rationale: Therapeutic plasma exchange (PLEX) for septic shock or sepsis-associated organ dysfunction ~~is one of the techniques of blood purification, aiming~~aims to normalize the plasma milieu of a systemically inflamed septic patient. Currently, no large RCTs have evaluated PLEX in pediatric septic shock or sepsis-associated organ dysfunction. Rimmer et al. performed a meta-analysis that included 4 small RCTs evaluating PLEX in adults (n=128) and pediatric (n=66) patients with sepsis and septic shock. PLEX was associated with reduced mortality in adults (RR 0.63, 95% CI 0.42, 0.96), but not in children (RR 0.96, 95% CI 0.28, 3.38) (461)~~(468)~~. However, b~~B~~ecause of the heterogeneity of the patient population, inclusion criteria, technical modalities of PLEX (filtration versus centrifugation), and types of replacement fluid (plasma versus albumin) in these 4 studies as well as the costs and potential risks, it ~~is difficult to make~~

~~a definitive conclusion~~PLEX cannot be routinely recommended as this time **(Supplemental Table ~~20~~30)**. ~~Currently, using the existing evidenced-based literature on the use of PLEX in "Sepsis with multi-organ failure,"~~ Similarly, the American Society for Apheresis recommended that the ~~for Apheresis gives a category III recommendation, which is "O~~"optimum role of apheresis therapy is not established" in sepsis with multi-organ failure~~. Decision making should be individualized~~ (462)~~(469)~~.

~~In pediatrics, three proof-of-concept studies on the use of PLEX in a specific inflammation phenotype of sepsis-induced multiple organ failure named TAMOF exist (470-472). Clinically,~~ TAMOF is an inflammatory phenotype of sepsis-induced multiple organ dysfunction in children that can be identified clinically by ~~patients develop~~ new-onset thrombocytopenia ~~in the setting of~~and evolving multiple organ ~~failure~~dysfunction (463, 464)~~(REF)~~. Autopsies performed on patients who died with TAMOF reveal~~ed~~ disseminated microvascular thromboses in various organs (463)~~(472)~~. These patients had~~ve~~ deficient activity of a disintegrin and metalloproteinase with thrombospondin type 1 motif (ADAMTS-13), elevated von Willebrand factor (VWF) activity~~ies~~, and the presence of ultra-large plasma VWF (463, 465)~~(472, 473)~~. ~~Thrombocytopenia in these patients results from widespread platelet aggregation and thrombotic microangiopathy caused, in part, by deficient proteolysis of ultra-large VWF and large plasma VWF. ADAMTS-13 functions to cleave VWF at a specific site to regulate VWF's multimeric size and adhesive properties~~Decreased activity of ADAMTS-13 leads to high circulating levels of ultra-large VWF that induce widespread platelet activation and thrombotic microangiopathy. ~~that cause platelet aggregation.~~ A number of inflammatory mediators are elevated in sepsis that can inhibit or ~~proteolytically~~ inactivate ADAMTS-13 including

interleukin (IL)-6, granulocyte elastase, plasmin, thrombin, plasma free hemoglobin, shigatoxins, and immunoglobulin ~~(Ig)~~G auto-antibody (466-471)~~(474-479)~~. ~~In a primate model, direct ADAMTS-13 inhibition by monoclonal antibodies results in disseminated microvascular thromboses and organ injures in the kidney, heart, and brain(219).~~

Three studies have examined the utility of PLEX in children with sepsis and TAMOF (463, 472, 473)~~(REF).~~ In the most recent ~~pediatric TAMOF registry~~and largest study (n=81), Fortenberry et al. reported ~~the largest prospective observational cohort study (n=81) on the use of PLEX for TAMOF. These investigators found~~ that PLEX was associated with lower 28-day mortality by multivariate analysis (aRR 0.45, 95% CI 0.23, 0.90) and by propensity score weighting (aRR, 0.46, 95% CI 0.22, 0.97) (472)~~(REF)~~. In ~~a second study, Sevketoglu et al reported a~~ a retrospective cohort study from the Turkish TAMOF Network (n=42), ~~that~~ PLEX was associated with lower 28-day mortality compared to the no PLEX group (27% versus 70%; p=0.004) ~~((473) (REF~~207~~)~~. In ~~a~~the third study, Nguyen et al ~~reported the first description of pediatric TAMOF (n=28) and a pilot study of PLEX for TAMOF (n=10).~~randomized 10 children to either PLEX or standard therapy (463)~~(REF).~~ The 5 patients who received PLEX had restoration of ADAMTS-13 activity and greater survival (5/5) ~~survived~~ compared to ~~only 1 of 5 in the non-PLEX group~~standard therapy (1/5, p<0.05) ~~(208)~~. Taken together, these data support ~~there is a~~ biologic rationale for the use of ~~plausibility in using~~ PLEX ~~for~~in TAMOF, ~~. TAMOF appears to be a specific inflammatory phenotype of sepsis-induced multiple organ failure and PLEX is thought to~~ i.e., the removale of pathologic ultra-large VWF and ADAMTS-13 inhibitors and ~~replenish~~restoration of ADAMTS-13 activity. Th~~e~~is approach of using PLEX is similar to ~~that used for~~ the rationale for using PLEX in

thrombotic thrombocytopenic purpura (474)~~(480)~~. ~~Hence, further studies and RCTs are needed.~~ While the panel acknowledges a potential benefit for PLEX and encourages an RCT to better define the utility of PLEX in children with sepsis and TAMOF, a recommendation could not be made based on existing data.

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).

Rationale: Renal replacement therapy is increasingly being used in PICUs for renal and non-renal conditions. The rationale for renal replacement therapy in septic shock includes impending or established fluid overload following initial resuscitation or for cytokine removal, reversal of coagulopathy, to buffer lactic acidosis, to address AKI, or a combination of these factors. Continuous renal replacement therapy (CRRT) may be useful for treating established fluid overload or to prevent further fluid overload while allowing liberal volume administration for nutrition, antimicrobials, and other medications, sedation, and transfusions. In addition, certain techniques of continuous blood purification may help to regulate systemic inflammation and promote kidney recovery (475)~~(481)~~. Fluid overload has been shown to cause increased morbidity and mortality in various intensive care settings and there is documented favorable association of CRRT in fluid overload (476)~~(482)~~.

