

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

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22
23 Supplemental digital content is available for this article. Direct URL citations appear in the printed text
24 and are provided in the HTML and PDF versions on this journal’s website.

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26
27 The following sponsoring organizations with formal liaison appointees endorse this guideline:

28
29 American Academy of Pediatrics; Australia and New Zealand Intensive Care Society, Canadian Critical
30 Care Society; European Society of Intensive Care Medicine; European Society of Paediatric and Neonatal
31 Intensive Care; Pediatric Infectious Disease Society; Scandinavian Society of Anaesthesiology and
32 Intensive Care Medicine; Society of Critical Care Medicine; UK Sepsis Trust; World Federation of
33 Pediatric Intensive and Critical Care Societies

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38 **Disclosures:** S. Weiss and M. Peters served as arbiters for conflict interest management and adjudication
39 throughout the guidelines process following standard operating procedures set forth by SCCM and
40 endorsed by ESICM. Disclosures were collected throughout guidelines development with verbal
41 disclosures and more formally using SCCM’s conflict of interest system where indicated. The following
42 disclosures were provided by the authors: S. Weiss participates as a member of the Shock Society; M.
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46 California state chapter executive board member for the American Thoracic Society (ATS), participates in
47 the Pediatric Acute Lung Injury and Sepsis Investigators Network, Grant funding from Gerber
48 Foundation; S. Nadel is the immediate past President of the European Society of Pediatric and Neonatal
49 Intensive Care Medicine (ESPNIC); J. Brierly serves as Past President of ESPNIC; E. Carrol is a member
50 of the NICE Diagnostic Advisory Committee and scientific panels through the National Institutes for
51 Health Research; I. Cheifetz is a volunteer for the American Association for Respiratory Care and the
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4 American Thoracic Society, he is an advisor to Philips, and a contributor to Up-to-Date; J. Cies received
5 grants and honoraria from Allergan, Merck, and Thermo Fisher Scientific and is a consultant for Atlantic
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10 S.p.A and AbbVie Inc., and travel grants from AbbVie, he has been a lecturer for Philips, Radiometer,
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27 College of Critical Care Medicine, Society of Critical Care Anesthesiologists, and the American Society
28 of Anesthesiologists, International Anesthesia Research Society; A. Randolph through her institution has
29 research support from Genentech, Inc. for influenza biomarkers, served as a consultant for Bristol Myers
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34 Governance Committee and special interest groups related to acute care nursing; J. Wolf receives research
35 support from Merck & Company, Astellas Pharma, and has grant support from Karius, Inc., Empatica
36 Inc., and Bluespark Technologies; J. Zimmerman received biomarker research funding from
37 Immunexpress and is Past President of SCCM; P. Tissieres provides consulting services for Baxter, Inc.

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4 acute therapies, Bristol-Myers Squibb Company, Chiesi Farmaceutici S.p.A., Faron Pharmaceuticals, has
5 research grants from bioMérieux, funding from La Jolla Pharmaceuticals, Chiesi Farmaceutici S.p.A., and
6 is President ESPNIC. All other authors, staff, and consultants have indicated they have no conflicts to
7 report.
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12 **Disclaimer:** The Society of Critical Care Medicine guidelines are intended for general information only,
13 are not medical advice, and do not replace professional advice, which should be sought for any medical
14 condition. The full disclaimer for guidelines can be accessed at
15 <https://www.sccm.org/Research/Guidelines/Guidelines>.
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19
20 **Funding:** These guidelines were solely funded by the European Society of Intensive Care Medicine and
21 the Society of Critical Care Medicine.
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24
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26 **Copyright form disclosure:** Dr. Weiss participates in Pediatric Acute Lung Injury and Sepsis
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33 implemented through the Network from intramural funding, governmental or other Foundation Grant
34 funding). Dr. Nadel received funding form La Jolla Pharmaceutical (consulting), and he participates in the
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46 receives funding from La Jolla Pharmaceuticals (consultant on the data safety monitoring board for a
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4 clinical trial of a sepsis therapeutic), and he participates in the American Thoracic Society (online journal
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8 American College of Emergency Physicians (Pediatric Emergency Medicine Committee member). Dr.
9 Javouhey received funding from CSL Behring (trial on Intravenous Immunoglobulins in toxic shock
10 syndrome in children). Dr. Karam participates in BloodNet, PALISI, ISBT, AABB, and CCCTG. Dr.
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14 member). Dr. Newth received funding from Philips Research North America (consulting concerning
15 monitoring in PICU), and he participates in the American Thoracic Society. Dr. Nishisaki's institutional
16 department receives an unrestricted grant from Nihon Kohden Inc (involves an activity to develop a
17 device to measure capillary refill time), and he participates in the Society for Simulation in Healthcare
18 and International Society for Pediatric Simulation. Dr. Nunnally participates in ACCM (Regent), SOCCA
19 (director), ASA (committee), IARS, and NYSA. Dr. Randolph's institution received funding from
20 Genentech, Inc. (influenza biomarker study research support); she has received funding from Bristol
21 Myers Squibb (consultant in 2017) and La Jolla Pharmaceuticals, Inc (design of pediatric septic shock
22 trial of angiotensin II); and she participates in the American Thoracic Society and the International Sepsis
23 Forum. Dr. Ranjit participates as the Chancellor of College of Pediatric Critical Care, India. Dr. Tume
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26 (Acute and Critical Care Special Interest Group). Dr. Williams participates in the Pediatric Cardiac
27 Intensive Care Society. Dr. Wolf received funding support for participation in industry-sponsored
28 research from Merck & Co Inc, Astellas Inc, and Cempra Pharmaceuticals Inc, and he received other
29 support from Karius, Empatica, and Bluespark Technologies. Dr. Zimmerman received funding from
30 Immunexpress, Seattle (sepsis biomarker research), and he participates in the AAP and Pediatric
31 Academic Society (PAS). Dr. Tissieres received funding from Baxter Inc (consulting, renal replacement
32 therapy) and Biomerieux Inc (research grant, biomarkers sepsis), and he participates in the Swiss
33 Intensive Care Society, Swiss Pediatric Society, and the French Society of Intensive Care. The remaining
34 authors have disclosed that they do not have any potential conflicts of interest.
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4 **ABSTRACT**

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7 **Objective:** To develop evidence-based recommendations for clinicians caring for
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9 children (including infants, school-aged children, and adolescents) with septic shock
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11 and other sepsis-associated organ dysfunction.
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14 **Design:** A panel of 49 international experts, representing 12 international
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16 organizations, as well as 3 methodologists and 3 public members was convened. Panel
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18 members assembled at key international meetings (for those panel members attending
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20 the conference), and a stand-alone meeting was held for all panel members in
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22 November 2018. A formal conflict-of-interest (COI) policy was developed at the onset of
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24 the process and enforced throughout. Teleconferences and electronic-based discussion
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26 among the chairs, co-chairs, methodologists, and group heads, as well as within
27
28 subgroups, served as an integral part of the guideline development process.
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33 **Methods:** The panel consisted of 6 subgroups: recognition and management of
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35 infection, hemodynamics and resuscitation, ventilation, endocrine and metabolic
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37 therapies, adjunctive therapies, and research priorities. We conducted a systematic
38
39 review for each Population, Intervention, Control, and Outcomes (PICO) question to
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41 identify the best available evidence, statistically summarized the evidence, and then
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43 assessed the quality of evidence using the Grading of Recommendations Assessment,
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45 Development, and Evaluation (GRADE) approach. We used the evidence-to-decision
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47 framework to formulate recommendations as strong or weak, or as a best practice
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49 statement. In addition, “in our practice” statements were included when evidence was
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51 inconclusive to issue a recommendation, but the panel felt that some guidance based
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53 on practice patterns may be appropriate.
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4 **Results:** The panel provided 77 statements on the management and resuscitation of
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6 children with septic shock and other sepsis-associated organ dysfunction. Overall, 6
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8 were strong recommendations, 49 were weak recommendations, and 9 were best-
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10 practice statements. For 13 questions, no recommendations could be made; but, for 10
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12 of these, “in our practice” statements were provided. In addition, 49 research priorities
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14 were identified.

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18 **Conclusions:** A large cohort of international experts was able to achieve consensus
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20 regarding many recommendations for the best care of children with sepsis,
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22 acknowledging that most aspects of care had relatively low quality of evidence resulting
23
24 in the frequent issuance of weak recommendations. Despite this challenge, these
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26 recommendations regarding the management of children with septic shock and other
27
28 sepsis-associated organ dysfunction provide a foundation for consistent care to improve
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30 outcomes and inform future research.

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

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4 The objective of the SCCM/ESICM *Surviving Sepsis Campaign International*
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6 *Guidelines for the Management of Septic Shock and Sepsis-associated Organ*
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8 *Dysfunction in Children* is to provide guidance for clinicians caring for children (including
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10 infants, school-aged children, and adolescents) with septic shock and other sepsis-
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12 associated organ dysfunction. We sought to leverage the expertise of a clinical and
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14 methodology team to create comprehensive evidence-based recommendations for the
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16 recognition and management of children with septic shock or other sepsis-associated
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18 acute organ dysfunction. Recommendations from these guidelines are based on the
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20 best current evidence but cannot replace the clinician’s decision-making capability when
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22 presented with a patient’s unique set of clinical variables. Recommendations are
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24 intended to guide “best practice” rather than to establish a treatment algorithm or to
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26 define standard of care. These guidelines are appropriate for treating septic shock and
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28 other sepsis-associated organ dysfunction in a hospital, emergency, or acute care
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30 setting, though some may be applicable elsewhere. Although recommendations were
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32 developed without consideration to availability of resources, we acknowledge that
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34 variation within and across health care systems and geographic regions will determine
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36 the practical application of these guidelines.
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45 Although several recommendations for the care of children with sepsis and septic
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47 shock have been previously published (14-16), these new guidelines are not intended to
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49 update or iterate on these prior documents. Instead, it was the aim of SCCM/ESICM
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51 *Surviving Sepsis Campaign* to provide an evidence-based approach to the management
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53 of septic shock and other sepsis-associated organ dysfunction in children using a
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4 comprehensive and transparent methodologic approach by a panel with geographic and
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6 professional diversity.
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10 11 **METHODOLOGY**

12 13 **Definitions**

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16 In 2005, the International Pediatric Sepsis Consensus Conference published
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18 definitions and criteria for sepsis, severe sepsis, and septic shock in children based on
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20 prevailing views of adult sepsis at the time with modifications for physiology based on
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22 age and maturational considerations (17). In 2016, new adult definitions and criteria
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24 were published (Sepsis-3) with *sepsis* defined as life-threatening organ dysfunction
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26 caused by a dysregulated host response to infection and *septic shock* the subset of
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28 sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of
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30 mortality (18). The term “severe sepsis” was replaced by this new definition of sepsis.
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32 Although application of Sepsis-3 to children has been attempted (19, 20), formal
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34 revisions to the 2005 pediatric sepsis definitions remain pending (21). Therefore, the
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36 majority of studies used to establish evidence for these guidelines referred to the 2005
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38 nomenclature in which severe sepsis was defined as a) ≥ 2 age-based systemic
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40 inflammatory response syndrome (SIRS) criteria, b) confirmed or suspected invasive
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42 infection, and c) cardiovascular dysfunction, acute respiratory distress syndrome
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44 (ARDS), or ≥ 2 non-cardiovascular organ system dysfunctions; and septic shock was
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46 defined as the subset with cardiovascular dysfunction, which included hypotension,
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48 treatment with a vasoactive medication, or impaired perfusion. However, studies that
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50 defined sepsis as severe infection leading to life-threatening organ dysfunction were
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4 included even if criteria used to define sepsis deviated from the 2005 consensus
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6 definitions.
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9 For the purposes of these guidelines, we define *septic shock* in children as
10 severe infection leading to cardiovascular dysfunction (including hypotension, need for
11 treatment with a vasoactive medication, or impaired perfusion) and *sepsis-associated*
12 *organ dysfunction* in children as severe infection leading to cardiovascular and/or non-
13 cardiovascular organ dysfunction. Because several methods to identify acute organ
14 dysfunction in children are currently available (17, 19, 20, 22, 23), we chose not to
15 require a specific definition or scheme for this purpose.
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28 **Scope of Patients**

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30 The panel intended these guidelines to apply to all patients from ≥ 37 weeks
31 gestation at birth to 18 years-of-age with severe sepsis or septic shock as defined by
32 the 2005 International Pediatric Sepsis Consensus Conference or inclusive of severe
33 infection leading to life-threatening organ dysfunction. Practically, all infants, children,
34 and adolescents with septic shock or other sepsis-associated acute organ dysfunction
35 are included in this scope. For simplicity, we will henceforth use the term “children” to
36 refer to infants, school-aged children, and adolescents in these guidelines.
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48 All recommendations apply to children with septic shock and other sepsis-
49 associated acute organ dysfunction unless specific qualifications, such as the subset
50 with immune compromise, are included in the recommendation. Even though these
51 guidelines are not intended to address the management of infection with or without
52 SIRS *when there is not associated acute organ dysfunction*, we recognize that sepsis
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4 exists as a spectrum and some children without known acute organ dysfunction may still
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6 benefit from similar therapies as those with known organ dysfunction. Finally,
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8 acknowledging that neonatal sepsis, especially in premature babies, may have distinct
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10 pathology, biology, and therapeutic considerations, newborns <37 weeks gestation are
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12 excluded from the scope of these guidelines. The panel sought to include term
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14 neonates (0-28 days) born at ≥ 37 weeks gestation within the scope of these guidelines
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16 because these infants may be recognized and resuscitated outside of a newborn
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18 nursery or neonatal intensive care unit. However, because the panel did not specifically
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20 address studies of neonates with perinatal infection or conditions that can be associated
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22 with neonatal sepsis (e.g., persistent pulmonary hypertension of the newborn), these
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24 guidelines do not address all management considerations for neonatal sepsis.
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33 **Application of Guidelines by Local Resource Availability**

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36 The intended target users of these guidelines are health professionals caring for
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38 children with septic shock or other sepsis-associated organ dysfunction in a hospital,
39
40 emergency, or other acute care setting. However, we acknowledge that many of the
41
42 recommendations are likely to apply to the care of children with septic shock and other
43
44 sepsis-associated organ dysfunction across a broad array of settings with adaptation to
45
46 specific environments and resource availability.
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51 These guidelines were largely developed without consideration of health care
52
53 resources (with some specific exceptions, e.g., fluid resuscitation), though we realize
54
55 that medical care for children with septic shock and other sepsis-associated organ
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57 dysfunction is necessarily carried out within the confines of locally available resources.
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4 The panel supports that these guidelines should constitute a general scheme of “best
5
6 practice,” but that translation to treatment algorithms or bundles and standards of care
7
8 will need to account for variation in the availability of local health care resources. The
9
10 panel acknowledges as well the need for future research to test the adaptation of
11
12 interventions to locally available resources.
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15 16 17 18 19 **Funding and Sponsorship**

20
21 All funding for the development of these guidelines was provided by SCCM and
22
23 ESICM. In addition, sponsoring organizations provided support for their members’
24
25 involvement.
26
27

28 29 30 31 **Selection and Organization of Panel Members**

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33 The selection of panel members was based on their expertise in specific aspects
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35 of pediatric sepsis. Co-chairs and co-vice chairs were appointed by the SCCM and
36
37 ESICM governing bodies; panel members were then recommended by the co-chairs
38
39 and co-vice chairs. Each panel member was required to be a practicing healthcare
40
41 professional with a focus on the acute and/or emergent care of critically ill children with
42
43 septic shock or other sepsis-associated acute organ dysfunction. Broad international
44
45 and multi-professional representation from critical and intensive care medicine,
46
47 emergency medicine, anesthesiology, neonatology, and infectious disease with
48
49 inclusion of physicians, nurses, pharmacists, and advanced practice providers as part of
50
51 the working group was ensured. Three members from the lay public were also included
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53 with a role to ensure that patient, family, and caregivers’ opinions were considered in
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4 prioritizing outcomes and finalizing recommendations that the clinicians proposed during
5
6 the development process. Panelists were recruited from a wide number of countries and
7
8 health care systems, including representation from resource-limited geographic areas. A
9
10 demographically diverse panel with regard to sex, race, and geography was assembled.
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12
13
14 Members were then allocated to specific groups based on their expertise.

15
16 The methodology team included trained methodologists from McMaster
17
18 University in Canada (WA, KC) and New York University in the United States (MN). The
19
20 team included methodologists with a health research methodology degree (MSc or
21
22 PhD) and/or advanced methodology training, all of whom are also practicing
23
24 intensivists. The methodology team provided methodological guidance and leadership
25
26 throughout the guideline development process.
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31 32 33 **Question Development and Outcome Prioritization**

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36 The panel was divided into groups: 1) recognition and management of infection,
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38 2) hemodynamics and resuscitation, 3) ventilation, 4) endocrine and metabolic
39
40 therapies, and 5) adjunctive therapies. A sixth subgroup was added to review research
41
42 priorities in pediatric sepsis.
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46 The co-chairs, co-vice chairs, and group heads made initial selections of the
47
48 topics. We included topics addressed in the 2016 SSC adult guidelines that were
49
50 relevant to children, as well as other key pediatric topics discussed in previously
51
52 published guidelines (14-16). The PICO format, which describes the population (P),
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54 intervention (I), control (C), and outcomes (O), was used for all guideline questions.
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58 Group heads, panel members, and methodologists reviewed and selected PICO
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4 questions considered important to guide care for children with septic shock or other
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6 sepsis-associated organ dysfunction. Panel members proposed additional PICO
7
8 questions of high priority and clinical relevance. For practical reasons, we excluded
9
10 several issues pertaining to general acute or critical illness that were not specific for
11
12 sepsis (e.g., head-of-bed positioning during invasive mechanical ventilation) and have
13
14 been addressed in other guidelines (e.g., Pediatric Acute Lung Injury Consensus
15
16 Conference [PALICC]) (24). However, topics with particular relevance to children with
17
18 septic shock or other sepsis-associated acute organ dysfunction were included in this
19
20 guideline, even if there was evaluation of similar or overlapping topics in previous
21
22 publications. The final decision regarding PICO question inclusion was reached by
23
24 discussion and consensus among the guideline panel leaders with input from panel
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26 members and the methodology team in each group.
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34 In adherence with the Grading of Recommendations Assessment, Development,
35
36 and Evaluation (GRADE) approach, panel members compiled a list of potential
37
38 outcomes for each PICO question. Subsequently, we electronically surveyed panel
39
40 members and asked them to rate each outcome on a scale of 1 (not important) to 9
41
42 (critically important). We selected only outcomes that were critical (mean of 7 or more)
43
44 for decision making, taking a patient's perspective. In addition, we presented all
45
46 selected outcomes to public members to ask for their input and feedback. The final list
47
48 of PICO questions is provided in **Supplemental Table 1**.
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55 **Search Strategy and Evidence Summation**

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4 For each PICO question, a professional medical librarian formulated the search
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6 strategy with input from the group heads, panel members, and methodologists.
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8 Searches utilized a combination of controlled vocabulary (e.g., “sepsis,” “bacterial
9
10 infections,” “critical illness,” “intensive care units,” “pediatrics,” “NICU,” “PICU,”
11
12 “emergency service”) and key words (e.g., “toxic shock,” “blood poisoning,” “acute
13
14 infection,” “child”) in the core search. Additional controlled vocabulary and key words
15
16 were incorporated to create separate strategies specific to the question posed.
17
18 Research design filters (e.g., systematic reviews/meta-analyses, randomized controlled
19
20 trials, observational studies) were also applied as appropriate. Only English language
21
22 studies were included. No date restrictions were imposed on the searches, but we
23
24 removed animal-only and opinion pieces from the results. The medical librarian
25
26 searched a minimum of two major databases (e.g., Cochrane Library,
27
28 PubMed/MEDLINE, or Embase) to identify relevant systematic reviews, clinical trials,
29
30 and observational studies published through May 1, 2017. As this was the inaugural
31
32 version of these guidelines for children, all publications up through May 1, 2017 were
33
34 considered. Key studies published after the conclusion of the initial literature search on
35
36 May 1, 2017 were incorporated into the evidence synthesis if identified by panel
37
38 members as important and relevant even if they were not part of the initial literature
39
40 review. We excluded articles published in abstract form, in a language other than
41
42 English, and those focused solely on pre-clinical data. Panel members, with input from
43
44 methodologists, used the Cochrane risk of bias tool to assess the risk of bias of
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46 randomized trials (25) and Newcastle-Ottawa Scale to assess risk of bias of non-
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48 randomized studies (26).
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4 When applicable, the methodologists used meta-analytic techniques to generate
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6 pooled estimates across two or more studies. For meta-analysis of randomized clinical
7
8 trials (RCTs), we used random-effects model and inverse variance method to pool
9
10 estimates across relevant studies. We reported relative risks (RR) and 95% confidence
11
12 interval (CI) for binary outcomes, and mean difference (MD) and 95% CI for continuous
13
14 outcomes. For observational data, we conducted meta-analyses if all individual studies
15
16 provided adjusted estimates and included both an intervention and a control arm using
17
18 a random-effects model and inverse variance method to pool adjusted odds ratio (OR)
19
20 across relevant studies. All analyses were conducted using RevMan software (Review
21
22 Manager, version 5.3, Copenhagen).
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31 **Formulation of Recommendations**

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33 The GRADE approach principles guided the assessment of quality of evidence
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35 from high to very low based on six domains: 1) risk of bias, 2) inconsistency, 3)
36
37 indirectness, 4) imprecision, 5) publication bias, and 6) assessment of the balance
38
39 between benefit and harm, patients' values and preferences, cost and resources, and
40
41 feasibility and acceptability of the intervention (27). Methodologists performed initial
42
43 assessments of quality of evidence and incorporated feedback from panel members to
44
45 generate final evidence profiles using GRADEpro GDT (28).
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51 The panel initially considered only research focused on pediatric patients using a
52
53 hierarchy of evidence (**Table 1**). Studies focusing on children with septic shock and
54
55 other sepsis-associated organ dysfunction were prioritized, though studies inclusive of
56
57 more general pediatric populations (e.g., all PICU patients) were considered for some
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4 questions on a case-by-case basis. If there were no studies or insufficient data in
5
6 children with sepsis or general pediatric illness, evidence from studies of adult patients
7
8 was considered using an *a priori* framework to determine appropriateness of indirect
9
10 evidence (**Figure 1**). Evidence from adult studies was generally down-graded due to
11
12 the indirectness of the evidence.
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15
16 In a series of webinars, methodologists reviewed the relevant data for each PICO
17
18 question with panel members to formulate initial recommendations. Each of the groups
19
20 used the Evidence-to-Decision (EtD) framework to facilitate transition from evidence to
21
22 the final recommendation. The EtD framework ensured that panel members took into
23
24 consideration not only the quality of evidence and magnitude of effect, but also balance
25
26 between benefits and harms, patients' values and preferences, resources, cost,
27
28 acceptability, and feasibility (28).
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34 We classified recommendations as strong or weak using the language "We
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36 recommend..." or "We suggest..." respectively. We judged a strong recommendation in
37
38 favor of an intervention to have desirable effects of adherence that will clearly outweigh
39
40 the undesirable effects. We judged a weak recommendation in favor of an intervention
41
42 to have desirable consequences of adherence that will probably outweigh the
43
44 undesirable consequences, but confidence is diminished either because the quality of
45
46 evidence was low or the benefits and risks were closely balanced. The implications of
47
48 calling a recommendation strong or weak are shown in **Table 2**. A strong
49
50 recommendation does not necessarily imply a standard of care, and circumstances may
51
52 exist in which a strong recommendation cannot or should not be followed for an
53
54 individual patient. We permitted strong recommendations *for* an intervention based on
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4 low or very low quality of evidence when the intervention had the potential to improve
5 survival and there was low risk for immediate harm. We permitted strong
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9 recommendations *against* an intervention based on low or very low quality of evidence
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11
12 when there was uncertain benefit but very likely or certain harm, including high costs
13
14 (29).

15
16 Best practice statements (BPS) were developed as ungraded strong
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18
19 recommendations within strict conditions suggested by the GRADE Working Group
20
21 **(Table 3)** (30). BPS were issued when the evidence could not be summarized or
22
23 assessed using GRADE methodology but the benefit or harm was deemed unequivocal.
24
25 In addition, when evidence was insufficient to make a recommendation, but the panel
26
27 felt that some guidance based on current practice patterns may be appropriate, we
28
29 issued an “in our practice” statement. The “in our practice statements” were developed
30
31 through a survey of panelists to ascertain their state of current practice. As such, “in our
32
33
34 practice” statements are intended only to describe current variation in care and are not
35
36 meant to be construed as recommendations.
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41 As new data are continuously generated, the Surviving Sepsis Campaign is
42
43 committed to ensuring that these guidelines are updated or affirmed every four years or
44
45 sooner if breaking and relevant evidence becomes available.
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50 **Voting Process**

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53 Panel members convened to review evidence and discuss recommendations in-
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55 person and through web conferences. Following the formulation of initial
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58 recommendations through discussion within subgroups, all panelists received links to
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4 evidence profiles and polls created using SurveyMonkey, Inc (Palo Alto, CA) to indicate
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6 agreement, disagreement, or abstention. Only panel members without relevant conflicts
7
8 of interest could vote. Voters could provide feedback for consideration in revising
9
10 statements. Panelists also deliberated during face-to-face meetings, during which
11
12 subgroups presented their draft statements for discussion. Up to three rounds of voting
13
14 were conducted throughout this process of deliberation in an attempt to achieve final
15
16 consensus. Acceptance of a statement required votes from 75% of the panel members
17
18 with an 80% agreement threshold.
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23 A summary of all statements determined by the panel is shown in **Appendix 1**.
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25 Evidence summaries and evidence profiles that informed the recommendations are
26
27 included in the online supplementary content. Links to specific tables and figures appear
28
29 within the relevant text.
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34 35 36 **Conflict of Interest Policy**

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38 Conflict-of-interest (COI) disclosures were sought through the Society of Critical
39
40 Care Medicine from all panelists and support personnel prior to commencing activities,
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42 with updates annually and as needed. The process relied solely on personal disclosure,
43
44 with clarifications sought when necessary, and centered primarily around potential
45
46 financial conflicts. The co-vice chairs reviewed all COI disclosures in accordance with
47
48 SCCM's standard operating procedures, sought clarification when necessary, and
49
50 worked with the co-chairs to recommend appropriate recusals. There was no industry
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52 input into or support of the guideline development process. No panelists received
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4 honoraria for any role in the guidelines process. Only librarians and a supporting project
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6 manager received compensation for their work.
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9 Seven individuals were identified with potential COIs, but only 3 were deemed
10 relevant to the final list of questions included in the scope of this guideline. These
11 individuals were asked to abstain from voting on the final recommendations involving
12 the potential COI. In addition, panel members were asked to voluntarily abstain from
13 voting on final recommendations if they had a potential academic COI (e.g., grant
14 application that could benefit from wording of a particular recommendation), though all
15 panel members were welcome to participate in the group discussions leading up to the
16 final recommendation to ensure that input was available from relevant experts.
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31 **A. SCREENING, DIAGNOSIS, AND SYSTEMATIC MANAGEMENT OF SEPSIS**

- 32
33 **1. In children who present as acutely unwell, we suggest implementing**
34 **systematic screening for timely recognition of septic shock and other**
35 **sepsis-associated organ dysfunction (weak recommendation, very low**
36 **quality of evidence).**
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43 **Remarks: Systematic screening needs to be tailored to the type of patients,**
44 **resources, and procedures within each institution. Evaluation for the**
45 **effectiveness and sustainability of screening should be incorporated as part of**
46 **this process.**
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52 **Rationale:** Systematic screening for sepsis in children is driven by the premise that
53 earlier recognition will lead to more timely initiation of therapy, which will translate to
54 improved morbidity and/or mortality. Screening tools are designed to increase reliability
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4 of sepsis recognition and empower health-care professionals to seek rapid medical
5
6 review. Rapid recognition of sepsis through standardized screening and procedures to
7
8 guide management of patients identified as at-risk for sepsis should be an essential
9
10 component of sepsis quality improvement (QI) programs. While the optimal method or
11
12 tool for screening is unclear, we suggest that screening tools be adapted to the type of
13
14 patients, resources, and processes within each institution.
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18
19 Several studies demonstrating that institutional sepsis QI efforts improve
20
21 outcomes have successfully incorporated screening tools (31-37). Most reported sepsis
22
23 screens were designed to prompt clinicians to prioritize review of patients that had
24
25 triggered the screen, hence the ultimate decision to treat or not remains with the
26
27 clinician. Although RCTs have evaluated the role of systematic screening algorithms to
28
29 recognize clinical deterioration in children more generally (38), high-quality trials on
30
31 pediatric sepsis recognition are lacking (39), and data are not sufficient to suggest any
32
33 particular screening tool, though several have been published (40-42) or shared on-line
34
35 (<http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx>).
36
37
38 Single-institution studies demonstrate that an electronic health record (EHR)-based
39
40 screening tool can yield high sensitivity and, when coupled with sequential clinician
41
42 assessment, improved specificity (43). For facilities that use an EHR, a step-wise
43
44 approach combining EHR-triggered alerts followed by clinician assessment has the
45
46 potential to shorten the time to sepsis recognition (41). Notably, no study was found on
47
48 systematic sepsis screening in low- and middle-income countries meeting the PICO
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4 Institutions should monitor and evaluate their practice following implementation of
5 sepsis screening (44). Robust QI balancing measures that should be assessed include
6 clinician response, anchoring bias, increased and/or inappropriate antimicrobial
7 prescriptions, fluid overload, increased PICU admissions and transfers to higher levels
8 of care, and health care utilization costs (45). Application of a screening tool requires
9 ongoing optimization of sensitivity and specificity, continuous improvement efforts to
10 maintain provider education and familiarity with the tool, and continual data acquisition
11 to monitor implementation and increase utilization (42). Finally, screening tools must
12 work well with existing or planned other early warning and rapid response systems (46,
13 47) that may also have inherent limitations (38, 48).

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31 **2. We were unable to issue a recommendation about using blood lactate**
32 **values to stratify children with suspected septic shock or other sepsis-**
33 **associated organ dysfunction into low- versus high-risk of having septic**
34 **shock or sepsis. However, in our practice, if lactate levels can be rapidly**
35 **obtained, we often measure blood lactate in children when evaluating for**
36 **septic shock and other sepsis-associated organ dysfunction.**

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45 **Rationale:** Blood lactate levels provide a valuable indirect marker of tissue
46 hypoperfusion (49). While increased lactate levels are not specific, they provide a
47 quantifiable surrogate for tissue hypoxia and can be rapidly obtained by point-of-care
48 tests available in many settings. In adults, blood lactate >2 mmol/L is now included
49 within the operational definition of septic shock as an indication of cellular/metabolic
50 dysfunction, and measurement of lactate is included in the Hour-1 Sepsis Bundle, with
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4 recommendations to repeat lactate measurement if the initial value exceeds 2
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6 mmol/L(18, 50, 51). In children, several observational studies have demonstrated an
7
8 association of elevated blood lactate levels with adverse outcomes in septic shock (11,
9
10 52-54). However, the optimal threshold to define *hyperlactatemia* remains unclear. In a
11
12 PICU study, the mortality rate for children with hypotension requiring vasopressors with
13
14 lactate >2 mmol/l was 32.0% compared to 16.1% if lactate was ≤2 mmol/l (11). Other
15
16 studies have shown that lactate levels >4 mmol/L are consistently associated with
17
18 mortality (52). Although blood lactate may be affected by the conditions of the blood
19
20 draw (e.g., use of a tourniquet), both venous and arterial lactate measurements
21
22 obtained have been shown to be independently associated with mortality in children
23
24 (55). In one prospective study in children, normalization of lactate within 2-4 hours of
25
26 presentation was associated with decreased risk of persistent organ dysfunction
27
28 (adjusted relative risk [RR] 0.47, 95% confidence interval [CI] 0.29, 0.78) (56). However,
29
30 no RCTs have tested whether initial or serial measurement of blood lactate directly
31
32 informs evaluation and/or management in children. Lactate levels should therefore be
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34 interpreted as part of a more comprehensive assessment of clinical status and
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36 perfusion.
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48 **3. We recommend implementing a protocol/guideline for management of**
49 **children with septic shock or other sepsis-associated organ dysfunction**
50 **(BPS).**
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54 **Rationale:** Institutional protocols have been shown to improve the speed and reliability
55
56 of care for children with septic shock or other sepsis-associated organ dysfunction.
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4 Studies reported improvements in mortality, length of stay, duration of organ
5
6 dysfunction, and development of new or progressive multiple organ dysfunction
7
8 syndrome (8, 32-34, 36, 57-61). Most of these studies have focused on timely delivery
9
10 of a “bundle of therapies” (e.g., blood culture, fluid bolus, and antibiotics). For example,
11
12 an analysis of 1179 children with sepsis across 54 hospitals in New York State found
13
14 that completion of a sepsis bundle within 1 hour was associated with lower risk-adjusted
15
16 odds ratio (aOR) of in-hospital mortality (0.59, 95% CI 0.38, 0.93, p=0.02) (8). In a
17
18 recent single institution study, bundle-compliant care in 1380 children with septic shock
19
20 was associated with a five-times lower mortality (OR 0.20, 95%-CI 0.07, 0.53) (33). In
21
22 another study, implementation of a sepsis protocol led to a substantial reduction in the
23
24 proportion of children who no longer had organ dysfunction on day 2 after presentation
25
26 (aOR 4.2, 95% CI 1.7, 10.4) (34). However, it should be noted that protocols studied to
27
28 date have variable components, many studies do not report adherence to specific items
29
30 within protocols, and only a few studies have attempted to adjust for initial illness
31
32 severity or other patient factors, making it difficult to summarize studies using the
33
34 GRADE approach. Therefore, because available evidence shows a strong and
35
36 consistent association that adherence to protocols reduces variability in care and
37
38 improves outcomes, we recommend implementing a protocol/guideline for management
39
40 of children with septic shock or other sepsis-associated organ dysfunction as a best
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42 practice.
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4 **4. We recommend obtaining blood cultures before initiating antimicrobial**
5 **therapy in situations where this does not substantially delay antimicrobial**
6 **administration (BPS).**
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11 **Rationale:** Blood cultures remain the most commonly used method to identify
12 bacteremia. Identification of a blood-borne pathogen can have significant clinical
13 implications on the type and duration of antimicrobial therapy and is an important
14 mechanism to recognize multidrug resistant pathogens (62). Thus, whenever possible,
15 blood cultures should be obtained prior to initiation of antimicrobial therapy in children
16 with severe sepsis or septic shock. Although no studies have directly measured the
17 effect of blood cultures alone on outcome in pediatric sepsis, several observational
18 studies have demonstrated that a bundled approach to initial resuscitation that includes
19 early blood cultures is associated with improved outcomes (8, 31, 33). If collection of the
20 blood cultures is likely to delay administration of antimicrobial therapy to the patient,
21 then administration of antimicrobials should take precedence, in view of the impact of
22 delayed antimicrobial administration on patient outcomes (63). However, because blood
23 cultures may be the only source of information identifying bacterial antibiotic
24 susceptibility, it is important to make all reasonable efforts to collect blood cultures
25 before timely antimicrobial administration. The collection of other biological specimens
26 to identify pathogens from non-blood sites (e.g. urine, cerebrospinal fluid, tracheal
27 aspirate, broncho-alveolar lavage, drainage from collections, etc.) should also happen
28 as soon as possible, and depending on the suspected site of infection, such specimens
29 may have a higher yield of pathogen identification than blood cultures. Clinicians should
30 also consider the epidemiology of pediatric infections in relation to age, sex, and host
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4 factors, such as comorbidities (64, 65). Specific patterns of pediatric bloodstream
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6 infections relating to age and comorbidities are well known, and approximately one out
7
8 of three bacteremia episodes are associated with organ dysfunction in a recent large
9
10 population-based study (65).
11
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14 Limitations of standard blood cultures include the time needed to grow and then
15
16 identify pathogens and their antibiotic sensitivities, as well as the effect of previous
17
18 therapy on diagnostic yield. New molecular technologies are becoming available to
19
20 facilitate earlier and faster microbiological diagnoses. Such techniques may be able to
21
22 identify a range of pathogens well before blood cultures are positive (66), and may
23
24 potentially identify pathogens even after the administration of antimicrobial therapy.
25
26 However, new molecular diagnostics are currently relatively expensive, are not sufficient
27
28 for all pathogens and antibiotic sensitivities, and are not universally available.
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34 35 36 **B. ANTIMICROBIAL THERAPY**