However, no high-quality studies in critically ill children with sepsis exist to directly determine whether RRT is definitively beneficial compared to diuretics and/or fluid restriction. Most of the data come from adult studies where outcomes have varied

from mortality to ICU length of stay and ventilator- and vasoactive-free days. One study addressed the timing of CRRT initiation in 27 children with sepsis and multiple organ dysfunction, demonstrating that CRRT was associated with survival when started within 48 hours of admission compared to those started on CRRT after 48 hours of admission (61% versus 33%, p<0.001). However, timing of CRRT initiation was at the discretion of the treating team, raising concern for confounding between groups, and all patients in both groups experienced normalization of kidney function (477)~~(483)~~ **(Supplemental Table ~~21~~31).**

The possible benefits of CRRT must also be weighed against potential risks, including the need for an invasive catheter, costs, limited availability in some centers, the need for clinician and nursing-specialist expertise, and the challenge of optimal timing (e.g., following resuscitation for fluid removal or earlier for acute cytokine clearance). Therefore, as the initial treatment strategy, we judge that fluid restriction and use of diuretics are reasonable in the presence of impending or established fluid overload with CRRT reserved as a second-line option 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.

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).

Rationale: High-volume hemofiltration (HVHF) for critically ill patients with septic shock and AKI is an appealing strategy for maintaining acid–base and fluid homeostasis, or for having a potential immunomodulatory effect in sepsis by removal of toxins and other inflammatory mediators, especially cytokines that contribute to organ injury and dysfunction.

In adults, use of higher CRRT flux rates (>35 mL/kg/hr filtration-dialysis), while initially encouraging, has not shown overall mortality benefit in subsequent RCTs and meta-analysis. A 2017 Cochrane review found no significant benefit in mortality, severity of organ dysfunction, LOS, or adverse effects with HVHF versus standard hemofiltration rates in critically ill adults (478)~~(484)~~. Notably, the results of this meta-analysis show that very few studies have been conducted to investigate the use of HVHF in critically ill patients with septic shock (four studies totaling 201 participants).

In a study involving 155 pediatric patients with severe sepsis, HVHF treatment did not significantly reduce 28-day mortality compared to standard volume CRRT. Moreover, there were no significant reductions in plasma levels of inflammatory mediators or in improving hemodynamic variables for HVHF. However, the incidence of hyperglycemia was significantly higher in HVHF group than in CVVH group (479)~~(485)~~ (**Supplemental Table ~~22~~32**).

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

Rationale: ECMO was introduced more than 40 years ago to support patients with reversible but severe cardiovascular and/or respiratory failure refractory to conventional medical therapy. As such, children with life-threatening sepsis-induced ARDS are often considered as candidates for ECMO rescue (480)~~(311)~~, and PALICC endorsed ECMO for the treatment of refractory hypoxia (24). The use of ECMO in pediatric sepsis has increased over the past decade (481, 482)~~(312, 313)~~; whether this has improved survival remains to be determined (483)~~(314)~~. To date, no RCT examining the effect of ECMO on outcome in pediatric sepsis has been published. In the absence of such data, using propensity score matching, Barbaro et al (484)~~(315)~~ reported that children with severe PARDS enrolled in the RESTORE trial had similar mortality rates when supported with ECMO (15/61, 25%) as compared with those who were not (18/61, 30%)(485)~~(316)~~ **(Supplemental Table ~~14~~33).** Research is underway to determine optimal pre-ECMO candidacy (486)~~(317)~~ as measures of renal, hepatic, neurologic, and hematologic dysfunction, and particularly the presence of blood stream infections, seem to discriminate mortality risk better than traditional pediatric severity of illness scores such as Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM), and Pediatric Logistic Organ Dysfunction (PELOD). Clearly, ECMO is not available worldwide, and transfer of highly unstable patients to higher levels of care that offer the therapy can carry substantial risk. However, adult and pediatric data suggest a potential association with improved mortality, particularly if transfer is to high volume ECMO centers (487, 488)~~(318, 319)~~.

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

Rationale: Several anecdotal reports of use of VA ECMO in the management of refractory septic shock in children exist. (The role of veno-venous [VV] ECMO for oxygenation/ventilation failure is addressed in the Ventilation section.) More recent reports suggest that VA ECMO may be associated with better survival than conventional therapy, and strategies to maximize flow rates to reverse shock and multiple organ dysfunction may play an important role (489, 490)~~(232, 233)~~. However, considerable concern surrounds the risks of this highly invasive therapy, such as hemorrhage and thromboembolic events.

The most recent and largest report of VA-ECMO in 44 pediatric patients with refractory septic shock secondary to bacterial, viral, or fungal infection admitted to 7 tertiary PICUs across 5 different countries compared their outcome to 120 children with refractory septic shock managed by conventional therapy (491)~~(234)~~. Inclusion in the study required children to meet 3 of 4 criteria for severe septic shock in the first 24 hours of their ICU stay: arterial pH ≤7.15, arterial lactate ≥4.0 mmol/L, base excess ≤ -10 mmol/L, and in-hospital cardiac arrest. Patients were excluded if they had cyanotic congenital heart disease, myocarditis, or an out-of-hospital cardiac arrest. The results showed no significant difference in survival to hospital discharge (50% in the VA ECMO cohort versus 40% in the conventional therapy cohort). Survival was significantly higher in patients who received high ECMO flows (>150 mL/kg/min at 4 hours after institution of ECMO) compared with children who received standard ECMO flows or no ECMO. ~~In~~

~~addition, among children who had suffered an in-hospital cardiac arrest, VA ECMO was associated with a 24% survival advantage~~ (**Supplemental Table ~~7~~34.**)~~.~~

The potential use of VA ECMO for refractory septic shock suggests that the definition of refractory septic shock (RSS) should be standardized across institutions. As yet, no universal definition of refractory septic shock in children exists. One published definition that could be applied is from the European Society of Paediatric and Neonatal Intensive Care (492)~~(235)~~. The suggested definition for RSS was ~~the association of: (1)~~ blood lactate >8 mmol/L or a 1 mmol/L lactate increase after 6 hours of resuscitation~~;~~ and ~~(2)~~ high vasoactive dependency (vasopressor-inotrope score >200), or ~~; and (3)~~ myocardial dysfunction~~,~~ defined as the occurrence of a resuscitation-responsive cardiac arrest in PICU or cardiac ultrasound findings with left ventricle ejection fraction <25% or a cardiac index <2.2 L/min/m^2. ~~This definition encompasses in-hospital cardiac arrest, and parameters that are associated with survival on VA-ECMO.~~

M. IMMUNOGLOBULINS

75. We suggest against the routine use of intravenous immune globulin (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.