37
38 **5. In children with septic shock, we recommend starting antimicrobial therapy**
39
40 **as soon as possible, within 1 hour of recognition (strong recommendation,**
41
42 **very low quality of evidence).**

43
44
45 **6. In children with sepsis-associated organ dysfunction but without shock, we**
46
47 **suggest starting antimicrobial therapy *as soon as possible* after appropriate**
48
49 **evaluation, within 3 hours of recognition (weak recommendation, very low**
50
51 **quality of evidence).**
52
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54
55 ***Rationale:*** Antimicrobials are the primary medical therapy that directly targets the
56
57 underlying cause of sepsis, and there is strong biologic rationale for rapid delivery of
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4 antimicrobials in patients with sepsis (67). Many QI initiatives have shown improved
5
6 pediatric sepsis outcomes with implementation of a bundle that includes rapid delivery
7
8 of intravenous antimicrobials (8, 32-34, 36, 57-61). Two retrospective observational
9
10 studies have also demonstrated an association of faster time to antimicrobial therapy
11
12 with reduced mortality for children with sepsis. The first study was an analysis of 130
13
14 children with sepsis (mortality of 12%), including 103 (79%) with septic shock, in which
15
16 the unadjusted OR for mortality among children with antimicrobials delivered within
17
18 versus after 60 minutes of sepsis recognition was 0.60 (95% CI 0.13 - 2.86) (63). The
19
20 second study was an analysis of 1179 children, including 69% with septic shock, where
21
22 completion of a sepsis bundle within 1 hour of sepsis recognition was associated with
23
24 decreased mortality (OR 0.59, 95% CI 0.38, 0.93, $p=0.02$); however, initiation of
25
26 antimicrobials alone by 1 hour of recognition was not associated with significant
27
28 mortality reduction (OR 0.78, 95% CI 0.55, 1.12, $p=0.18$) (8). When the adjusted OR of
29
30 these 2 studies were pooled, there was a possible reduction in mortality (OR 0.77, 95%
31
32 CI 0.55, 1.08) (**Supplemental Table 2, Supplemental Figure 1.**) Other secondary end-
33
34 points reported in the literature have also been associated with shorter time to initiation
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36 of antimicrobial therapy, including reduced length of stay, shorter duration of organ
37
38 dysfunction, and reduced development of new or progressive multiple organ dysfunction
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40 syndrome (8, 32-34, 36, 57-61). Moreover, indirect evidence from adult sepsis generally
41
42 supports a benefit to starting antimicrobial therapy as soon as possible after recognition
43
44 of septic shock (68-73). Thus, timely antimicrobial therapy—ideally administered as part
45
46 of a more comprehensive bundle of initial care—should be the goal for children with
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48 septic shock.
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4 The definition of “timely” in this context represents an area of controversy relating
5
6 to challenges in the accurate recognition of patients with sepsis and septic shock and
7
8 the need to consider balancing QI metrics such as unnecessary antimicrobial usage
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10 (67, 74, 75). One pediatric study (63) indicated a dose-response gradient such that the
11
12 longer time to antimicrobial therapy, the higher the mortality. Yet the mortality increase
13
14 reached significance only when antimicrobials were administered >3 hours in
15
16 comparison to <3 hours, whereas the mortality of patients receiving antimicrobials within
17
18 <1 hour was not different from those receiving antimicrobials within <3 hours in that
19
20 relatively small study. The second, larger pediatric study demonstrated a significant
21
22 decrease in mortality if antimicrobials were administered within 1 hour, but only in the
23
24 context of a bundle that included a blood culture and fluid bolus. (8) Thus, available
25
26 pediatric studies do not provide a clear time cut-off after which the risk of mortality or
27
28 other adverse outcomes increases, but rather support that there is likely to be an
29
30 incremental risk for harm as time to antimicrobial initiation increases, in particular
31
32 beyond 3 hours. Notably, the benefit of antimicrobial therapy within 1 hour of recognition
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34 has been most prominent in cohorts with a predominance of septic shock (as compared
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36 to sepsis without shock) patients (8, 63).
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46 Based on limited pediatric evidence and indirect evidence from adult studies, the
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48 panel supported that, in children *with septic shock*, antimicrobial therapy should be
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50 initiated as soon as possible and ideally within 1 hour of recognition. Suspicion of septic
51
52 shock can usually be guided by clinical findings rapidly ascertained through history and
53
54 physical examination. While our recommendation to ideally administer antimicrobial
55
56 administration within 1 hour of recognition of septic shock establishes a tangible goal
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4 that emphasizes the importance of early antimicrobial therapy and assists clinicians in
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6 prioritizing bedside care, this cut-point should not be misconstrued as a known
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8 biological truth. Thus, dichotomous time-based metrics of the quality of care for children
9
10 with sepsis, while pragmatic and potentially useful to trend, may be of less value than
11
12 use of continuous variables such as median time to antimicrobials. Despite a very low
13
14 quality of evidence on this topic, we provide a strong recommendation because the
15
16 panel concluded that most patients would accept and most clinicians should seek to
17
18 initiate antimicrobial therapy as soon as possible after recognition of septic shock in
19
20 most situations.
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26 For children *without clinical signs of shock*, the panel acknowledged that the
27
28 diagnosis of sepsis-associated organ dysfunction has additional challenges related to
29
30 the need to discriminate those with true sepsis from among a large number presenting
31
32 with suspected infection (67). In view of the available evidence, we suggest starting
33
34 antimicrobial therapy *as soon as possible* after sepsis recognition, while allowing up to 3
35
36 hours for appropriate diagnostic investigation for patients *without clinical signs of shock*
37
38 and for those with an uncertain diagnosis. However, the diagnostic evaluation should be
39
40 performed expeditiously and, if and when the evaluation supports a likely infection or
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42 evidence of septic shock or other sepsis-associated organ dysfunction becomes
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44 manifest, antimicrobial therapy should be immediately administered.
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53 **7. We recommend empiric broad-spectrum therapy with one or more**
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55 **antimicrobials to cover all likely pathogens (BPS).**
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4 **8. Once the pathogen(s) and sensitivities are available, we recommend**
5 **narrowing empiric antimicrobial therapy coverage (BPS).**
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9 **9. If no pathogen is identified, we recommend narrowing or stopping empiric**
10 **antimicrobial therapy according to clinical presentation, site of infection,**
11 **host risk factors, and adequacy of clinical improvement in discussion with**
12 **infectious disease and/or microbiological expert advice (BPS).**
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19 **Rationale:** Sepsis mortality is associated with delays to *appropriate* antimicrobial
20 therapy, and hence optimal treatment for sepsis relies on accurate selection of
21 antimicrobials to ensure activity against the major pathogens (50, 63, 71, 76). *Empiric*
22 *therapy* refers to the initial choice of antimicrobials pending microbiological results
23 (Table 4) and is based on the predicted likelihood of bacterial pathogens. Empiric
24 therapy should cover a broad range of pathogens that are likely to cause the infection,
25 acknowledging that, in rare circumstances, this may not fully cover very unusual
26 pathogens. *Broad-spectrum therapy* refers to the use of *single- or multi-drug*
27 antimicrobial therapy with activity against multiple groups of bacteria/pathogens. Broad-
28 spectrum therapy is recommended for initial empiric therapy of children with septic
29 shock or sepsis-associated organ dysfunction to increase the likelihood that the initial
30 empirical therapy is effective against the causative pathogens.
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48 The initial choice of empiric antimicrobials should take into account the specific
49 clinical history (e.g., age, site of infection, concomitant disease states, comorbid
50 conditions, indwelling devices). Patients with recent or current hospital exposure should
51 receive empiric therapy that considers known infection or colonization, as well as any
52 recent antimicrobial exposure. Institutions or regions should identify the most
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4 appropriate first-line single-agent antimicrobial, taking into account anatomic site of
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6 infection, age, local epidemiology, and host comorbidity and risk factors (e.g.,
7
8 ceftriaxone is recommended for community-acquired sepsis by the National Institute for
9
10 Health and Care Excellence (NICE) in the United Kingdom) (16). For complex patients
11
12 or those recently or currently in hospital, the choice of empiric antimicrobials should also
13
14 take into account concomitant underlying diseases, chronic organ failure, indwelling
15
16 devices, the presence of immunosuppression or other form of immunocompromise,
17
18 recent known infection or colonization with specific pathogens, and recent receipt of
19
20 antimicrobials (65, 77, 78). When available, an infectious diseases clinician should be
21
22 consulted. Other non-bacterial pathogens that are suspected as a cause of infection
23
24 should also be targeted as part of initial antimicrobial therapy on a case-by-case basis.
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31 Sepsis in children is most commonly due to gram-negative or gram-positive
32
33 bacteria, although the relative prevalence of these pathogens varies by age, geographic
34
35 region, location (community versus hospital) of sepsis onset, and other patient factors.
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37 Invasive fungal infections are largely restricted to immunocompromised patients and
38
39 pre-term infants. Certain specific conditions put patients at risk for atypical or resistant
40
41 pathogens, thus requiring specific empiric regimens. For example, neutropenic patients
42
43 are at risk for an especially wide range of potential pathogens, including resistant gram-
44
45 negative bacilli and *Candida* species, and neonates are at risk of sepsis caused by
46
47 *listeria monocytogenes* and disseminated herpes simplex virus (HSV). Children with
48
49 chronic conditions treated in hospital settings are prone to sepsis with resistant bacteria
50
51 such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant
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53 enterococci (VRE). For children at risk for multidrug-resistant bacterial infections,
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4 empiric broad-spectrum antimicrobial regimens may require more than one agent to
5
6 broadly cover such potential pathogens.
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9 For specific empiric broad-spectrum antimicrobial therapy, the reader is directed
10 to published resources (77, 79) and the need to consider patient history, allergies, local
11 epidemiology, and suspected site/source of infection. However, general suggestions
12 can be provided here. For previously healthy children with community-acquired sepsis,
13 a third-generation cephalosporin (e.g., ceftriaxone) may be sufficient. Vancomycin
14 should be added in settings where MRSA or ceftriaxone-resistant pneumococci are
15 prevalent, and addition of an aminoglycoside or substitution of a carbapenem is
16 appropriate in settings where ceftriaxone resistance is common in gram-negative
17 bacteria (80). For immunocompromised patients or hospital-acquired sepsis,
18 antimicrobial therapy should begin with an anti-pseudomonal third- or higher-generation
19 cephalosporin (e.g., cefepime), a broad-spectrum carbapenem (e.g., meropenem,
20 imipenem/cilastatin), or an extended-range penicillin/ β -lactamase inhibitor combination
21 (e.g., piperacillin/tazobactam) (79). For neonates, therapy should also include ampicillin
22 for listeria and consideration for empiric acyclovir if there is a clinical concern for HSV
23 (77). For patients with a suspected or documented intra-abdominal source of infection,
24 therapy should include broad coverage for gastrointestinal pathogens, including
25 anaerobic bacteria, with either an extended-range penicillin/ β -lactamase inhibitor
26 combination or carbapenem, or addition of clindamycin or metronidazole. For patients
27 who present with sepsis complicating an influenza-like illness during the local influenza
28 season, empiric antiviral therapy should be started while awaiting the respiratory virus
29 testing (81, 82). Patients at higher risk of antibiotic-resistant infection because of past
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4 infection or colonization, local epidemiology, or recent broad-spectrum antibiotic use
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6 should receive an individually tailored empiric therapeutic regimen (83). In cases of
7
8 suspected toxic shock syndrome or necrotizing fasciitis, empiric treatment should
9
10 include clindamycin or lincomycin to limit toxin production and enhance bacterial
11
12 clearance (84). Finally, for sepsis treated in regions endemic for rickettsial or parasitic
13
14 pathogens (e.g., malaria), clinicians should consider adding relevant empiric coverage.
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19 *Targeted or definitive therapy* refers to the antimicrobial regimen targeted to a
20
21 specific pathogen(s) after microbiologic identification. As with empiric therapy,
22
23 targeted/definitive therapy may be single- or multi-drug therapy, but should not be
24
25 broader than required to treat the specific pathogen(s) after microbiologic identification
26
27 (85, 86). Risks of unnecessary continuation of broad-spectrum antibiotic and other
28
29 antimicrobial therapy include direct side effects and toxicities (such as the nephrotoxicity
30
31 or ototoxicity of aminoglycosides), infection with *Clostridioides difficile* (formerly
32
33 *Clostridium*) or fungal pathogens, and promotion of antimicrobial resistance in the
34
35 patient and in the community. In addition, unnecessary exposure to antibiotics may lead
36
37 to alteration of the human microbiome early in life, the impact of which is poorly
38
39 understood but has been associated with worse outcomes such as necrotizing
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41 enterocolitis in newborns.
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48 Because most microbiological cultures show significant growth within 24 to 36
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50 hours of collection when a pathogen is present (87), empiric treatment should be re-
51
52 evaluated after no more than 48 hours following initiation. If no pathogen is identified
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54 *and* bacterial/fungal infection is deemed unlikely, clinicians should stop empiric
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56 antimicrobial therapy to reduce unnecessary exposure to antibiotics/antifungals.
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4 However, many children with a clinical diagnosis of septic shock do not have a
5
6 pathogen isolated (5, 6). Patients with negative bacterial microbiological results may
7
8 have false-negative tests due to antibiotic pre-treatment, absence of bacteremia (e.g.,
9
10 bacterial pneumonia despite true bacterial infection), or sepsis related to viral infections
11
12 (88). Thus, the decision to continue, narrow, or stop antimicrobial therapy must often be
13
14 made on the basis of clinician judgment and indirect clinical information, taking into
15
16 account the clinical presentation, site and type of infection, host risk factors, and
17
18 adequacy of clinical improvement. Complex patients should be discussed with pediatric
19
20 infectious diseases and/or microbiology specialists to ensure likely pathogens are
21
22 treated and that antibiotics and other antimicrobials are stopped when they are no
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24 longer necessary.
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33 **10. In children without immune compromise and without high risk for**
34 **multidrug-resistant pathogens, we suggest against the routine use of**
35 **empiric multiple antimicrobials directed against the same pathogen for the**
36 **purpose of synergy (weak recommendation, very low quality of evidence).**
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43 **Remarks: In certain situations, such as confirmed or strongly suspected group B**
44 **streptococcal sepsis, use of empiric multiple antimicrobials directed against the**
45 **same pathogen for the purpose of synergy may be indicated.**
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50 **11. In children with immune compromise and/or at high risk for multidrug-**
51 **resistant pathogens, we suggest using empiric multi-drug therapy when**
52 **septic shock or other sepsis-associated organ dysfunction is**
53 **present/suspected (weak recommendation, very low quality of evidence).**
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4 **Rationale:** The selection of an empiric antimicrobial regimen requires consideration of
5
6 a patient's underlying disease state, potential history of prior infections and colonization
7
8 with multidrug-resistant organisms (MDROs), presence of immunosuppression, and
9
10 possible recent antimicrobial use, as well as local pathogen prevalence and
11
12 susceptibility profile(50, 89, 90). Empiric therapy may be single- or multi-drug, but
13
14 should be broad spectrum in nature as defined in Table 4. For select patients or with
15
16 concern for particular types of infection, this may necessitate adding a glycopeptide
17
18 (i.e., vancomycin) to ensure empiric coverage of methicillin-resistant *Staphylococcus*
19
20 *aureus* (MRSA) or a second gram-negative agent (e.g., aminoglycoside in addition to a
21
22 beta-lactam or second/third-generation cephalosporin) when antibiotic resistance is a
23
24 concern. However, routinely including an aminoglycoside or a glycopeptide for synergy
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26 or “double-coverage” as part of an empiric regimen is not supported by the available
27
28 data (90-101).
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36 A recent Cochrane review evaluated beta-lactam monotherapy versus beta-
37
38 lactam and aminoglycoside combination regimens for sepsis and included 69 trials
39
40 accounting for 7863 participants, including neonatal and pediatric patients(89). In trials
41
42 where the mono- and multidrug arm used the same beta-lactam, no difference in clinical
43
44 outcomes was observed between study groups. In studies where the monotherapy arm
45
46 contained a beta-lactam of broader spectrum than the multidrug arm, monotherapy
47
48 showed a possible benefit for all-cause mortality (OR 0.85, 95% CI 0.71, 1.01) and a
49
50 significant advantage for clinical failure (OR 0.75, 95% CI 0.67, 0.84) (89). Additionally,
51
52 indirect evidence from adults with sepsis including 13 RCTs comparing empirical mono-
53
54 versus combination antibiotic therapy suggests mortality and other outcomes are not
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4 improved by empiric combination therapy (91). Therefore, many children with septic
5 shock and other sepsis-associated organ dysfunction do not require empiric multi-drug
6 therapy. Clinicians should continually re-evaluate the local epidemiology and resistance
7 rates to ensure monotherapy remains appropriate (89).
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14 Certain clinical scenarios, however, may necessitate multi-drug antimicrobial
15 therapy. For example, in patients at high risk for resistant gram-negative infections with
16 sepsis, combining a beta- lactam/beta-lactamase inhibitor agent (i.e.,
17 piperacillin/tazobactam combination) with an aminoglycoside (i.e., gentamicin) can be
18 considered, not for synergy, but for expanded coverage to treat both susceptible and
19 resistant pathogens until final identification and susceptibilities are known (102-104).
20 Additionally, a synergistic multi-drug regimen may be appropriate in select settings,
21 even for targeted/definitive therapy, such as device-associated infections, enterococcal
22 endocarditis, staphylococcal endocarditis, group B streptococcal sepsis, and
23 carbapenem-resistant Enterobacteriaceae infections (105, 106).
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38 Pediatric patients with cancer and transplant recipients have a substantial degree
39 of immunosuppression and represent a population at higher risk for colonization and
40 infection with multi-drug resistant organisms (107, 108). The 2017 guidelines for the
41 management of fever and neutropenia (FN) in children with cancer and hematopoietic
42 stem-cell transplantation recommended monotherapy with an anti-pseudomonas beta-
43 lactam, a fourth-generation cephalosporin, or a carbapenem as empiric therapy in high-
44 risk pediatric patients with FN (79). The three RCTs in high-risk pediatric FN comparing
45 monotherapy with aminoglycoside-containing combination therapy found no significant
46 differences in failure rates, infection-related mortality, or overall mortality (79, 109, 110).
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4 The meta-analysis also confirmed the efficacy and safety of monotherapy without the
5 addition of an aminoglycoside. However, the 2017 guidelines on the management of
6 children with FN did recommend addition of a second gram-negative agent and/or a
7 glycopeptide when resistant organisms were suspected for patients who are clinically
8 unstable (i.e., septic shock) and in centers with a high rate of resistant pathogens (79).
9
10 Therefore, for children with septic shock or other sepsis-associated organ dysfunction
11 who have immune compromise and/or are at high risk for multidrug-resistant pathogens,
12 we suggest empiric multi-drug therapy.
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16 Currently, specific resistance rate thresholds do not exist to help clinicians decide
17 when the addition of a glycopeptide or second gram-negative agent for sepsis or septic
18 shock is necessary. The US guidelines for the management of community-acquired
19 pneumonia in adults suggest a 25% rate of high-level macrolide resistance in the
20 community as the threshold beyond which macrolides should not be used (111, 112).
21
22 Additionally, current guidelines from the Infectious Diseases Society of America
23 recommend an alternative antibiotic for skin and soft tissue infections if the local
24 clindamycin resistance rate is greater than 10% (113). Considering the current rates of
25 morbidity and mortality for patients with sepsis or septic shock, a local or regional
26 antimicrobial resistance rate exceeding 10% is probably a prudent threshold for the
27 addition of a second agent if that pathogen is suspected(5, 63).
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53 **12. We recommend using antimicrobial dosing strategies that have been**
54 **optimized based on published pharmacokinetic/pharmacodynamic**
55 **principles and with consideration of specific drug properties (BPS).**
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4 **Rationale:** Sepsis may alter the pharmacokinetics and pharmacodynamics of
5
6 antimicrobials. Therefore, antimicrobial dosing should be individualized to deliver
7
8 effective and timely treatment of life-threatening infection, while at the same time limiting
9
10 adverse medication effects. Sub-therapeutic dosing can lead to failure to clear the
11
12 infection, prolong organ dysfunction, and can lead to the development of antimicrobial
13
14 resistance. A substantial proportion of sepsis patients are at risk for altered drug
15
16 metabolism and/or clearance, including those with kidney and hepatic dysfunction and
17
18 those treated with extracorporeal therapies (114). In particular, continuous renal
19
20 replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) both
21
22 lead to profound alteration of antimicrobial clearance, requiring individual dose
23
24 adaptation (115). Therapeutic drug monitoring (TDM), where available, can permit
25
26 individualized antimicrobial dosing to achieve maximal effect while minimizing toxicity
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28 (116).
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36 Examples of sepsis and septic shock-related altered pharmacokinetics include
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38 increased volume of distribution as a result of fluid therapy and capillary leak (V_d) (117),
39
40 decreased antimicrobial clearance as a result of altered renal and hepatic organ
41
42 perfusion and organ dysfunction (118), and higher unbound drug levels due to
43
44 hypoalbuminemia leading to increased clearance(119). Hepatic dysfunction impairs the
45
46 metabolism of lipophilic and highly albumin bound antibiotics, leading to drug
47
48 accumulation and toxicity. In renal dysfunction, time-dependent antibiotics cleared by
49
50 the kidneys, such as the beta-lactams, require reduced dosing frequency.
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56 The 3 main determinants of antimicrobial efficacy are: a) the time during which
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58 the concentration of the drug remains above the minimum inhibitory concentration (MIC)
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4 of the causative pathogen ($T > MIC$) (time-dependent antibiotics); b) the peak
5
6 concentration to MIC ratio (C_{max}/MIC) (concentration-dependent antibiotics); and c) the
7
8 ratio of the 24-hour area under the concentration-time curve divided by the MIC
9
10 (AUC_{24}/MIC) (concentration-dependent with time-dependence antibiotics). The main
11
12 classes of time-dependent antibiotics include beta-lactams (penicillins, cephalosporins,
13
14 carbapenems, monobactams) and lincosamides (clindamycin and lincomycin). For
15
16 amoxicillin-clavulanic acid, current published dosing regimens in critically ill children can
17
18 result in sub-therapeutic concentrations in the early period of sepsis due to augmented
19
20 renal clearance (120, 121). In sepsis, the use of continuous or extended infusions with
21
22 loading doses, as opposed to intermittent dosing, may lead to improved outcomes in
23
24 patients treated with beta-lactam antibiotics (122).
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31 The main classes of concentration-dependent antibiotics include
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33 aminoglycosides and metronidazole. In some centers, drug concentrations measured
34
35 within 60 minutes before or after administration of aminoglycosides are used to estimate
36
37 the C_{min} and C_{max} , respectively, and together with the MIC of the pathogen, can help to
38
39 guide appropriate antimicrobial dosing (119). Concentration-dependent antibiotics may
40
41 require an altered dosing frequency to maximize bacterial killing by preserving the
42
43 C_{max}/MIC .
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48 Glycopeptides, oxazolidinones, fluoroquinolones, polymyxins, daptomycin,
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50 azithromycin, and tigecycline are examples of concentration-dependent with time-
51
52 dependent antibiotics. For vancomycin, this can mean higher doses, but that comes
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54 with an increased risk of toxicity. For this reason, continuous vancomycin infusions may
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56 be considered to achieve optimal concentrations in some patients (123). For
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4 concentration-dependent with time-dependent antibiotics, dose optimization involves
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6 adjusting the dosing interval rather than administered dose (119).
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11 **13. In children with septic shock or sepsis-associated organ dysfunction who**
12 **are receiving antimicrobials, we recommend daily assessment (e.g., clinical,**
13 **laboratory assessment) for de-escalation of antimicrobial therapy (BPS).**
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19 **Remarks: This assessment should include a review of the ongoing indication for**
20 **empiric antimicrobial therapy after the first 48 hours that is guided by**
21 **microbiologic results and in response to clinical improvement and/or evidence of**
22 **infection resolution. This recommendation applies to patients being treated with**
23 **empiric, targeted, and combination therapy.**
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31 **Rationale:** The misuse and overuse of broad-spectrum antimicrobials in health care,
32 the community, veterinary medicine, and the environment have contributed to a global
33 public health emergency (124). De-escalation of antimicrobials, where appropriate, is
34 warranted to minimize adverse effects of unnecessarily prolonged administration. To
35 date, quality improvement efforts in adults have shown that safe and effective
36 antimicrobial de-escalation can be achieved by daily assessment and discussion (125,
37 126).
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48 Several host biomarkers have also been proposed to aid in the safe de-
49 escalation of antimicrobial therapy. In adults with severe infections and sepsis,
50 procalcitonin has been shown to successfully guide de-escalation (127-131) with an
51 associated improved mortality (132). Similar reductions in length of antimicrobial
52 therapy have also been safely achieved in neonatal populations (133) using
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4 procalcitonin as a guide. In the United Kingdom, the NICE committee concluded that in
5
6 emergency room and critical care settings, procalcitonin testing shows promise but
7
8 currently insufficient evidence is available to recommend the routine adoption of
9
10 procalcitonin-guided antimicrobial de-escalation (www.nice.org.uk/guidance/dg18).
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14 Although a relationship between antimicrobial stewardship programs (ASP) and a
15
16 decrease in antimicrobial resistance has not yet been shown, studies suggest that
17
18 inpatient pediatric ASPs may reduce antimicrobial usage without contributing to adverse
19
20 patient outcomes (124). The “Start Smart - Then Focus” work from Public Health
21
22 England suggests a pragmatic approach of the 5 “antimicrobial prescribing decision”
23
24 options to include: 1) stop antimicrobials if there is no evidence of infection, 2) switch
25
26 antimicrobials from intravenous to oral, 3) change antimicrobials – ideally to a narrower
27
28 spectrum – or broader if required, 4) continue and document next review date or stop
29
30 date, and 5) outpatient parenteral antimicrobial therapy (134). De-escalating
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32 antimicrobial therapy must be based in sound clinical judgment and needs to be
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34 adapted to local epidemiology and identified resistance patterns.
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43 **14. We recommend determining the duration of antimicrobial therapy**
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45 **according to the site of infection, microbial etiology, response to treatment,**
46
47 **and ability to achieve source control (BPS).**
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50 **Rationale:** The main purposes of antimicrobial therapy in patients with sepsis are to
51
52 reduce the pathogen load rapidly and to prevent recurrence. Important determinants of
53
54 the required duration of antimicrobial therapy include site of infection, ability to drain or
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56 remove fixed infectious foci, choice of antimicrobial therapy, time to clearance of
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4 positive cultures, the nature of the causative pathogen, and the integrity of the host
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6 immune response. There is no evidence that severity of sepsis is an important
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8 determinant of optimal duration of therapy because illness severity is not expected to
9
10 affect clearance of infection.
11
12

13
14 The optimal duration of antimicrobial therapy can differ by site of infection
15
16 because of a high pathogen burden, poor antimicrobial penetration, or presence of
17
18 difficult-to-eradicate microbial biofilms at the site. For example, longer duration of
19
20 therapy is typically required for treatment of endocarditis, undrained abscesses, and
21
22 prosthetic joint infection without device removal (135-137). Characteristics of the
23
24 causative organism that may affect optimal duration of therapy include resistance or
25
26 decreased susceptibility to front-line antimicrobials and propensity to cause deep-
27
28 seated or difficult-to-eradicate infection. For example, optimal duration of treatment for
29
30 endocarditis caused by methicillin-susceptible *Staphylococcus aureus* may be shorter
31
32 than for that caused by methicillin-resistant *Staphylococcus aureus* (137). Similarly,
33
34 although 7-10 days of therapy is appropriate for treatment of uncomplicated gram
35
36 negative bacteremia in immunocompetent hosts (138, 139), uncomplicated *S. aureus*
37
38 bacteremia requires a longer course of therapy to effect cure (140-142), likely because
39
40 of unrecognized seeding (143). Integrity of host immunity may also affect clearance of
41
42 infection, so antimicrobial therapy for infection in neutropenic pediatric patients with
43
44 cancer is often continued until resolution of neutropenia (79).
45
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53 A systematic review evaluated studies describing duration of treatment for
54
55 clinically and microbiologically-documented infections in children and provides
56
57 evidence-based clinical guidelines for optimal duration of antimicrobial therapy for
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4 specific conditions(144). Given the lack of studies on the duration of antimicrobial
5
6 therapy for pediatric patients with sepsis specifically, we refer to this previously
7
8 published guideline as best evidence. Importantly, there are no data to support that the
9
10 presence of organ dysfunction or a higher initial illness severity necessitates longer
11
12 therapy for specific infection types (other than attention to how such organ dysfunction
13
14 may affect antimicrobial pharmacokinetics and pharmacodynamics).
15
16
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19 Observational studies suggest that longer exposure to antibiotics is associated
20
21 with risk of potential adverse events including necrotizing enterocolitis in very low
22
23 birthweight infants (145), candidemia in hospitalized children (146, 147), development of
24
25 antimicrobial resistance (148) and *Clostridioides difficile* (formerly *Clostridium*) infection
26
27 (149). Several meta-analyses, RCTs, and observational studies have compared long-
28
29 versus short-duration antibiotic therapy for serious infections (141, 145, 150-168). Most
30
31 studies suggest that shorter courses were associated with similar clinical outcomes
32
33 compared to longer durations; these include neonatal bacteremia (159, 164),
34
35 pyelonephritis (169), uncomplicated bacterial meningitis (155, 156, 160-162, 165, 166),
36
37 and pneumonia (170, 171). In contrast to these infections, some studies have identified
38
39 scenarios where longer durations of antimicrobial therapy is superior. For example, an
40
41 RCT suggested that 14 days of antibiotic therapy was superior to 7 days for treatment of
42
43 neonates with *Staphylococcus aureus* bacteremia (141), and an observational study
44
45 suggested that >10 days was superior to ≤10 days of antibiotic therapy in children
46
47 treated for gram-negative bacteremia without removal of a pre-existing CVC (163).
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57 **C. SOURCE CONTROL**

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4 **15. We recommend that emergent source control intervention be implemented**
5 **as soon possible after a diagnosis of an infection amenable to a source**
6 **control procedure is made (BPS).**
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11 **Remarks: Appropriate diagnostic testing to identify the site of infection and**
12 **microbial etiology should be performed, and advice from specialist teams (e.g.,**
13 **infectious diseases, surgery) should be sought, as appropriate, in order to**
14 **prioritize interventions needed to achieve source control.**
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21 **16. We recommend removal of intravascular access devices that are**
22 **confirmed to be the source of sepsis or septic shock after other vascular**
23 **access has been established and depending on the pathogen and the**
24 **risks/benefits of a surgical procedure (strong recommendation, low quality**
25 **of evidence).**
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33 **Rationale:** Source control is defined as physical modalities taken to control or remove
34 the source of infection or to prevent spread of the infection systemically or to adjacent
35 tissues (172). Source control may include percutaneous or deep abscess drainage,
36 drainage of an empyema, septic joint, or subperiosteal abscess, removal of infected
37 hardware or central venous catheters (CVCs), or debridement of necrotizing soft-tissue
38 infection. The adult SSC guidelines recommend source control as soon as is reasonably
39 feasible after resuscitation, ideally within 6-12 hours of diagnosis (50). Waiting for
40 patients to clinically stabilize prior to intervention is not recommended, as delaying
41 adequate source control may lead to further clinical deterioration (6). While source
42 control as an adjunct to antimicrobial and other medical therapy has been best
43 described for abdominal infections in adults and has been associated with reduction in
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4 mortality (173), the role of source control for pediatric sepsis has been less well
5
6 elucidated (174).
7

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9 The importance of source control in children has been shown for skin and deep
10
11 tissue abscesses and necrotizing fasciitis (174-176). Despite the relative paucity of
12
13 pediatric data, source control is an important facet of treatment of sepsis, and should
14
15 not be delayed. Larger collections containing infected material often are poorly
16
17 penetrated by intravenous antimicrobials and contribute to direct and hematogenous
18
19 spread, ongoing inflammation, and organ dysfunction.
20
21

22
23 A common, but potentially preventable, source of infection is central line-
24
25 associated bloodstream infections (CLABSI). Delayed removal of a CVC in neonates
26
27 and in patients with fungemia or Enterobacteriaceae bacteremia increases the risk of
28
29 death or slows recovery (177-180). Removal of a CVC that is the source of infection is
30
31 therefore generally warranted unless extenuating circumstances exist. Fungal infection
32
33 dictates immediate removal, while in case of coagulase negative *Staphylococcus spp* or
34
35 clinically stable patients with infection caused by gram-negative rods, infections can
36
37 often be initially treated through the CVC as a temporizing measure. The decision to
38
39 remove the CVC, or not, should ultimately be made based on the pathogen
40
41 suspected/recovered and host factors, such as immune status. (**Supplemental Table**
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48 **3.)**
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50 51 52 53 54 55 **D. FLUID THERAPY** 56

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58 **17. In healthcare systems with availability of intensive care, we**

59
60 **suggest administering up to 40-60 mL/kg in bolus fluid (10-20 mL/kg per**
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4 bolus) over the first hour, titrated to clinical markers of cardiac output and
5
6 discontinued if signs of fluid overload develop, for the initial resuscitation
7
8 of children with septic shock or other sepsis-associated organ dysfunction
9
10 (weak recommendation, low quality of evidence).
11
12

13
14 18. In healthcare systems with no availability of intensive care and *in the*
15
16 *absence of hypotension*, we recommend against bolus fluid administration
17
18 while starting maintenance fluids (strong recommendation, high quality of
19
20 evidence).
21
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23
24 19. In healthcare systems with no availability of intensive care, *if hypotension*
25
26 *is present*, we suggest administering up to 40 mL/kg in bolus fluid (10-20
27
28 mL/kg per bolus) over the first hour with titration to clinical markers of
29
30 cardiac output and discontinued if signs of fluid overload develop (weak
31
32 recommendation, low quality of evidence).
33
34

35
36 **Remarks:** Clinical markers of cardiac output may include heart rate, blood
37
38 pressure, capillary refill time, level of consciousness, and urine output. In all
39
40 settings, the need for fluid administration should be guided by frequent
41
42 reassessment of clinical markers of cardiac output, serial blood lactate
43
44 measurement and advanced monitoring, when available. Signs of fluid overload
45
46 that should limit further fluid bolus therapy may include clinical signs of
47
48 pulmonary edema or new or worsening hepatomegaly.
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53 **Rationale:**
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4 Effective fluid resuscitation in septic shock can correct hypovolemia caused by capillary
5 leak, vasodilation, and fluid losses. Without maintenance of adequate atrial filling
6 pressures, cardiac output will fall and organ perfusion will be compromised.
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11 Three RCTs of different volume resuscitation strategies in children with septic
12 shock in settings in which advanced supportive care (e.g., intubation, mechanical
13 ventilation, and intensive care) was accessible have been published (181-183). These
14 studies have a combined total of only 316 children and showed no difference in
15 mortality between the restrictive and liberal fluid resuscitation groups (**Supplemental**
16 **Table 4, Supplemental Figure 2**).
17
18

19
20
21 In geographic settings in which advanced supportive care, including mechanical
22 ventilation, is limited and/or intensive care is not routinely accessible, the only large-
23 scale RCT of different bolus fluid volume resuscitation strategies in severe infection in
24 children was the Fluid Expansion as Supportive Therapy (FEAST) study (**Supplemental**
25 **Table 4, Supplemental Figure 2**) (184). The FEAST study was conducted in Africa in a
26 low-resource setting without access to PICU admission. Children between 60 days and
27 12 years of age with a severe febrile illness and abnormal perfusion were randomized to
28 either rapid volume expansion with 20 mL/kg of intravenous 0.9% saline or 5% albumin
29 or no bolus with maintenance fluid only (control group). Among the 3141 study
30 participants, malaria and anemia were highly prevalent. Overall, the RCT demonstrated
31 a lower mortality after 48 hours in children receiving conservative fluid therapy (i.e., no
32 bolus fluid, maintenance fluid only) than among those given liberal initial fluid therapy
33 (i.e., 20 mL/kg fluid bolus with maintenance fluid) with a RR of 0.72 (95% CI 0.57, 0.9).
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Notably, 29 additional children enrolled with severe hypotension (systolic blood

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4 pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in
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6 children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age) were
7
8 treated with 40 mL/kg fluid bolus per the planned protocol without randomization to the
9
10 control group. One additional child who was randomized to the control group also
11
12 received a 40 mL/kg fluid bolus due to severe hypotension.
13
14