Rationale: The proposed rationale for IVIG in severe infections is to boost passive immunity through neutralization of bacterial toxins, promoting opsonization of bacteria, and inhibition of immune cell proliferation and inflammatory mediators. However, IVIG

has considerable batch-to-batch variability and its true biologic activity is not clear. There are no high-quality studies of IVIG in critically ill children with sepsis, and small observational studies have reported conflicting results (493)~~(486)~~. An RCT of polyclonal IVIG in 100 children with sepsis demonstrated a reduction in mortality (28% versus 44%), LOS (6 versus 9 days), and less progression to complications (8% versus 32%)(494)~~(487)~~. However, a more recent multicenter trial of polyclonal IVIG in 3,493 neonates with suspected or proven serious infection found no significant differences in mortality or major disability (495)~~(488)~~. Other studies have been carried out with specific monoclonal antibodies (e.g., monoclonal antibody against endotoxin in children with meningococcal septic shock), but there are no definitive data to support general benefit of polyclonal immunoglobulin in neonates or children with septic shock at this time. Data from adult patients with septic shock also do not support a routine benefit of IVIG (496)~~(489)~~, though administration of IgM- and IgA-enriched polyclonal IVIG has shown possible efficacy (497)~~(490)~~. **(Supplemental Table ~~23~~35.)**

For patients with toxic shock syndrome, especially those with streptococcal etiology, polyclonal IVIG may have clinical utility (498)~~(491)~~. Other potential pediatric populations that may benefit from IVIG in sepsis are those with necrotizing fasciitis (though evidence in adults does not support use (499, 500)~~(492)~~), and those with primary humoral immunodeficiencies or immunocompromised with documented low immunoglobulin levels.

N. 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%.

Rationale: Stress ulcer prophylaxis should not be routinely administered to children with septic shock or other sepsis-associated organ dysfunction, as evidence for benefit is lacking (501)~~(493)~~ and may increase risk of adverse effects, such as pneumonia or *Clostridioides difficile* (formerly *Clostridium)* infection (502)~~(494)~~. Rather than routine, universal administration of stress-ulcer prophylaxis, individual patients should be assessed for the presence of risk factors of clinically important gastrointestinal bleeding. These include multiple organ dysfunction(503)~~(495)~~, prolonged mechanical ventilation (>48 hours), coagulopathy, persistent shock, and treatment with corticosteroids and non-steroidal anti-inflammatory agents(504)~~(496)~~.

The risk of GI bleeding is also reduced by mucosal protection introduced by gastric feeding. Early enteral nutrition could therefore be a viable alternative to pharmacological stress-ulcer prophylaxis. A meta-analysis of 1836 adult patients reported that, in the presence of enteral nutrition, pharmacological stress ulcer prophylaxis did not significantly change the risk of GI bleeding. Notably, in those patients who received enteral nutrition and were treated with stress ulcer prophylaxis,

the risk of pneumonia was increased compared to patients on parenteral nutrition (OR 2.81, 95% CI 1.2, 6.6)(505)~~(497)~~ **(Supplemental Table ~~24~~36).**

77. We suggest against routine deep vein thrombosis (DVT) 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).

Rationale: An open-label RCT of low molecular weight heparin to prevent CVC-associated thrombosis in the PICU was terminated early because of poor recruitment (506)~~(498)~~. Eleven (14.1%) of 78 patients randomized to reviparin had DVT proven on venogram versus 10 (12.5%) of 80 controls (OR 1.15, 95% CI 0.42, 3.23). Three adverse events (major bleed or death) all occurred in the control group and no deaths occurred because of venous thromboembolism **(Supplemental Table 37)**. A subsequent systematic review found the quality of evidence to be low and that the efficacy of low molecular weight heparin in preventing CVC-associated thrombosis is unknown (507)~~(499)~~. It is important to highlight that these studies were specific to children with CVCs who may or may not have had sepsis and that they may not apply to the general thromboembolic risk in children with sepsis.

While CVCs represent the principal risk factor for DVT in infants (508)~~(500)~~, older children may have other risk factors. For example, the risk of DVT increases in adolescence, obesity, cancer, and in those with multiple medical conditions, especially

renal and cardiac disease (509, 510)~~(501, 502)~~. At present, it is unknown whether certain high-risk populations of children with sepsis may benefit from DVT prophylaxis.

KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES

This report from the SSC pediatric guidelines panel covers 5 main topic areas (i.e., early recognition and infection, hemodynamics, ventilation, endocrine and metabolic therapies, and adjunctive therapies) with a total of 76 recommendations arising from 67 PICO questions. On review of these evidence-based analyses, it is clear that, for many PICO questions, the literature review failed to identify sufficient data to develop strong (or even weak in some instances) recommendations for critically ill children with septic shock or other sepsis-associated organ dysfunction. These SSC pediatric guidelines, at the same time, also identified gaps that can inform future research opportunities. As new research populates the evidence-base, it can then be used to develop future iterations of the SSC pediatric guidelines, creating a cycle designed to grow the evidence and increase the number of strong recommendations in the future. Further clarity is needed from both informative pathophysiology studies as well as well-designed RCTs, and the panelists have listed these in the text. The design of meaningful and effective future research should be informed by the needs identified by the collective clinical expertise within the panel.

Overall, the process of developing the SSC-pediatric guidelines generated at least ~~27~~ 29 pathophysiology questions warranting further study and ~~22~~23 RCTs (i.e., total of ~~49~~52 studies). We presented these questions as research opportunities, but have not yet prioritized these opportunities into a formal research agenda (**Table 6**). We

envisionage that many of the 27 pathophysiology questions can be taken up by individual research groups and we hope that the SSC children's guidelines document will serve as a template of current evidence and how best to fill the gaps in our knowledge. In contrast, the necessary RCTs will need a coordinated national/international effort and our community will need to prioritize the most appropriate studies at different phases of management (i.e., recognition, fluid resuscitation, first 48 hours, etc.).