15
16 For children with septic shock diagnosed by abnormal perfusion or hypotension
17
18 in healthcare systems with availability of advanced supportive and intensive care, and in
19
20 the absence of signs of fluid overload, the panel suggests administering up to 40-60
21
22 mL/kg fluid bolus therapy in the first hour of resuscitation. Fluid resuscitation should be
23
24 titrated to clinical markers of cardiac output and discontinued if signs of fluid overload
25
26 develop. Clinical markers of cardiac output can include heart rate, capillary refill, and
27
28 urine output. Although no high-quality RCTs demonstrate clear superiority of this
29
30 practice, numerous observational studies have reported improved patient outcomes with
31
32 routine administration of up to 40-60 mL/kg fluid bolus therapy in the first hour of
33
34 resuscitation (8, 32, 33, 36, 185-188). The panel provides only a weak recommendation
35
36 for this resuscitation strategy in healthcare systems with availability of intensive care
37
38 because a more restrictive fluid resuscitation strategy has not been shown to be inferior
39
40 in this setting and indirect data (184) indicate harm from rapid fluid boluses in other
41
42 settings. For this recommendation, the panel judged the balance of observational data
43
44 supporting initial fluid bolus therapy to outweigh an indirect suggestion of harm because
45
46 the generalizability of the FEAST trial to healthcare systems with availability of
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48 advanced supportive and intensive care is not clear.
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4 For children with septic shock without signs of fluid overload in low-resource
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6 settings where advanced supportive and intensive care is not available, the panel
7
8 recommends against bolus fluid administration, while starting maintenance fluids, in the
9
10 first hour *if hypotension is not present*, and suggests administering up to 40 mL/kg in
11
12 bolus fluid (10-20 mL/kg per bolus) over the first hour *if hypotension is present*. The
13
14 strong recommendation against bolus fluid *if hypotension is not present* was based on
15
16 the FEAST trial, in which rapid bolus fluid in the first hour of resuscitation increased
17
18 mortality compared to maintenance fluids only.
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23 For the subset of children with septic shock *and hypotension*, we suggest
24
25 cautious administration of fluid bolus therapy in low-resource settings because there are
26
27 insufficient data to conclude that fluid resuscitation is not beneficial in children with
28
29 septic shock *and hypotension*. In the FEAST study, all children with *severe* hypotension
30
31 were treated with 40 mL/kg of bolus fluid (184) and so it is not known if fluid bolus
32
33 therapy was beneficial or harmful in this subgroup of children. It should also be noted
34
35 that children with gastroenteritis were excluded from FEAST, as ongoing fluid losses
36
37 should be replaced with intravenous or oral rehydration as indicated. A recent analysis
38
39 of children with *moderate* hypotension who were randomized to either fluid bolus or
40
41 maintenance fluid in the FEAST trial was published after completion of our initial
42
43 systematic review but considered by the panel to be potentially influential (189). In this
44
45 analysis, only children with moderate hypotension were included because children with
46
47 severe hypotension were not allocated to the control (no bolus) arm. Fluid bolus therapy
48
49 in children with moderate hypotension was not beneficial or harmful compared to
50
51 maintenance fluid only (RR of death = 1.48, 95% CI 0.61–3.66, p=0.41). Although
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4 children who were reclassified as meeting all three WHO shock criteria of cold
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6 extremities, prolonged capillary refill >3 seconds, and weak, fast pulse (14) had 48%
7
8 mortality in the bolus groups versus 20% mortality in the control group, this difference
9
10 was not statistically significant (p=0.07). These cases were a very small proportion of
11
12 the total FEAST trial participants (only 72 [2.3%] had moderate hypotension and 65
13
14 [2%] met the full WHO shock criteria), and no data were provided about differential
15
16 patient characteristics between these very small *post hoc* subgroups to assess for
17
18 potential confounding. Therefore, until further data are available, the panel suggests
19
20 cautious administration of fluid bolus therapy for the subset of children with septic shock
21
22 *and hypotension* in low-resource settings as a weak recommendation based on low
23
24 quality of evidence.
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31 Although a suggestion of *up to* 40 mL/kg was included for hypotensive shock in
32
33 low-resource settings because this volume was administered to children with severe
34
35 hypotension in the FEAST study, fluid administration should always be titrated to clinical
36
37 markers of cardiac output and discontinued if signs of fluid overload develop. For
38
39 purposes of this weak recommendation, hypotension can be defined as a) systolic blood
40
41 pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in
42
43 children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age (184)
44
45 or b) by the WHO criteria of cold extremities *with* prolonged capillary refill >3 seconds
46
47 *and* weak, fast pulse (14). Although the panel did not review different approaches to
48
49 fluid bolus therapy in hypotensive children in low-resource settings, WHO recommends
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51 10-20 mL/kg of isotonic crystalloid over 30-60 minutes, followed by an additional 10
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4 mL/kg over 30 minutes if condition has not improved and signs of fluid overload, cardiac
5
6 failure, or neurological deterioration have not developed (14).
7
8

9 Fluid boluses may be administered as 10 or 20 mL/kg, according to clinician preference.
10

11 To facilitate rapid intravenous fluid administration (as well as other intravenous
12
13 therapies, such as antimicrobials and vasoactive medications), clinicians should
14
15 consider alternative methods of vascular access if initial attempts at peripheral vein
16
17 cannulation are not immediately successful. Intraosseous access is rapid and effective
18
19 and recommended by Pediatric Advanced Life Support (PALS), Advanced Pediatric Life
20
21 Support (APLS), and the International Liaison Committee on Resuscitation (ILCOR).
22
23

24 Ultrasound-guided peripheral intravenous catheter placement, CVCs, and umbilical
25
26 venous catheter access are alternatives if the skills are immediately available (190,
27
28 191). In all healthcare systems, repeat boluses should only be administered after
29
30 reassessment of hemodynamic status if shock has not resolved and signs of fluid
31
32 overload are not present.
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38 Although fluid bolus therapy should be discontinued if signs of fluid overload are
39
40 present or develop, early recognition of fluid overload by clinical examination is a
41
42 challenge in children. Identifying fluid overload is especially difficult in young children, in
43
44 whom crackles (rales) are often absent even in the context of gross pulmonary edema.
45
46 Worsening respiratory status, particularly increasing respiratory rate, radiographic
47
48 evidence of pulmonary edema in an intubated patient, or new or expanding
49
50 hepatomegaly may be the only clues of evolving fluid overload. Bedside ultrasound may
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52 also be helpful to assess fluid overload, as there is emerging evidence to suggest that a
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4 “full” inferior vena cava with minimal variation across the respiratory cycle demonstrated
5
6 on ultrasound indicates a fluid-replete circulation (192).
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11 **20. We suggest using crystalloids, rather than albumin, for the initial**
12
13 **resuscitation of children with septic shock or other sepsis-associated organ**
14
15 **dysfunction (weak recommendation, moderate quality of evidence).**
16
17

18
19 **Remarks:** Although there is no difference in outcomes, this recommendation
20
21 **takes into consideration cost and other barriers of administering albumin**
22
23 **compared to crystalloids.**
24
25

26 **Rationale:** The FEAST trial investigated 3141 African children with infection and
27
28 impaired perfusion, who were randomly assigned to resuscitation with 5% human
29
30 albumin solution or 0.9% saline boluses or no boluses on admission to the hospital.
31
32 Although both the albumin and 0.9% saline arms exhibited higher mortality than the no
33
34 bolus arm, comparing human albumin solution to 0.9% saline (RR 1.02, 95% CI 0.8,
35
36 1.28) showed no difference in mortality (184). In the absence of any clear benefit of
37
38 albumin administration in children with sepsis, and in view of the additional costs in
39
40 comparison to crystalloids, problems of availability, and the potential risk of blood-borne
41
42 infection, we suggest against the routine use of albumin for initial fluid resuscitation in
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44 children with sepsis.
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53 **21. We suggest using balanced/buffered crystalloids, rather than 0.9% saline,**
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55 **for the initial resuscitation of children with septic shock or other sepsis-**
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4 **associated organ dysfunction (weak recommendation, very low quality of**
5
6 **evidence).**
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9 **Rationale:** Increasing evidence from observational studies and RCTs in adults
10 suggests that resuscitation with crystalloid fluids containing high chloride concentrations
11 (e.g., 0.9% saline) is associated with hyperchloremic acidosis, systemic inflammation,
12 acute kidney injury, coagulopathy, and mortality when compared to resuscitation with
13 more balanced/buffered crystalloids (e.g., lactated Ringer's, PlasmaLyte) (193).
14
15

16 Although no pediatric RCTs compare balanced/buffered crystalloids to 0.9% saline,
17 there are 2 large observational studies in children with sepsis (194, 195). They included
18 a total of 30,532 children with sepsis, 2100 of whom received only balanced/buffered
19 crystalloids for the first 72 hours of hospital admission, and 28,432 who received 0.9%
20 saline (**Supplemental Table 5**). These studies showed that use of balanced/buffered
21 crystalloids was associated with lower mortality (OR 0.79, 95% CI 0.65, 0.95) but not
22 AKI (OR 0.98, 95% CI 0.94-1.02) (194, 195). Indirect evidence from adult patients,
23 including two large RCTs, also demonstrates benefit with balanced/buffered crystalloids
24 over 0.9% saline, with adult patients who received larger volumes of fluid and those with
25 sepsis exhibiting the greatest benefit (193, 196). Taken together, these data support
26 that the desirable consequences of balanced/buffered crystalloids probably outweigh
27 the undesirable consequences (including cost), especially in those who require large
28 volume of fluid resuscitation. Therefore, pending further high-quality pediatric data, we
29 suggest that balanced/buffered crystalloids should generally be preferred over 0.9%
30 saline for resuscitation of children with septic shock or other sepsis-associated organ
31 dysfunction without a specific indication for an alternative fluid type (e.g., 0.9% saline
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4 may be preferred in patients with hyponatremia or concern for increased intracranial
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6 pressure).

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

14
15 **Rationale:** No studies compare starches with other fluids in children. However, in
16 adults with severe sepsis and septic shock (**Supplemental Table 6**), two large RCTs
17 showed increased risk of mortality, coagulopathy, and AKI in patients receiving
18 hydroxyethyl starch (HES) (197, 198). A meta-analysis further confirmed the risk of
19 harm with HES (199). In the US, the Food and Drug Administration (FDA) has restricted
20 the use of HES (200) and the European Medicines Agency has recommended complete
21 suspension of its use (201). Therefore, we strongly recommend against the use of HES
22 in children with sepsis.
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41 **23. We suggest against using gelatin in the resuscitation of children with**
42 **septic shock or other sepsis-associated organ dysfunction (weak**
43 **recommendation, low quality of evidence).**

44
45 **Rationale:** One RCT of gelatin-derived fluid in pediatric septic shock compared it to
46 0.9% saline in 60 patients. The estimates were imprecise, and showed no difference in
47 mortality, days of using vasoactive medications, or AKI between the two groups (202)
48 (**Supplemental Table 7**). In the absence of any data indicating benefit of gelatin in
49 children, we suggest against its use in pediatric sepsis.
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7 **E. HEMODYNAMIC MONITORING**
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9 **24. We were unable to issue a recommendation about whether to target mean**
10 **arterial blood pressure (MAP) at the 5th or 50th percentile for age in children**
11 **with septic shock and other sepsis-associated organ dysfunction. However,**
12 **in our practice, we target MAP to between the 5th and 50th percentile or >50th**
13 **percentile for age.**
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21 ***Rationale:*** While no data from RCTs support specific hemodynamic targets in children,
22 evidence suggests that targeting MAP of approximately 65 mmHg (5th percentile) in
23 adults with septic shock may be beneficial (203). In the absence of evidence from
24 RCTs, we were unable to reach consensus to recommend a specific MAP target for
25 children. However, in our practice, 37% of panel members reported targeting MAP
26 between the 5th and 50th percentile for age and 45% reported targeting MAP >50th
27 percentile for age. Many panelists also commented that lower blood pressures are
28 acceptable if other hemodynamic parameters (e.g., mental status, perfusion, urine
29 output, lactate) are improving. RCTs to define optimal hemodynamic targets, including
30 MAP, are urgently required to inform practice in pediatric sepsis. In settings where direct
31 measurement of MAP is less reliable, systolic blood pressure provides a reasonable
32 alternative.
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50 A previous recommendation to target perfusion pressure (MAP minus central
51 venous pressure [CVP]) lacks supporting data (204). Prioritizing CVP measurement is
52 also impractical during early resuscitation (such as in most pediatric emergency
53 departments); CVP also provides an unreliable assessment of left ventricular preload.
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7 **25. We suggest not using bedside clinical signs in isolation to categorize**
8 **septic shock in children as “warm” or “cold” (weak recommendation, very**
9 **low quality of evidence).**

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

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23 **Remarks: Advanced hemodynamic monitoring may include cardiac**
24 **output/cardiac index, systemic vascular resistance, or central venous oxygen**
25 **saturation (ScvO₂).**

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31 ***Rationale:*** The ACCM previously recommended clinical assessment of children
32 in septic shock to differentiate “warm” versus “cold” shock based on extremity
33 temperature, capillary refill, pulse strength, diastolic blood pressure, and pulse pressure.
34 Depending on “warm” or “cold” classification, different resuscitation strategies were
35 suggested (e.g., fluid and vasopressors for “warm” shock and inotropes for “cold”
36 shock). However, a number of observational studies have demonstrated very poor
37 correlation of clinical assessments with cardiac index and systemic vascular resistance
38 as measured by advanced monitoring (205-210). Indeed, many children who appeared
39 to have “warm” shock by clinical examination had evidence of myocardial dysfunction,
40 thus demonstrating the challenge of using clinical signs alone to direct therapy. Hence,
41 we suggest not attempting to make this distinction using clinical assessments alone,
42 though this categorical distinction may be helpful if advanced hemodynamic monitoring
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4 is available to assess patient physiology more accurately. Examples of advanced
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6 monitoring include invasive arterial blood pressure monitoring with pulse contour
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8 analysis, ultrasound Doppler of the ascending or descending thoracic aorta
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10 (suprasternal or esophageal Doppler), cardiac ultrasound/echocardiography (211), or
11
12 measurement of ScvO₂ (212). All of these parameters (other than ScvO₂) will provide
13
14 additional assessment of cardiac index and/or systemic vascular resistance index
15
16 beyond clinical signs, which may then be used to direct and titrate treatment. There is
17
18 also emerging evidence that fluid responsiveness may be predicted by aortic blood flow
19
20 peak velocity variation (ΔV_{peak}) in mechanically ventilated children (213). In an RCT of
21
22 90 children admitted to a PICU in Egypt, addition of serial echocardiography provided
23
24 early recognition of septic myocardial dysfunction and hypovolemia that was not
25
26 apparent on clinical assessment and resulted in faster shock reversal, less fluid
27
28 overload, shorter LOS, and lower mortality compared with the group without serial
29
30 echocardiography (211). When advanced hemodynamic monitoring is available, it is
31
32 appropriate to target the normal range for parameters such as cardiac index, systemic
33
34 vascular resistance index, stroke index, and ScvO₂ (**Table 5**). No evidence supports
35
36 targeting a supranormal range of cardiac index.
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45
46 Until recently, adult guidelines have recommended early goal-directed therapy
47
48 (EGDT) based on the protocol published by Rivers et al in 2001(214). This
49
50 recommendation described the use of a series of “goals” that included CVP and ScvO₂.
51
52 This approach is no longer recommended following a failure to show reduction in
53
54 mortality in 3 subsequent large multicenter RCTs (215-217). In children, there has only
55
56 been one small RCT supporting the use of a protocolized approach including targeting
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4 ScvO₂ > 70%. This study included 102 children with fluid-refractory septic shock and
5
6 showed a reduced risk of death (RR 0.3, 95% CI 0.13, 0.68) from a very high baseline
7
8 mortality of 39% (26). No high-quality RCTs have investigated other hemodynamic
9
10 variables to guide therapy in children (**Supplemental Table 8, Supplemental Figure**
11
12 **3**).
13
14

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18
19 **27. We suggest using trends in blood lactate levels, in addition to clinical**
20
21 **assessment, to guide resuscitation of children with septic shock and other**
22
23 **sepsis-associated organ dysfunction (weak recommendation, very low**
24
25 **quality of evidence).**
26
27

28
29 **Remarks: In children with an elevated blood lactate, repeat testing that reveals a**
30
31 **persistent elevation in blood lactate may indicate incomplete hemodynamic**
32
33 **resuscitation and should prompt efforts, as needed, to further promote**
34
35 **hemodynamic stability.**
36
37

38 **Rationale:** Although blood lactate is not a direct measure of tissue perfusion, increased
39
40 lactate is associated with worse outcomes in children (11). Only one pediatric
41
42 observational study of lactate-guided resuscitation, which included 77 children with
43
44 sepsis in the ED, was available (**Supplemental Table 9**). This study showed that
45
46 lactate normalization was associated with a decreased risk of persistent organ
47
48 dysfunction (RR 0.46, 95% CI 0.29, 0.73; adjusted RR 0.47, 95% CI 0.29, 0.78) (56).
49
50 There is also indirect evidence from adult sepsis, with six RCTs (total of 1007 patients)
51
52 evaluating lactate-guided resuscitation of patients with septic shock (218-223). The
53
54 pooled estimates across all RCTs showed significant reduction in mortality compared to
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4 resuscitation without lactate monitoring (RR 0.66, 95% CI 0.55, 0.81) (**Supplemental**
5
6 **Table 9**). Therefore, while there was not sufficient evidence to propose a
7
8 recommendation to measure lactate to differentiate low- versus high-risk of sepsis
9
10 among children with infection or suspected infection (see Recommendation 2), we do
11
12 suggest that blood lactate levels be used to help guide resuscitation of children with
13
14 established septic shock or other sepsis-associated organ dysfunction.
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21 **F. VASOACTIVE MEDICATIONS**

22
23 **28. We suggest using epinephrine, rather than dopamine, in children with**
24
25 **septic shock (weak recommendation, low quality of evidence).**

26
27 **29. We suggest using norepinephrine, rather than dopamine, in children with**
28
29 **septic shock (weak recommendation, very low quality of evidence).**

30
31 **30. We were unable to issue a recommendation for a specific first-line**
32
33 **vasoactive infusion for children with septic shock. However, in our practice,**
34
35 **we select either epinephrine or norepinephrine as the first-line vasoactive**
36
37 **infusion guided by clinician preference, individual patient physiology, and**
38
39 **local system factors.**

40
41 **31. We were unable to issue a recommendation about initiating vasoactive**
42
43 **agents through peripheral access in children with septic shock. However, in**
44
45 **our practice, we often or sometimes administer a dilute concentration of the**
46
47 **initial vasoactive medication through a peripheral vein if central venous**
48
49 **access is not readily accessible.**
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4 **Remarks: It is reasonable to begin vasoactive infusions after 40-60 mL/kg of fluid**
5
6 **resuscitation if the patient continues to have evidence of abnormal perfusion, or**
7
8 **sooner if fluid overload develops or other concerns for fluid administration are**
9
10 **present. Either epinephrine or norepinephrine may be administered through a**
11
12 **peripheral vein (or intraosseous, if in place) if central venous access is not**
13
14 **readily accessible. Dopamine may be substituted as the first-line vasoactive**
15
16 **infusion, administered either peripherally or centrally, if epinephrine or**
17
18 **norepinephrine is not readily available.**
19
20
21
22

23 **Rationale:** Epinephrine and norepinephrine both have vasopressor and inotropic
24 effects, are widely used, and are effective in treating children with fluid-refractory septic
25 shock. No studies directly compare epinephrine with norepinephrine. However,
26 epinephrine has been compared to dopamine in two RCTs in children with fluid-
27 refractory septic shock (224, 225). Across both studies, epinephrine was associated
28 with a lower risk of mortality (RR 0.63, 95% CI 0.40, 0.99) and more organ failure-free
29 days among survivors by day 28 (MD 4 more days, 95% CI 2.0 to 6.0) (**Supplemental**
30 **Table 10, Supplemental Figure 4**).
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43 Norepinephrine has not been studied in children with septic shock, but in a
44 randomized trial of norepinephrine versus saline in sedated, mechanically ventilated
45 children, mortality was not different between groups (RR 0.50 95% CI 0.10-2.43,
46 **Supplemental Table 11a**) but the norepinephrine group showed higher urine output
47 (p=0.016) and improved blood pressure (p=0.04) suggesting improved perfusion relative
48 to saline (226). Evidence from adult trials (**Supplemental Table 11b**) shows a lower
49 mortality rate (RR, 0.93 95% CI 0.86-1.00) and lower incidence of arrhythmias (RR 0.48
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4 95% CI 0.40-0.58]) with norepinephrine than with dopamine, and no difference in
5
6 mortality with epinephrine than with norepinephrine (RR, 0.96 95% CI 0.77-1.21) (227).
7
8

9 Evidence is insufficient to recommend either epinephrine or norepinephrine as
10 the initial vasoactive agent for children with fluid-refractory septic shock. In a survey of
11 our panel members, an equal number used epinephrine and norepinephrine as the first-
12 line vasoactive medication with a general preference for epinephrine to treat myocardial
13 dysfunction and low cardiac output and for norepinephrine to increase systemic
14 vascular resistance. It therefore seems reasonable to use either epinephrine or
15 norepinephrine as the initial vasoactive agent, with the choice made based on individual
16 patient physiology, clinician preference, and local system factors. Once cardiac
17 ultrasound/echocardiography or other advanced monitoring is available, selection of
18 vasoactive therapy should be driven by individual patient physiology.
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33 No pediatric data identify when shock becomes “fluid-refractory” and, thus, to
34 guide when to start vasoactive infusions. However, excessive fluid resuscitation can
35 lead to fluid overload, which has been associated with increased mortality in critically ill
36 children (228). A trial comparing a fluid-sparing strategy with early initiation of
37 vasoactive medications compared to a fluid-liberal resuscitation strategy is currently
38 ongoing (SQUEEZE trial, Clinical Trials.gov NCT03080038). Until further data are
39 available, we consider it reasonable to begin vasoactive infusions after 40-60 mL/kg of
40 fluid resuscitation if the patient continues to have evidence of abnormal perfusion.
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52 Additional fluid resuscitation may be concurrently administered if the patient
53 demonstrates physiologic improvement following each fluid bolus and without signs of
54 fluid overload.
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4 All vasoactive agents, including norepinephrine, may be initiated through
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6 peripheral venous (or intraosseous, if in place) access if central venous access is not
7
8 readily available to avoid delays in therapy (229, 230). However, central venous access
9
10 should be obtained as soon as reasonably practicable. In our practice, 82% of panel
11
12 members reported at least sometimes administering the initial vasoactive infusion
13
14 peripherally if central venous or intraosseous access was not readily available,
15
16 particularly in the emergency department or other non-PICU settings. Most panelists
17
18 preferred epinephrine or dopamine to norepinephrine if peripheral infusion was needed.
19
20 Although epinephrine or norepinephrine is the preferred first-line medication, dopamine
21
22 may be substituted as the first-line vasoactive infusion, administered either peripherally
23
24 or centrally, if neither epinephrine nor norepinephrine is readily available.
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34 **32. We suggest either adding vasopressin or further titrating catecholamines in**
35
36 **children with septic shock who require high-dose catecholamines (weak**
37
38 **recommendation, low quality of evidence).**
39
40

41 **Remarks: No consensus was achieved on the optimal threshold for initiating**
42
43 **vasopressin. Therefore, this decision should be made according to individual**
44
45 **clinician preference.**
46
47

48 **Rationale:** Vasopressin-receptor agonists (vasopressin or terlipressin) have been
49
50 studied in three RCTs in children (**Supplemental Table 12**). Vasopressin was
51
52 compared with saline in one study in children with vasodilatory shock (231) and in one
53
54 study of children with severe lung disease (232). Terlipressin was compared with usual
55
56 care in children with septic shock (233). The mortality rate (RR, 1.14 [0.80-1.62]) and
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4 ischemic events (RR, 1.56; 95% CI, 0.41-5.91) were higher vasopressin/terlipressin.
5
6 There were fewer vasoactive-free days with vasopressin (median 25.2d in AVP (IQR
7
8 0.0-28.3), median 27.5d in control (IQR 23.1-28.9). In six RCTs in adults, renal
9
10 replacement therapy was required less often with vasopressin (RR, 0.74 95% CI 0.51-
11
12 1.08) (234). Weighing the benefit of avoiding renal replacement therapy against the
13
14 potential harm from ischemic events and the non-significant difference in mortality, we
15
16 suggest that vasopressin may be added or catecholamines may be further titrated in
17
18 children on high doses of catecholamines.
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26 **33. We were unable to issue a recommendation about adding an inodilator in**
27
28 **children with septic shock and cardiac dysfunction despite other vasoactive**
29
30 **agents. However, in our practice, we sometimes use inodilators in children**
31
32 **with septic shock and evidence of persistent hypoperfusion and cardiac**
33
34 **dysfunction despite other vasoactive agents.**
35
36
37

38 **Rationale:** There are no RCTs of inodilators (including milrinone, dobutamine, or
39
40 levosimendan) in children with septic shock with persistent hypoperfusion and cardiac
41
42 dysfunction. A report of two children described improvement in cardiac output with
43
44 addition of inodilators (235). A case series of 10 children with meningococcal septic
45
46 shock treated with milrinone described improved core-to-peripheral temperature
47
48 gradient, with stable blood pressure and no change in acidosis (236). These data were
49
50 not sufficient to formulate a recommendation. However, in our practice, 77% of panel
51
52 members reported at least sometimes using inodilators in children with septic shock
53
54 who had evidence of persistent hypoperfusion and cardiac dysfunction despite other
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4 vasoactive agents, typically in a PICU with advanced hemodynamic monitoring
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6 available.
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10 **G. VENTILATION**

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13 **34. We were unable to issue a recommendation about whether to intubate**
14
15 **children with fluid-refractory, catecholamine-resistant septic shock.**

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17
18 **However, in our practice, we commonly intubate children with fluid-**
19
20 **refractory, catecholamine-resistant septic shock without respiratory failure.**

21
22
23 **Rationale:** There are no RCTs and/or observational studies of children receiving early
24
25 intubation for refractory shock without respiratory failure compared to delayed or no
26
27 intubation for the same condition, nor is there suitable indirect evidence to substantiate
28
29 a formal recommendation. However, it is well understood that a high metabolic demand
30
31 from refractory shock typically indicated by progressive lactic acidemia and end-organ
32
33 dysfunction can be, at least in part, mitigated by early invasive mechanical ventilation
34
35 even without clinical symptoms of acute pulmonary edema or respiratory failure (237-
36
37 239). Moreover, chest radiograph findings can “lag” behind clinical deterioration (240,
38
39 241) such that patients with refractory shock and a “negative” chest radiograph may still
40
41 progress toward more overt acute respiratory distress syndrome (ARDS). Lung
42
43 ultrasound may provide an alternative tool to chest radiograph in detecting lung
44
45 pathology, but its utility to identify which sepsis patients may benefit from early
46
47 mechanical ventilation is not yet clear(242-245). For these reasons, 48% of panel
48
49 members often or always and 35% sometimes intubate children with fluid-refractory,
50
51 catecholamine-resistant septic shock even in the absence of clear respiratory failure,
52
53 while 17% rarely or never do so. Of note, when intubating, caution should be exercised
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4 to avoid worsening hypotension or precipitating cardiac arrest as medications used for
5
6 inducing anesthesia at the time of tracheal intubation, along with conversion from
7
8 spontaneous breathing to use of positive pressure ventilation, may result in a transient
9
10 deterioration in patient hemodynamics. The panel does recognize that in some settings,
11
12 invasive mechanical ventilation may not be available or feasible—or may even be
13
14 detrimental. In these instances, transport of the patient to a higher level of care can be
15
16 life-saving.
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23
24 **35. We suggest not to use etomidate when intubating children with septic**
25
26 **shock or other sepsis-associated organ dysfunction (weak**
27
28 **recommendation, low quality of evidence).**
29

30
31 **Rationale:** Etomidate is a short-acting intravenous anesthetic agent that has been
32
33 used for inducing anesthesia and sedation for tracheal intubation in patients with
34
35 unstable hemodynamics. However, concerns regarding the drug's effect on adrenal
36
37 function have been raised in adult studies. No RCTs exist in critically ill children with or
38
39 without sepsis comparing etomidate to another anesthesia/sedative regimen. Two
40
41 observational studies included children. One study from 1984 (246) enrolled acutely
42
43 injured adults and children (44 intubated with etomidate versus 90 intubated with a
44
45 benzodiazepine and opioid). A more recent study (247) enrolled children with
46
47 meningococcal sepsis or septic shock with 23 intubated with etomidate as compared to
48
49 37 intubated with any other combination of sedatives. While caution must be taken
50
51 given the small sample size, each of these studies reported higher mortality after use of
52
53 etomidate (pooled OR 4.51, 95% CI 1.82, 11.16) (**Supplemental Table 13**). In addition,
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4 den Brinker et al (247) reported a significant association of etomidate with adrenal
5
6 insufficiency, with cortisol to adrenocorticotropin hormone (ACTH) ratios decreasing by
7
8 83% after etomidate exposure. Indirect evidence is available from 4 RCTs in adults
9
10 (248-251). In the largest of these trials, Jabre et al (251) compared 234 critically ill
11
12 adults intubated with etomidate to 235 intubated with an alternative medication regimen
13
14 and found higher adrenal insufficiency in the etomidate group (OR 1.79, 95% CI 1.37,
15
16 2.36). Pooled odds of all 4 adult studies was 1.89 (95% CI 1.47, 2.44) with all studies
17
18 suggesting significantly increased risk of adrenal insufficiency after etomidate
19
20 administration. Importantly, this effect was seen even after 1 dose of etomidate.
21
22 Unfortunately, there is no conclusive evidence to recommend an optimal alternative
23
24 induction agent to etomidate, though ketamine and fentanyl are routinely available and
25
26 can offer favorable hemodynamic profiles in the setting of shock.
27
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36 **36. We suggest a trial of non-invasive mechanical ventilation (over invasive**
37
38 **mechanical ventilation) in children with sepsis-induced pediatric ARDS**
39
40 **(PARDS) without a clear indication for intubation and who are responding to**
41
42 **initial resuscitation (weak recommendation, very low quality of evidence)**
43
44

45 **Remarks: When non-invasive mechanical ventilation is initiated, clinicians should**
46
47 **carefully and frequently re-evaluate the patient's condition.**
48
49

50 **Rationale:** Non-invasive mechanical ventilation with continuous positive airway
51
52 pressure ventilation (CPAP) or bi-level positive airway pressure ventilation (BiPAP) may
53
54 allow for decreased work of breathing and improved oxygenation in the face of sepsis-
55
56 induced PARDS. Therefore, it is possible to avoid intubation in sepsis patients who are
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3
4 identified early with mild PARDS physiology and no evidence of advancing end-organ
5
6 dysfunction. However, no RCTs in either critically ill children or children with sepsis-
7
8 induced PARDS compare the effect of non-invasive ventilation to invasive mechanical
9
10 ventilation on clinical outcomes. Observational studies have tested whether non-
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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

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4 2015 PALICC (262) and 2017 Pediatric Mechanical Ventilation Consensus Conference
5
6 (PEMVECC)(263) guidelines.
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11 **37. We suggest using high positive end-expiratory pressure (PEEP) in children**
12 **with sepsis-induced PARDS (weak recommendation, very low quality of**
13 **evidence)**
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19 **Remarks: The exact level of high PEEP has not been tested or determined in**
20 **PARDS patients. Some RCTs and observational studies in PARDS have used and**
21 **advocated for use of the ARDS-network PEEP to fractional inspired oxygen (FiO₂)**
22 **grid though adverse hemodynamic effects of high PEEP may be more prominent**
23 **in children with septic shock.**
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31 **Rationale:** PEEP helps to prevent alveolar collapse, restore end-expiratory lung
32 volume, and improve mean airway pressures, all of which help to improve adequate
33 oxygenation in PARDS patients and minimize unnecessary use of high FiO₂. Adult
34 ARDS patients have been successfully managed with judicious and strict application of
35 a PEEP/FiO₂ grid, initially implemented in the ARDS-network ARMA trial (264). This grid
36 has been applied in children with PARDS enrolled in RCTs (265), but a pediatric-
37 specific PEEP/FiO₂ grid has not been determined or validated. In 2017, a multi-center
38 observational study by the Collaborative Pediatric Critical Care Research Network
39 reported that pediatric critical care clinicians almost uniformly limit PEEP to 10 cm H₂O
40 irrespective of oxygenation and FiO₂ (266). This is in contrast to the PEMVECC (263)
41 and PALICC (24) recommendations for use of PEEP in excess of 15 cm H₂O for severe
42 PARDS patients. Our panel reviewed several observational studies of PARDS patients,
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4 all published since 2007, each including 12-30% sepsis-induced PARDS (266-278). The
5
6 largest, a multicenter study by Khemani et al (278), evaluated 1,134 PARDS patients of
7
8 whom 26% were managed with lower PEEP relative to ARDSnet protocol and
9
10 experienced greater mortality than those managed in accordance with a higher PEEP
11
12 strategy as recommended by the ARDSnet PEEP/FiO₂ grid (**Supplemental Table 14**).
13
14 After adjustment for relevant co-morbidities, pediatric patients managed with a PEEP
15
16 strategy at or above that recommended by the ARDSnet low PEEP/FiO₂ grid had a
17
18 decreased odds of death compared to children managed with PEEP lower than that
19
20 recommended by the ARDSnet low PEEP/FiO₂ grid (adjusted OR 0.50, 95% CI 0.31-
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22 0.81).
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29 The panel concluded that PEEP levels >10 cm H₂O may be necessary with
30
31 progressive hypoxemia, with the precise amount of “high” PEEP carefully titrated for
32
33 each individual while attending to the potential adverse hemodynamic effects of
34
35 increasing intrathoracic pressure in children with septic shock. Therefore, although the
36
37 optimal approach to setting PEEP has not yet been determined in children with PARDS,
38
39 carefully increasing PEEP for children with sepsis-induced PARDS who require FiO₂
40
41 exceeding 60% and/or exhibit ongoing hypoxemia is reasonable, rather than continuing
42
43 to manage such children with a low- or moderate- PEEP strategy of ≤10 cm H₂O.
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50
51 **38. We cannot suggest for or against the use of recruitment maneuvers in**
52
53 **children with sepsis-induced PARDS and refractory hypoxemia.**
54

55 **Remarks: If a recruitment maneuver is considered, the use of a stepwise,**
56
57 **incremental and decremental PEEP titration maneuver is preferred over sustained**
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4 **inflation techniques that have not been optimized through direct testing in**
5
6 **PARDS patients. All PARDS patients must be carefully monitored for tolerance of**
7
8 **the maneuver.**
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11 **Rationale:** ARDS is characterized by decreased lung compliance, risk for atelectasis,
12 and increased intrapulmonary shunt. Recruitment maneuvers have been used in both
13 children and adults temporarily to increase transpulmonary pressure to recruit lung units
14 with the goal of improving both oxygenation and ventilation. Most recruitment
15 maneuvers include either sustained inflation or a step-wise incremental or decremental
16 PEEP titration methodology. However, many clinicians and researchers remain
17 concerned that the optimal strategy for lung recruitment has not been determined and
18 injudicious implementation of recruitment maneuvers can result in hemodynamic
19 compromise (279), hypercarbia (280), and/or ventilator-induced lung injury (281).
20
21 PEMVECC did not recommend use of recruitment maneuvers in children, citing an
22 overall lack of evidence in this area (263). In contrast, the 2015 PALICC provided a
23 weak recommendation in favor of recruitment maneuvers with prioritization of a slow
24 stepwise incremental and decremental PEEP method (24).
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43 Two observational studies are potentially informative about use of recruitment
44 maneuvers in children with sepsis-induced PARDS (269, 270). (**Supplemental Table**
45 **15.**) First, Boriosi et al (282) enrolled 21 children with lung injury, of whom 66% had
46 sepsis, and used incremental PEEP recruitment maneuvers. Patients experienced
47 improved oxygenation as measured by both the partial pressure of oxygen in arterial
48 blood to FiO₂ ratio (PaO₂/FiO₂ or P/F) and alveolar-to-arterial oxygen (A-a O₂) gradient
49 for the 4 hours after recruitment. Second, Duff et al (283) enrolled 32 children and used
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4 the sustained inflation technique, which also resulted in improved oxygenation for the
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6 ensuing 6 hours. However, neither study tested the association of recruitment
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8 maneuvers with clinical outcomes, such as ventilator days or mortality. Consequently,
9
10 despite the potential for benefit for some patients coupled with the possibility of harm
11
12 (284, 285), insufficient data do not allow us to recommend either for or against
13
14 recruitment maneuvers in sepsis-induced PARDS patients at this time.
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21 **39. We suggest a trial of prone positioning in children with sepsis and severe**
22
23 **PARDS (weak recommendation, low quality of evidence)**

24 **Remarks: Research trials in adults with ARDS and children with PARDS have**
25
26 **emphasized prone positioning for at least 12 hours per day, as tolerated.**

27
28 **Rationale:** Prone positioning almost uniformly improves oxygenation in adults with
29
30 ARDS and children with PARDS. While the exact mechanisms continue to be
31
32 elucidated, prone position has been shown to recruit areas of collapsed, de-recruited
33
34 lung with resultant improved elastance, decreased lung stress and strain, and improved
35
36 functional residual capacity (286). Given that pulmonary perfusion is thought to be
37
38 consistent both dorsally and ventrally, an improvement in lung aeration can be met with
39
40 continued perfusion, thereby reducing ventilation-perfusion mismatching (287). Most
41
42 recent RCTs in adults support use of prone positioning as a potentially life-saving
43
44 management strategy (**Supplemental Table 16**), especially in those meeting severe
45
46 ARDS criteria (i.e., P/F <150 mmHg) (288). This benefit is seen particularly in patients
47
48 who are positioned for prolonged periods of time, most commonly reported as 12-20
49
50 hours per day. Two pediatric RCTs tested the use of prone positioning in PARDS
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4 patients (265, 289). Pooled analyses of these two studies yielded a RR of 0.99 (95% CI
5
6 0.36, 2.69) for mortality in prone positioning as compared to supine positioning for this
7
8 patient population (**Supplemental Table 16, Figure 6**). Importantly, no serious adverse
9
10 events were reported in these trials, although the prone positioning methodology was
11
12 protocolized in each with particular attention to avoid accidental endotracheal extubation
13
14 and pressure injury. PALICC (24) did not recommend routine use of prone positioning in
15
16 PARDS patients but suggested its consideration in severe PARDS. The panel noted
17
18 that the National Institutes of Health (NIH) has approved and funded an international
19
20 RCT of prone positioning in severe PARDS (ClinicalTrials.gov identifier NCT02902055).
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29 **40. We recommend against the routine use of inhaled nitric oxide (iNO) in all**
30
31 **children with sepsis-induced PARDS (strong recommendation, low quality of**
32
33 **evidence).**
34

35
36 **41. We suggest using iNO as a rescue therapy in children with sepsis-induced**
37
38 **PARDS and refractory hypoxemia after other oxygenation strategies have**
39
40 **been optimized (weak recommendation, moderate quality of evidence)**
41

42
43 **Rationale:** The presumptive mechanism of sepsis-induced PARDS involves alveolar
44
45 epithelial injury, vascular endothelial injury, and activation of inflammatory, fibrosis, and
46
47 coagulation cascades. As such, PARDS is not a disease process primarily of pulmonary
48
49 arterial hypertension, the therapeutic target of iNO therapy, and so is not recommended
50
51 for routine use in children with sepsis-associated PARDS. Nonetheless, many PARDS
52
53 patients have co-morbidities that include risk for pulmonary hypertension (e.g., chronic
54
55 lung disease after prematurity, congenital heart disease after repair or palliation) or
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4 clinical features, such as acidemia and hypoxemia, that increase pulmonary arterial
5
6 pressures. Thus, inhaled nitric oxide therapy may be considered in children with
7
8 documented pulmonary hypertension or severe right ventricular dysfunction (241,
9
10 290)(REF). Such use of iNO in sepsis must be balanced against its lack of availability or
11
12 high cost in many areas of the world and, that once in place, iNO use carries a potential
13
14 patient safety consideration as inadvertent and abrupt discontinuation of the therapy
15
16 can result in a rapid and potentially life-threatening rebound pulmonary hypertensive
17
18 crisis.
19
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23
24 Several small RCTs (291-293) and observational studies have described
25
26 significant improvement in oxygenation after iNO therapy (294). Many, but not all, of
27
28 these studies include patients with sepsis (292, 293, 295-298), and few analyze longer
29
30 term, clinically relevant outcomes such as mortality. A 2016 Cochrane review indicated
31
32 no mortality benefit from iNO administration (RR 0.78, 95% CI 0.51, 1.18) in 3RCTs
33
34 (299). Our analysis of two recent observational studies, one conducted in children on
35
36 ECMO and another in children with severe PARDS, respectively, suggest possible
37
38 increased mortality risk (296, 298), whereas one RCT of 55 PARDS patients indicated
39
40 improved duration of mechanical ventilation in PARDS survivors (293) (**Supplemental**
41
42 **Table 17, Supplemental Figure 7**) Taken together, these data do not support *routine*
43
44 use of iNO in all children with sepsis-induced PARDS but do raise the potential for
45
46 benefit as an emergency rescue therapy for severe, sepsis-induced PARDS with
47
48 refractory hypoxemia after other oxygenation strategies have been optimized.
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4 However, when iNO is used, we agree with the PALICC recommendation that
5
6 “assessment of benefit must be undertaken promptly and serially to minimize toxicity
7
8 and to eliminate continued use without established effect” (24). These
9
10 recommendations align with the 2004 guidelines for use of iNO therapy in neonates and
11
12 children issued by the European Society for Pediatric and Neonatal Intensive Care
13
14 (300), PALICC guidelines (24), and a 2017 Cochrane review (294) as no relevant
15
16 change in evidence has become available.
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23
24 **42. We were unable to issue a recommendation to use high-frequency**
25
26 **oscillatory ventilation (HFOV) versus conventional ventilation in children with**
27
28 **sepsis-induced PARDS. However, in our practice, there is no preference to**
29
30 **use or not use HFOV in patients with severe PARDS and refractory hypoxia.**
31
32

33 ***Rationale:*** HFOV provides a sustained mean airway pressure with superimposed high
34
35 frequency, pendelluft-type, oscillatory breaths that may improve oxygenation in patients
36
37 with moderate-to-severe lung disease while minimizing barotrauma, volutrauma, and
38
39 atelectrauma. However, the most efficacious timing of application, optimal settings, and
40
41 ideal population of patients likely to benefit have not been well established. HFOV may
42
43 be difficult to apply effectively in centers with little experience, and is not universally
44
45 available. Despite these practical limitations, both PALICC (24) and PEMVECC (263)
46
47 endorsed cautionary use of HFOV as an alternative type therapy in patients with severe
48
49 PARDS. In our panel, clinicians who use versus those who do not use HFOV in patients
50
51 with severe PARDS and refractory hypoxia were nearly evenly distributed.
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4 Application of HFOV in adult ARDS patients has yielded concerning results due to a
5
6 potentially increased mortality observed in the adult OSCILLATE RCT (301) and a
7
8 neutral result in the adult OSCAR RCT (302). Pediatric data include 2 observational
9
10 studies with a non-HFOV control group and 3 randomized trials. In the two
11
12 observational studies, oxygenation improved with HFOV relative to conventional
13
14 ventilation but there was a non-significant trend toward increased mortality (Guo et al:
15
16 34.6% versus 22.7%, adjusted OR 2.74, 95% CI 0.52, 14.6; Bateman et al: 25% versus
17
18 17%, adjusted OR 1.28, 95% CI 0.92, 1.79)(303, 304). Among three small RCTs,
19
20 however, a trend toward reduced mortality in those managed with HFOV was observed
21
22 (pooled RR 0.77, 95% CI 0.43, 1.36)(305-307). A large, multi-center, international RCT
23
24 of HFOV compared to conventional mechanical ventilation in severe PARDS patients,
25
26 including children with and without sepsis, is underway and will seek to address many of
27
28 these issues ([www.clinicaltrials.gov/ NCT02902055](http://www.clinicaltrials.gov/NCT02902055)).

37
38 **43. We suggest using neuromuscular blockade in children with sepsis and**
39
40 **severe PARDS (weak recommendation, very low quality of evidence)**

41
42 **Remarks: The exact duration of neuromuscular blockade to use in severe PARDS**
43
44 **patients has not been determined to date. Most of the adult RCT data and**
45
46 **pediatric observational data support treatment for 24-48 hours after ARDS onset.**

47
48 **Rationale:** Indirect evidence from 3 adult RCTs (308-310) found that early use of
49
50 neuromuscular blocking agents (NMBAs) for up to 48 hours in adults with severe ARDS,
51
52 defined as PaO₂/FiO₂ ratio <150 mmHg, improved 90-day survival and shortened
53
54 duration of mechanical ventilation without increasing muscle weakness. In a multi-
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4 center double-blind RCT (310), 340 patients with early severe ARDS, meeting criteria
5 within 48 hours, were randomized to receive either cisatracurium besylate or placebo
6
7 once adequately sedated. After adjustment for baseline PaO₂/FiO₂, plateau pressure,
8
9 and the Simplified Acute Physiology Score, the cisatracurium group had a hazard ratio
10
11 for death at 90 days of 0.68 (95% CI 0.48, 0.98) compared to the placebo group. Early
12
13 use of NMBA was also associated with decreased organ system dysfunction, less air
14
15 leak, and a decreased pro-inflammatory response (311). These findings remained
16
17 consistent when combined with earlier smaller studies from the same group of
18
19 investigators in a meta-analysis. However, a more recent adult trial of early
20
21 neuromuscular blockade in those with moderate to severe ARDS was stopped for futility
22
23 at the second interim analysis (enrollment of 1006 patients) with a 90-day mortality
24
25 difference of 42.5% in the intervention limb versus 42.8% in the control limb. In this
26
27 study, the intervention group received continuous cisatracurium and deep sedation for
28
29 48 hours compared to the control arm that received lighter sedation targets (Richmond
30
31 Agitation Scale of 0 to -1). Both limbs received low tidal volume ventilation with high
32
33 PEEP strategy. Notably, only 13.8% of patients enrolled in ROSE had non-pulmonary
34
35 sepsis as a primary diagnosis.
36
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39 In pediatrics, there are no prospective data regarding the use of NMBA in
40
41 PARDS (with or without sepsis), although there is an ongoing pediatric trial in the
42
43 Netherlands (Clinical Trials.Gov NCT02902055). In one large retrospective study of 317
44
45 children with PARDS, of whom 23% experienced sepsis-induced PARDS (312),
46
47 mortality was lower in those children treated with neuromuscular blockade (8.8% versus
48
49 17.7%). However, duration of mechanical ventilation was longer in the treatment group
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4 and proportion with neuromuscular weakness was not assessed (**Supplemental Table**
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7 **18**).

10 H. CORTICOSTEROIDS

12 **44. We suggest against using intravenous hydrocortisone to treat children**
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14
15 **with septic shock if fluid resuscitation and vasopressor therapy are able to**
16
17 **restore hemodynamic stability (weak recommendation, low quality of**
18
19 **evidence).**

22 **45. We suggest that either intravenous hydrocortisone or no hydrocortisone**
23
24
25 **may be used if adequate fluid resuscitation and vasopressor therapy are not**
26
27 **able to restore hemodynamic stability (weak recommendation, low quality of**
28
29 **evidence).**

31
32 **Rationale:** A potential role for intravenous hydrocortisone as adjunctive therapy for
33
34 septic shock is supported by various roles of cortisol in homeostasis and the stress
35
36 response. For example, cortisol directly decreases reuptake of norepinephrine (313),
37
38 augments beta-adrenergic receptor sensitivity in the heart, and enhances calcium
39
40 availability in myocardial and vascular smooth muscle cells (314) promoting myocardial
41
42 contractility and vasoconstriction, respectively. Cortisol helps to inhibit prostacyclin and
43
44 endogenous nitric oxide production, resulting in increased vascular tone (315),
45
46 modulation of capillary leak (316), and augmentation of the beta-adrenergic receptor in
47
48 the heart (315). However, potential adverse side effects of corticosteroid therapy include
49
50 hyperglycemia (317, 318), catabolism-related diffuse neuromuscular weakness
51
52 (including the diaphragm) (319, 320), and hospital-acquired infections (321). These
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4 effects may be under-appreciated in critically ill patients, but can contribute to worse
5
6 outcomes (322).
7

8
9 At least one pediatric (323) and several adult (324) interventional trials examining
10
11 adjunctive corticosteroids for septic shock have concluded that this drug class hastens
12
13 resolution of shock. Of the four adult, high-quality contemporary RCTs, two reported a
14
15 mortality reduction and two did not (325-329). A recent meta-analysis of 42 RCTs
16
17 including 9,969 adults and 225 children with sepsis found that corticosteroids possibly
18
19 result in a small reduction in short-term mortality (RR 0.93, 95% CI 0.84, 1.03), long-
20
21 term mortality (0.94, 95% CI 0.89, 1.00), faster resolution of shock, and shorter LOS,
22
23 while also possibly increasing the risk of neuromuscular weakness (RR 1.21, 95% CI
24
25 1.01, 1.52) (330). Despite a weak recommendation to treat sepsis with hydrocortisone
26
27 based on the findings noted in the overall meta-analysis (331), the pediatric studies
28
29 enrolled a combined small number of subjects, reported inconsistent conclusions, had
30
31 methodologic limitations, and did not demonstrate an overall mortality reduction (323,
32
33 332-334). **(Supplemental Table 19).**
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41 Observational cohort studies have reported either harm or no benefit with
42
43 hydrocortisone in children with septic shock (5, 335-339). For example, a retrospective
44
45 analysis of the REsearching severe Sepsis and Organ dysfunction in children: a gLobal
46
47 perspectivE (RESOLVE) trial of activated protein C in pediatric sepsis found no
48
49 differences in mortality, duration of mechanical ventilation and vasoactive-inotropic
50
51 support, or PICU stay among 193 children who received and 284 who did not receive
52
53 open-labeled corticosteroids (336). Despite the *post hoc* analysis, age, sex, PRISM-III
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55 scores, baseline number of dysfunctional organs, and baseline Pediatric Overall
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4 Performance Category scores did not differ between corticosteroid-treated and
5
6 corticosteroid non-treated groups.
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9 Several pediatric and adult studies have attempted to use random cortisol and/or
10 cosyntropin-stimulated cortisol serum concentrations to identify which patients with
11 septic shock may benefit from hydrocortisone therapy, but reliable cutoffs have not been
12 clearly identified. Challenges relate to variability in 1) the cortisol assay itself; 2) cortisol
13 metabolism (11-beta-hydroxysteroid dehydrogenase) during sepsis; 3) corticosteroid-
14 binding globulin concentrations; and 4) multiple tissue (e.g., elastase, anti-glucocorticoid
15 compounds) and cellular (e.g., glucocorticoid receptor) factors. Therefore, use of
16 random cortisol or stimulation tests to guide corticosteroid prescription in children with
17 septic shock cannot be recommended as this time. However, for any patient with a
18 clinical concern for primary adrenal insufficiency (e.g., a patient with significant and
19 unexplained hypoglycemia, hyponatremia, and/or hyperkalemia), a high-dose
20 cosyntropin-stimulation test should be performed. Interpretation should focus on the
21 baseline serum ACTH concentration (above normal indicating primary adrenal
22 insufficiency) and the 60-minute stimulated serum cortisol concentration (<18 µg/dL
23 indicating primary adrenal insufficiency) (340).
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45 In summary, no high-quality investigations currently support or refute the routine
46 use of adjunctive corticosteroids for pediatric septic shock or other sepsis-associated
47 organ dysfunction. At the time of this publication, an RCT is in progress to examine the
48 potential risks and benefits of adjunctive hydrocortisone for fluid and vasoactive-
49 inotropic recalcitrant septic shock in children. However, this uncertainty does not apply
50 to children presenting with septic shock or other sepsis-associated organ dysfunction
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4 who also have acute or chronic corticosteroid exposure, hypothalamic-pituitary-adrenal
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6 axis disorders, congenital adrenal hyperplasia or other corticosteroid-related
7
8 endocrinopathies, or have recently been treated with ketoconazole or etomidate, for
9
10 whom prescription of stress-dose hydrocortisone is indicated, with or without evaluation
11
12 of the adrenal axis (341).
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19 I. ENDOCRINE AND METABOLIC

20
21 **46. We recommend against insulin therapy to maintain a blood glucose target**
22
23 **at or below 140 mg/dL (7.8 mmol/L) (strong recommendation, moderate**
24
25 **quality of evidence).**
26
27

28
29 **47. We were unable to issue a recommendation regarding what blood glucose**
30
31 **range to target for children with septic shock or other sepsis-associated**
32
33 **organ dysfunction. However, in our practice, there was consensus to target**
34
35 **blood glucose levels below 180 mg/dL (10 mmol/L) but there was not**
36
37 **consensus about the lower limit of the target range.**
38
39

40
41 **Rationale:** While hyperglycemia has been associated with poor outcomes in numerous
42
43 studies of critically ill children and adults, three prospective multicenter randomized
44
45 clinical trials of glucose control to a low target range (including 50-80, 70-100, 72-126,
46
47 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
48
49 clinical benefit in children (342-344) (**Supplemental Table 20**). One single-center RCT
50
51 did show substantial mortality benefit, but there was a high rate of severe hypoglycemia
52
53 and the higher target range cohort had substantially higher blood glucose levels than
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58 those used in the other multicenter RCTs (345). A trial involving children with burn
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4 injuries, a unique PICU population, demonstrated no mortality benefit, but did find a
5
6 significant reduction in morbidity (346). Notably, all trials included sepsis patients but
7
8 none targeted them exclusively. Meta-analyses of all published prospective trials in
9
10 children have shown no clinical benefits overall, but showed a substantially higher risk
11
12 of hypoglycemia when using insulin therapy to maintain a glucose target below 140
13
14 mg/dL (7.8mmol/L) (347, 348). Even brief episodes of severe hypoglycemia during
15
16 septic shock in children may be a risk factor for poor long-term developmental outcomes
17
18 (349-352).
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24 Treating hyperglycemia ≥ 180 mg/dL (≥ 10 mmol/L) may be desirable as incidence
25
26 of insulin-induced hypoglycemia in the studied pediatric cohorts with targets of 140-180
27
28 mg/dL (7.8-10.0 mmol/L) is extremely low. There are, however, no direct comparisons
29
30 between treatment to < 180 mg/dL (10.0 mmol/L) and no treatment. Therefore, evidence
31
32 cannot definitively guide this therapeutic target. However, given that the guidelines for
33
34 adults recommend an upper limit of 180 mg/dL (10 mmol/L) and given the lack of harm
35
36 demonstrated in the pediatric trials with those targets, treating children with septic shock
37
38 or other sepsis-associated organ dysfunction with intravenous insulin with a goal upper
39
40 blood glucose target of 180 mg/dL (10 mmol/L) is reasonable. The lower target, i.e., the
41
42 glucose concentration below which insulin infusion should be discontinued, has also not
43
44 been specifically studied, but is reasonable to set at 140-150 mg/dL (7.8-8.3 mmol/L),
45
46 based on similar principles. In a survey of our panel members, 32.5% always or often
47
48 and 17.5% sometimes target glucose levels between 140 and 180 mg/dL. Regardless of
49
50 the glucose target, the overriding goal during insulin therapy should be avoidance of
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52 hypoglycemia.
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7 **48. We were unable to issue a recommendation as to whether to target normal**
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9 **blood calcium levels in children with septic shock or sepsis-associated**
10
11 **organ dysfunction. However, in our practice, we often target normal**
12
13 **calcium levels for children with septic shock requiring vasoactive infusion**
14
15 **support.**
16
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18
19 **Rationale:** Calcium has an essential role in nearly all cellular processes, including
20
21 myocardial contractility and vasomotor tone. As such, intracellular and circulating levels
22
23 of calcium are tightly regulated. During septic shock, derangements in calcium
24
25 regulation frequently occur in critically ill adults and children. However, a systematic
26
27 review of adult literature found no evidence to support treating hypocalcemia of critical
28
29 illness (353). Calcium supplementation may actually worsen organ dysfunction and is
30
31 correlated with adverse outcomes in critically ill adult patients receiving PN (354).
32
33 Although the prevalence of hypocalcemia in critically ill children has been reported to
34
35 be up to 75% and is associated with organ dysfunction (355), no studies in children with
36
37 septic shock have investigated the effect of calcium supplementation to treat
38
39 hypocalcemia. However, in our practice, 65% of panel members always or often and
40
41 20% sometimes target normal calcium levels with parenteral calcium administration in
42
43 children with septic shock requiring vasoactive infusion support. Only 15% of panel
44
45 members rarely or never target normal calcium levels.
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4 **49. We suggest against the routine use of levothyroxine in children with septic**
5 **shock and other sepsis-associated organ dysfunction in a sick euthyroid**
6 **state (weak recommendation, low quality of evidence).**
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10
11 **Rationale:** Critically ill children, similar to adults, develop low tri-iodothyronine (T3) and
12 low normal thyroxine (T4) concentrations without the compensatory rise in thyroid
13 stimulating hormone (TSH) that is typical of the “sick euthyroid” state or
14 hypothyroxinemia of non-thyroidal illness (356). The decrease in T3 is due both to
15 increased thyroid hormone turnover and to decreased de-iodination of T4 to T3, with
16 redirection of T4 metabolism toward higher levels of biologically inactive reverse T3.
17 The magnitude of the drop in T3 within the first 24 hours of illness reflects the severity of
18 illness (357). Although of theoretical benefit, few trials of thyroid hormone replacement
19 have been conducted in critically ill children and none in children with sepsis. Two
20 prospective RCTs in children undergoing cardiac surgery (without sepsis) showed no
21 difference in mortality, vasoactive days, or PICU LOS (358, 359). One open-label study
22 in premature neonates also showed no difference in clinical outcomes (360). Taken
23 together, there are no direct data to inform a recommendation for children with sepsis,
24 and no indirect data from other critically ill children to support a recommendation for the
25 routine use of levothyroxine in children with septic shock and other sepsis-associated
26 organ dysfunction in a sick euthyroid state.
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53 **50. We suggest either antipyretic therapy or a permissive approach to fever in**
54 **children with septic shock or other sepsis-associated organ dysfunction**
55 **(weak recommendation, moderate quality of evidence).**
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4 **Rationale:** Fever is a complex physiologic response associated with sepsis, and it
5
6 remains unclear whether fever is a beneficial (361) or a harmful (362) response to
7
8 infection. Potential benefits include inhibiting the growth of some pathogens and
9
10 increased neutrophil production and lymphocyte proliferation. Conversely, fever is
11
12 associated with an increased metabolic rate (which may or may not have detrimental
13
14 effects in patients with sepsis) and may impair some components of immune function.
15
16 Fever can also make patients uncomfortable (363). Thus, the putative benefits of
17
18 maintaining normothermia by treating fever are unclear.
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23
24 No direct evidence for or against the use of antipyretics in febrile children with
25
26 sepsis-associated organ dysfunction exists. Rather, the panel had to consider indirect
27
28 data extrapolated from studies in adults. One systematic review of adult patients studied
29
30 the use of antipyretics and physical cooling methods included 8 RCTs (1507 patients)
31
32 and 8 observational studies (17,432 patients) (364). This study had 28-day mortality as
33
34 the primary outcome, with additional outcomes of early mortality (i.e., death on or prior
35
36 to day 14), frequency of acquisition of hospital-acquired infection, frequency of shock
37
38 reversal, and mean changes in body temperature, heart rate, and minute ventilation. No
39
40 difference was noted in 28-day mortality. Effects on early mortality differed between the
41
42 randomized (favored reduced mortality with antipyretic therapy) and observational
43
44 (favored increased mortality with antipyretic therapy) studies. While antipyretic therapy
45
46 successfully decreased body temperature, there was no effect on heart rate, minute
47
48 ventilation, shock reversal, or acquisition of nosocomial infections. This study did not
49
50 assess outcome measures of patient comfort. Based on available data, we are not able
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52 to recommend the optimal approach to fever in children with sepsis. However, it is
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4 reasonable to provide antipyretic therapy to optimize patient comfort, to reduce
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6 metabolic demand under certain clinical scenarios (e.g., refractory shock, pulmonary
7
8 hypertension), and to reduce extreme body temperatures.
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11 12 13 14 15 16 **J. NUTRITION** 17

18
19 **51. We were unable to issue a recommendation regarding early**
20
21 **hypocaloric/trophic enteral feeding followed by slow increase to full enteral**
22
23 **feeding versus early full enteral feeding in children with septic shock or**
24
25 **sepsis-associated organ dysfunction without contraindications to enteral**
26
27 **feeding. However, in our practice, there is a preference to commence early**
28
29 **enteral nutrition within 48 hours of admission in children with septic shock**
30
31 **or sepsis-associated organ dysfunction who have no contraindications to**
32
33 **enteral nutrition and to increase enteral nutrition in a stepwise fashion until**
34
35 **nutritional goals are met.**
36
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41 **Rationale:** No studies examine the enteral nutrition advancement strategy in children
42
43 with septic shock or other sepsis-associated organ dysfunction. Indirect evidence from a
44
45 small RCT in critically ill children examines early (6-24 hour) versus late enteral nutrition
46
47 (>24 hour) in, respectively, 57 and 52 children (365). Early enteral feeding had no effect
48
49 on duration of PICU stay, but a trend toward better survival in the early feeding group
50
51 (30% in early feeding versus 48% in late feeding, $p=0.07$) was shown. There is also
52
53 indirect evidence from the EDEN trial in adults (366) in which 200 patients were
54
55 randomized to receive either trophic or full enteral feeding for the first 6 days. This study
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4 demonstrated no difference in number of ventilator-free days, mortality at 60 days, or
5
6 infectious complications, but trophic enteral feeding was associated with less
7
8 gastrointestinal intolerance. Because neither of these studies was conclusive nor
9
10 directly studied children with septic shock or other sepsis-associated organ dysfunction,
11
12 no evidence-based recommendation could be made by the panel. However, in critically
13
14 ill children, a stepwise approach to increasing enteral feeds has been shown to reduce
15
16 time needed to reach nutritional goals (367-370). In our practice, 60% of panel
17
18 members always or often and 20% sometimes commence early enteral feeding within
19
20 48 hours of admission in children with septic shock or sepsis-associated organ
21
22 dysfunction who have no contraindications to enteral nutrition, while 20% of panel
23
24 members rarely or never pursue this practice.
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33 **52. We suggest not withholding enteral feeding solely on the basis of**
34 **vasoactive-inotropic medication administration (weak recommendation, low**
35 **quality of evidence).**
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41 **Remarks: Enteral feeding is not contraindicated in children with septic shock**
42 **after adequate hemodynamic resuscitation who no longer require escalating**
43 **doses of vasoactive agents or in whom weaning of vasoactive agents has started.**
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48 **Rationale:** We reviewed indirect evidence from three observational studies (two
49
50 retrospective and one prospective) in post-operative/cardiac pediatric populations.
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52
53 These studies reported that enteral feeding was tolerated in patients on non-
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55 escalating/weaning doses of vasoactive agents without increased adverse effects or
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57 gastrointestinal complications (371-373). In another study of 339 critically ill children,
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4 there was no association between enteral feeding and the development of severe
5
6 gastrointestinal outcomes such as vomiting, diarrhea, abdominal distension, bleeding,
7
8 necrotizing enterocolitis, or perforation (371). However, in the report, the decision to
9
10 start enteral nutrition may have been biased by the clinical condition of the patient. In a
11
12 retrospective study of 52 critically ill children, the use of vasoactive medications was not
13
14 associated with an increase in feeding intolerance or gastrointestinal complications
15
16 (372). In a prospective observational study of critically ill children who received post-
17
18 pyloric feeding, 44/65 (67.7%) of patients with shock and 284/461 (61.6%) of patients
19
20 without shock received enteral nutrition within 48 hours. Although gastrointestinal
21
22 complications were more common in children admitted with shock, no association
23
24 between the incidence of digestive tract complications and early (first 48 hours) or late
25
26 administration of post-pyloric enteral nutrition was reported (373). Based on these
27
28 studies which, while providing indirect evidence, all consistently found that enteral
29
30 feeding was not associated with harm, we recommend not to withhold enteral nutrition
31
32 solely because vasoactive-inotropic medications are being used. Current evidence
33
34 supports starting enteral nutrition in hemodynamically stable patients who are no longer
35
36 requiring fluid resuscitation or escalating doses of vasoactive agents.
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48 **53. We suggest enteral nutrition as the preferred method of feeding and that**
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50 **parenteral nutrition may be withheld in the first 7 days of PICU admission in**
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52 **children with septic shock or other sepsis-associated organ dysfunction**
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54 **(weak recommendation, moderate quality of evidence).**
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4 **Rationale:** No studies have been published on this specific issue of nutrition in children
5
6 with septic shock or other sepsis-associated organ dysfunction. However, in a general
7
8 cohort of 1440 critically ill children enrolled in the international multicenter RCT of
9
10 pediatric early versus late PN in critical illness (374), withholding parenteral nutrition
11
12 during the first week in PICU when enteral nutrition was less than 80% of prescribed
13
14 goal was clinically superior to providing supplemental parental nutrition within 24 hours
15
16 of admission (375). Secondary analyses of the PEPaNIC trial showed that withholding
17
18 PN was also beneficial in term neonates and children who were undernourished at
19
20 admission (376, 377), though withholding parenteral nutrition in term neonates was also
21
22 associated with increased risk of severe hypoglycemia (376). A long-term follow-up 2
23
24 years after PICU admission showed that withholding parenteral nutrition for 1 week did
25
26 not affect survival, anthropometrics, or health status, but did improve certain domains of
27
28 neurocognitive development (378). Although the results of the PEPaNIC trial
29
30 corroborated the findings from adult RCTs, the optimal timing of parenteral nutrition in
31
32 the critically ill child with sepsis is still not clear (374, 379-381). Our recommendation is
33
34 based on one trial and therefore, the evidence to withhold PN in the first 7 days of PICU
35
36 admission is of moderate certainty and must be explored further using pragmatic timing
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38 for PN in the first week, particularly in severely malnourished patients and neonates.
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50 **54. We suggest against supplementation with specialized lipid emulsions in**
51 **children with septic shock or other sepsis-associated organ dysfunction**
52 **(weak recommendation, very low quality of evidence).**
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4 **Rationale:** In two RCTs evaluating immunomodulatory formulas, including lipid
5 emulsions, in critically ill children, outcomes were not significantly different (382, 383).
6
7 One RCT was terminated during interim analysis because of unlikely benefit in the
8
9 intervention arm (383). In another small RCT, use of enteral feeding supplemented with
10
11 or without omega-3 fatty acids in 120 critically ill children with sepsis was investigated
12
13 (384). Univariate analyses showed a significant difference in inflammatory mediators
14
15 and reduction in PICU LOS, but these outcome benefits were not evident in the
16
17 multivariable analyses. Taken together, although promising, insufficient evidence is
18
19 available to support routine supplementation in pediatric sepsis with specialized lipid
20
21 emulsions.
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31 **55. We suggest against the routine measurements of gastric residual volumes**
32
33 **(GRV) in children with septic shock or other sepsis-associated organ**
34
35 **dysfunction (weak recommendation, low quality of evidence).**
36
37

38 **Rationale:** Although routine measurement of GRV is a relatively common practice in
39
40 PICUs, there is no direct evidence in pediatric sepsis. In a two-center observational
41
42 cohort study of critically ill children admitted with a variety of diagnoses, one center
43
44 reported routine use of GRV monitoring while the other center did not practice GRV
45
46 measurements (385). The center that advanced enteral nutrition without routine
47
48 measurements of GRV did not have an increase in the incidence of vomiting, ventilator
49
50 acquired pneumonia, or necrotizing enterocolitis in comparison with the other PICU
51
52 **(Supplemental Table 21)**. Although there are likely some children for whom measuring
53
54 GRV would likely be useful (e.g., gastroparesis, omphalocele, gastroschisis), no
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4 evidence supports routine measurements in all patients at this time and, if measured,
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6 GRV is not sufficient to diagnose EN intolerance.
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11 **56. We suggest administering enteral feeds through a gastric tube, rather than**
12 **a post-pyloric feeding tube, to children with septic shock or other sepsis-**
13 **associated organ dysfunction who have no contraindications to enteral**
14 **feeding (weak recommendation, low quality of evidence)**
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21 **Rationale:** In 3 small RCTs, gastric versus post-pyloric enteral feeding were compared
22 in mechanically-ventilated children with a variety of diagnoses (386-388). The outcomes
23 reported included lower caloric achievement with gastric feeding and delayed start of
24 enteral feeding with post-pyloric feeding (386, 387). No significant difference was found
25 in the incidence of ventilator-associated pneumonia between gastric and post-pyloric
26 feeding (388). On the basis of these studies, there is no clear evidence that post-pyloric
27 feeding is beneficial and there is concern for potential harm through delayed
28 optimization of enteral nutrition. Therefore, we suggest that feeding with a gastric tube is
29 physiologic and, based on current evidence, the preferred method for enteral nutrition.
30 Post-pyloric feeding may be considered in patients in whom gastric feeding is either
31 contraindicated (e.g., high-risk for aspiration) or was not tolerated/advanced, and as a
32 result, nutritional goals were unable to be met.
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53 **57. We suggest against the routine use of prokinetic agents for the treatment**
54 **of feeding intolerance in children with septic shock or other sepsis-**
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4 **associated organ dysfunction (weak recommendation, low quality of**
5
6 **evidence).**
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9 **Rationale:** Prokinetic agents, such as metoclopramide and erythromycin, are often
10 used in the PICU in an effort to reduce feeding intolerance (389). Indirect evidence for
11 this question was provided from the only pediatric randomized control trial, which was a
12 combined intervention of enteral zinc, selenium, glutamine, and intravenous
13 metoclopramide. In critically ill children, this combined intervention failed to reduce the
14 development of sepsis or incidence of hospital-acquired infection in immunocompetent
15 children, although the intervention including metoclopramide did reduce the rate of
16 hospital-acquired infection and sepsis in immunocompromised children. However, the
17 application of this study to children who already have sepsis is not clear. Prokinetic
18 agents are also not without risk as they have been associated with prolongation of the
19 QT interval and ventricular arrhythmias (390-392). Further investigation is needed to
20 determine if prokinetic agents are beneficial in patients with sepsis, particularly in
21 immunocompromised children.
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43 **58. We suggest against the use of selenium in children with septic shock or**
44 **other sepsis-associated organ dysfunction (weak recommendation, low**
45 **quality of evidence).**
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50 **Rationale:** Although clinical research examining the use of selenium among critically ill
51 neonates and adults has been done (**Supplemental Table 22**), there no data regarding
52 selenium supplementation as potential adjunctive therapy for pediatric sepsis. Selenium
53 plays a key role as a cofactor for glutathione peroxidase, iodothyronine deiodinase, and
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4 thioredoxin (393); accordingly, selenium deficiency could affect thyroid metabolism and
5
6 the response to oxidative stress during critical illness. Moreover, low serum selenium
7
8 concentrations are common in critical illness (394, 395) and infection (396), and have
9
10 been associated with measures of oxidative stress in neonates (397) and adults (398).
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14 A systematic review of investigations examining selenium supplementation in
15
16 preterm neonates reported improved outcomes, including reduction in occurrence of
17
18 sepsis (399). Similarly, a published systematic review and meta-analysis of the effect of
19
20 parenteral selenium supplementation in critically ill adult sepsis patients concluded that
21
22 this intervention reduced risk of mortality (400), but when the meta-analysis was
23
24 updated to include the results of a more recent RCT, there was no difference in
25
26 mortality in those treated with or without selenium supplementation (50). In an
27
28 interventional trial examining the potential benefit of zinc, selenium, glutamine, and
29
30 metoclopramide administration to critically ill children, there was no reduction in the
31
32 primary outcome measure, namely, time until the first episode of nosocomial
33
34 infection/sepsis (383). Based on lack of interventional trials examining selenium
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36 supplementation in the setting of pediatric sepsis and sepsis-associated organ
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38 dysfunction, we suggest against its use as a weak recommendation.
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48 **59. We suggest against the use of glutamine supplementation in children with**
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50 **septic shock or other sepsis-associated organ dysfunction (weak**
51
52 **recommendation, low quality of evidence).**