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Figure 1

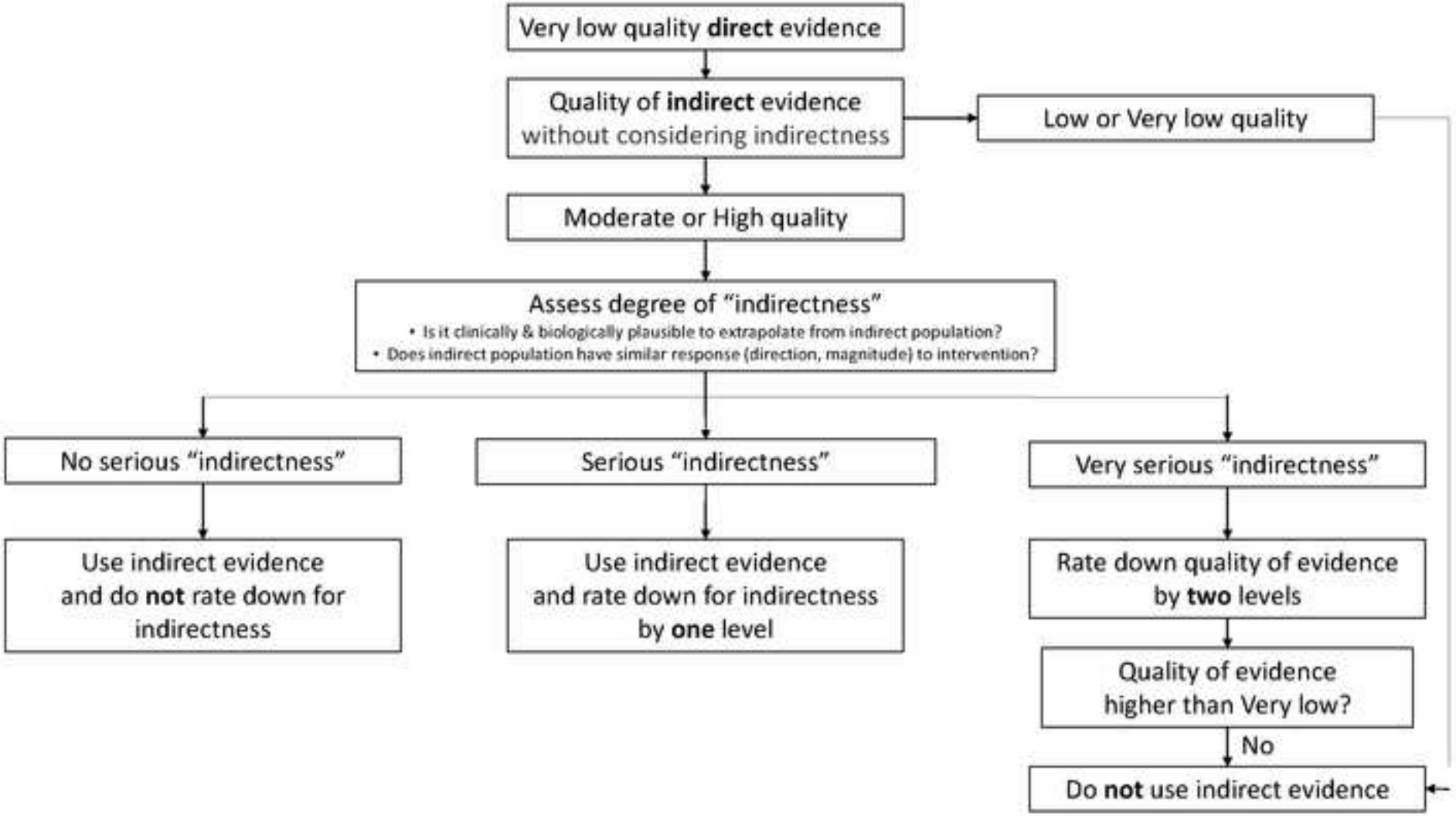

Table 1: Determination of the Quality of Evidence

Underlying methodology

1. High: Systematic reviews, RCTs
2. Moderate: Downgraded RCTs or upgraded observational studies
3. Low: Well-conducted prospective observational cohort studies
4. Very Low: Downgraded observational cohort studies, case-control studies, case series or expert opinion or other evidence

Factors that may decrease the strength of evidence

1. Methodologic features of available RCTs suggesting high likelihood of bias
2. Inconsistency of results, including problems with subgroup analyses
3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias

Factors that may increase the strength of evidence

1. Large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders)
2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)
3. Dose-response gradient

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Table 2: Implications of the Strength of Recommendation

Category	Strength	Quality of evidence	Implications to patients	Implications to clinicians	Implications to policymakers
Strong recommendation	Strong	Usually High or Moderate	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Can be adapted as policy in most situations, including for use as performance indicators
Weak recommendation	Weak	Any	The majority of individuals in this situation would want the suggested course of action, but many would not	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances, such as patients' or family's values and preferences	Policies will likely be variable
Best practice statement	Strong	Ungraded	Same as strong recommendation	Same as strong recommendation	Same as strong recommendation
In our practice statement	Not a recommendation	N/A	N/A	N/A	N/A

Table 2: Implications of the Strength of Recommendation

Category	Strength	Quality of evidence	Implications to patients	Implications to clinicians	Implications to policymakers
Strong recommendation	Strong	Usually High or Moderate	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Can be adapted as policy in most situations, including for use as performance indicators
Weak recommendation	Weak	Any	The majority of individuals in this situation would want the suggested course of action, but many would not	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances, such as patients' or family's values and preferences	Policies will likely be variable
Best practice statement	Strong	Ungraded	Same as strong recommendation	Same as strong recommendation	Same as strong recommendation
In our practice statement	Not a recommendation	N/A	N/A	N/A	N/A

Table 3: Criteria for Best Practice Statement

Criteria for Best Practice Statement	
1	Is the statement clear and actionable?
2	Is the message necessary?
3	Is the net benefit (or harm) unequivocal?
4	Is the evidence difficult to collect and summarize?
5	Is the rationale explicit?
6	Is this better to be formally GRADEd?

Modified from Guyatt GH, Schunemann HJ, Djulbegovic B, Akl EA. Guideline panels should not GRADE good practice statements. J Clin Epidemiol. 2015;68(5):597-600

Table 4: Definitions for Empiric, Targeted/Definitive, Broad-spectrum, and Multiple Drug Antimicrobial Therapy

Term	Definition	Comment
Empiric antimicrobial therapy	Initial antimicrobial therapy started for suspected infection in the absence of definitive microbiologic pathogen identification.	Empiric therapy may consist of single or multiple agents but should be broad spectrum in nature. Empiric antimicrobial therapy should be based on local, regional, or national pathogen epidemiology and patient risk factors.
Targeted/Definitive antimicrobial therapy	Antimicrobial therapy targeted to specific pathogen(s), usually after microbiologic identification.	Targeted/Definitive therapy may consist of single or multiple agents, but should not be broader than required to treat the specific pathogen(s) after microbiologic identification .
Broad-spectrum antimicrobial therapy	An antimicrobial regimen with activity against multiple different groups of bacteria or other pathogens considered to be likely causes of the clinical presentation.	Broad-spectrum antimicrobial therapy may consist of single or multiple agents.
Multiple-drug antimicrobial therapy	More than one antimicrobial agent is needed to either a) expand the spectrum of coverage to include additional pathogens (eg, vancomycin for MRSA; b) decrease the likelihood of resistance to any particular single agent (eg, for patients with known or high-risk for MDRO); or c) provide synergy to treat a suspected or known pathogen.	