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55 **Rationale:** During catabolic stress, the human body is unable to produce adequate
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57 quantities of glutamine and, therefore, its essential role as a fuel source for enterocytes
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4 and immune cells is diminished. Over the past two decades, several investigations of
5
6 glutamine administration alone and in various combinations with other nutritional
7
8 supplements have been conducted in critically ill populations (383, 401-407), including
9
10 those with sepsis(402, 408-410). Contemporary studies have not found glutamine in any
11
12 form (enteral or parenteral) and/or in combination with other nutritional elements to
13
14 significantly improve morbidity or mortality in critically ill infants, children, and adults,
15
16 including those with sepsis (411-413) (**Supplemental Table 23**). However, single
17
18 element studies administering only glutamine to children with sepsis and septic shock
19
20 are scarce. An RCT by Jordan et al (404) randomized children (49 control; 49
21
22 interventional) with sepsis and septic shock for the purpose of examining oxidative
23
24 stress and inflammatory response. This investigation supports earlier studies in broader
25
26 populations finding no differences in PICU ($p=0.062$) or hospital LOS ($p= 0.09$) or
27
28 hospital mortality ($p=0.31$). Two other studies of glutamine administration in combination
29
30 with other elements to children with septic shock and critical illness are available (383,
31
32 402). The RCT by Briassoulis et al (402) examined children with septic shock receiving
33
34 glutamine in combination with arginine, antioxidants, and omega-3 fatty acids. Although
35
36 the main outcome of change in cytokines showed some promise, no difference was
37
38 noted between groups for hospital survival (80% versus 87%) or LOS (10.4 ± 2.2 versus
39
40 11.4 ± 2.5 days) (15). Carcillo et al (383) randomized 283 subjects from 8 PICUs to a
41
42 control group receiving whey protein formula or an intervention group receiving formula
43
44 with zinc, selenium, glutamine and IV metoclopramide supplementation. There was no
45
46 difference between hospital-acquired infections and clinical sepsis per 100 days
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48 ($p=0.81$), PICU LOS ($p= 0.16$), or 28-day mortality (8/139 [5.8%] versus 15/145
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4 [10.3%]). Subjects from this trial were also categorized by immune status with the
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6 suggestion that immune status may play a role in the effectiveness of nutritional
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8 supplemental, including glutamine (414). However, no direct evidence regarding
9
10 glutamine supplementation in children with sepsis exists; hence, we suggest against the
11
12 use of glutamine therapy in children with septic shock or other sepsis-associated organ
13
14 dysfunction until further data become available.
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21 **60. We suggest against the use of arginine in the treatment of children with**
22
23 **septic shock or other sepsis-associated organ dysfunction (weak**
24
25 **recommendation, very low quality of evidence).**
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28 **Rationale:** Reduced availability of arginine in sepsis may lead to decreased
29
30 endogenous nitric oxide synthesis, loss of microcirculatory regulation, and altered
31
32 immune response (415-417). In the only pediatric RCT of arginine supplementation in
33
34 children with sepsis (418), ten children received infusions of arginine and had enhanced
35
36 arginine oxidation and increased nitric oxide levels, but no clinical outcomes were
37
38 reported. In indirect data from adult studies, RCTs of L-arginine supplementation have
39
40 been small and have reported both positive and negative effects on mortality (419-423).
41
42 One trial in septic adults found decreased mortality(421), but other studies found no
43
44 benefit or increased mortality in adults with sepsis(419, 422, 423). Some authors found
45
46 improvement in secondary outcomes in patients with sepsis, such as reduced infectious
47
48 complications and shorter LOS, but the relevance of these findings and their
49
50 applicability to children with sepsis in the face of potential harm is unclear. Hence, in the
51
52 absence of evidence of demonstrated benefit, we suggest against the use of arginine
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4 therapy in children with sepsis-associated organ dysfunction until further data become
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6 available.
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11 **61. We suggest against using zinc supplementation in children with septic**
12 **shock and other sepsis-associated organ dysfunction (weak**
13 **recommendation, very low quality of evidence).**
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19 **Rationale:** Alterations in zinc homeostasis and associations between zinc levels and
20 outcomes have been reported in the critically ill. Benefits of zinc supplementation have
21 been shown in some forms of infectious illnesses. However, no trials of zinc
22 supplementation in children with sepsis have been conducted. One RCT in critically ill
23 children comparing daily supplementation with zinc, selenium, glutamine, and
24 metoclopramide versus whey protein was stopped during interim analysis due to futility
25 (383). Based on conflicting studies in the adult literature, routine supplementation of
26 zinc is not recommended in nutritional guidelines for critically ill adults (424). Future
27 RCTs examining the optimal timing and dose of zinc in children with sepsis and septic
28 shock and its impact on immune response and clinical outcomes might help answer this
29 question.
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48 **62. We suggest against the use of ascorbic acid (vitamin C) in the treatment of**
49 **children with septic shock or other sepsis-associated organ dysfunction**
50 **(weak recommendation, very low quality of evidence).**
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55 **Rationale:** Ascorbic acid (vitamin C) has multiple physiologic functions. Most
56 importantly in the setting of sepsis, vitamin C is an antioxidant and neutralizes reactive
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4 oxygen and nitrogen radicals, inhibits activation of pro-inflammatory cytokines,
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6 increases endogenous vasopressor synthesis, and inhibits bacterial replication (425-
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8 427). Adults with sepsis frequently have very low levels of vitamin C. In one study, 88%
9
10 of adults with septic shock had hypovitaminosis C (428). Small studies in adults suggest
11
12 that treatment of septic patients with vitamin C may improve organ dysfunction (429)
13
14 and reduce mortality (430). Vitamin C has also been used as a component of
15
16 combination therapy, typically with thiamine and corticosteroids, in adults with sepsis
17
18 (431). One study compared such treatment in 47 adult patients with sepsis to historical
19
20 control patients (432). Treatment was associated with decreased hospital mortality (OR
21
22 0.13, 95% CI 0.04, 0.48), shorter duration of vasopressor therapy, and improved organ
23
24 dysfunction scores (**Supplemental Table 24**).
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31 Currently, there are no data on the use of vitamin C in critically ill children or in
32
33 pediatric sepsis. The prevalence of low vitamin C levels in septic children is unknown,
34
35 and no studies have investigated the effect of vitamin C supplementation, either alone
36
37 or in combination with other agents, in the treatment of pediatric sepsis.
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43 **63. We suggest against the use of thiamine to treat children with sepsis-**
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45 **associated organ dysfunction (weak recommendation, low quality of**
46
47 **evidence).**
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50 **Rationale:** Thiamine is a crucial factor in cellular metabolism. In its active form,
51
52 thiamine pyrophosphate (TPP) is an essential coenzyme used to generate energy
53
54 (ATP) from glucose. The human body does not produce thiamine and, with a short half-
55
56 life and small body stores, thiamine deficiency can develop within days of critical illness
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4 and inadequate nutrition, resulting in impaired oxidative and carbohydrate metabolism.
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6 Low blood concentrations of thiamine have been reported on admission of critically ill
7
8 children and adults with sepsis and septic shock (433-435). A study examining thiamine
9
10 deficiency in children admitted to the PICU showed that low blood thiamine
11
12 concentration in those with severe sepsis or septic shock was associated with mortality
13
14 (OR 8.40, 95% CI 1.38, 51.0)(434). In an RCT of 88 adults with septic shock
15
16 **(Supplemental Table 25)**, there were no differences between treatment with thiamine
17
18 versus placebo for the primary outcome of change in lactate levels or the secondary
19
20 outcomes of mortality, shock reversal, and LOS (433). However, on *post hoc* analysis,
21
22 thiamine treatment in the subgroup with thiamine deficiency on admission was
23
24 associated with lower lactate level within 24 hours and lower mortality (p=0.047).
25
26 However, more evidence is needed to recommend whether thiamine supplementation
27
28 should be used to treat children with septic shock or other sepsis-associated organ
29
30 dysfunction. Also, it may be important for this evidence to be considered in the context
31
32 of thiamine status at PICU admission.
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42 **64. We suggest against the acute repletion of vitamin D deficiency (VDD) for**
43 **treatment of septic shock or other sepsis-associated organ dysfunction**
44 **(weak recommendation, very low quality of evidence).**
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49 **Rationale:** A systematic review and meta-analysis of 17 studies including 2,783
50
51 patients showed that approximately half of critically ill children have VDD (25-hydroxy
52
53 vitamin D [25(OH)D] level < 50 nmol/L or <20 ng/mL) at PICU admission (190). Further,
54
55 VDD was associated with higher illness severity, multiple organ dysfunction, and
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57 mortality across these studies. Six of these studies focused on or separately analyzed
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4 children with sepsis (436-440). Three studies reported a greater need for vasoactive
5 agents in VDD children (436-438), although mortality across these six studies was not
6 associated with VDD (436-440) (**Supplemental Table 26**).
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11 Vitamin D levels are lowered by fluid resuscitation, which can confound the
12 association with illness severity and disease complications (437). In addition, free or
13 bioavailable 1,25(OH)₂D is the active form which is influenced by the level of vitamin D
14 binding protein (VDBP) and a patient's VDBP genotype, which was not estimated or
15 measured in prior studies (441). Although vitamin D levels are a potentially modifiable
16 risk factor via supplementation, a meta-analysis of rapid normalization of vitamin D
17 levels concluded that it is best achieved using loading therapy that takes into account
18 disease status, determines baseline vitamin D level, and considers patient weight (442-
19 444). A loading dose >300,000 IU should be avoided outside of RCTs evaluating risk
20 and benefit.
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25 Hypervitaminosis D is associated with hypercalcemia and other severe
26 complications (445) and vitamin D overdoses can be fatal (446). No current data
27 support that rapid acute correction of VDD is an effective treatment in septic shock or
28 improves outcomes of septic children. Further, measurement of 25(OH)₂D levels is not
29 currently a standard component of sepsis care and methods of accurately measuring
30 bioavailable vitamin D are not yet widely validated. However, if VDD is diagnosed,
31 repletion should occur as a usual part of general holistic pediatric care according to
32 recommended guidelines independently of the presence of sepsis (447).
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4 **65. We suggest against transfusion of red blood cells if the blood hemoglobin**
5 **concentration is ≥ 7 g/dL in hemodynamically stabilized children with septic**
6 **shock or other sepsis-associated organ dysfunction (weak**
7 **recommendation, low quality of evidence).**

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

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

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31 **Rationale:** The only study evaluating specific red blood cell (RBC) transfusion
32 thresholds in children with sepsis is a *post hoc* subgroup analysis of the Transfusion
33 Requirements in the Pediatric Intensive Care Unit (TRIPICU) study (448)
34 **(Supplemental Table 27)**. This study included 137 stabilized critically ill children (MAP
35 > 2 standard deviations below normal for age and cardiovascular support not increased
36 for at least 2 hours before enrollment) with sepsis, with a hemoglobin ≤ 9.5 g/dL within 7
37 days after PICU admission. Patients were randomized to receive RBCs if hemoglobin
38 decreased to either < 7.0 g/dL (restrictive group) or 9.5 g/dL (liberal group). No
39 differences were found between the restrictive versus liberal group in the primary
40 endpoint of new or progressive multiple organ dysfunction syndrome (18.8% versus
41 19.1%) or mortality ($p=0.44$). These results are similar to those from primary analysis of
42 the TRIPICU study (449), as well as in adults (450). Our suggestion against transfusion
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4 if hemoglobin is >7 g/dL in hemodynamically-stable children with sepsis parallels the
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6 TAXI recommendations (451).
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9 Insufficient data are available to guide red blood cell transfusion therapy in
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11 children with unstable septic shock. Two pediatric RCTs did demonstrate decreased
12
13 mortality when red blood transfusion to goal hemoglobin ≥ 10 (hematocrit >30%) was
14
15 included as part of an early goal-directed therapy algorithm targeting ScvO₂, but the
16
17 impact of each individual component, including red blood transfusion, is unclear (212,
18
19 452). In critically ill adults, the Transfusion Requirements in Septic Shock (TRISS) trial
20
21 randomized 998 subjects with septic shock to either a transfusion threshold hemoglobin
22
23 of 7 g/dL or 9 g/dL (453). At randomization, all patients had hypotension (mean arterial
24
25 pressure <70 mmHg) and/or were being treated with vasopressors. Ninety-day mortality
26
27 showed no differences (relative risk, 0.94; 95%CI 0.78-1.09), suggesting that a
28
29 restrictive transfusion strategy in hemodynamically unstable septic adults was safe.
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33 **(Supplemental Table 27.)** The SSC recommends that RBC transfusion in adults occur
34
35 only when hemoglobin concentration decreases to <7.0 g/dL in the absence of
36
37 extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute
38
39 hemorrhage (strong recommendation, high quality of evidence)(50). This adult
40
41 recommendation is also valid for hemodynamically unstable patients.
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48 However, in the absence of pediatric data, we are not able to provide a
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50 recommendation for critically ill children with unstable septic shock.
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55 **67. We suggest against prophylactic platelet transfusion based solely on**
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57 **platelet levels in non-bleeding children with septic shock or other sepsis-**
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4 **associated organ dysfunction and thrombocytopenia (weak**
5 **recommendation, very low quality of evidence).**
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9 **Rationale:** One observational study demonstrated an association between the
10 administration of platelet transfusions to critically ill children and worse clinical outcomes
11 **(Supplemental Table 28)**, including longer ICU LOS, progressive organ dysfunction,
12 and increased mortality (454). Indirect evidence can be found in an RCT of 660 infants
13 born at less than 34 weeks gestational age, the majority of whom were treated for
14 sepsis, that compared a platelet transfusion threshold of 50,000 /mm³ (high threshold)
15 with 25,000 /mm³ (low threshold)(455). More infants in the high- versus low-threshold
16 group received at least one platelet transfusion (90% vs 53%). More adverse events,
17 including new major bleeding or death, were also seen in the high threshold group (OR
18 1.57, 95% CI 1.06, 2.32).
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33 Although existing evidence does not support a platelet threshold at which
34 transfusion is absolutely indicated, the risk of spontaneous bleeding may be greater at
35 lower platelet counts, e.g., <10-20,000 /mm³. In addition, some populations of
36 thrombocytopenic critically ill children may have a relatively high risk of bleeding, such
37 as those with oncological diagnoses or those receiving ECMO. Because the threshold
38 at which the benefits of platelet transfusion outweigh the risks is unknown, clinical
39 judgment based on patient risk factors for bleeding in addition to the measured platelet
40 level must be exercised carefully.
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55 **68. We suggest against prophylactic plasma transfusion in non-bleeding**
56 **children with septic shock or other sepsis-associated organ dysfunction**
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4 **and coagulation abnormalities (weak recommendation, very low quality of**
5
6 **evidence).**
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8
9 **Remarks: Prophylactic plasma transfusion refers to situations in which there is**
10 **an abnormality in laboratory coagulation testing but no active bleeding.**
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14 **Rationale:** No direct data exist to inform a recommendation about plasma transfusion in
15
16 pediatric sepsis. One RCT evaluates prophylactic plasma transfusion in critically ill
17
18 children without sepsis. Pieters et al randomized 81 children <2 years of age requiring
19
20 primary repair of craniosynostosis to receive plasma using either a prophylactic (in
21
22 absence of bleeding) or reactive (when the patient was bleeding) strategy (456). The
23
24 prophylactic plasma transfusion group received a significantly higher volume of plasma
25
26 compared to the reactive group (29.7 mL/kg versus 16.1 mL/kg, $p < 0.001$). Despite an
27
28 improvement in coagulation values in the prophylactic group, there was no difference in
29
30 PRBC transfusion requirements or blood loss between the two groups. **(Supplemental**
31
32 **Table 29)** Additionally, a meta-analysis published in 2012 that included 80 RCTs
33
34 (mostly in adults) concluded that there was no consistent evidence for benefit of
35
36 prophylactic plasma transfusion across a range of indications that were evaluated (457).
37
38 Observational studies in critically ill children have shown that plasma transfusions are
39
40 associated with worse clinical outcomes (458, 459). Furthermore, plasma transfusion
41
42 frequently fails to correct abnormal coagulation tests in critically ill adults and children
43
44 (459, 460). We therefore suggest against prophylactic plasma transfusions for children
45
46 with septic shock and other sepsis-associated organ dysfunction who are not bleeding.
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55 However, some specific patient populations might benefit from prophylactic
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57 plasma transfusions, such as patients with worsening coagulation tests at high risk for
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4 disseminated intravascular coagulopathy (DIC), children with comorbid cancer, or
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6 children with sepsis on extracorporeal life support (ECLS).
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11 **L. PLASMA EXCHANGE, RENAL REPLACEMENT, AND EXTRACORPOREAL**
12
13 **SUPPORT**
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16 **69. We suggest against using plasma exchange in children with septic shock**
17
18 **or other sepsis-associated organ dysfunction without thrombocytopenia-**
19 **associated multiple organ failure (TAMOF) (weak recommendation, very low**
20 **quality of evidence)**
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26 **70. We cannot suggest for or against the use of plasma exchange in children**
27
28 **with septic shock or other sepsis-associated organ dysfunction with**
29 **TAMOF.**
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32
33 **Rationale:** Therapeutic plasma exchange (PLEX) for septic shock or sepsis-associated
34 organ dysfunction aims to normalize the plasma milieu of a systemically inflamed septic
35 patient. Currently, no large RCTs have evaluated PLEX in pediatric septic shock or
36 sepsis-associated organ dysfunction. Rimmer et al. performed a meta-analysis that
37 included 4 small RCTs evaluating PLEX in adults (n=128) and pediatric (n=66) patients
38 with sepsis and septic shock. PLEX was associated with reduced mortality in adults (RR
39 0.63, 95% CI 0.42, 0.96), but not in children (RR 0.96, 95% CI 0.28, 3.38) (461).
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50 However, because of the heterogeneity of the patient population, inclusion criteria,
51 technical modalities of PLEX (filtration versus centrifugation), and types of replacement
52 fluid (plasma versus albumin) in these 4 studies as well as the costs and potential risks,
53 it PLEX cannot be routinely recommended as this time (**Supplemental Table 30**).
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4 Similarly, the American Society for Apheresis recommended that the "optimum role of
5
6 apheresis therapy is not established" in sepsis with multi-organ failure (462).
7
8

9 TAMOF is an inflammatory phenotype of sepsis-induced multiple organ
10
11 dysfunction in children that can be identified clinically by new-onset thrombocytopenia
12
13 and evolving multiple organ dysfunction (463, 464). Autopsies performed on patients
14
15 who died with TAMOF revealed disseminated microvascular thromboses in various
16
17 organs (463). These patients had deficient activity of a disintegrin and metalloproteinase
18
19 with thrombospondin type 1 motif (ADAMTS-13), elevated von Willebrand factor (VWF)
20
21 activity, and the presence of ultra-large plasma VWF (463, 465). Decreased activity of
22
23 ADAMTS-13 leads to high circulating levels of ultra-large VWF that induce widespread
24
25 platelet activation and thrombotic microangiopathy. A number of inflammatory
26
27 mediators are elevated in sepsis that can inhibit or inactivate ADAMTS-13 including
28
29 interleukin (IL)-6, granulocyte elastase, plasmin, thrombin, plasma free hemoglobin,
30
31 shigatoxins, and immunoglobulin G auto-antibody (466-471).
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38 Three studies have examined the utility of PLEX in children with sepsis and
39
40 TAMOF (463, 472, 473). In the most recent and largest study (n=81), Fortenberry et al.
41
42 reported that PLEX was associated with lower 28-day mortality by multivariate analysis
43
44 (aRR 0.45, 95% CI 0.23, 0.90) and by propensity score weighting (aRR, 0.46, 95% CI
45
46 0.22, 0.97) (472). In a retrospective cohort study from the Turkish TAMOF Network
47
48 (n=42), PLEX was associated with lower 28-day mortality compared to the no PLEX
49
50 group (27% versus 70%; p=0.004) (473)). In the third study, Nguyen et al randomized
51
52 10 children to either PLEX or standard therapy (463). The 5 patients who received
53
54 PLEX had restoration of ADAMTS-13 activity and greater survival (5/5) compared to
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4 standard therapy (1/5, p<0.05). Taken together, these data support a biologic rationale
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6 for the use of PLEX in TAMOF, i.e., the removal of pathologic ultra-large VWF and
7
8 ADAMTS-13 inhibitors and restoration of ADAMTS-13 activity. This approach of using
9
10 PLEX is similar to the rationale for using PLEX in thrombotic thrombocytopenic purpura
11
12 (474). While the panel acknowledges a potential benefit for PLEX and encourages an
13
14 RCT to better define the utility of PLEX in children with sepsis and TAMOF, a
15
16 recommendation could not be made based on existing data.
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23 **71. We suggest using renal replacement therapy to prevent or treat fluid**
24
25 **overload in children with septic shock or other sepsis-associated organ**
26
27 **dysfunction who are unresponsive to fluid restriction and diuretic therapy**
28
29 **(weak recommendation, very low quality of evidence).**
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31

32 **Rationale:** Renal replacement therapy is increasingly being used in PICUs for renal
33
34 and non-renal conditions. The rationale for renal replacement therapy in septic shock
35
36 includes impending or established fluid overload following initial resuscitation or for
37
38 cytokine removal, reversal of coagulopathy, to buffer lactic acidosis, to address AKI, or
39
40 a combination of these factors. Continuous renal replacement therapy (CRRT) may be
41
42 useful for treating established fluid overload or to prevent further fluid overload while
43
44 allowing liberal volume administration for nutrition, antimicrobials, and other
45
46 medications, sedation, and transfusions. In addition, certain techniques of continuous
47
48 blood purification may help to regulate systemic inflammation and promote kidney
49
50 recovery (475). Fluid overload has been shown to cause increased morbidity and
51
52 mortality in various intensive care settings and there is documented favorable
53
54 association of CRRT in fluid overload (476).
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4 However, no high-quality studies in critically ill children with sepsis exist to
5 directly determine whether RRT is definitively beneficial compared to diuretics and/or
6 fluid restriction. Most of the data come from adult studies where outcomes have varied
7 from mortality to ICU length of stay and ventilator- and vasoactive-free days. One study
8 addressed the timing of CRRT initiation in 27 children with sepsis and multiple organ
9 dysfunction, demonstrating that CRRT was associated with survival when started within
10 48 hours of admission compared to those started on CRRT after 48 hours of admission
11 (61% versus 33%, $p < 0.001$). However, timing of CRRT initiation was at the discretion of
12 the treating team, raising concern for confounding between groups, and all patients in
13 both groups experienced normalization of kidney function (477) (**Supplemental Table**
14 **31**).

15
16 The possible benefits of CRRT must also be weighed against potential risks,
17 including the need for an invasive catheter, costs, limited availability in some centers,
18 the need for clinician and nursing-specialist expertise, and the challenge of optimal
19 timing (e.g., following resuscitation for fluid removal or earlier for acute cytokine
20 clearance). Therefore, as the initial treatment strategy, we judge that fluid restriction and
21 use of diuretics are reasonable in the presence of impending or established fluid
22 overload with CRRT reserved as a second-line option to prevent or treat fluid overload
23 in children with septic shock or other sepsis-associated organ dysfunction who are
24 unresponsive to fluid restriction and diuretic therapy.

25
26 **72. We suggest against high-volume hemofiltration over standard**
27 **hemofiltration in children with septic shock or other sepsis-associated**

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4 **organ dysfunction who are treated with renal replacement therapy (weak**
5
6 **recommendation, low quality of evidence).**
7

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

21 In adults, use of higher CRRT flux rates (>35 mL/kg/hr filtration-dialysis), while
22 initially encouraging, has not shown overall mortality benefit in subsequent RCTs and
23 meta-analysis. A 2017 Cochrane review found no significant benefit in mortality, severity
24 of organ dysfunction, LOS, or adverse effects with HVHF versus standard hemofiltration
25 rates in critically ill adults (478). Notably, the results of this meta-analysis show that very
26 few studies have been conducted to investigate the use of HVHF in critically ill patients
27 with septic shock (four studies totaling 201 participants).
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38 In a study involving 155 pediatric patients with severe sepsis, HVHF treatment
39 did not significantly reduce 28-day mortality compared to standard volume CRRT.
40 Moreover, there were no significant reductions in plasma levels of inflammatory
41 mediators or in improving hemodynamic variables for HVHF. However, the incidence of
42 hyperglycemia was significantly higher in HVHF group than in CVVH group (479)
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51 **(Supplemental Table 32).**
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4 **73. We suggest using veno-venous extracorporeal membrane oxygenation**
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6 **(ECMO) in children with sepsis-induced PARDS and refractory hypoxia**
7
8 **(weak recommendation, very low quality of evidence)**
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10
11 **Rationale:** ECMO was introduced more than 40 years ago to support patients with
12 reversible but severe cardiovascular and/or respiratory failure refractory to conventional
13 medical therapy. As such, children with life-threatening sepsis-induced ARDS are often
14 considered as candidates for ECMO rescue (480), and PALICC endorsed ECMO for the
15 treatment of refractory hypoxia (24). The use of ECMO in pediatric sepsis has increased
16 over the past decade (481, 482); whether this has improved survival remains to be
17 determined (483). To date, no RCT examining the effect of ECMO on outcome in
18 pediatric sepsis has been published. In the absence of such data, using propensity
19 score matching, Barbaro et al (484) reported that children with severe PARDS enrolled
20 in the RESTORE trial had similar mortality rates when supported with ECMO (15/61,
21 25%) as compared with those who were not (18/61, 30%)(485) **(Supplemental Table**
22 **33)**. Research is underway to determine optimal pre-ECMO candidacy (486) as
23 measures of renal, hepatic, neurologic, and hematologic dysfunction, and particularly
24 the presence of blood stream infections, seem to discriminate mortality risk better than
25 traditional pediatric severity of illness scores such as Pediatric Risk of Mortality
26 (PRISM), Pediatric Index of Mortality (PIM), and Pediatric Logistic Organ Dysfunction
27 (PELOD). Clearly, ECMO is not available worldwide, and transfer of highly unstable
28 patients to higher levels of care that offer the therapy can carry substantial risk.
29 However, adult and pediatric data suggest a potential association with improved
30 mortality, particularly if transfer is to high volume ECMO centers (487, 488).
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7 **74. We suggest using veno-arterial (VA) ECMO as a rescue therapy in children**
8 **with septic shock only if refractory to all other treatments (weak**
9 **recommendation, very low quality of evidence).**
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13 **Rationale:** Several anecdotal reports of use of VA ECMO in the management of
14 refractory septic shock in children exist. (The role of veno-venous [VV] ECMO for
15 oxygenation/ventilation failure is addressed in the Ventilation section.) More recent
16 reports suggest that VA ECMO may be associated with better survival than
17 conventional therapy, and strategies to maximize flow rates to reverse shock and
18 multiple organ dysfunction may play an important role (489, 490). However,
19 considerable concern surrounds the risks of this highly invasive therapy, such as
20 hemorrhage and thromboembolic events.
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33 The most recent and largest report of VA-ECMO in 44 pediatric patients with
34 refractory septic shock secondary to bacterial, viral, or fungal infection admitted to 7
35 tertiary PICUs across 5 different countries compared their outcome to 120 children with
36 refractory septic shock managed by conventional therapy (491). Inclusion in the study
37 required children to meet 3 of 4 criteria for severe septic shock in the first 24 hours of
38 their ICU stay: arterial pH ≤ 7.15 , arterial lactate ≥ 4.0 mmol/L, base excess ≤ -10
39 mmol/L, and in-hospital cardiac arrest. Patients were excluded if they had cyanotic
40 congenital heart disease, myocarditis, or an out-of-hospital cardiac arrest. The results
41 showed no significant difference in survival to hospital discharge (50% in the VA ECMO
42 cohort versus 40% in the conventional therapy cohort). Survival was significantly higher
43 in patients who received high ECMO flows (>150 mL/kg/min at 4 hours after institution
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4 of ECMO) compared with children who received standard ECMO flows or no ECMO
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7 **(Supplemental Table 34.)**

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9 The potential use of VA ECMO for refractory septic shock suggests that the
10 definition of refractory septic shock (RSS) should be standardized across institutions. As
11 yet, no universal definition of refractory septic shock in children exists. One published
12 definition that could be applied is from the European Society of Paediatric and Neonatal
13 Intensive Care (492). The suggested definition for RSS was blood lactate >8 mmol/L or
14 a 1 mmol/L lactate increase after 6 hours of resuscitation and high vasoactive
15 dependency (vasopressor-inotrope score >200), or myocardial dysfunction defined as
16 the occurrence of a resuscitation-responsive cardiac arrest in PICU or cardiac
17 ultrasound findings with left ventricle ejection fraction <25% or a cardiac index <2.2
18 L/min/m².

32 33 34 35 **M. IMMUNOGLOBULINS**

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38 **75. We suggest against the routine use of intravenous immune globulin (IVIG)**
39
40 **in children with septic shock or other sepsis-associated organ dysfunction**
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42 **(weak recommendation, low quality of evidence).**

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45 **Remarks: Although routine use of IVIG is not recommended, select patients may**
46
47 **benefit from such treatment.**

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49
50 **Rationale:** The proposed rationale for IVIG in severe infections is to boost passive
51 immunity through neutralization of bacterial toxins, promoting opsonization of bacteria,
52 and inhibition of immune cell proliferation and inflammatory mediators. However, IVIG
53 has considerable batch-to-batch variability and its true biologic activity is not clear.
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4 There are no high-quality studies of IVIG in critically ill children with sepsis, and small
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6 observational studies have reported conflicting results (493). An RCT of polyclonal IVIG
7
8 in 100 children with sepsis demonstrated a reduction in mortality (28% versus 44%),
9
10 LOS (6 versus 9 days), and less progression to complications (8% versus 32%)(494).
11
12 However, a more recent multicenter trial of polyclonal IVIG in 3,493 neonates with
13
14 suspected or proven serious infection found no significant differences in mortality or
15
16 major disability (495). Other studies have been carried out with specific monoclonal
17
18 antibodies (e.g., monoclonal antibody against endotoxin in children with meningococcal
19
20 septic shock), but there are no definitive data to support general benefit of polyclonal
21
22 immunoglobulin in neonates or children with septic shock at this time. Data from adult
23
24 patients with septic shock also do not support a routine benefit of IVIG (496), though
25
26 administration of IgM- and IgA-enriched polyclonal IVIG has shown possible efficacy
27
28 (497). **(Supplemental Table 35.)**

29
30 For patients with toxic shock syndrome, especially those with streptococcal
31
32 etiology, polyclonal IVIG may have clinical utility (498). Other potential pediatric
33
34 populations that may benefit from IVIG in sepsis are those with necrotizing fasciitis
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36 (though evidence in adults does not support use (499, 500)), and those with primary
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38 humoral immunodeficiencies or immunocompromised with documented low
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40 immunoglobulin levels.
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53 **N. PROPHYLAXIS**

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55 **76. We suggest against the routine use of stress ulcer prophylaxis in critically**
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57 **ill children with septic shock or other sepsis-associated organ dysfunction,**
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4 **except for high-risk patients (weak recommendation, very low quality of**
5
6 **evidence).**
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9 **Remarks: Although *routine* stress-ulcer prophylaxis is not recommended, some**
10
11 **high-risk patients may benefit from stress ulcer prophylaxis. Studies have**
12
13 **supported benefit of stress-ulcer prophylaxis when baseline rate of clinically**
14
15 **important bleeding is approximately 13%.**
16
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19 **Rationale:** Stress ulcer prophylaxis should not be routinely administered to children
20
21 with septic shock or other sepsis-associated organ dysfunction, as evidence for benefit
22
23 is lacking (501) and may increase risk of adverse effects, such as pneumonia or
24
25 *Clostridioides difficile* (formerly *Clostridium*) infection (502). Rather than routine,
26
27 universal administration of stress-ulcer prophylaxis, individual patients should be
28
29 assessed for the presence of risk factors of clinically important gastrointestinal bleeding.
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31 These include multiple organ dysfunction(503), prolonged mechanical ventilation
32
33 (>48 hours), coagulopathy, persistent shock, and treatment with corticosteroids and
34
35 non-steroidal anti-inflammatory agents(504).
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41 The risk of GI bleeding is also reduced by mucosal protection introduced by
42
43 gastric feeding. Early enteral nutrition could therefore be a viable alternative to
44
45 pharmacological stress-ulcer prophylaxis. A meta-analysis of 1836 adult patients
46
47 reported that, in the presence of enteral nutrition, pharmacological stress ulcer
48
49 prophylaxis did not significantly change the risk of GI bleeding. Notably, in those
50
51 patients who received enteral nutrition and were treated with stress ulcer prophylaxis,
52
53 the risk of pneumonia was increased compared to patients on parenteral nutrition (OR
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55 2.81, 95% CI 1.2, 6.6)(505) **(Supplemental Table 36).**
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7 **77. We suggest against routine deep vein thrombosis (DVT) prophylaxis**
8
9 **(mechanical or pharmacologic) in critically ill children with septic shock or**
10 **other sepsis-associated organ dysfunction, but potential benefits may**
11 **outweigh risks and costs in specific populations (weak recommendation,**
12 **low quality of evidence).**
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19 **Rationale:** An open-label RCT of low molecular weight heparin to prevent CVC-
20 associated thrombosis in the PICU was terminated early because of poor recruitment
21 (506). Eleven (14.1%) of 78 patients randomized to reviparin had DVT proven on
22 venogram versus 10 (12.5%) of 80 controls (OR 1.15, 95% CI 0.42, 3.23). Three
23 adverse events (major bleed or death) all occurred in the control group and no deaths
24 occurred because of venous thromboembolism (**Supplemental Table 37**). A
25 subsequent systematic review found the quality of evidence to be low and that the
26 efficacy of low molecular weight heparin in preventing CVC-associated thrombosis is
27 unknown (507). It is important to highlight that these studies were specific to children
28 with CVCs who may or may not have had sepsis and that they may not apply to the
29 general thromboembolic risk in children with sepsis.
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45 While CVCs represent the principal risk factor for DVT in infants (508), older
46 children may have other risk factors. For example, the risk of DVT increases in
47 adolescence, obesity, cancer, and in those with multiple medical conditions, especially
48 renal and cardiac disease (509, 510). At present, it is unknown whether certain high-risk
49 populations of children with sepsis may benefit from DVT prophylaxis.
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60 **KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES**

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4 This report from the SSC pediatric guidelines panel covers 5 main topic areas
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6 (i.e., early recognition and infection, hemodynamics, ventilation, endocrine and
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8 metabolic therapies, and adjunctive therapies) with a total of 76 recommendations
9
10 arising from 67 PICO questions. On review of these evidence-based analyses, it is clear
11
12 that, for many PICO questions, the literature review failed to identify sufficient data to
13
14 develop strong (or even weak in some instances) recommendations for critically ill
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16 children with septic shock or other sepsis-associated organ dysfunction. These SSC
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18 pediatric guidelines, at the same time, also identified gaps that can inform future
19
20 research opportunities. As new research populates the evidence-base, it can then be
21
22 used to develop future iterations of the SSC pediatric guidelines, creating a cycle
23
24 designed to grow the evidence and increase the number of strong recommendations in
25
26 the future. Further clarity is needed from both informative pathophysiology studies as
27
28 well as well-designed RCTs, and the panelists have listed these in the text. The design
29
30 of meaningful and effective future research should be informed by the needs identified
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32 by the collective clinical expertise within the panel.
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41 Overall, the process of developing the SSC-pediatric guidelines generated at
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43 least 29 pathophysiology questions warranting further study and 23 RCTs (i.e., total of
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45 52 studies). We presented these questions as research opportunities, but have not yet
46
47 prioritized these opportunities into a formal research agenda (**Table 6**). We envision that
48
49 many of the pathophysiology questions can be taken up by individual research groups
50
51 and we hope that the SSC children's guidelines document will serve as a template of
52
53 current evidence and how best to fill the gaps in our knowledge. In contrast, the
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55 necessary RCTs will need a coordinated national/international effort and our community
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4 will need to prioritize the most appropriate studies at different phases of management
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7 (i.e., recognition, fluid resuscitation, first 48 hours, etc.).
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9

10 11 12 **Acknowledgments** 13

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16 The authors wish to thank Darlene Barkman, MA, and Janna Pogers, PT, MPT,
17
18 NCS, CSRS for their sensitive and insightful comments from the perspective of parents
19
20 of children with sepsis. Their input, particularly related to ranking the importance of
21
22 outcomes to consider through the literature search, provided valuable direction to the
23
24 panel. The authors also wish to thank Rebecca Skidmore and James D. Medd for their
25
26 dedication as they conducted the literature searches for the five panels. Their
27
28 experience and professionalism contributed greatly to the final publication. Finally,
29
30 appreciation is extended to Deborah L. McBride for project management and editorial
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32 support.
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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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22
23 Supplemental digital content is available for this article. Direct URL citations appear in the printed text
24 and are provided in the HTML and PDF versions on this journal’s website.

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26
27 The following sponsoring organizations with formal liaison appointees endorse this guideline:

28
29 American Academy of Pediatrics; Australia and New Zealand Intensive Care Society, Canadian Critical
30 Care Society; European Society of Intensive Care Medicine; European Society of Paediatric and Neonatal
31 Intensive Care; Pediatric Infectious Disease Society; Scandinavian Society of Anaesthesiology and
32 Intensive Care Medicine; Society of Critical Care Medicine; UK Sepsis Trust; World Federation of
33 Pediatric Intensive and Critical Care Societies

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38 **Disclosures:** S. Weiss and M. Peters served as arbiters for conflict interest management and adjudication
39 throughout the guidelines process following standard operating procedures set forth by SCCM and
40 endorsed by ESICM. Disclosures were collected throughout guidelines development with verbal
41 disclosures and more formally using SCCM’s conflict of interest system where indicated. The following
42 disclosures were provided by the authors: S. Weiss participates as a member of the Shock Society; M.
43 Peters serves as Vice Chair of the UK PICS study group; M. Agus is active as a volunteer in the
44 American Academy of Pediatrics, Pediatric Academic Societies, American Pediatric Society, Society for
45 Pediatric Research, and The American Society for Clinical Investigation; H. Flori is a Michigan and
46 California state chapter executive board member for the American Thoracic Society (ATS), participates in
47 the Pediatric Acute Lung Injury and Sepsis Investigators Network, Grant funding from Gerber
48 Foundation; S. Nadel is the immediate past President of the European Society of Pediatric and Neonatal
49 Intensive Care Medicine (ESPNIC); J. Brierly serves as Past President of ESPNIC; E. Carrol is a member
50 of the NICE Diagnostic Advisory Committee and scientific panels through the National Institutes for
51 Health Research; I. Cheifetz is a volunteer for the American Association for Respiratory Care and the
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4 American Thoracic Society, he is an advisor to Philips, and a contributor to Up-to-Date; J. Cies received
5 grants and honoraria from Allergan, Merck, and Thermo Fisher Scientific and is a consultant for Atlantic
6 Diagnostic Lab Liaison committee; A. Cruz has provided testimony for legal cases involving children
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8 Medical President-elect on the Executive Committee of ESPNIC, he served as a consultant and lecturer
9 on the external advisory board and received research and educational grants from Chiesi Farmaceutici
10 S.p.A and AbbVie Inc., and travel grants from AbbVie, he has been a lecturer for Philips, Radiometer,
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16 for the American Board of Pediatrics; P. Ishimine serves on various boards: American Board of
17 Emergency Medicine, and is a member of the American College of Emergency Physicians; E. Javouhey
18 received funding from the CSL Behring company for a trial on intravenous immunoglobulins in toxic
19 shock syndrome in children; O. Karam is the chair of BloodNet; M. Kneyber is scientific chair of
20 ESPNIC; G. MacLaren serves on the Executive Committee of the Extracorporeal Life Support
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24 the Society for Simulation in Healthcare and the International Society for Pediatric Simulation, he has
25 also a portion of his time supported by a grant from Nihon Kohden device development for capillary refill
26 time measurement; M. Nunnally reports service on committees and board seats for the SCCM's American
27 College of Critical Care Medicine, Society of Critical Care Anesthesiologists, and the American Society
28 of Anesthesiologists, International Anesthesia Research Society; A. Randolph through her institution has
29 research support from Genentech, Inc. for influenza biomarkers, served as a consultant for Bristol Myers
30 Squibb in 2017 pediatric sepsis trial design, and is a consultant for La Jolla Pharmaceuticals design of
31 pediatric septic shock trial angiotensin II; S. Ranjit is Chancellor of the College of Pediatric Critical Care
32 Medicine India; L. Tume is Nursing President for ESPNIC and serves on the UK PICS Scientific and
33 Education Committees; J. Verger serves on the American Association of Critical-Care Nurses
34 Governance Committee and special interest groups related to acute care nursing; J. Wolf receives research
35 support from Merck & Company, Astellas Pharma, and has grant support from Karius, Inc., Empatica
36 Inc., and Bluespark Technologies; J. Zimmerman received biomarker research funding from
37 Immunexpress and is Past President of SCCM; P. Tissieres provides consulting services for Baxter, Inc.

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4 acute therapies, Bristol-Myers Squibb Company, Chiesi Farmaceutici S.p.A., Faron Pharmaceuticals, has
5 research grants from bioMérieux, funding from La Jolla Pharmaceuticals, Chiesi Farmaceutici S.p.A., and
6 is President ESPNIC. All other authors, staff, and consultants have indicated they have no conflicts to
7 report.
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11
12 **Disclaimer:** The Society of Critical Care Medicine guidelines are intended for general information only,
13 are not medical advice, and do not replace professional advice, which should be sought for any medical
14 condition. The full disclaimer for guidelines can be accessed at
15 <https://www.sccm.org/Research/Guidelines/Guidelines>.
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19
20 **Funding:** These guidelines were solely funded by the European Society of Intensive Care Medicine and
21 the Society of Critical Care Medicine.
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25
26 **Copyright form disclosure:** Dr. Weiss participates in Pediatric Acute Lung Injury and Sepsis
27 Investigators (PALISI) and Shock Society. Dr. Peters participates in the UK PICS study group (vice-
28 chair) and has testified as an expert witness in cases of clinical negligence, causation of injuries. Dr. Agus
29 participates in the AAP, PAS, APS, and SPR, and he has testified as an expert witness in cases related to
30 ICU and/or endocrinology in children. Dr. Flori participates in American Thoracic Society State Chapter
31 (Executive Board Member - Michigan and California State Chapters) and Pediatric Acute Lung Injury
32 and Sepsis Investigators (PALISI) Network (Steering committee member for various studies being
33 implemented through the Network from intramural funding, governmental or other Foundation Grant
34 funding). Dr. Nadel received funding from La Jolla Pharmaceutical (consulting), and he participates in the
35 ESPNIC (Medical President). Dr. Brierley participates in the ESPNIC. Dr. Carrol participates in NICE
36 (Diagnostic advisory Committee panel) and NIHR (two scientific panels, i4i and DTF). Dr. Cheifetz
37 participates in AARC and ATS (volunteer activities) and has testified as an expert witness for medical
38 malpractice cases. Dr. Cies received funding from Allergan, Merck, Thermo Fisher Scientific, and
39 Atlantic Diagnostic Laboratories (consultant), and he participates in Pediatric Pharmacy Advocacy Group
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45 England Clinical Reference Group for commissioning paediatric specialist medicine care. Dr. Hall
46 receives funding from La Jolla Pharmaceuticals (consultant on the data safety monitoring board for a
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4 clinical trial of a sepsis therapeutic), and he participates in the American Thoracic Society (online journal
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6 participates in SAEM (Consensus Conference Co-Chair), American Board of Pediatrics/American Board
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8 American College of Emergency Physicians (Pediatric Emergency Medicine Committee member). Dr.
9 Javouhey received funding from CSL Behring (trial on Intravenous Immunoglobulins in toxic shock
10 syndrome in children). Dr. Karam participates in BloodNet, PALISI, ISBT, AABB, and CCCTG. Dr.
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13 Parenteral and Enteral Nutrition (ASPEN) (president). Dr. Møller participates in the SSAI (board
14 member). Dr. Newth received funding from Philips Research North America (consulting concerning
15 monitoring in PICU), and he participates in the American Thoracic Society. Dr. Nishisaki's institutional
16 department receives an unrestricted grant from Nihon Kohden Inc (involves an activity to develop a
17 device to measure capillary refill time), and he participates in the Society for Simulation in Healthcare
18 and International Society for Pediatric Simulation. Dr. Nunnally participates in ACCM (Regent), SOCCA
19 (director), ASA (committee), IARS, and NYSA. Dr. Randolph's institution received funding from
20 Genentech, Inc. (influenza biomarker study research support); she has received funding from Bristol
21 Myers Squibb (consultant in 2017) and La Jolla Pharmaceuticals, Inc (design of pediatric septic shock
22 trial of angiotensin II); and she participates in the American Thoracic Society and the International Sepsis
23 Forum. Dr. Ranjit participates as the Chancellor of College of Pediatric Critical Care, India. Dr. Tume
24 participates in ESPNIC (Nursing President) and the UK PICS Scientific and Education Committee. Dr.
25 Verger participates in the AACN (Cert. Corp. Governance Committee) and the Academy of Nursing
26 (Acute and Critical Care Special Interest Group). Dr. Williams participates in the Pediatric Cardiac
27 Intensive Care Society. Dr. Wolf received funding support for participation in industry-sponsored
28 research from Merck & Co Inc, Astellas Inc, and Cempra Pharmaceuticals Inc, and he received other
29 support from Karius, Empatica, and Bluespark Technologies. Dr. Zimmerman received funding from
30 Immunexpress, Seattle (sepsis biomarker research), and he participates in the AAP and Pediatric
31 Academic Society (PAS). Dr. Tissieres received funding from Baxter Inc (consulting, renal replacement
32 therapy) and Biomerieux Inc (research grant, biomarkers sepsis), and he participates in the Swiss
33 Intensive Care Society, Swiss Pediatric Society, and the French Society of Intensive Care. The remaining
34 authors have disclosed that they do not have any potential conflicts of interest.
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4 **ABSTRACT**

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7 **Objective:** To develop evidence-based recommendations for clinicians caring for
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9 children (including infants, school-aged children, and adolescents) with septic shock
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11 and other sepsis-associated organ dysfunction.
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14 **Design:** A panel of 49 international experts, representing 12 international
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16 organizations, as well as 3 methodologists and 3 public members was convened. Panel
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18 members assembled at key international meetings (for those panel members attending
19
20 the conference), and a stand-alone meeting was held for all panel members in
21
22 November 2018. A formal conflict-of-interest (COI) policy was developed at the onset of
23
24 the process and enforced throughout. Teleconferences and electronic-based discussion
25
26 among the chairs, co-chairs, methodologists, and group heads, as well as within
27
28 subgroups, served as an integral part of the guideline development process.
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33 **Methods:** The panel consisted of 6 subgroups: recognition and management of
34
35 infection, hemodynamics and resuscitation, ventilation, endocrine and metabolic
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37 therapies, adjunctive therapies, and research priorities. We conducted a systematic
38
39 review for each Population, Intervention, Control, and Outcomes (PICO) question to
40
41 identify the best available evidence, statistically summarized the evidence, and then
42
43 assessed the quality of evidence using the Grading of Recommendations Assessment,
44
45 Development, and Evaluation (GRADE) approach. We used the evidence-to-decision
46
47 framework to formulate recommendations as strong or weak, or as a best practice
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49 statement. In addition, “in our practice” statements were included when evidence was
50
51 inconclusive to issue a recommendation, but the panel felt that some guidance based
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53 on practice patterns may be appropriate.
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4 | **Results:** The panel provided 77~~6~~ statements on the management and resuscitation of
5 | children with septic shock and other sepsis-associated organ dysfunction. Overall, 6~~5~~
6 | were strong recommendations, 49 were weak recommendations, and 9 were best-
7 | practice statements. For 13 questions, no recommendations could be made; but, for 10
8 | of these, “in our practice” statements were provided. In addition, 49 research priorities
9 | were identified.
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12 | **Conclusions:** A large cohort of international experts was able to achieve consensus
13 | regarding many recommendations for the best care of children with sepsis,
14 | acknowledging that most aspects of care had relatively low quality of evidence resulting
15 | in the frequent issuance of weak recommendations. Despite this challenge, these
16 | recommendations regarding the management of children with septic shock and other
17 | sepsis-associated organ dysfunction provide a foundation for consistent care to improve
18 | outcomes and inform future research.
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21 | **Key Words:** evidence-based medicine; Grading of Recommendations Assessment,
22 | Development, and Evaluation criteria; guidelines; infection; pediatrics; sepsis; septic
23 | shock; Surviving Sepsis Campaign.
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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.

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4 | The objective of the SCCM/ESICM *Surviving Sepsis Campaign International*
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6 | *Guidelines for the Management of Septic Shock and Sepsis-Associated-associated*
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8 | *Organ Dysfunction in Children* is to provide guidance for clinicians caring for children
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10 | (including infants, school-aged children, and adolescents) with septic shock and other
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12 | sepsis-associated organ dysfunction. We sought to leverage the expertise of a clinical
13 |
14 | and methodology team to create comprehensive evidence-based recommendations for
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16 | the recognition and management of children with septic shock or other sepsis-
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18 | associated acute organ dysfunction. Recommendations from these guidelines are
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20 | based on the best current evidence but cannot replace the clinician’s decision-making
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22 | capability when presented with a patient’s unique set of clinical variables.
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26 | Recommendations are intended to guide “best practice” rather than to establish a
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28 | treatment algorithm or to define standard of care. These guidelines are appropriate for
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30 | treating septic shock and other sepsis-associated organ dysfunction in a hospital,
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32 | emergency, or acute care setting, though some may be applicable elsewhere. Although
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34 | recommendations were developed without consideration to availability of resources, we
35 |
36 | acknowledge that variation within and across health care systems and geographic
37 |
38 | regions will determine the practical application of these guidelines.
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42 | Although several recommendations for the care of children with sepsis and septic
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44 | shock have been previously published (14-16), these new guidelines are not intended to
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46 | update or iterate on these prior documents. Instead, it was the aim of SCCM/ESICM
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48 | *Surviving Sepsis Campaign* to provide an evidence-based approach to the management
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50 | of septic shock and other sepsis-associated organ dysfunction in children using a
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4 | comprehensive and transparent methodologic approach by a panel with geographic and
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10 | 11 | **METHODOLOGY**

12 | 13 | **Definitions and Scope**

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16 | In 2005, the International Pediatric Sepsis Consensus Conference published
17 | definitions and criteria for sepsis, severe sepsis, and septic shock in children based on
18 | prevailing views of adult sepsis at the time with modifications for physiology based on
19 | age and maturational considerations (17). ~~Of note, by these criteria, septic shock in~~
20 | ~~children is defined as cardiovascular dysfunction (i.e., abnormal perfusion) with or~~
21 | ~~without hypotension.~~ In 2016, new adult definitions and criteria were published (Sepsis-
22 | 3) with *sepsis* defined as life-threatening organ dysfunction caused by a dysregulated
23 | host response to infection and *septic shock* the subset of sepsis with circulatory and
24 | cellular/metabolic dysfunction associated with a higher risk of mortality (18). The term
25 | “severe sepsis” was replaced by this new definition of sepsis. Although application of
26 | Sepsis-3 to children has been attempted (19, 20), formal revisions to the 2005 pediatric
27 | sepsis definitions remain pending (21). Therefore, the majority of studies used to
28 | establish evidence for these guidelines in the literature was expected to referred to the
29 | 2005 nomenclature in which severe sepsis ~~in children~~ was defined as a) ≥ 2 age-based
30 | systemic inflammatory response syndrome (SIRS) criteria, b) confirmed or suspected
31 | invasive infection, and c) cardiovascular dysfunction, acute respiratory distress
32 | syndrome (ARDS), or ≥ 2 non-cardiovascular organ system dysfunctions; ~~and~~. ~~S~~septic
33 | shock ~~in children~~ was defined as the subset with cardiovascular dysfunction, which
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4 included hypotension, treatment with a vasoactive medication, or impaired perfusion.
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6 However, studies that defined sepsis as severe infection leading to life-threatening
7 organ dysfunction were included even if criteria used to define sepsis deviated from the
8 2005 consensus definitions.
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14 For the purposes of these guidelines, we define *septic shock* in children as
15 severe infection leading to cardiovascular dysfunction (including hypotension, need for
16 treatment with a vasoactive medication, or impaired perfusion) and *sepsis-associated*
17 organ dysfunction in children as severe infection leading to cardiovascular and/or non-
18 cardiovascular organ dysfunction. Because several methods to identify acute organ
19 dysfunction in children are currently available (17, 19, 20, 22, 23), we chose not to
20 require a specific definition or scheme for this purpose.
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31 | 32 | 33 Scope of Patients 34 |

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36 ~~Given that the definition of sepsis as “life-threatening organ dysfunction caused~~
37 ~~by a dysregulated host response to infection” is generally applicable to children and in~~
38 ~~anticipation of an update to pediatric sepsis definitions, t~~The panel identified the scope
39 ~~of these intended these~~ guidelines to ~~include apply to~~ all patients from ~~≥37 weeksweeks~~
40 gestation at birth to 18 years-of-age with severe sepsis or septic shock as defined by
41 the 2005 International Pediatric Sepsis Consensus Conference or inclusive of severe
42 infection leading to life-threatening organ dysfunction. Practically, all infants, children,
43 and adolescents with septic shock or other sepsis-associated acute organ dysfunction
44 are included in this scope. For simplicity, we will henceforth use the term “children” to
45 refer to infants, school-aged children, and adolescents in these guidelines.
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4 ~~Thus, a~~All recommendations apply to children with septic shock and other
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6 sepsis-associated acute organ dysfunction unless specific qualifications, such as the
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8 subset with immune compromise, are included in the recommendation. Even though
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10 these guidelines are not intended to address the management of infection with or
11
12 without SIRS *when there is not associated acute organ dysfunction*, we recognize that
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14 sepsis exists as a spectrum and some children without known acute organ dysfunction
15
16 may still benefit from similar therapies as those with known organ dysfunction. ~~Because~~
17
18 ~~several methods to identify acute organ dysfunction in children are currently available,~~
19
20 ~~(17, 19, 20, 22, 23) we chose not to require a specific definition or scheme for this~~
21
22 ~~purpose.~~ Finally, acknowledging that neonatal sepsis, especially in premature babies,
23
24 may have distinct pathology, biology, and therapeutic considerations, ~~studies that~~
25
26 ~~focused exclusively on~~ newborns <37 weeks gestation ~~were~~are excluded from the
27
28 scope of these guidelines. The panel sought to include term neonates (0-28 days) born
29
30 at ≥37 weeks gestation within the scope of these guidelines because these infants may
31
32 be recognized and resuscitated outside of a newborn nursery or neonatal intensive care
33
34 unit. However, because the panel did not specifically address studies of neonates with
35
36 perinatal infection or conditions that can be associated with neonatal sepsis (e.g.,
37
38 persistent pulmonary hypertension of the newborn), these guidelines do not address all
39
40 management considerations for neonatal sepsis.

Application of Guidelines by Local Resource Availability

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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,

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4 | emergency, or other acute care setting. However, we acknowledge that many of the
5 |
6 | recommendations are likely to apply to the care of children with septic shock and other
7 |
8 | sepsis-associated organ dysfunction across a broad array of settings with adaptation to
9 |
10 | specific environments and resource availability.
11 |

12 |
13 | ~~In addition, t~~hese guidelines were largely ~~considered developed~~ without
14 |
15 | consideration of health care resources (with some specific exceptions, e.g., fluid
16 |
17 | resuscitation), though we realize that medical care for children with septic shock and
18 |
19 | other sepsis-associated organ dysfunction is necessarily carried out within the confines
20 |
21 | of locally available resources. The panel supports that these guidelines should
22 |
23 | constitute a general scheme of “best practice,” but that translation to treatment
24 |
25 | algorithms or bundles and standards of care will need to account for variation in the
26 |
27 | availability of local health care resources. The panel acknowledges as well the need for
28 |
29 | future research to test the adaptation of interventions to locally available resources.
30 |
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32 | 33 | 34 | **Funding and Sponsorship** 35 |

36 |
37 | All funding for the development of these guidelines was provided by SCCM and
38 |
39 | ESICM. In addition, sponsoring organizations provided support for their members’
40 |
41 | involvement.
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44 | 45 | 46 | **Selection and Organization of Panel Members** 47 |

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49 | The selection of panel members was based on their expertise in specific aspects
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51 | of pediatric sepsis. Co-chairs and co-vice chairs were appointed by the SCCM and
52 |
53 | ESICM governing bodies; panel members were then recommended by the co-chairs
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3
4 and co-vice chairs. Each panel member was required to be a practicing healthcare
5
6 professional with a focus on the acute and/or emergent care of critically ill children with
7
8 septic shock or other sepsis-associated acute organ dysfunction. Broad international
9
10 and multi-professional representation from critical and intensive care medicine,
11
12 emergency medicine, anesthesiology, neonatology, and infectious disease with
13
14 inclusion of physicians, nurses, pharmacists, and advanced practice providers as part of
15
16 the working group was ensured. Three members from the lay public were also included
17
18 with a role to ensure that patient, family, and caregivers' opinions were considered in
19
20 prioritizing outcomes and finalizing recommendations that the clinicians proposed during
21
22 the development process. Panelists were recruited from a wide number of countries and
23
24 health care systems, including representation from resource-limited geographic areas. A
25
26 demographically diverse panel with regard to sex, race, and geography was assembled.
27
28 Members were then allocated to specific groups based on their expertise.
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35
36 The methodology team included trained methodologists from McMaster
37
38 University in Canada (WA, KC) and New York University in the United States (MN). The
39
40 team included methodologists with a health research methodology degree (MSc or
41
42 PhD) and/or advanced methodology training, all of whom are also practicing
43
44 intensivists. The methodology team provided methodological guidance and leadership
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46 throughout the guideline development process.
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53 **Question Development and Outcome Prioritization**

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55 The panel was divided into groups: 1) recognition and management of infection,
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57 2) hemodynamics and resuscitation, 3) ventilation, 4) endocrine and metabolic
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4 therapies, and 5) adjunctive therapies. A sixth subgroup was added to review research
5
6 priorities in pediatric sepsis.
7

8
9 The co-chairs, co-vice chairs, and group heads made initial selections of the
10 topics. We included topics addressed in the 2016 SSC adult guidelines that were
11 relevant to children, as well as other key pediatric topics discussed in previously
12 published guidelines (14-16). The PICO format, which describes the population (P),
13
14 intervention (I), control (C), and outcomes (O), was used for all guideline questions.
15
16 Group heads, panel members, and methodologists reviewed and selected PICO
17
18 questions considered important to guide care for children with septic shock or other
19
20 sepsis-associated organ dysfunction. Panel members proposed additional PICO
21
22 questions of high priority and clinical relevance. For practical reasons, we excluded
23
24 several issues pertaining to general acute or critical illness that were not specific for
25
26 sepsis (e.g., head-of-bed positioning during invasive mechanical ventilation) and have
27
28 been addressed in other guidelines (e.g., Pediatric Acute Lung Injury Consensus
29
30 Conference [PALICC]) (24). However, topics with particular relevance to children with
31
32 septic shock or other sepsis-associated acute organ dysfunction were included in this
33
34 guideline, even if there was evaluation of similar or overlapping topics in previous
35
36 publications. The final decision regarding PICO question inclusion was reached by
37
38 discussion and consensus among the guideline panel leaders with input from panel
39
40 members and the methodology team in each group.
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53 In adherence with the Grading of Recommendations Assessment, Development,
54 and Evaluation (GRADE) approach, panel members compiled a list of potential
55
56 outcomes for each PICO question. Subsequently, we electronically surveyed panel
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4 members and asked them to rate each outcome on a scale of 1 (not important) to 9
5
6 (critically important). We selected only outcomes that were critical (mean of 7 or more)
7
8 for decision making, taking a patient's perspective. In addition, we presented all
9
10 selected outcomes to public members to ask for their input and feedback. The final list
11
12 of PICO questions is provided in **Supplemental Table 1**.
13
14
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19 **Search Strategy and Evidence Summation**

21 For each PICO question, a professional medical librarian formulated the search
22
23 strategy with input from the group heads, panel members, and methodologists.
24
25 Searches utilized a combination of controlled vocabulary (e.g., "sepsis," "bacterial
26
27 infections," "critical illness," "intensive care units," "pediatrics," "NICU," "PICU,"
28
29 "emergency service") and key words (e.g., "toxic shock," "blood poisoning," "acute
30
31 infection," "PICU," "child") in the core search. Additional controlled vocabulary and key
32
33 words were incorporated to create separate strategies specific to the question posed.
34
35 Research design filters (e.g., systematic reviews/meta-analyses, randomized controlled
36
37 trials, observational studies) were also applied as appropriate. Only English language
38
39 studies were included. No date restrictions were imposed on the searches, but we
40
41 removed animal-only and opinion pieces from the results. The medical librarian
42
43 searched a minimum of two major databases (e.g., Cochrane Library,
44
45 PubMed/MEDLINE, or Embase) to identify relevant systematic reviews, clinical trials,
46
47 and observational studies published through May 1, 2017. As this was the inaugural
48
49 version of these guidelines for children, all publications up through May 1, 2017 were
50
51 considered. Key studies published after the conclusion of the initial literature search on
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4 | May 1, 2017 were incorporated into the evidence synthesis if identified by panel
5 | members as important and relevant even if they were not part of the initial literature
6 | review. We excluded articles published in abstract form, in a language other than
7 | English, and those focused solely on pre-clinical data. ~~After finalizing the searches for~~
8 | ~~each PICO question, panel members screened the titles and abstracts, reviewed full~~
9 | ~~text of potentially relevant articles, and abstracted relevant data using a standardized~~
10 | ~~form.~~ Panel members, with input from methodologists, used the Cochrane risk of bias
11 | tool to assess the risk of bias of randomized trials (25) and Newcastle-Ottawa Scale to
12 | assess risk of bias of non-randomized studies (26).
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26 | When applicable, the methodologists used meta-analytic techniques to generate
27 | pooled estimates across two or more studies. For meta-analysis of randomized clinical
28 | trials (RCTs), we used random-effects model and inverse variance method to pool
29 | estimates across relevant studies. We reported relative risks (RR) and 95% confidence
30 | interval (CI) for binary outcomes, and mean difference (MD) and 95% CI for continuous
31 | outcomes. For observational data, we conducted meta-analyses if all individual studies
32 | provided adjusted estimates and included both an intervention and a control arm using
33 | a random-effects model and inverse variance method to pool adjusted odds ratio (OR)
34 | across relevant studies. All analyses were conducted using RevMan software (Review
35 | Manager, version 5.3, Copenhagen).
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51 | 52 | 53 | **Formulation of Recommendations**

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55 | The GRADE approach principles guided the assessment of quality of evidence
56 | from high to very low ~~and were used to determine the strength of recommendations.~~
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4 ~~The GRADE approach to assess the quality of evidence is~~ based on ~~the evaluation of~~
5
6 six domains: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, 5)
7
8 publication bias, and 6) ~~other criteria, followed by~~ assessment of the balance between
9
10 benefit and harm, patients' values and preferences, cost and resources, and feasibility
11
12 and acceptability of the intervention (27). Methodologists performed initial assessments
13
14 of quality of evidence and incorporated feedback from panel members to generate final
15
16 evidence profiles using GRADEpro GDT (28).
17
18
19
20

21
22 The panel initially considered only research focused on pediatric patients using
23
24 ~~the following~~ a hierarchy of evidence: ~~systematic reviews of randomized trials, individual~~
25
26 ~~RCTs, systematic reviews of observational studies, and prospective observational~~
27
28 ~~studies (Table 1). Evidence from RCTs started as high-quality but could be~~
29
30 ~~downgraded due to concerns within the above 6 GRADE criteria. Evidence from~~
31
32 ~~observational studies began as low-quality that could be upgraded on the basis of a~~
33
34 ~~large magnitude of effect or other factors. If none of these study designs were available,~~
35
36 ~~the panel considered retrospective observational studies, case-control studies, and~~
37
38 ~~large case series.~~ Studies focusing on children with septic shock and other sepsis-
39
40 associated organ dysfunction were prioritized, though studies inclusive of more general
41
42 pediatric populations (e.g., all PICU patients) were considered for some questions on a
43
44 case-by-case basis. If there were no studies or insufficient data in children with sepsis
45
46 or general pediatric illness, evidence ~~of~~ from studies of adult patients was considered
47
48 using an *a priori* framework to determine appropriateness of indirect evidence (Figure
49
50 1). For PICO questions in which adult data were deemed appropriate to consider, the
51
52 same hierarchy of evidence was applied, though the quality of evidence from adult
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4 | studies was generally down-graded due to the indirectness of the evidence. ~~To~~
5 |
6 | ~~streamline this process across the groups, we developed and used a framework to help~~
7 |
8 | ~~guide whether indirect evidence was appropriate to use (Figure 1).~~
9 |

10 |
11 | In a series of webinars, methodologists reviewed the relevant data for each PICO
12 | question with panel members to formulate initial recommendations. Each of the groups
13 | used the Evidence-to-Decision (EtD) framework to facilitate transition from evidence to
14 | the final recommendation. The EtD framework ensured that panel members took into
15 | consideration not only the quality of evidence and magnitude of effect, but also balance
16 | between benefits and harms, patients' values and preferences, resources, cost,
17 | acceptability, and feasibility (28).
18 |

19 | We classified recommendations as strong or weak using the language "We
20 | recommend..." or "We suggest..." respectively. ~~We used the strength of a~~
21 | ~~recommendation to reflect our confidence about whether the desirable consequences of~~
22 | ~~the adherence to the intervention would outweigh the undesirable consequences. Thus,~~
23 | ~~w~~We judged a strong recommendation in favor of an intervention to have desirable
24 | effects of adherence that will clearly outweigh the undesirable effects. We judged a
25 | weak recommendation in favor of an intervention to have desirable consequences of
26 | adherence that will probably outweigh the undesirable consequences, but confidence is
27 | diminished either because the quality of evidence was low or the benefits and risks
28 | were closely balanced. The implications of calling a recommendation strong or weak are
29 | shown in Table 2. ~~are that most patients would accept that intervention and that most~~
30 | ~~clinicians should use it in most situations (Table 2). However, a~~ strong
31 | recommendation does not necessarily imply a standard of care, and circumstances may
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4 exist in which a strong recommendation cannot or should not be followed for an
5
6 individual patient. ~~We judged a weak recommendation in favor of an intervention to~~
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8 ~~have desirable consequences of adherence that will probably outweigh the undesirable~~
9
10 ~~consequences, but confidence is diminished either because the quality of evidence was~~
11
12 ~~low or the benefits and risks were closely balanced. We anticipate that a weak~~
13
14 ~~recommendation, while still relevant for most patients in most settings, will be more~~
15
16 ~~heavily influenced by clinical circumstances and patients' values than a strong~~
17
18 ~~recommendation. We permitted strong recommendations for an intervention based on~~
19
20 ~~low or very low quality of evidence when the intervention had the potential to improve~~
21
22 ~~survival and there was low- risk for immediate harm. We permitted strong~~
23
24 ~~recommendations against an intervention based on low or very low quality of evidence~~
25
26 ~~when there was uncertain benefit but very likely or certain harm, including high costs~~
27
28 ~~We permitted strong recommendations based on low or very low quality of evidence for~~
29
30 ~~life-threatening scenarios or when there was uncertain benefit but very likely or certain~~
31
32 ~~harm~~ (29).

33
34 Best practice statements (BPS) were developed as ungraded strong
35
36 recommendations within strict conditions suggested by the GRADE Working Group
37
38 (Table 3) (30). BPS were issued when the evidence could not be summarized or
39
40 assessed using GRADE methodology but the benefit or harm was deemed unequivocal.
41
42 In addition, when ~~the evidence was lacking or~~ was insufficient to make a
43
44 recommendation, but the panel felt that some guidance based on current practice
45
46 patterns may be appropriate, we issued ~~a number of an~~ “in our practice” statements. The
47
48 “in our practice statements” were developed through a survey of panelists to ascertain
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4 their state of current practice ~~for PICO questions without sufficient evidence to formulate~~
5 ~~a recommendation, but identified as common enough scenarios to ascertain the extent~~
6 ~~of agreement among panelists' clinical practice.~~ As such, “in our practice” statements
7
8
9 are intended only to describe current variation in care and are not meant to be
10
11
12 construed as recommendations. ~~We summarize the implication of statements or~~
13
14 ~~recommendations in Table 2.~~
15
16
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18
19 As new data are continuously generated, the Surviving Sepsis Campaign is
20
21 committed to ensuring that these guidelines are updated or affirmed every four years or
22
23 sooner if breaking and relevant evidence becomes available.
24
25

26 27 28 **Voting Process**

29
30 Panel members convened to review evidence and discuss recommendations ~~at~~
31
32 ~~key international meetings (for those panel members attending the conference), and a~~
33
34 ~~stand-alone meeting was held for all panel members in Hamilton, Ontario, Canada in~~
35
36 ~~November 2018 in-person and through web conferences.~~ Following the formulation of
37
38
39 initial recommendations through discussion within subgroups, all panelists received
40
41
42 links to evidence profiles and polls created using SurveyMonkey, Inc (Palo Alto, CA) to
43
44
45 indicate agreement, disagreement, or abstention. Only panel members without relevant
46
47
48 conflicts of interest could vote. Voters could provide feedback for consideration in
49
50
51 revising statements. Panelists also deliberated during face-to-face meetings, during
52
53
54 which subgroups presented their draft statements for discussion. Up to three rounds of
55
56
57 voting were conducted throughout this process of deliberation in an attempt to achieve
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4 final consensus. Acceptance of a statement required votes from 75% of the panel
5
6 members with an 80% agreement threshold.
7
8

9 A summary of all statements determined by the panel is shown in **Appendix 1**.
10
11 Evidence summaries and evidence profiles that informed the recommendations are
12
13 included in the online [Supplementary-supplementary Contentcontent](#). Links to specific
14
15 tables and figures appear within the relevant text.
16
17
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19
20

21 **Conflict of Interest Policy**

22

23
24 Conflict-of-interest (COI) disclosures were sought through the Society of Critical
25
26 Care Medicine from all panelists and support personnel prior to commencing activities,
27
28 with updates annually and as needed. The process relied solely on personal disclosure,
29
30 with clarifications sought when necessary, and centered primarily around potential
31
32 financial conflicts. The co-vice chairs reviewed all COI disclosures in accordance with
33
34 SCCM's standard operating procedures, sought clarification when necessary, and
35
36 worked with the co-chairs to recommend appropriate recusals. There was no industry
37
38 input into or support of the guideline development process. No panelists received
39
40 honoraria for any role in the guidelines process. Only librarians and a supporting project
41
42 manager received compensation for their work.
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49 Seven individuals were identified with potential COIs, but only 3 were deemed
50
51 relevant to the final list of questions included in the scope of this guideline. These
52
53 individuals were asked to abstain from voting on the final recommendations involving
54
55 the potential COI. In addition, panel members were asked to voluntarily abstain from
56
57 voting on final recommendations if they had a potential academic COI (e.g., grant
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4 | application that could benefit from wording of a particular recommendation), though all
5 |
6 | panel members were welcome to participate in the group discussions leading up to the
7 |
8 | final recommendation to ensure that input was available from relevant experts.
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14 | **A. SCREENING, DIAGNOSIS, AND SYSTEMATIC MANAGEMENT OF**
15 |
16 | **SEPSIS RECOGNITION AND MANAGEMENT**
17 |

- 18 |
19 | **1. In children who present as acutely unwell, we suggest implementing**
20 |
21 | **systematic screening for timely recognition of septic shock and other**
22 |
23 | **sepsis-associated organ dysfunction (weak recommendation, very low**
24 |
25 | **quality of evidence).**
26 |

27 |
28 | **Remarks: Systematic screening needs to be tailored to the type of patients,**
29 |
30 | **resources, and procedures within each institution. Evaluation for the**
31 |
32 | **effectiveness and sustainability of screening should be incorporated as part of**
33 |
34 | **this process.**
35 |

36 |
37 | ***Rationale:*** Systematic screening for sepsis in children is driven by the premise that
38 |
39 | earlier recognition will lead to more timely initiation of therapy, which will translate to
40 |
41 | improved morbidity and/or mortality. Screening tools are designed to increase reliability
42 |
43 | of sepsis recognition and empower health-care professionals to seek rapid medical
44 |
45 | review. Rapid recognition of sepsis through standardized screening and procedures to
46 |
47 | guide management of patients identified as at-risk for sepsis should be an essential
48 |
49 | component of sepsis quality improvement (QI) programs. While the optimal method or
50 |
51 | tool for screening is unclear, we suggest that screening tools be adapted to the type of
52 |
53 | patients, resources, and processes within each institution.
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4 | Several studies demonstrating that institutional sepsis QI efforts improve
5 |
6 | outcomes have successfully incorporated screening tools (31-37). Most reported sepsis
7 |
8 | screens were designed to prompt clinicians to prioritize review of patients that had
9 |
10 | triggered the screen, hence the ultimate decision to treat or not remains with the
11 |
12 | clinician. Although RCTs have evaluated the role of systematic screening algorithms to
13 |
14 | recognize clinical deterioration in children more generally (38), high-quality trials on
15 |
16 | pediatric sepsis recognition are lacking (39), and data are not sufficient data to suggest
17 |
18 | any particular screening tool, though several have been published (40-42) or shared on-
19 |
20 | line (<http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx>).
21 |
22 | Single-institution studies demonstrate that an electronic health record (EHR)-based
23 |
24 | screening tool can yielded high sensitivity and, when coupled with sequential clinician
25 |
26 | assessment, improved specificity (43). For facilities that use an EHR, a step-wise
27 |
28 | approach combining EHR-triggered alerts followed by clinician assessment ~~thus~~ has the
29 |
30 | potential to shorten the time to sepsis recognition (41). Notably, no study was found on
31 |
32 | systematic sepsis screening in low- and middle-income countries meeting the PICO
33 |
34 | criteria.
35 |
36 |
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38 |
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41 |