MRSA, methicillin-resistant *Staphyloccocus aureus*; MDRO, multi-drug resistant organism

Table 5: Normal Ranges for Advanced Monitoring

Parameter	Formula	Normal range	Units
Cardiac index	CI = CO / body surface area	3.5–5.5	$L/min/m^2$
Stroke index	SI = CI / heart rate	30–60	mL/m^2
Systemic vascular resistance index	SVRI = 80 x (MAP - CVP) / CI	800–1600	$dyne\text{-}s/cm^5/m^2$

CI, cardiac index; CO, cardiac output; SI, stroke index; SVRI, systemic vascular resistance index
MAP, mean arterial pressure; CVP, central venous pressure

Table 6: Knowledge Gaps and Research Opportunities (refer to numbered recommendations in Guidelines and Appendix 1)

Subgroup	Pathophysiology	Clinical trials
A. Screening, Diagnosis, and Systematic Management of Sepsis: 4 pathophysiology studies and 2 RCTs	1. QI screening tool algorithms to recognize clinical deterioration (see Rec 1) 2. Define the optimal level of hyperlactatemia (see Rec 2) 3. Protocol/guideline for management (see Rec 3) 4. New molecular technologies in identifying pathogens before blood culture positivity or after antibiotic administration (see Rec 4)	1. Pediatric sepsis recognition (see Rec 1) 2. Initial or serial measurement of blood lactate directly informs evaluation and/or management (see Rec 2)
B. Antimicrobial Therapy: 7 pathophysiology studies	1. The definition of "timely" antimicrobials in a bundle of initial care (see Recs 5 and 6) 2. QI metrics to assess unnecessary antimicrobials (see Rec 7) 3. Antimicrobial resistance rate thresholds to help decide when the addition of a glycopeptide or second gram-negative agent is necessary (see Rec 10 and 11) 4. Alteration in the pharmacokinetics and pharmacodynamics of antimicrobials (see Rec 12) 5. The relationship between antimicrobial stewardship programs and a decrease in antimicrobial resistance (see Rec 13) 6. The use of procalcitonin as a guide to antimicrobial therapy and relationship to outcome (see Rec 13) 7. The determinants of optimal duration of antimicrobial therapy (see Rec 14)	
C. Source Control: 1 pathophysiology studies	1. Role of source control (see Rec 15 and 16)	
D. Fluid Therapy: 1 pathophysiology study and 2 RCTs	1. Features of early recognition of fluid overload (see Rec 17-19)	1. Clinical markers of cardiac output to guide fluid resuscitation (see Rec 17-19) 2. Balanced crystalloid versus 0.9% saline (see Rec 21)
E. Hemodynamic Monitoring: 2 RCTs		1. Specific hemodynamic targets (>5th versus >50th MAP percentile) (see Rec 24) 2. Lactate-guided resuscitation (see Rec 27)

F. Vasoactive Medications: 3 pathophysiology studies	1. The choice of first-line vasoactive infusion (see Rec 30) 2. The optimal threshold for using continuous infusion of vasopressin (see Rec 32) 3. The use and effects of inodilators (see Rec 33)	
G. Ventilation: 4 pathophysiology studies and 5 RCTs	1. Non-invasive modalities to identify the need for early mechanical ventilation (see Rec 36) 2. Does early non-invasive mechanical ventilation versus invasive mechanical ventilation in sepsis-induced PARDS mitigate the need for subsequent invasive mechanical ventilation (see Rec 36) 3. The optimal approach to setting PEEP in mechanical ventilation for sepsis-induced PARDS (see Rec 37) 4. The use of recruitment maneuvers in mechanical ventilation for sepsis-induced PARDS (see Rec 38)	1. Early- versus delayed-endotracheal intubation for refractory shock without respiratory failure (see Rec 34) 2. During mechanical ventilation, low- versus moderate-PEEP strategy for sepsis-induced PARDS (see Rec 37) 3. During mechanical ventilation, prone positioning in sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 39) 4. HFOV versus conventional mechanical ventilation in sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 42) 5. NMBA during mechanical ventilation for sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 43)
H. Corticosteroids: 1 RCT		1. Adjunctive corticosteroids for refractory septic shock (see Rec 45)
I. Endocrine and metabolic therapies: 2 pathophysiology studies and 1 RCT	1. The optimal glucose target (between 140 and 180 mg/dL) necessitating control with insulin in children with septic shock or other sepsis-associated organ dysfunction (see Rec 47) 2. Hypocalcemia and supplements in children with septic shock or other sepsis-associated organ dysfunction (see Rec 48)	1. Fever management in children with septic shock or other sepsis-associated organ dysfunction (see Rec 50)
J. Nutrition: 3 pathophysiology studies and 7 RCTs	1. Lipid solution effects on inflammatory physiology (see Rec 54) 2. The role of prokinetic agents in immunocompromised children with septic shock or other sepsis-associated organ dysfunction (see Rec 57)	1. Early- versus late- enteral nutrition in children with septic shock or other sepsis-associated organ dysfunction (see Recs 51, 52, and 53) 2. Bolus versus continuous enteral feeding in children with septic

	3. The prevalence of low serum vitamin C levels in children with septic shock or other sepsis-associated organ dysfunction (see Rec 62)	shock or other sepsis-associated organ dysfunction (see Rec 51, 52, and 53) 3. Enteral nutrition versus parenteral supplementation of nutritional intake in the first 7 days of management of children with septic shock or other sepsis-associated organ dysfunction (see Rec 53) 4. Dietary supplements (selenium, glutamine, arginine, zinc) in children with septic shock or other sepsis-associated organ dysfunction (see Recs 58, 59, 60, and 61) 5. Vitamin C supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 62) 6. Thiamine deficiency, and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 63) 7. Vitamin D deficiency and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 64)
K. Blood Products: 2 pathophysiology studies	1. Optimal hemoglobin level in children with septic shock or other sepsis-associated organ dysfunction (see Recs 65 and 66) 2. The threshold at which the benefits of platelet transfusion outweigh the risks in children with septic shock or other sepsis-associated organ dysfunction (see Rec 67)	
L. Plasma Exchange, Renal Replacement, and Extracorporeal Support: 2 pathophysiology studies and 2 RCTs	1. Optimal timing and approach for ECMO in refractory shock (see Rec 74) 2. To define optimal pre-ECMO candidacy (see Recs 73 and 74)	1. Plasma exchange in children with septic shock or sepsis-associated organ dysfunction with thrombocytopenia-associated organ failure (see Rec 70) 2. Renal replacement therapy versus diuretics in the first 48 hours in children with septic shock or other sepsis-associated organ dysfunction (see Recs 71-72)

M. Immunoglobulins		
N. Prophylaxis: 1 RCT		1. Stress ulcer prophylaxis in relation to feeding in children with septic shock or other sepsis-associated organ dysfunction (see Rec 76)

RCT, randomized clinical trial; Rec, recommendation number; MAP, mean arterial pressure; PARDS, pediatric acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; HFOV, high-frequency oscillatory ventilation; NMBA, neuromuscular blocking agent; ECMO, extracorporeal membrane oxygenation

Table 6: Knowledge Gaps and Research Opportunities (refer to numbered recommendations in Guidelines and Appendix 1)