42 | Institutions should monitor and evaluate their practice following implementation of
43 |
44 | sepsis screening (44). Robust QI balancing measures that should be assessed include
45 |
46 | clinician response, anchoring bias, increased and/or inappropriate antimicrobial
47 |
48 | prescriptions, fluid overload, increased PICU admissions and transfers to higher levels
49 |
50 | of care, and health care utilization costs (45). Application of a screening tool requires
51 |
52 | ongoing optimization of sensitivity and specificity, continuous improvement efforts to
53 |
54 | maintain provider education and familiarity with the tool, and continual data acquisition
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4 | to monitor implementation and increase utilization (42). Finally, screening tools must
5 |
6 | work well with existing or planned other early warning and rapid response systems (46,
7 |
8 | 47) that may also have inherent limitations (38, 48).
9 |

10 |
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12 |
13 |
14 | **2. We were unable to issue a recommendation about using blood lactate**
15 |
16 | **values to stratify children with suspected septic shock or other sepsis-**
17 |
18 | **associated organ dysfunction into low- versus high-risk of having septic**
19 |
20 | **shock or sepsis. However, in our practice, if lactate levels can be rapidly**
21 |
22 | **obtained, we often measure blood lactate in children when evaluating for**
23 |
24 | **septic shock and other sepsis-associated organ dysfunction.**
25 |
26 |

27 |
28 | **Rationale:** Blood lactate levels provide a valuable indirect marker of tissue
29 |
30 | hypoperfusion (49) ~~and can contribute to the early recognition, diagnosis, and~~
31 | ~~management of pediatric septic shock (17).~~ While increased lactate levels are not
32 |
33 | specific, they provide a quantifiable surrogate for tissue hypoxia and can be rapidly
34 |
35 | obtained by point-of-care tests available in many settings. In adults, blood lactate >2
36 |
37 | mmol/L is now included within the operational definition of septic shock as an indication
38 |
39 | of cellular/metabolic dysfunction, and measurement of lactate is included in the Hour-1
40 |
41 | Sepsis Bundle, with recommendations to repeat lactate measurement if the initial value
42 |
43 | exceeds 2 mmol/L (18, 50, 51). In children, several observational studies have
44 |
45 | demonstrated an association of elevated blood lactate levels with adverse outcomes in
46 |
47 | septic shock (11, 52-54). However, the optimal threshold to define *hyperlactatemia*
48 |
49 | remains unclear. In a PICU study, the mortality rate for children with hypotension
50 |
51 | requiring vasopressors with lactate >2 mmol/l was 32.0% compared to 16.1% if lactate
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4 | was ≤ 2 mmol/l (11). Other studies have shown that lactate levels >4 mmol/L are
5 |
6 | consistently associated with mortality (52). Although blood lactate may be affected by
7 |
8 | the conditions of the blood draw (e.g., use of a tourniquet), both venous and arterial
9 |
10 | lactate measurements obtained have been shown to be independently associated with
11 |
12 | mortality in children (55). In ~~a retrospective~~ one prospective pediatric study in children,
13 |
14 | normalization of lactate within 2-4 hours of presentation was associated with decreased
15 |
16 | risk of persistent organ dysfunction (adjusted relative risk [RR] 0.47, 95% confidence
17 |
18 | interval [CI] 0.29, 0.78) (56). However, no ~~pediatric~~ RCTs have tested whether initial or
19 |
20 | serial measurement of blood lactate directly informs evaluation and/or management in
21 |
22 | children. Lactate levels should therefore be interpreted as part of a more
23 |
24 | comprehensive assessment of clinical status and perfusion.
25 |
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34 | **3. We recommend implementing a protocol/guideline for management of**
35 |
36 | **children with septic shock or other sepsis-associated organ dysfunction**
37 |
38 | **(BPS).**
39 |

40 | **Rationale:** Institutional protocols have been shown to improve the speed and reliability
41 |
42 | of care for children with septic shock or other sepsis-associated organ dysfunction.
43 |
44 | Studies reported improvements in mortality, length of stay, duration of organ
45 |
46 | dysfunction, and development of new or progressive multiple organ dysfunction
47 |
48 | syndrome (8, 32-34, 36, 57-61). Most of these studies have focused on timely delivery
49 |
50 | of a “bundle of therapies” (e.g., blood culture, fluid bolus, and antibiotics). For example,
51 |
52 | an analysis of 1179 children with sepsis across 54 hospitals in New York State found
53 |
54 | that completion of a sepsis bundle within 1 hour was associated with lower risk-adjusted
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4 odds ratio (aOR) of in-hospital mortality (0.59, 95% CI 0.38, 0.93, p=0.02) (8). In a
5
6 recent single institution study, bundle-compliant care in 1380 children with septic shock
7
8 was associated with a five-times lower mortality (OR 0.20, 95%-CI 0.07, 0.53) (33). In
9
10 another study, implementation of a sepsis protocol led to a substantial reduction in the
11
12 proportion of children who no longer had organ dysfunction on day 2 after presentation
13
14 (aOR 4.2, 95% CI 1.7, 10.4) (34). However, it should be noted that protocols studied to
15
16 date have variable components, many studies do not report adherence to specific items
17
18 within protocols, and only a few studies have attempted to adjust for initial illness
19
20 severity or other patient factors, making it difficult to summarize studies using the
21
22 GRADE approach. Therefore, because available evidence shows a strong and
23
24 consistent association that adherence to protocols reduces variability in care and
25
26 improves outcomes, we recommend implementing a protocol/guideline for management
27
28 of children with septic shock or other sepsis-associated organ dysfunction as a best
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30 practice.
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41 **4. We recommend obtaining blood cultures before initiating antimicrobial**
42 **therapy in situations where this does not substantially delay antimicrobial**
43 **administration (BPS).**
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48 **Rationale:** Blood cultures remain the most commonly used method to identify
49
50 bacteremia. Identification of a blood-borne pathogen can have significant clinical
51
52 implications on the type and duration of antimicrobial therapy and is an important
53
54 mechanism to recognize multidrug resistant pathogens (62). Thus, whenever possible,
55
56 blood cultures should be obtained prior to initiation of antimicrobial therapy in children
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4 | with severe sepsis or septic shock. Although no studies have directly measured the
5 |
6 | effect of blood cultures alone on outcome in pediatric sepsis, several observational
7 |
8 | studies have demonstrated that a bundled approach to initial resuscitation that includes
9 |
10 | early blood cultures is associated with improved outcomes (8, 31, 33). If collection of the
11 |
12 | blood cultures is likely to delay administration of antimicrobial therapy to the patient,
13 |
14 | then administration of antimicrobials should take precedence, in view of the impact of
15 |
16 | delayed antimicrobial administration on patient outcomes (63). However, **increased**
17 |
18 | **mortality is associated with increased time to initiation of appropriate antimicrobial**
19 |
20 | **therapy (63), and in many settings, because** blood cultures may be the only source of
21 |
22 | information identifying bacterial antibiotic susceptibility, **it is important to make all**
23 |
24 | **reasonable efforts to collect blood cultures before timely antimicrobial administration.**
25 |

26 |
27 | The collection of other biological specimens to identify pathogens from non-blood sites
28 |
29 | (e.g. urine, cerebrospinal fluid, tracheal aspirate, broncho-alveolar lavage, drainage
30 |
31 | from collections, etc.) should also happen as soon as possible, and depending on the
32 |
33 | suspected site of infection, such specimens may have a higher yield of pathogen
34 |
35 | identification than blood cultures. Clinicians should also consider the epidemiology of
36 |
37 | pediatric infections in relation to age, sex, and host factors, such as comorbidities (64,
38 |
39 | 65). Specific patterns of pediatric bloodstream infections relating to age and
40 |
41 | comorbidities are well known, and approximately one out of three bacteremia
42 |
43 | episodes are associated with organ dysfunction in a recent large population-based
44 |
45 | study (65).
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48 | Limitations of standard blood cultures include the time needed to grow and then
49 |
50 | identify pathogens and their antibiotic sensitivities, as well as the effect of previous
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4 therapy on diagnostic yield. New molecular technologies are becoming available to
5 facilitate earlier and faster microbiological diagnoses. Such techniques may be able to
6 identify a range of pathogens well before blood cultures are positive (66), and may
7 potentially identify pathogens even after the administration of antimicrobial therapy.
8
9 However, new molecular diagnostics are currently relatively expensive, are not sufficient
10 for all pathogens and antibiotic sensitivities, and are not universally available.
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21 **B. ANTIMICROBIAL THERAPY**

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

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

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41 ***Rationale:*** Antimicrobials are the primary medical therapy that directly targets the
42 underlying cause of sepsis, and there is strong biologic rationale for rapid delivery of
43 antimicrobials in patients with sepsis (67). Many QI initiatives have shown improved
44 pediatric sepsis outcomes with implementation of a bundle that includes rapid delivery
45 of intravenous antimicrobials (8, 32-34, 36, 57-61). Two retrospective observational
46 studies have also demonstrated an association of faster time to antimicrobial therapy
47 with reduced mortality for children with sepsis. The first study was an analysis of 130
48 children with sepsis (mortality of 12%), including 103 (79%) with septic shock, in which
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4 the unadjusted OR for mortality ~~for~~among children ~~where~~with antimicrobials ~~were~~
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6 delivered within versus after 60 minutes of sepsis recognition was ~~reduced with an~~
7
8 ~~unadjusted OR of~~ 0.60 (95% CI 0.13 - 2.86) (63). The second study was an analysis of
9
10 1179 children, including 69% with septic shock, where completion of a sepsis bundle
11
12 within 1 hour of sepsis recognition was associated with decreased mortality (OR 0.59,
13
14 95% CI 0.38, 0.93, p=0.02); however, initiation of antimicrobials alone by 1 hour of
15
16 recognition was not associated with significant mortality reduction (OR 0.78, 95% CI
17
18 0.55, 1.12, p=0.18) (8). When the adjusted OR of these 2 studies were pooled, there
19
20 was a possible reduction in mortality (OR 0.77, 95% CI 0.55, 1.08) (**Supplemental**
21
22 **Table 2, Supplemental Figure 1, Table 2**). Other secondary end-points reported in the
23
24 literature have also been associated with shorter time to initiation of antimicrobial
25
26 therapy, including reduced length of stay, shorter duration of organ dysfunction, and
27
28 reduced development of new or progressive multiple organ dysfunction syndrome (8,
29
30 32-34, 36, 57-61). Moreover, indirect evidence from adult sepsis generally supports a
31
32 benefit to starting antimicrobial therapy as soon as possible after recognition of septic
33
34 shock (68-73). Thus, timely antimicrobial therapy—ideally administered as part of a
35
36 more comprehensive bundle of initial care—should be the goal for children with septic
37
38 shock.
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48 The definition of “timely” in this context represents an area of controversy relating
49
50 to challenges in the accurate recognition of patients with sepsis and septic shock and
51
52 the need to consider balancing QI metrics such as unnecessary antimicrobial usage
53
54 (67, 74, 75). One pediatric study (63) indicated a dose-response gradient such that the
55
56 longer time to antimicrobial therapy, the higher the mortality. Yet the mortality increase
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4 reached significance only when antimicrobials were administered >3 hours in
5
6 comparison to <3 hours, whereas the mortality of patients receiving antimicrobials within
7
8 <1 hour was not different from those receiving antimicrobials within <3 hours in that
9
10 relatively small study. The second, larger pediatric study demonstrated a significant
11
12 decrease in mortality if antimicrobials were administered within 1 hour, but only in the
13
14 context of a bundle that included a blood culture and fluid bolus. (8) Thus, available
15
16 pediatric studies do not provide a clear time cut-off after which the risk of mortality or
17
18 other adverse outcomes increases, but rather support that there is likely to be an
19
20 incremental risk for harm as time to antimicrobial initiation increases, in particular
21
22 beyond 3 hours. Notably, the benefit of antimicrobial therapy within 1 hour of recognition
23
24 has been most prominent in cohorts with a predominance of septic shock (as compared
25
26 to sepsis without shock) patients (8, 63).
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34 Based on limited pediatric evidence and indirect evidence from adult studies, the
35
36 panel supported that, in children *with septic shock*, antimicrobial therapy should be
37
38 initiated as soon as possible and ideally within 1 hour of recognition. Suspicion of septic
39
40 shock can usually be guided by clinical findings rapidly ascertained through history and
41
42 physical examination. While our recommendation to ideally administer antimicrobial
43
44 administration within 1 hour of recognition of septic shock establishes a tangible goal
45
46 that emphasizes the importance of early antimicrobial therapy and assists clinicians in
47
48 prioritizing bedside care, this cut-point should not be misconstrued as a known
49
50 biological truth. Thus, dichotomous time-based metrics of the quality of care for children
51
52 with sepsis, while pragmatic and potentially useful to trend, may be of less value than
53
54 use of continuous variables such as median time to antimicrobials. Despite a very low
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4 quality of evidence on this topic, we provide a strong recommendation because the
5
6 panel concluded that most patients would accept and most clinicians should seek to
7
8 initiate antimicrobial therapy as soon as possible after recognition of septic shock in
9
10 most situations.
11
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14 For children *without clinical signs of shock*, the panel acknowledged that the
15
16 diagnosis of sepsis-associated organ dysfunction has additional challenges related to
17
18 the need to discriminate those with true sepsis from among a large number presenting
19
20 with suspected infection (67). In view of the available evidence, we suggest starting
21
22 antimicrobial therapy *as soon as possible* after sepsis recognition, while allowing up to 3
23
24 hours for appropriate diagnostic investigation for patients *without clinical signs of shock*
25
26 and for those with an uncertain diagnosis. However, the diagnostic evaluation should be
27
28 performed expeditiously and, if and when the evaluation supports a likely infection or
29
30 evidence of septic shock or other sepsis-associated organ dysfunction becomes
31
32 manifest, antimicrobial therapy should be immediately administered.
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- 41 **7. We recommend empiric broad-spectrum therapy with one or more**
42 **antimicrobials to cover all likely pathogens (BPS).**
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45 **8. Once the pathogen(s) and sensitivities are available, we recommend**
46 **narrowing empiric antimicrobial therapy coverage (BPS).**
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50 **9. If no pathogen is identified, we recommend narrowing or stopping empiric**
51 **antimicrobial therapy according to clinical presentation, site of infection,**
52 **host risk factors, and adequacy of clinical improvement in discussion with**
53 **infectious disease and/or microbiological expert advice (BPS).**
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4 | **Rationale:** Sepsis mortality is associated with delays to *appropriate* antimicrobial
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6 | therapy, and hence optimal treatment for sepsis relies on accurate selection of
7 |
8 | antimicrobials to ensure activity against the major pathogens (50, 63, 71, 76). *Empiric*
9 |
10 | *therapy* refers to the initial choice of antimicrobials pending microbiological results
11 |
12 | (**Table 4**) and is based on the predicted likelihood of bacterial pathogens. Empiric
13 |
14 | therapy should cover a broad range of pathogens that are likely to cause the infection,
15 |
16 | acknowledging that, in rare circumstances, this may not fully cover very unusual
17 |
18 | pathogens. *Broad-spectrum therapy* refers to the use of *single- or multi-drug*
19 |
20 | antimicrobial therapy with activity against multiple groups of bacteria/pathogens. Broad-
21 |
22 | spectrum therapy is recommended for initial empiric therapy of children with septic
23 |
24 | shock or sepsis-associated organ dysfunction to increase the likelihood that the initial
25 |
26 | empirical therapy is effective against the causative pathogens.
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34 | The initial choice of empiric antimicrobials should take into account the specific
35 |
36 | clinical history (e.g., age, site of infection, concomitant disease states, comorbid
37 |
38 | conditions, indwelling devices). Patients with recent or current hospital exposure should
39 |
40 | receive empiric therapy that considers known infection or colonization, as well as any
41 |
42 | recent antimicrobial exposure. Institutions or regions should identify the most
43 |
44 | appropriate first-line single-agent antimicrobial, taking into account anatomic site of
45 |
46 | infection, age, local epidemiology, and host comorbidity and risk factors (e.g.,
47 |
48 | ceftriaxone is recommended for community-acquired sepsis by the National Institute for
49 |
50 | Health and Care Excellence (NICE) in the United Kingdom) (16). For complex patients
51 |
52 | or those recently or currently in hospital, the choice of empiric antimicrobials should also
53 |
54 | take into account ~~the specific clinical history such as the clinical syndrome/site of~~
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4 | ~~infection~~, concomitant underlying diseases, chronic organ failure, indwelling devices, the
5 |
6 | presence of immunosuppression or other form of immunocompromise, recent known
7 |
8 | infection or colonization with specific pathogens, and recent receipt of antimicrobials
9 |
10 | (65, 77, 78). When available, an infectious diseases clinician should be consulted.
11 |
12 | Other non-bacterial pathogens that are suspected as a cause of infection should also be
13 |
14 | targeted as part of initial antimicrobial therapy on a case-by-case basis.
15 |
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19 | Sepsis in children is most commonly due to gram-negative or gram-positive
20 |
21 | bacteria, although the relative prevalence of these pathogens varies by age, geographic
22 |
23 | region, location (community versus hospital) of sepsis onset, and other patient factors.
24 |

25 |
26 | Invasive fungal infections are largely restricted to immunocompromised patients and
27 |
28 | pre-term infants. Certain specific conditions put patients at risk for atypical or resistant
29 |
30 | pathogens, thus requiring specific empiric regimens. For example, neutropenic patients
31 |
32 | are at risk for an especially wide range of potential pathogens, including resistant gram-
33 |
34 | negative bacilli and *Candida* species, and neonates are at risk of sepsis caused by
35 |
36 | *listeria monocytogenes* and disseminated herpes simplex virus (HSV). Children with
37 |
38 | chronic conditions treated in hospital settings are prone to sepsis with resistant bacteria
39 |
40 | such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant
41 |
42 | enterococci (VRE). For children at risk for multidrug-resistant bacterial infections,
43 |
44 | empiric broad-spectrum antimicrobial regimens may require more than one agent to
45 |
46 | broadly cover such potential pathogens.
47 |
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52 | For specific empiric broad-spectrum antimicrobial therapy, the reader is directed
53 |
54 | to published resources (77, 79) and the need to consider patient history, allergies, local
55 |
56 | epidemiology, and suspected site/source of infection. However, general suggestions
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4 can be provided here. For previously healthy children with community-acquired sepsis,
5
6 a third-generation cephalosporin (e.g., ceftriaxone) may be sufficient. Vancomycin
7
8 should be added in settings where MRSA or ceftriaxone-resistant pneumococci are
9
10 prevalent, and addition of an aminoglycoside or substitution of a carbapenem is
11
12 appropriate in settings where ceftriaxone resistance is common in gram-negative
13
14 bacteria (80). For immunocompromised patients or hospital-acquired sepsis,
15
16 antimicrobial therapy should begin with an anti-pseudomonal third- or higher-generation
17
18 cephalosporin (e.g., cefepime), a broad-spectrum carbapenem (e.g., meropenem,
19
20 imipenem/cilastatin), or an extended-range penicillin/β-lactamase inhibitor combination
21
22 (e.g., piperacillin/tazobactam) (79). For neonates, therapy should also include ampicillin
23
24 for listeria and consideration for empiric acyclovir if there is a clinical concern for HSV
25
26 (77). For patients with a suspected or documented intra-abdominal source of infection,
27
28 therapy should include broad coverage for gastrointestinal pathogens, including
29
30 anaerobic bacteria, with either an extended-range penicillin/β-lactamase inhibitor
31
32 combination or carbapenem, or addition of clindamycin or metronidazole. For patients
33
34 who present with sepsis complicating an influenza-like illness during the local influenza
35
36 season, empiric antiviral therapy should be started while awaiting the respiratory virus
37
38 testing (81, 82). Patients at higher risk of antibiotic-resistant infection because of past
39
40 infection or colonization, local epidemiology, or recent broad-spectrum antibiotic use,
41
42 should receive an individually tailored empiric therapeutic regimen (83). In cases of
43
44 suspected toxic shock syndrome or necrotizing fasciitis, empiric treatment should
45
46 include clindamycin or lincomycin to limit toxin production and enhance bacterial
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4 | clearance (84). Finally, for sepsis treated in regions endemic for rickettsial or parasitic
5 | pathogens (e.g., malaria), clinicians should consider adding relevant empiric coverage.
6 |
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8 |

9 | *Targeted or definitive therapy* refers to the antimicrobial regimen targeted to a
10 | specific pathogen(s) after microbiologic identification. As with empiric therapy,
11 | targeted/definitive therapy may be single- or multi-drug therapy, but should not be
12 | broader than required to treat the specific pathogen(s) after microbiologic identification
13 | (85, 86)(79, 80). Risks of unnecessary continuation of broad-spectrum antibiotic and
14 | other antimicrobial therapy include direct side effects and toxicities (such as the
15 | nephrotoxicity or ototoxicity of aminoglycosides), infection with *Clostridioides difficile*
16 | (formerly *Clostridium*) or fungal pathogens, and promotion of antimicrobial resistance in
17 | the patient and in the community. In addition, unnecessary exposure to antibiotics may
18 | lead to alteration of the human microbiome early in life, the impact of which is poorly
19 | understood but has been associated with worse outcomes such as necrotizing
20 | enterocolitis in newborns.
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38 | Because most microbiological cultures show significant growth within 24 to 36
39 | hours of collection when a pathogen is present (87)(84), empiric treatment should be re-
40 | evaluated after no more than 48 hours following initiation. If no pathogen is identified
41 | *and* bacterial/fungal infection is deemed unlikely, clinicians should stop empiric
42 | antimicrobial therapy to reduce unnecessary exposure to antibiotics/antifungals.
43 | However, many children with a clinical diagnosis of septic shock do not have a
44 | pathogen isolated (5, 6). Patients with negative bacterial microbiological results may
45 | have false-negative tests due to antibiotic pre-treatment, absence of bacteremia (e.g.,
46 | bacterial pneumonia despite true bacterial infection), or sepsis related to viral infections
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4 | [\(88\)\(82\)](#). Thus, the decision to continue, narrow, or stop antimicrobial therapy must
5 |
6 | often be made on the basis of clinician judgment and indirect clinical information, taking
7 |
8 | into account the clinical presentation, site and type of infection, host risk factors, and
9 |
10 | adequacy of clinical improvement. Complex patients should be discussed with pediatric
11 |
12 | infectious diseases and/or microbiology specialists to ensure likely pathogens are
13 |
14 | treated and that antibiotics and other antimicrobials are stopped when they are no
15 |
16 | longer necessary.
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24 | **10. In children without immune compromise and without high risk for**
25 |
26 | **multidrug-resistant pathogens, we suggest against the routine use of**
27 |
28 | **empiric multiple antimicrobials directed against the same pathogen for the**
29 |
30 | **purpose of synergy (weak recommendation, very low quality of evidence).**
31 |

32 |
33 | **Remarks:** In certain situations, such as confirmed or strongly suspected group B
34 |
35 | streptococcal sepsis, use of empiric multiple antimicrobials directed against the
36 |
37 | same pathogen for the purpose of synergy may be indicated.
38 |
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40 |
41 | **11. In children with immune compromise and/or at high risk for multidrug-**
42 |
43 | **resistant pathogens, we suggest using empiric multi-drug therapy when**
44 |
45 | **septic shock or other sepsis-associated organ dysfunction is**
46 |
47 | **present/suspected (weak recommendation, very low quality of evidence).**
48 |
49 |

50 | **Rationale:** The selection of an empiric antimicrobial regimen requires consideration of
51 |
52 | a patient's underlying disease state, potential history of prior infections and colonization
53 |
54 | with multidrug-resistant organisms (MDROs), presence of immunosuppression, and
55 |
56 | possible recent antimicrobial use, as well as local pathogen prevalence and
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4 | susceptibility profile [\(50, 89, 90\)](#)~~(50, 83, 84)~~. Empiric therapy may be single- or multi-
5 |
6 | drug, but should be broad spectrum in nature as defined in Table 4. For select patients
7 |
8 | or with concern for particular types of infection, this may necessitate adding a
9 |
10 | glycopeptide (i.e., vancomycin) to ensure empiric coverage of methicillin-resistant
11 |
12 | *Staphylococcus aureus* (MRSA) or a second gram-negative agent (e.g., aminoglycoside
13 |
14 | in addition to a beta-lactam or second/third-generation cephalosporin) when antibiotic
15 |
16 | resistance is a concern. However, routinely including an aminoglycoside or a
17 |
18 | glycopeptide for synergy or “double-coverage” as part of an empiric regimen is not
19 |
20 | supported by the available data [\(90-101\)](#)~~(84-95)~~.

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26 | A recent Cochrane review evaluated beta-lactam monotherapy versus beta-
27 |
28 | lactam and aminoglycoside combination regimens for sepsis and included 69 trials
29 |
30 | accounting for 7863 participants, including neonatal and pediatric patients [\(89\)](#)~~(83)~~. In
31 |
32 | trials where the mono- and multidrug arm used the same beta-lactam, no difference in
33 |
34 | clinical outcomes was observed between study groups. In studies where the
35 |
36 | monotherapy arm contained a beta-lactam of broader spectrum than the multidrug arm,
37 |
38 | monotherapy ~~suggested~~ showed a possible benefit for all-cause mortality (OR 0.85,
39 |
40 | 95% CI 0.71, 1.01) and a significant advantage for clinical failure (OR 0.75, 95% CI
41 |
42 | 0.67, 0.84) [\(89\)](#)~~(83)~~. Additionally, indirect evidence from adults with sepsis including 13
43 |
44 | RCTs comparing empirical mono- versus combination antibiotic therapy suggests
45 |
46 | mortality and other outcomes are not improved by empiric combination therapy [\(91\)](#)~~(85)~~.
47 |
48 | Therefore, many children with septic shock and other sepsis-associated organ
49 |
50 | dysfunction do not require empiric multi-drug therapy. Clinicians should continually re-
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4 | evaluate the local epidemiology and resistance rates to ensure monotherapy remains
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6 | appropriate [\(89\)\(83\)](#).
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9 | Certain clinical scenarios, however, may necessitate multi-drug antimicrobial
10 | therapy. For example, in patients [s](#) at high risk for resistant gram-negative infections with
11 | sepsis, combining a beta- lactam/beta-lactamase inhibitor agent (i.e.,
12 | piperacillin/tazobactam combination) with an aminoglycoside (i.e., gentamicin) can be
13 |
14 | considered, not for synergy, but for expanded coverage to treat both susceptible and
15 | resistant pathogens until final identification and susceptibilities are known [\(102-104\)\(96-](#)
16 | [98\)](#). Additionally, a synergistic multi-drug regimen may be appropriate in select settings,
17 | even for targeted/definitive therapy, such as device-associated infections, enterococcal
18 | endocarditis, staphylococcal endocarditis, group B streptococcal sepsis, and
19 | carbapenem-resistant Enterobacteriaceae infections [\(105, 106\)\(99, 100\)](#).
20 |
21 |

22 | Pediatric patients with cancer and transplant recipients have a substantial degree
23 | of immunosuppression and represent a population at higher risk for colonization and
24 | infection with multi-drug resistant organisms [\(107, 108\)\(101, 102\)](#). The 2017 guidelines
25 | for the management of fever and neutropenia (FN) in children with cancer and
26 | hematopoietic stem-cell transplantation recommended monotherapy with an anti-
27 | pseudomonas beta-lactam, a fourth-generation cephalosporin, or a carbapenem as
28 | empiric therapy in high-risk pediatric patients with FN [\(79\)\(103\)](#). The three RCTs in
29 | high-risk pediatric FN comparing monotherapy with aminoglycoside-containing
30 | combination therapy found no significant differences in failure rates, infection-related
31 | mortality, or overall mortality [\(79, 109, 110\)\(103-105\)](#). The meta-analysis also confirmed
32 | the efficacy and safety of monotherapy without the addition of an aminoglycoside.
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4 However, the 2017 guidelines on the management of children with FN did recommend
5 addition of a second gram-negative agent and/or a glycopeptide when resistant
6 organisms were suspected for patients who are clinically unstable (i.e., septic shock)
7 and in centers with a high rate of resistant pathogens [\(79\)\(403\)](#). Therefore, for children
8 with septic shock or other sepsis-associated organ dysfunction who have immune
9 compromise and/or are at high risk for multidrug-resistant pathogens, we suggest
10 empiric multi-drug therapy.
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21 Currently, specific resistance rate thresholds do not exist to help clinicians decide
22 when the addition of a glycopeptide or second gram-negative agent for sepsis or septic
23 shock is necessary. The US guidelines for the management of community-acquired
24 pneumonia in adults suggest a 25% rate of high-level macrolide resistance in the
25 community as the threshold beyond which macrolides should not be used [\(111,](#)
26 [112\)\(406, 407\)](#). Additionally, current guidelines from the Infectious Diseases Society of
27 America recommend an alternative antibiotic for skin and soft tissue infections if the
28 local clindamycin resistance rate is greater than 10% [\(113\)\(408\)](#). Considering the
29 current rates of morbidity and mortality for patients with sepsis or septic shock, a local
30 or regional antimicrobial resistance rate exceeding 10% is probably a prudent threshold
31 for the addition of a second agent if that pathogen is suspected(5, 63).
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50 **12. We recommend using antimicrobial dosing strategies that have been**
51 **optimized based on published pharmacokinetic/pharmacodynamic**
52 **principles and with consideration of specific drug properties (BPS).**
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4 | **Rationale:** Sepsis may alter the pharmacokinetics and pharmacodynamics of
5 |
6 | antimicrobials. Therefore, antimicrobial dosing should be individualized to deliver
7 |
8 | effective and timely treatment of life-threatening infection, while at the same time limiting
9 |
10 | adverse medication effects. Sub-therapeutic dosing can lead to failure to clear the
11 |
12 | infection, prolong organ dysfunction, and can lead to the development of antimicrobial
13 |
14 | resistance. A substantial proportion of sepsis patients are at risk for altered drug
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16 | metabolism and/or clearance, including those with kidney and hepatic dysfunction and
17 |
18 | those treated with extracorporeal therapies [\(114\)\(409\)](#). In particular, continuous renal
19 |
20 | replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) both
21 |
22 | lead to profound alteration of antimicrobial clearance, requiring individual dose
23 |
24 | adaptation [\(115\)\(410\)](#). Therapeutic drug monitoring (TDM), where available, can permit
25 |
26 | individualized antimicrobial dosing to achieve maximal effect while minimizing toxicity
27 |
28 | [\(116\)\(411\)](#).

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36 | Examples of sepsis and septic shock-related altered pharmacokinetics include
37 |
38 | increased volume of distribution as a result of fluid therapy and capillary leak (V_d)
39 |
40 | [\(117\)\(412\)](#), decreased antimicrobial clearance as a result of altered renal and hepatic
41 |
42 | organ perfusion and organ dysfunction [\(118\)\(413\)](#), and higher unbound drug levels due
43 |
44 | to hypoalbuminemia leading to increased clearance [\(119\)\(414\)](#). Hepatic dysfunction
45 |
46 | impairs the metabolism of lipophilic and highly albumin bound antibiotics, leading to
47 |
48 | drug accumulation and toxicity. In renal dysfunction, time-dependent antibiotics cleared
49 |
50 | by the kidneys, such as the beta-lactams, require reduced dosing frequency.