Subgroup ~~expertise~~	Pathophysiology	Clinical trials
A. Screening, ~~diagnosis~~Diagnosis, and ~~systematic~~ Systematic ~~management~~ Management of ~~sepsis~~Sepsis: 4 pathophysiology studies and 2 RCTs	1. QI screening tool algorithms to recognize clinical deterioration (see Rec 1) 2. Define the optimal level of hyperlactatemia (see Rec 2) 3. Protocol/guideline for management (see Rec 3) 4. New molecular technologies in identifying pathogens before blood culture positivity or after antibiotic administration (see Rec 4)	1. Pediatric sepsis recognition (see Rec 1) 2. Initial or serial measurement of blood lactate directly informs evaluation and/or management (see Rec 2)
B. Antimicrobial Therapy: ~~5~~7 pathophysiology studies	1. The definition of "timely" antimicrobials in a bundle of initial care (see Recs 5 and 6) 2. QI metrics to assess unnecessary antimicrobials (see Rec 7) 3. Antimicrobial resistance rate thresholds to help decide when the addition of a glycopeptide or second gram-negative agent is necessary (see Rec 10 and 11) 4. Alteration in the pharmacokinetics and pharmacodynamics of antimicrobials (see Rec 12) 5. The relationship between antimicrobial stewardship programs and a decrease in antimicrobial resistance (see Rec ~~15~~13) 6. The use of procalcitonin as a guide to antimicrobial therapy and relationship to outcome (see Rec ~~15~~13) 7. The determinants of optimal duration of antimicrobial therapy (see Rec ~~16~~14)	
C. Source Control: ~~3~~1 pathophysiology studies	1. ~~The r~~Role of source control (see Rec ~~13~~ 15 and ~~14~~16)	
D. Fluid Therapy: 1 pathophysiology study and 42 RCTs	1. Features of early recognition of fluid overload (see Rec ~~18~~17-19)	1. Clinical markers of cardiac output to guide fluid resuscitation (see Rec ~~18~~17-19) ~~1.~~ Balanced crystalloid versus 0.9% saline (see Rec 21) ~~Specific hemodynamic targets (>5th versus >50th MAP percentile) (see Rec 19)~~

		~~Balanced crystalloid versus 0.9% saline (see Rec 21)~~ 2. ~~Lactate-guided resuscitation (see Rec 22)~~
E. Hemodynamic Monitoring: ~~1~~2 RCTs		~~1. Balanced crystalloid versus 0.9% saline (see Rec 24)~~ 1. Specific hemodynamic targets (>5th versus >50th MAP percentile) (see Rec 24) 2. Lactate-guided resuscitation (see Rec 27)
F. Vasoactive Medications: 3 pathophysiology studies	1. The choice of first-line vasoactive infusion (see Rec 30~~29~~) 2. The optimal threshold for using continuous infusion of vasopressin (see Rec ~~31~~32) 3. The use and effects of inodilators (see Rec ~~32~~33)	
G. Ventilation: ~~5~~ 4 pathophysiology studies and 5 RCTs	1. Non-invasive modalities to identify the need for early mechanical ventilation (see Rec 36) 2. Does early non-invasive mechanical ventilation versus invasive mechanical ventilation in sepsis-induced PARDS mitigate the need for subsequent invasive mechanical ventilation (see Rec 36) 3. The optimal approach to setting PEEP in mechanical ventilation for sepsis-induced PARDS (see Rec 37) 4. The use of recruitment maneuvers in mechanical ventilation for sepsis-induced PARDS (see Rec 38)	1. Early- versus delayed-endotracheal intubation for refractory shock without respiratory failure (see Rec 34) ~~2.~~ During mechanical ventilation, low- versus moderate-PEEP strategy for sepsis-induced PARDS (see Rec 37) 2. 3. During mechanical ventilation, prone positioning in sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 39) ~~)~~ ~~4.~~ HFOV versus conventional mechanical ventilation in sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 42) 4. ~~5.~~ 4.5. NMBA during mechanical ventilation for sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 43)
H. Corticosteroids: 1 RCT	~~To define optimal pre-ECMO candidacy (see Recs 33 and 44)~~	1. Adjunctive corticosteroids for refractory septic shock (see Rec~~s~~ 45~~ and 46~~)

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I. Endocrine and metabolic therapies: ~~5 pathophysiology studies and 9 RCTs~~2 pathophysiology studies and 1 RCT	~~1. Lipid solution effects on inflammatory physiology (see Rec 50)~~ 1. The optimal glucose target (between 140 and 180 mg/dL) necessitating control with insulin in children with septic shock or other sepsis-associated organ dysfunction (see Recs~~ 46 and~~ 47) Hypocalcemia and supplements in children with septic shock or other sepsis-associated organ dysfunction (see Rec 48) ~~1.~~2.	1. Fever management in children with septic shock or other sepsis-associated organ dysfunction (see Rec 50) ~~1. Adjunctive corticosteroids for refractory septic shock (see Recs 45 and 46)~~ ~~1. Early- versus late- enteral nutrition in children with septic shock or other sepsis-associated organ dysfunction (see Recs 47, 48, and 49)~~ ~~1. Bolus versus continuous enteral feeding in children with septic shock or other sepsis-associated organ dysfunction (see Rec 47, 48 and 49)~~ ~~1. Enteral nutrition versus parenteral supplementation of nutritional intake in the first 7 days of management of children with septic shock or other sepsis-associated organ dysfunction (see Rec 49)~~
J. Nutrition: 3 pathophysiology studies and ~~8~~7 RCTs	1. Lipid solution effects on inflammatory physiology (see Rec 54) The role of prokinetic agents in immunocompromised children with septic shock or other sepsis-associated organ dysfunction (see Rec ~~53~~57) ~~1. Lipid solution effects on inflammatory physiology (see Rec 54)~~ 2. ~~1.~~ ~~2. The optimal glucose target (between 140 and 180 mg/dL) necessitating control with insulin in children with septic shock or other sepsis-associated organ dysfunction (see Recs 54 and 55)~~ ~~3. Hypocalcemia and supplements in children with septic shock or other sepsis-associated organ dysfunction (see Rec 60)~~ ~~2.~~3.~~3.~~ The prevalence of low serum vitamin C levels in children with septic shock or other sepsis-associated organ dysfunction (see Rec ~~63~~62)	1. ~~1.~~Early- versus late- enteral nutrition in children with septic shock or other sepsis-associated organ dysfunction (see Recs 51, 52, and 53) 2. ~~2.~~Bolus versus continuous enteral feeding in children with septic shock or other sepsis-associated organ dysfunction (see Rec 51, 52, and 53) 3. Enteral nutrition versus parenteral supplementation of nutritional intake in the first 7 days of management of children with septic shock or other sepsis-associated organ dysfunction (see Rec 53) ~~1.~~4. ~~4.~~ Dietary supplements (selenium, glutamine, arginine, zinc) in children with septic shock or other sepsis-associated organ dysfunction (see Recs ~~56~~58, ~~57~~59, ~~58~~60, and ~~59~~61)

		~~2. Fever management in children with septic shock or other sepsis-associated organ dysfunction (see Rec 62)~~ ~~3.~~5. Vitamin C supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec ~~63~~62) ~~4.~~6. Thiamine deficiency, and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec ~~64~~63) ~~5.~~7. ~~8.~~ V~~DD~~itamin D deficiency~~,~~ and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec ~~65~~64)
K. Blood Products: 2 pathophysiology studies	1. Optimal hemoglobin level in children with septic shock or other sepsis-associated organ dysfunction (see Recs 6~~6~~5 and 6~~7~~6) 2. The threshold at which the benefits of platelet transfusion outweigh the risks in children with septic shock or other sepsis-associated organ dysfunction (see Rec 6~~7~~8)	
L. Plasma Exchange, Renal Replacement, and Extracorporeal Support: 2 pathophysiology studies and 2 RCTs	1. Optimal timing and approach for ~~extracorporeal membrane oxygenation~~ECMO in refractory shock (see Rec 74) ~~1.~~2. To define optimal pre-ECMO candidacy (see Recs 73 and 74)	1. Plasma exchange in children with septic shock or sepsis-associated organ dysfunction with thrombocytopenia-associated organ failure (see Rec 70~~ and 71~~) 2. ~~CRRT~~ Renal replacement therapy versus diuretics in the first 48 hours in children with septic shock or other sepsis-associated organ dysfunction (see Recs 71-72)
M. Immunoglobulins		
N. Prophylaxis: 1 RCT		1. Stress ulcer prophylaxis in relation to feeding in children with septic shock or other sepsis-associated organ dysfunction (see Rec 76)

RCT, randomized clinical trial; Rec, recommendation number; MAP, mean arterial pressure; PARDS, pediatric acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; HFOV, high-frequency oscillatory ventilation; NMBA, neuromuscular blocking agent; ECMO, extracorporeal membrane oxygenation

Appendix 1: Summary of Guidelines

A. 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). PICO 1 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-versus high-risk of having septic shock or sepsis. PICO 2
3. We *recommend* implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction (BPS). PICO 3
4. We *recommend* obtaining blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (BPS). PICO 4
B. ANTIMICROBIAL THERAPY
5. In children with septic shock, we *recommend* starting antimicrobial therapy as soon as possible, within 1 hour of recognition (strong recommendation, very low quality of evidence). PICO 6
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 hours of recognition (weak recommendation, very low quality of evidence). PICO 6
7. We *recommend* empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (BPS). PICO 5
8. Once the pathogen(s) and sensitivities are available, we *recommend* narrowing empiric antimicrobial therapy coverage (BPS). PICO 5
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). PICO 5
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). PICO 8/9 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). PICO 8/9

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). PICO 7

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). PICO 11

    Remarks: This assessment should include a review of the ongoing indication for empiric antimicrobial therapy after the first 48 hours 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 *recommen*d determining the duration of antimicrobial therapy according to the site of infection, microbial etiology, response to treatment, and ability to achieve source control (BPS). PICO 10

C. 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). 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). PICO 13

D. 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). PICO 17

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). PICO 17

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). PICO 17

    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). PICO 15

    Remarks: Although there is no difference in outcomes, this recommendation takes into consideration cost and other barriers of administering albumin compared to 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). PICO 14

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) PICO 16

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). PICO 16

E. HEMODYNAMIC MONITORING

24. We were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5^{th} or 50^{th} percentile for age in children with septic shock and other sepsis-associated organ dysfunction. PICO 21

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). PICO 20

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). PICO 18

    Remarks: Advanced hemodynamic monitoring may include cardiac output/cardiac index, systemic vascular resistance, or central venous oxygen saturation ($ScvO_2$).

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). PICO 19

    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

F. VASOACTIVE MEDICATIONS

28. We *suggest* using epinephrine, rather than dopamine, in children with septic shock (weak recommendation, low quality of evidence). PICO 22

29. We *suggest* using norepinephrine, rather than dopamine, in children with septic shock (weak recommendation, very low quality of evidence). PICO 23

30. We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock. PICO 22/23

31. We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock. PICO 26

    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). PICO 25

    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. PICO 24

G. VENTILATION

34. We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock. PICO 27

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). PICO 28

36. We *suggest* a trial of non-invasive mechanical ventilation (over invasive mechanical ventilation) in children with sepsis-induced pediatric ARDS (PARDS) without a clear indication for intubation and who are responding to initial resuscitation (weak recommendation, very low quality of evidence). PICO 29

    Remarks: When non-invasive mechanical ventilation is initiated, clinicians should carefully and frequently re-evaluate the patient's condition.

37. We *suggest* using high positive end-expiratory pressure (PEEP) in children with sepsis-induced PARDS (weak recommendation, very low quality of evidence). PICO 30

    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 fractional inspired oxygen (FiO_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. PICO 31

    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). PICO 32

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

40. We *recommend* against the routine use of inhaled nitric oxide (iNO) in all children with sepsis-induced PARDS (strong recommendation, low quality of evidence). PICO 33

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). PICO 33

42. We were unable to issue a recommendation to use high-frequency oscillatory ventilation (HFOV) versus conventional ventilation in children with sepsis-induced PARDS. PICO 34

43. We *suggest* using neuromuscular blockade in children with sepsis and severe PARDS (weak recommendation, very low quality of evidence). PICO 35

    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 hours after ARDS onset.

H. CORTICOSTEROIDS

44. We *suggest* against using intravenous 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). PICO 47

45. We *suggest* that either intravenous 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). PICO 47

I. 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). PICO 52/60

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. PICO 52/60

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. PICO 62

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). PICO 63

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). PICO 64

J. NUTRITION

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

52. We *suggest* not withholding enteral feeding solely on the basis of vasoactive-inotropic medication administration (weak recommendation, low quality of evidence). PICO 48

    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 days of PICU admission in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence). PICO 49/50

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). PICO 53

55. We *suggest* against the routine measurements of gastric residual volumes (GRV) in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). PICO 54

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). PICO 55

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). PICO 56

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). PICO 57

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). PICO 58

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). PICO 59

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). PICO 61

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). PICO 65

63. We *suggest* against the use of thiamine to treat children with sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). PICO 66

64. We *suggest* against the acute repletion of vitamin D deficiency (VDD) for treatment of septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence). PICO 67

K. BLOOD PRODUCTS

65. We *suggest* against transfusion of red blood cells 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). PICO 38

    Remarks: According to the 2018 Transfusion and Anemia Expertise Initiative (TAXI) guidelines, for the purposes of red blood cell transfusion, "hemodynamically stabilized" is defined as a mean arterial blood pressure higher than 2 standard deviations below normal for age and no increase in vasoactive medications for at least 2 hours.

66. We cannot make a recommendation regarding hemoglobin transfusion thresholds for critically ill children with unstable septic shock. PICO 38

67. We *suggest* against prophylactic platelet transfusion based solely on platelet levels in non-bleeding children with septic shock or other sepsis-associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence). PICO 40

68. We *suggest* against prophylactic plasma transfusion in non-bleeding children with septic shock or other sepsis-associated organ dysfunction and coagulation abnormalities (weak recommendation, very low quality of evidence). PICO 39

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

L. 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 thrombocytopenia-associated multiple organ failure (TAMOF) (weak recommendation, very low quality of evidence). PICO 37

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. PICO 37

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). PICO 43

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). PICO 44

73. We *suggest* using veno-venous (VV) extracorporeal membrane oxygenation (ECMO) in children with sepsis-induced PARDS and refractory hypoxia (weak recommendation, very low quality of evidence). PICO 36

74. We *suggest* using veno-arterial (VA) ECMO as a rescue therapy in children with septic shock only if refractory to all other treatments (weak recommendation, very low quality of evidence). PICO 45

M. IMMUNOGLOBULINS

75. We *suggest* against the routine use of intravenous immune globulin (IVIG) in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). PICO 46

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

N. 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). PICO 41

    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 (DVT) 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). PICO 42

Appendix 1: Summary of Guidelines

A. ~~RECOGNITION AND MANAGEMENT~~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). PICO 1 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-versus high-risk of having septic shock or sepsis. PICO 2
3. We *recommend* implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction (BPS). PICO 3
4. We *recommend* obtaining blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (BPS). PICO 4
B. ANTIMICROBIAL THERAPY
5. In children with septic shock, we *recommend* starting antimicrobial therapy as soon as possible, within 1 hour of recognition (strong recommendation, very low quality of evidence). PICO 6
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 hours of recognition (weak recommendation, very low quality of evidence). PICO 6
7. We *recommend* empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (BPS). PICO 5
8. Once the pathogen(s) and sensitivities are available, we *recommend* narrowing empiric antimicrobial therapy coverage (BPS). PICO 5
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). PICO 5
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). PICO 8/9 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). PICO 8/9

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). PICO 7

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). PICO 11

    Remarks: This assessment should include a review of the ongoing indication for empiric antimicrobial therapy after the first 48 hours 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). PICO 10

C. 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). 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). PICO 13

~~17. 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). PICO 11~~

~~Remarks: This assessment should include a review of the ongoing indication for empiric antimicrobial therapy after the first 48 hours 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.~~

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~~D~~B. FLUID THERAPY~~HEMODYNAMICS AND RESUSCITATION~~

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). PICO 17

~~In healthcare systems with no availability of intensive care, we *suggest* administering up to 20 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, moderate 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). PICO 17

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). PICO 17

    Remarks: Clinical markers of cardiac output may include heart rate, blood pressure, capillary refill time, level of consciousness, and urine output. In all settings, ~~T~~the need for ~~bolus~~ fluid administration should be guided by frequent reassessment of clinical markers of cardiac output, serial blood lactate measurement and advanced monitoring, when available. ~~Even in low-resource settings, the subset of children with septic shock *and hypotension* should receive cautious fluid bolus therapy.~~ 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). PICO 15

    Remarks: Although there is no difference in outcomes, this recommendation takes into consideration cost and other barriers of administering albumin compared to 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). PICO 14

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) PICO 16

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). PICO 16

E. HEMODYNAMIC MONITORING

24. We were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5th or 50th percentile for age in children with septic shock and other sepsis-associated organ dysfunction. PICO 21

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). PICO 20

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). PICO 18
    Remarks: Advanced hemodynamic monitoring may include cardiac output/cardiac index, systemic vascular resistance, or central venous oxygen saturation ($ScvO_2$).

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). PICO 19

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

F. VASOACTIVE MEDICATIONS

28. We *suggest* using epinephrine, rather than dopamine, in children with septic shock (weak recommendation, low quality of evidence). PICO 22
29. We *suggest* using norepinephrine, rather than dopamine, in children with septic shock (weak recommendation, very low quality of evidence). PICO 23
30. We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock. PICO 22/23
31. We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock. PICO 26

    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). PICO 25

    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. PICO 24

    ~~We *suggest* using veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) as a rescue therapy in children with septic shock only if refractory to all other treatments (weak recommendation, very low quality of evidence). PICO 45~~

~~C~~G. VENTILATION

34. We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock. PICO 27
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). PICO 28
36. We *suggest* a trial of non-invasive mechanical ventilation (over invasive mechanical ventilation) in children with sepsis-induced pediatric ARDS (PARDS) without a clear indication for intubation and who are responding to initial resuscitation (weak recommendation, very low quality of evidence). PICO 29

    Remarks: When non-invasive mechanical ventilation is initiated, clinicians should carefully and frequently re-evaluate the patient's condition.
37. We *suggest* using high positive end-expiratory pressure (PEEP) in children with sepsis-induced PARDS (weak recommendation, very low quality of evidence). PICO 30

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 fractional inspired oxygen (FiO_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. PICO 31

    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). PICO 32

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

40. We *recommend* against the routine use of inhaled nitric oxide (iNO) in all children with sepsis-induced PARDS (strong recommendation, low quality of evidence). PICO 33

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). PICO 33

42. We were unable to issue a recommendation to use high-frequency oscillatory ventilation (HFOV) versus conventional ventilation in children with sepsis-induced PARDS. PICO 34

43. We *suggest* using neuromuscular blockade in children with sepsis and severe PARDS (weak recommendation, very low quality of evidence). PICO 35

    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 hours after ARDS onset.

~~We *suggest* using veno-venous ECMO in children with sepsis-induced PARDS and refractory hypoxia (weak recommendation, very low quality of evidence). PICO 36~~

~~D~~H. CORTICOSTEROIDS

44. We *suggest* against using intravenous 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). PICO 47

45. We *suggest* that either intravenous 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). PICO 47

I. 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). PICO 52/60

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. PICO 52/60

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. PICO 62

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). PICO 63

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). PICO 64

J. NUTRITION

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

52. We *suggest* not withholding enteral feeding solely on the basis of vasoactive-inotropic medication administration (weak recommendation, low quality of evidence). PICO 48

    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 days of PICU admission in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence). PICO 49/50

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). PICO 53

55. We *suggest* against the routine measurements of gastric residual volumes (GRV) in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). PICO 54

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). PICO 55

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77. We *suggest* against routine deep vein thrombosis (DVT) 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). PICO 42