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55 | The 3 main determinants of antimicrobial efficacy are: a) the time during which
56 |
57 | the concentration of the drug remains above the minimum inhibitory concentration (MIC)
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4 of the causative pathogen ($T > MIC$) (time-dependent antibiotics); b) the peak
5 concentration to MIC ratio (C_{max}/MIC) (concentration-dependent antibiotics); and c) the
6
7 ratio of the 24-hour area under the concentration-time curve divided by the MIC
8
9 (AUC_{24}/MIC) (concentration-dependent with time-dependence antibiotics). The main
10
11 classes of time-dependent antibiotics include beta-lactams (penicillins, cephalosporins,
12
13 carbapenems, monobactams) and lincosamides (clindamycin and lincomycin). For
14
15 amoxicillin-clavulanic acid, current published dosing regimens in critically ill children can
16
17 result in sub-therapeutic concentrations in the early period of sepsis due to augmented
18
19 renal clearance [\(120, 121\)](#)~~(115, 116)~~. In sepsis, the use of continuous or extended
20
21 infusions with loading doses, as opposed to intermittent dosing, may lead to improved
22
23 outcomes in patients treated with beta-lactam antibiotics [\(122\)](#)~~(117)~~.
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30
31 The main classes of concentration-dependent antibiotics include
32
33 aminoglycosides and metronidazole. In some centers, drug concentrations measured
34
35 within 60 minutes before or after administration of aminoglycosides are used to estimate
36
37 the C_{min} and C_{max} , respectively, and together with the MIC of the pathogen, can help to
38
39 guide appropriate antimicrobial dosing [\(119\)](#)~~(114)~~. Concentration-dependent antibiotics
40
41 may require an altered dosing frequency to maximize bacterial killing by preserving the
42
43 C_{max}/MIC .
44
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48 Glycopeptides, oxazolidinones, fluoroquinolones, polymixins, daptomycin,
49
50 azithromycin, and tigecycline are examples of concentration-dependent with time-
51
52 dependent antibiotics. For vancomycin, this can mean higher doses, but that comes
53
54 with an increased risk of toxicity. For this reason, continuous vancomycin infusions may
55
56 be considered to achieve optimal concentrations in some patients [\(123\)](#)~~(118)~~. For
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4 concentration-dependent with time-dependent antibiotics, dose optimization involves
5
6 adjusting the dosing interval rather than administered dose [\(119\)\(114\)](#).
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11 **13. In children with septic shock or sepsis-associated organ dysfunction who**
12 **are receiving antimicrobials, we recommend daily assessment (e.g., clinical,**
13 **laboratory assessment) for de-escalation of antimicrobial therapy (BPS).**
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19 **Remarks: This assessment should include a review of the ongoing indication for**
20 **empiric antimicrobial therapy after the first 48 hours that is guided by**
21 **microbiologic results and in response to clinical improvement and/or evidence of**
22 **infection resolution. This recommendation applies to patients being treated with**
23 **empiric, targeted, and combination therapy.**
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31 **Rationale:** The misuse and overuse of broad-spectrum antimicrobials in health care,
32 the community, veterinary medicine, and the environment have contributed to a global
33 public health emergency [\(124\)\(128\)](#). De-escalation of antimicrobials, where appropriate,
34 is warranted to minimize adverse effects of unnecessarily prolonged administration. To
35 date, quality improvement efforts in adults have shown that safe and effective
36 antimicrobial de-escalation can be achieved by daily assessment and discussion [\(125,](#)
37 [126\)\(129, 130\)](#).
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48 Several host biomarkers have also been proposed to aid in the safe de-
49 escalation of antimicrobial therapy. In adults with severe infections and sepsis,
50 procalcitonin has been shown to successfully guide de-escalation [\(127-131\)\(131-135\)](#)
51 with an associated improved mortality [\(132\)\(136\)](#). Similar reductions in length of
52 antimicrobial therapy have also been safely achieved in neonatal populations [\(133\)\(137\)](#)
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4 using procalcitonin as a guide. In the United Kingdom, the NICE committee concluded
5 that in emergency room and critical care settings, procalcitonin testing shows promise
6 but currently insufficient evidence is available to recommend the routine adoption of
7 procalcitonin-guided antimicrobial de-escalation (www.nice.org.uk/guidance/dg18).
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14 Although a relationship between antimicrobial stewardship programs (ASP) and a
15 decrease in antimicrobial resistance has not yet been shown, studies suggest that
16 inpatient pediatric ASPs may reduce antimicrobial usage without contributing to adverse
17 patient outcomes [\(124\)\(128\)](#). The “Start Smart - Then Focus” work from Public Health
18 England suggests a pragmatic approach of the 5 “antimicrobial prescribing decision”
19 options to include: 1) stop antimicrobials if there is no evidence of infection, 2) switch
20 antimicrobials from intravenous to oral, 3) change antimicrobials – ideally to a narrower
21 spectrum – or broader if required, 4) continue and document next review date or stop
22 date, and 5) outpatient parenteral antimicrobial therapy [\(134\)\(138\)](#). De-escalating
23 antimicrobial therapy must be based in sound clinical judgment and needs to be
24 adapted to local epidemiology and identified resistance patterns.
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43 **14. We recommend determining the duration of antimicrobial therapy**
44 **according to the site of infection, microbial etiology, response to treatment,**
45 **and ability to achieve source control (BPS).**
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50 **Rationale:** The main purposes of antimicrobial therapy in patients with sepsis are to
51 reduce the pathogen load rapidly and to prevent recurrence. Important determinants of
52 the required duration of antimicrobial therapy include site of infection, ability to drain or
53 remove fixed infectious foci, choice of antimicrobial therapy, time to clearance of
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4 | positive cultures, the nature of the causative pathogen, and the integrity of the host
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6 | immune response. There is no evidence that severity of sepsis is an important
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8 | determinant of optimal duration of therapy because illness severity is not expected to
9 |
10 | affect clearance of infection.
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14 | The optimal duration of antimicrobial therapy can differ by site of infection
15 |
16 | because of a high pathogen burden, poor antimicrobial penetration, or presence of
17 |
18 | difficult-to-eradicate microbial biofilms at the site. For example, longer duration of
19 |
20 | therapy is typically required for treatment of endocarditis, undrained abscesses, and
21 |
22 | prosthetic joint infection without device removal [\(135-137\)](#)~~(139-141)~~. Characteristics of
23 |
24 | the causative organism that may affect optimal duration of therapy include resistance or
25 |
26 | decreased susceptibility to front-line antimicrobials and propensity to cause deep-
27 |
28 | seated or difficult-to-eradicate infection. For example, optimal duration of treatment for
29 |
30 | endocarditis caused by methicillin-susceptible *Staphylococcus aureus* may be shorter
31 |
32 | than for that caused by methicillin-resistant *Staphylococcus aureus* [\(137\)](#)~~(141)~~.
33 |
34 | Similarly, although 7-10 days of therapy is appropriate for treatment of uncomplicated
35 |
36 | gram negative bacteremia in immunocompetent hosts [\(138, 139\)](#)~~(142, 143)~~,
37 |
38 | uncomplicated *S. aureus* bacteremia requires a longer course of therapy to effect cure
39 |
40 | [\(140-142\)](#)~~(144-146)~~, likely because of unrecognized seeding [\(143\)](#)~~(147)~~. Integrity of
41 |
42 | host immunity may also affect clearance of infection, so antimicrobial therapy for
43 |
44 | infection in neutropenic pediatric patients with cancer is often continued until resolution
45 |
46 | of neutropenia [\(79\)](#)~~(103)~~.
47 |
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50 | A systematic review evaluated studies describing duration of treatment for
51 |
52 | clinically and microbiologically-documented infections in children and provides
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4 | evidence-based clinical guidelines for optimal duration of antimicrobial therapy for
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6 | specific conditions [\(144\)](#)~~(148)~~. Given the lack of studies on the duration of antimicrobial
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8 | therapy for pediatric patients with sepsis specifically, we refer to this previously
9 |
10 | published guideline as best evidence. Importantly, there are no data to support that the
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12 | presence of organ dysfunction or a higher initial illness severity necessitates longer
13 |
14 | therapy for specific infection types (other than attention to how such organ dysfunction
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16 | may affect antimicrobial pharmacokinetics and pharmacodynamics).
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21 | Observational studies suggest that longer exposure to antibiotics is associated
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23 | with risk of potential adverse events including necrotizing enterocolitis in very low
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25 | birthweight infants [\(145\)](#)~~(149)~~, candidemia in hospitalized children [\(146, 147\)](#)~~(150, 151)~~,
26 |
27 | development of antimicrobial resistance [\(148\)](#)~~(152)~~ and *Clostridioides difficile* (formerly
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29 | *Clostridium*) infection [\(149\)](#)~~(153)~~. Several meta-analyses, RCTs, and observational
30 |
31 | studies have compared long- versus short-duration antibiotic therapy for serious
32 |
33 | infections [\(141, 145, 150-168\)](#)~~(145, 149, 154-172)~~. Most studies suggest that shorter
34 |
35 | courses were associated with similar clinical outcomes compared to longer durations;
36 |
37 | these include neonatal bacteremia [\(159, 164\)](#)~~(163, 168)~~, pyelonephritis [\(169\)](#)~~(173)~~,
38 |
39 | uncomplicated bacterial meningitis [\(155, 156, 160-162, 165, 166\)](#)~~(159, 160, 164-166,~~
40 |
41 | [169, 170\)](#), and pneumonia [\(170, 171\)](#)~~(174, 175)~~. In contrast to these infections, some
42 |
43 | studies have identified scenarios where longer durations of antimicrobial therapy is
44 |
45 | superior. For example, an RCT suggested that 14 days of antibiotic therapy was
46 |
47 | superior to 7 days for treatment of neonates with *Staphylococcus aureus* bacteremia
48 |
49 | [\(141\)](#)~~(145)~~, and an observational study suggested that >10 days was superior to ≤10
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4 | days of antibiotic therapy in children treated for gram-negative bacteremia without
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6 | removal of a pre-existing CVC [\(163\)](#)~~(167)~~.
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10 | 11 | **C. SOURCE CONTROL** 12 | 13 |

14 | **15. We recommend that emergent source control intervention be implemented**
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16 | **as soon possible after a diagnosis of an infection amenable to a source**
17 |
18 | **control procedure is made (BPS).**
19 |

20 | **Remarks: Appropriate diagnostic testing to identify the site of infection and**
21 |
22 | **microbial etiology should be performed, and advice from specialist teams (e.g.,**
23 |
24 | **infectious diseases, surgery) should be sought, as appropriate, in order to**
25 |
26 | **prioritize interventions needed to achieve source control.**
27 |
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29 | **16. We recommend removal of intravascular access devices that are**
30 |
31 | **confirmed to be the source of sepsis or septic shock after other vascular**
32 |
33 | **access has been established and depending on the pathogen and the**
34 |
35 | **risks/benefits of a surgical procedure (strong recommendation, low quality**
36 |
37 | **of evidence).**
38 |

39 | **Rationale:** Source control is defined as physical modalities taken to control or remove
40 |
41 | the source of infection or to prevent spread of the infection systemically or to adjacent
42 |
43 | tissues [\(172\)](#)~~(119)~~. Source control may include percutaneous or deep abscess
44 |
45 | drainage, drainage of an empyema, septic joint, or subperiosteal abscess, removal of
46 |
47 | infected hardware or central venous catheters (CVCs), or debridement of necrotizing
48 |
49 | soft-tissue infection. The adult SSC guidelines recommend source control as soon as is
50 |
51 | reasonably feasible after resuscitation, ideally within 6-12 hours of diagnosis (50).
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4 | Waiting for patients to clinically stabilize prior to intervention is not recommended, as
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6 | delaying adequate source control may lead to further clinical deterioration (6). While
7 |
8 | source control as an adjunct to antimicrobial and other medical therapy has been best
9 |
10 | described for abdominal infections in adults and has been associated with reduction in
11 |
12 | mortality [\(173\)\(120\)](#), the role of source control for pediatric sepsis has been less well
13 |
14 | elucidated [\(174\)\(121\)](#).
15 |
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19 | The importance of source control in children has been shown for skin and deep
20 |
21 | tissue abscesses and necrotizing fasciitis [\(174-176\)\(121-123\)](#). Despite the relative
22 |
23 | paucity of pediatric data, source control is an important facet of treatment of sepsis, and
24 |
25 | should not be delayed. Larger collections containing infected material often are poorly
26 |
27 | penetrated by intravenous antimicrobials and contribute to direct and hematogenous
28 |
29 | spread, ongoing inflammation, and organ dysfunction.
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33 | A common, but potentially preventable, source of infection is central line-
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35 | associated bloodstream infections (CLABSI). Delayed removal of a CVC in neonates
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37 | and in patients with fungemia or Enterobacteriaceae bacteremia increases the risk of
38 |
39 | death or slows recovery [\(177-180\)\(124-127\)](#). Removal of a CVC that is the source of
40 |
41 | infection is therefore generally warranted unless extenuating circumstances exist.
42 |
43 | Fungal infection dictates immediate removal, while in case of coagulase negative
44 |
45 | *Staphylococcus spp* or clinically stable patients with infection caused by gram-negative
46 |
47 | rods, infections can often be initially treated through the CVC as a temporizing measure.
48 |
49 | The decision to remove the CVC, or not, should ultimately be made based on the
50 |
51 | pathogen suspected/recovered and host factors, such as immune status.
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55 | **(Supplemental Table 3.)**
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9 **D. HEMODYNAMICS AND RESUSCITATION FLUID THERAPY**

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11 **17. In healthcare systems with availability of intensive care, we**
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13 **suggest administering up to 40-60 mL/kg in bolus fluid (10-20 mL/kg per**
14 **bolus) over the first hour, titrated to clinical markers of cardiac output and**
15 **discontinued if signs of fluid overload develop, for the initial resuscitation**
16 **of children with septic shock or other sepsis-associated organ dysfunction**
17 **(weak recommendation, low quality of evidence).**

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26 **~~18. In healthcare systems with no availability of intensive care, we suggest~~**
27 **~~administering up to 20 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the~~**
28 **~~first hour, titrated to clinical markers of cardiac output and discontinued if~~**
29 **~~signs of fluid overload develop, for the initial resuscitation of children with~~**
30 **~~septic shock or other sepsis-associated organ dysfunction (weak~~**
31 **~~recommendation, moderate quality of evidence).~~** **In healthcare systems with**
32 **no availability of intensive care and *in the absence of hypotension*, we**
33 **recommend against bolus fluid administration while starting maintenance**
34 **fluids (strong recommendation, high quality of evidence).**

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

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4 **Remarks:** Clinical markers of cardiac output may include heart rate, blood
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6 pressure, capillary refill time, level of consciousness, and urine output. In all
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8 settings, the need for bolus fluid administration should be guided by frequent
9
10 reassessment of clinical markers of cardiac output, serial blood lactate
11
12 measurement and advanced monitoring, when available. Even in low-resource
13
14 settings, the subset of children with septic shock and hypotension should receive
15
16 cautious fluid bolus therapy. Signs of fluid overload that should limit further fluid
17
18 bolus therapy may include clinical signs of pulmonary edema or new or
19
20 worsening hepatomegaly. ~~Clinical markers of cardiac output may include heart~~
21 ~~rate, blood pressure, capillary refill time, level of consciousness, and urine~~
22 ~~output. The need for bolus fluid administration should be guided by frequent~~
23 ~~reassessment of clinical markers of cardiac output, serial blood lactate~~
24 ~~measurement and advanced monitoring, when available. Even in low-resource~~
25 ~~settings, the subset of children with septic shock and hypotension should receive~~
26 ~~cautious fluid bolus therapy. Signs of fluid overload may include clinical signs of~~
27 ~~pulmonary edema or new or worsening hepatomegaly.~~

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43 **Rationale:**

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45 Septic shock is characterized by abnormal perfusion, including tachycardia, decreased
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47 blood pressure, prolonged capillary refill, organ dysfunction and increased serum lactate
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49 (17). ~~Effective fluid resuscitation in septic shock can correct relative hypovolemia,~~
50
51 ~~caused by capillary leak, and vasodilation, and fluid losses. Without maintenance of~~
52
53 ~~adequate atrial filling pressures, cardiac output will fall and organ perfusion will be~~
54
55 ~~compromised. However, the cardiovascular physiology in childhood septic shock is~~
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4 variable. In older children, particularly those with healthcare-acquired infections (e.g.,
5 CLABSIs), a vasodilatory picture may dominate with tachycardia, hypotension, bounding
6 pulses, warm peripheries, and flash capillary refill. In younger children with community-
7 acquired infection (e.g., meningococcal sepsis), the phenotype is more likely to be one
8 of impaired cardiac output due to the direct effects of bacterial toxins and inflammatory
9 mediators on myocardial cell function and profound vasoconstriction (176). In this latter
10 case the presentation may be with tachycardia, hypotension, cold peripheries, and
11 prolonged capillary refill. Although observational studies have generally supported a role
12 for fluid resuscitation in children with septic shock (8, 32, 33, 35, 177-180), the optimal
13 rate, volume, and timing of fluid resuscitation across such variable physiologic
14 presentations has not been conclusively demonstrated.

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

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

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4 60 days and 12 years of age with a severe febrile illness and abnormal perfusion were
5 randomized to either rapid volume expansion with 20 mL/kg of intravenous 0.9% saline
6 or 5% albumin or no bolus with maintenance fluid only (control group). Among the 3141
7 study participants, malaria and anemia were highly prevalent. Overall, the RCT
8 demonstrated a lower mortality after 48 hours in children receiving conservative fluid
9 therapy (i.e., no bolus fluid, maintenance fluid only) than among those given liberal
10 initial fluid therapy (i.e., 20 mL/kg fluid bolus with maintenance fluid) with a RR of 0.72
11 (95% CI 0.57, 0.9). Notably, 29 additional children enrolled with severe hypotension
12 (systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60
13 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of
14 age) were treated with 40 mL/kg fluid bolus per the planned protocol without
15 randomization to the control group. One additional child who was randomized to the
16 control group also received a 40 mL/kg fluid bolus due to severe hypotension. The
17 FEAST study has resulted in some reluctance to use a high-volume fluid resuscitation
18 strategy in critically ill children, even in settings in which intensive care is available.

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41 For children with septic shock diagnosed by abnormal perfusion or hypotension
42 in healthcare systems with availability of advanced supportive and intensive care, and in
43 the absence of signs of fluid overload, the panel suggests administering up to 40-60
44 mL/kg fluid bolus therapy in the first hour of resuscitation. Fluid resuscitation should be
45 in health care systems with availability of advanced supportive and intensive care,
46 titrated to clinical markers of cardiac output and discontinued if signs of fluid overload
47 develop. Clinical markers of cardiac output can include heart rate, capillary refill, and
48 urine output. Although no high-quality RCTs support demonstrate clear superiority of
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4 this practice, several numerous observational studies investigating this approach to
5 resuscitation have reported improved patient outcomes with routine administration of up
6 to 40-60 mL/kg fluid bolus therapy in the first hour of resuscitation (8, 32, 33, 36, 177-
7 179, 185)(8, 32, 33, 36, 185-188). Notably, †The panel provides only a weak
8 recommendation for this resuscitation strategy in healthcare systems with availability of
9 intensive care given that because a more restrictive fluid resuscitation strategy has not
10 been shown to be inferior in this setting and indirect data (184)(184) indicate harm
11 from rapid fluid boluses in other settings. , indeed, may be superior in health care
12 systems with limited availability of advanced supportive and intensive care, as seen in
13 the FEAST trial. For this recommendation, the panel judged the balance of
14 observational data supporting initial fluid bolus therapy to outweigh an indirect
15 suggestion of harm because the generalizability of the FEAST trial to healthcare
16 systems with availability of advanced supportive and intensive care is not clear. A weak
17 recommendation (i.e., suggestion) to administer up to 40-60 mL/kg in bolus fluid therapy
18 over the first hour indicates the panel's judgment that the majority of individuals in this
19 situation would want this course of action, but different choices are likely to be
20 appropriate for different patients and therapy should be tailored to the individual
21 patient's circumstances.

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

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4 | suggestion to limit initial fluid bolus resuscitation to 20 mL/kg in the first hour for children
5 | in low-resource settings where advanced supportive and intensive care is not available.

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

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

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

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4 hypotension were not allocated to the control (no bolus) arm. Fluid bolus therapy in
5 children with moderate hypotension was not beneficial or harmful compared to
6 maintenance fluid only (RR of death = 1.48, 95% CI 0.61–3.66, p=0.41). Although
7 children who were reclassified as meeting all three WHO shock criteria of cold
8 extremities, prolonged capillary refill >3 seconds, and weak, fast pulse (14)(14) had
9 48% mortality in the bolus groups versus 20% mortality in the control group, this
10 difference was not statistically significant (p=0.07). These cases were a very small
11 proportion of the total FEAST trial participants (only 72 [2.3%] had moderate
12 hypotension and 65 [2%] met the full WHO shock criteria), and no data were provided
13 about differential patient characteristics between these very small *post hoc* subgroups
14 to assess for potential confounding. Therefore, until further data are available, the panel
15 suggests cautious administration of fluid bolus therapy for the subset of children with
16 septic shock and hypotension in low-resource settings as a weak recommendation
17 based on low quality of evidence.

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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

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

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4 warm peripheries, and flash capillary refill. In younger children with community-acquired
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6 infection (e.g., meningococcal sepsis), the phenotype is more likely to be one of
7
8 impaired cardiac output due to the direct effects of bacterial toxins and inflammatory
9
10 mediators on myocardial cell function and profound vasoconstriction (176). In this latter
11
12 case the presentation may be with tachycardia, hypotension, cold peripheries, and
13
14 prolonged capillary refill. Although observational studies have generally supported a role
15
16 for fluid resuscitation in children with septic shock (8, 32, 33, 35, 177-180), the optimal
17
18 rate, volume, and timing of fluid resuscitation across such variable physiologic
19
20 presentations has not been conclusively demonstrated.
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29 Three RCTs of different volume resuscitation strategies in children with septic shock in
30
31 settings in which advanced supportive care (e.g., intubation, mechanical ventilation, and
32
33 intensive care) was accessible have been published (181-183). These studies have a
34
35 combined total of only 316 children and showed no difference in mortality between the
36
37 restrictive and liberal fluid resuscitation groups.
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41 In geographic settings in which advanced supportive care is limited and/or intensive
42
43 care is not routinely accessible, the only large-scale RCT of different bolus fluid volume
44
45 resuscitation strategies in severe infection in children was the Fluid Expansion as
46
47 Supportive Therapy (FEAST) study (184). The FEAST study was conducted in Africa, in
48
49 a low-resource setting without access to PICU admission. Among the 3141 study
50
51 participants, malaria and anemia were highly prevalent. Overall, the RCT demonstrated
52
53 a lower mortality after 48 hours in children receiving conservative fluid therapy (i.e., no
54
55 bolus fluid, maintenance fluid only) than among those given liberal initial fluid therapy
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4 | ~~(i.e., 20 mL/kg fluid bolus with maintenance fluid) with a RR of 0.72 (95% CI 0.57, 0.9).~~

5 |
6 | ~~The FEAST study has resulted in some reluctance to use a high-volume fluid~~
7 | ~~resuscitation strategy in critically ill children, even in settings in which intensive care is~~
8 | ~~available.~~

9 |
10 | ~~The panel suggests administering up to 40-60 mL/kg fluid bolus therapy in the first hour~~
11 | ~~of resuscitation in health care systems with availability of advanced supportive and~~
12 | ~~intensive care, titrated to clinical markers of cardiac output and discontinued if signs of~~
13 | ~~fluid overload develop. Clinical markers of cardiac output can include heart rate,~~
14 | ~~capillary refill, and urine output. Although no high-quality RCTs support this practice,~~
15 | ~~several observational studies investigating this approach to resuscitation have reported~~
16 | ~~improved patient outcomes with routine administration of up to 40-60 mL/kg fluid bolus~~
17 | ~~therapy in the first hour of resuscitation (8, 32, 33, 36, 177-179, 185). Notably, the panel~~
18 | ~~provides only a weak recommendation given that a more restrictive fluid resuscitation~~
19 | ~~strategy has not been shown to be inferior and, indeed, may be superior in health care~~
20 | ~~systems with limited availability of advanced supportive and intensive care, as seen in~~
21 | ~~the FEAST trial. A weak recommendation (i.e., suggestion) to administer up to 40-60~~
22 | ~~mL/kg in bolus fluid therapy over the first hour indicates the panel's judgment that the~~
23 | ~~majority of individuals in this situation would want this course of action, but different~~
24 | ~~choices are likely to be appropriate for different patients and therapy should be tailored~~
25 | ~~to the individual patient's circumstances.~~

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

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4 treatment of circulatory impairment in low-resource settings (14). A weak
5 recommendation (i.e., suggestion) to administer up to 20 mL/kg in bolus fluid in
6 healthcare systems with limited availability of advanced supportive and intensive care
7 indicates the panel's uncertainty of whether this amount of fluid may cause harm in
8 some patients without severe hypotension. Notably, no data support that such a
9 restrictive approach to fluid resuscitation is beneficial in children with septic shock and
10 hypotension, as even the subset of children in the FEAST study with severe febrile
11 illness and hypotension were treated with 40 mL/kg of bolus fluid. (184) Therefore,
12 cautious administration of fluid bolus therapy should be considered for the subset of
13 children with septic shock and hypotension in low-resource settings. The WHO
14 recommends 10-20 mL/kg of isotonic crystalloid over 30-60 minutes, followed by an
15 additional 10 mL/kg over 30 minutes if condition has not improved (14).
16
17 Fluid boluses may be administered as 10 or 20 mL/kg, according to clinician preference.
18
19 To facilitate rapid intravenous fluid administration (as well as other intravenous
20 therapies, such as antimicrobials and vasoactive medications), clinicians should
21 consider alternative methods of vascular access if initial attempts at peripheral vein
22 cannulation are not immediately successful. Intraosseous access is rapid and effective
23 and recommended by Pediatric Advanced Life Support (PALS), Advanced Pediatric Life
24 Support (APLS), and the International Liaison Committee on Resuscitation (ILCOR).
25
26 Ultrasound-guided peripheral intravenous catheter placement, CVCs, and umbilical
27 venous catheter access are alternatives if the skills are immediately available (186,
28 187). In all healthcare systems, repeat boluses should only be administered after
29 reassessment of hemodynamic status and if shock has not resolved.
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4 | Although fluid bolus therapy should be discontinued if signs of fluid overload are
5 | present or develop, early recognition of fluid overload by clinical examination is a
6 | challenge in children. Identifying fluid overload is especially difficult in young children, in
7 | whom crackles (rales) are often absent even in the context of gross pulmonary edema.
8 | Worsening respiratory status, particularly increasing respiratory rate, radiographic
9 | evidence of pulmonary edema in an intubated patient, or new or expanding
10 | hepatomegaly may be the only clues of evolving fluid overload. Bedside ultrasound may
11 | also be helpful to assess fluid overload, as there is emerging evidence to suggest that a
12 | “full” inferior vena cava with minimal variation across the respiratory cycle demonstrated
13 | on ultrasound indicates a fluid-replete circulation [\(192\)\(188\)](#).
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31 | **20. We suggest using crystalloids, rather than albumin, for the initial**
32 | **resuscitation of children with septic shock or other sepsis-associated organ**
33 | **dysfunction (weak recommendation, moderate quality of evidence).**
34 |
35 |

36 | **Remarks:** Although there is no difference in outcomes, this recommendation
37 | **takes into consideration cost and other barriers of administering albumin**
38 | **compared to crystalloids.**
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41 | **Rationale:** The FEAST trial investigated 3141 African children with infection and
42 | impaired perfusion, who were randomly assigned to resuscitation with 5% human
43 | albumin solution or 0.9% saline boluses or no boluses on admission to the hospital.
44 | Although both the albumin and 0.9% saline arms exhibited higher mortality than the no
45 | bolus arm, comparing human albumin solution to 0.9% saline (RR 1.02, 95% CI 0.8,
46 | 1.28) showed no difference in mortality [\(184\)\(184\)](#). In the absence of any clear benefit
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4 | of albumin administration in children with sepsis, and in view of the additional costs in
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6 | comparison to crystalloids, problems of availability, and the potential risk of blood-borne
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8 | infection, we suggest against the routine use of albumin for initial fluid resuscitation in
9 |
10 | children with sepsis.
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16 | **21. We suggest using balanced/buffered crystalloids, rather than 0.9% saline,**
17 |
18 | **for the initial resuscitation of children with septic shock or other sepsis-**
19 | **associated organ dysfunction (weak recommendation, very low quality of**
20 | **evidence).**
21 |
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25 | ***Rationale:*** Increasing evidence from observational studies and RCTs in adults
26 |
27 | suggests that resuscitation with crystalloid fluids containing high chloride concentrations
28 |
29 | (e.g., 0.9% saline) is associated with hyperchloremic acidosis, systemic inflammation,
30 |
31 | acute kidney injury, coagulopathy, and mortality when compared to resuscitation with
32 |
33 | more balanced/buffered crystalloids (e.g., lactated Ringer's, PlasmaLyte) [\(193\)](#)~~(209)~~.
34 |
35 | Although no pediatric RCTs compare ~~balanced~~balanced/buffered crystalloids to 0.9%
36 |
37 | saline, there are 2 large observational studies in children with sepsis [\(194, 195\)](#)~~(210,~~
38 |
39 | [211\)](#). They included a total of 30,532 children with sepsis, 2100 of whom received only
40 |
41 | ~~balanced~~balanced/buffered crystalloids for the first 72 hours of hospital admission, and
42 |
43 | 28,432 who received 0.9% saline [\(Supplemental Table 5\)](#). These studies showed that
44 |
45 | use of ~~balanced~~balanced/buffered crystalloids was associated with lower mortality (OR
46 |
47 | 0.79, 95% CI 0.65, 0.95) but not AKI (OR 0.98, 95% CI 0.94-1.02) [\(194, 195\)](#)~~(210, 211)~~.
48 |
49 | Indirect evidence from adult patients, including two large RCTs, also demonstrates
50 |
51 | benefit with ~~balanced~~balanced/buffered crystalloids over 0.9% saline, with adult patients
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4 who received larger volumes of fluid and those with sepsis exhibiting the greatest
5
6 benefit [\(193, 196\)](#)~~(209, 212)~~. Taken together, these data support that the desirable
7
8 consequences of ~~balanced~~[balanced/buffered](#) crystalloids probably outweigh the
9
10 undesirable consequences (including cost), especially in those who require large
11
12 volume of fluid resuscitation. Therefore, pending further high-quality pediatric data, we
13
14 suggest that ~~balanced~~[balanced/buffered](#) crystalloids should generally be preferred over
15
16 0.9% saline for resuscitation of children with septic shock or other sepsis-associated
17
18 organ dysfunction without a specific indication for an alternative fluid type (e.g., 0.9%
19
20 saline may be preferred in patients with hyponatremia or concern for increased
21
22 intracranial pressure).
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31 **22. We recommend against using starches in the acute resuscitation of**
32
33 **children with septic shock or other sepsis-associated organ dysfunction**
34
35 **(strong recommendation, moderate quality of evidence).**
36
37

38 **Rationale:** No studies compare starches with other fluids in children. However, in
39
40 adults with severe sepsis and septic shock [\(Supplemental Table 6\)](#), two large RCTs
41
42 showed increased risk of mortality, coagulopathy, and AKI in patients receiving
43
44 hydroxyethyl starch (HES) [\(197, 198\)](#)~~(213, 214)~~. A meta-analysis further confirmed the
45
46 risk of harm with HES [\(199\)](#)~~(215)~~. In the US, the Food and Drug Administration (FDA)
47
48 has restricted the use of HES [\(200\)](#)~~(216)~~ and the European Medicines Agency has
49
50 recommended complete suspension of its use [\(201\)](#)~~(217)~~. Therefore, we strongly
51
52 recommend against the use of HES in children with sepsis.
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4 | **23. We suggest against using gelatin in the resuscitation of children with**
5 | **septic shock or other sepsis-associated organ dysfunction (weak**
6 | **recommendation, low quality of evidence).**
7 |
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10 | **Rationale:** One RCT of gelatin-derived fluid in pediatric septic shock compared it to
11 | 0.9% saline in 60 patients. The estimates were imprecise, and showed no difference in
12 | mortality, days of using vasoactive medications, or AKI between the two groups
13 | [\(202\)\(218\)](#) (**Supplemental Table 57**). In the absence of any data indicating benefit of
14 | gelatin in children, we suggest against its use in pediatric sepsis.
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19 | **E. HEMODYNAMIC MONITORING**

20 | **24. We were unable to issue a recommendation about whether to target mean**
21 | **arterial blood pressure (MAP) at the 5th or 50th percentile for age in children**
22 | **with septic shock and other sepsis-associated organ dysfunction. However,**
23 | **in our practice, we target MAP to between the 5th and 50th percentile or >50th**
24 | **percentile for age.**
25 |

26 | **Rationale:** While no data from RCTs support specific hemodynamic targets in children,
27 | evidence suggests that targeting MAP of approximately 65 mmHg (5th percentile) in
28 | adults with septic shock may be beneficial [\(203\)\(189\)](#). In the absence of evidence from
29 | RCTs, we were unable to reach consensus to recommend a specific MAP target for
30 | children. However, in our practice, 37% of panel members reported targeting MAP
31 | between the 5th and 50th percentile for age and 45% reported targeting MAP >50th
32 | percentile for age. Many panelists also commented that lower blood pressures are
33 | acceptable if other hemodynamic parameters (e.g., mental status, perfusion, urine
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4 | output, lactate) are improving. RCTs to define optimal hemodynamic targets, including
5 |
6 | MAP, are urgently required to inform practice in pediatric sepsis. In settings where direct
7 |
8 | measurement of MAP is less reliable, systolic blood pressure provides a reasonable
9 |
10 | alternative.
11 |

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13 |
14 | A previous recommendation to target perfusion pressure (MAP minus central
15 |
16 | venous pressure [CVP]) lacks supporting data [\(204\)\(199\)](#). Prioritizing CVP
17 |
18 | measurement is also impractical during early resuscitation (such as in most pediatric
19 |
20 | emergency departments); CVP also provides an unreliable assessment of left
21 |
22 | ventricular preload.
23 |
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28 | **25. We suggest not using bedside clinical signs in isolation to categorize**
29 |
30 | **septic shock in children as “warm” or “cold” (weak recommendation, very**
31 |
32 | **low quality of evidence).**
33 |

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35 |
36 | **26. We suggest using advanced hemodynamic variables, when available, in**
37 |
38 | **addition to bedside clinical variables to guide the resuscitation of children**
39 |
40 | **with septic shock or other sepsis-associated organ dysfunction (weak**
41 |
42 | **recommendation, low quality of evidence).**
43 |
44 |

45 | **Remarks: Advanced hemodynamic monitoring may include cardiac**
46 |
47 | **output/cardiac index, systemic vascular resistance, or central venous oxygen**
48 |
49 | **saturation (ScvO₂).**
50 |

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53 | **Rationale:** The ACCM previously recommended clinical assessment of children
54 |
55 | in septic shock to differentiate “warm” versus “cold” shock based on extremity
56 |
57 | temperature, capillary refill, pulse strength, diastolic blood pressure, and pulse pressure.
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4 | Depending on “warm” or “cold” classification, different resuscitation strategies were
5 |
6 | suggested (e.g., fluid and vasopressors for “warm” shock and inotropes for “cold”
7 |
8 | shock). However, a number of observational studies have demonstrated very poor
9 |
10 | correlation of clinical assessments with cardiac index and systemic vascular resistance
11 |
12 | as measured by advanced monitoring [\(205-210\)](#)~~(191-196)~~. Indeed, many children who
13 |
14 | appeared to have “warm” shock by clinical examination had evidence of myocardial
15 |
16 | dysfunction, thus demonstrating the challenge of using clinical signs alone to direct
17 |
18 | therapy. Hence, we suggest not attempting to make this distinction using clinical
19 |
20 | assessments alone, though this categorical distinction may be helpful if advanced
21 |
22 | hemodynamic monitoring is available to assess patient physiology more accurately.
23 |
24 | Examples of advanced monitoring include invasive arterial blood pressure monitoring
25 |
26 | with pulse contour analysis, ultrasound Doppler of the ascending or descending thoracic
27 |
28 | aorta (suprasternal or esophageal Doppler), cardiac ultrasound/echocardiography
29 |
30 | [\(211\)](#)~~(197)~~, or measurement of ScvO₂ [\(212\)](#)~~(187)~~. All of these parameters (other than
31 |
32 | ScvO₂) will provide additional assessment of cardiac index and/or systemic vascular
33 |
34 | resistance index beyond clinical signs, which may then be used to direct and titrate
35 |
36 | treatment. There is also emerging evidence that fluid responsiveness may be predicted
37 |
38 | by aortic blood flow peak velocity variation (ΔV_{peak}) in mechanically ventilated
39 |
40 | children [\(213\)](#)~~(198)~~. In an RCT of 90 children admitted to a PICU in Egypt, addition of
41 |
42 | serial echocardiography provided early recognition of septic myocardial dysfunction and
43 |
44 | hypovolemia that was not apparent on clinical assessment and resulted in faster shock
45 |
46 | reversal, less fluid overload, shorter LOS, and lower mortality compared with the group
47 |
48 | without serial echocardiography [\(211\)](#)~~(197)~~. When advanced hemodynamic monitoring
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4 | is available, it is appropriate to target the normal range for parameters such as cardiac
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6 | index, systemic vascular resistance index, stroke index, and ScvO₂ (Table 5). No
7 |
8 | evidence supports targeting a supranormal range of cardiac index.
9 |

10 |
11 | Until recently, adult guidelines have recommended early goal-directed therapy
12 | (EGDT) based on the protocol published by Rivers et al in 2001(214)(199). This
13 |
14 | recommendation described the use of a series of “goals” that included CVP and ScvO₂.
15 |
16 | This approach is no longer recommended following a failure to show reduction in
17 |
18 | mortality in 3 subsequent large multicenter RCTs (215-217)(200-202). ~~These findings
19 | may reflect important improvements in sepsis resuscitation protocols in general,
20 | meaning EGDT (as described by Rivers et al.) no longer offers a significant advantage.~~

21 |
22 | In children, there has only been one small RCT supporting the use of a protocolized
23 |
24 | approach including targeting ScvO₂ > 70%. This study included 102 children with fluid-
25 |
26 | refractory septic shock and showed a reduced risk of death (RR 0.3, 95% CI 0.13, 0.68)
27 |
28 | from a very high baseline mortality of 39% (26)(26). No high-quality RCTs have
29 |
30 | investigated other hemodynamic variables to guide therapy in children (Supplemental
31 |
32 | **Table 8, Supplemental Figure 3**).
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38 | **27. We suggest using trends in blood lactate levels, in addition to clinical**
39 |
40 | **assessment, to guide resuscitation of children with septic shock and other**
41 |
42 | **sepsis-associated organ dysfunction (weak recommendation, very low**
43 |
44 | **quality of evidence).**

45 |
46 | **Remarks: In children with an elevated blood lactate, repeat testing that reveals a**
47 |
48 | **persistent elevation in blood lactate may indicate incomplete hemodynamic**
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4 **resuscitation and should prompt efforts, as needed, to further promote**
5
6 **hemodynamic stability.**
7

8
9 ***Rationale:*** Although blood lactate is not a direct measure of tissue perfusion, increased
10 lactate is associated with worse outcomes in children (11). Only one pediatric
11 observational study of lactate-guided resuscitation, which included 77 children with
12 sepsis in the ED, was available (**Supplemental Table 9**). This study showed that
13 lactate normalization was associated with a decreased risk of persistent organ
14 dysfunction (RR 0.46, 95% CI 0.29, 0.73; adjusted RR 0.47, 95% CI 0.29, 0.78) (56).
15

16
17 There is also indirect evidence from adult sepsis, with six RCTs (total of 1007 patients)
18 evaluating lactate-guided resuscitation of patients with septic shock ([218-223](#))(~~[203-208](#)~~).
19

20
21 The pooled estimates across all RCTs showed significant reduction in mortality
22 compared to resuscitation without lactate monitoring (RR 0.66, 95% CI 0.55, 0.81)
23

24 (**Supplemental Table 9**). Therefore, while there was not sufficient evidence to propose
25

26 a recommendation to measure lactate to differentiate low- versus high-risk of sepsis
27 among children with infection or suspected infection (see **recommendation**
28

29 **Recommendation #2**), we do suggest that blood lactate levels be used to help guide
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31 resuscitation of children with established septic shock or other sepsis-associated organ
32 dysfunction.
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50 **F. VASOACTIVE MEDICATIONS**

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53 **28. We suggest using epinephrine, rather than dopamine, in children with**
54 **septic shock (weak recommendation, low quality of evidence).**
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4 | **29. We suggest using norepinephrine, rather than dopamine, in children with**
5 | **septic shock (weak recommendation, very low quality of evidence).**
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9 | **30. We were unable to issue a recommendation for a specific first-line**
10 | **vasoactive infusion for children with septic shock. However, in our practice,**
11 | **we select either epinephrine or norepinephrine as the first-line vasoactive**
12 | **infusion guided by clinician preference, individual patient physiology, and**
13 | **local system factors.**
14 |
15 |

16 | **31. We were unable to issue a recommendation about initiating vasoactive**
17 | **agents through peripheral access in children with septic shock. However, in**
18 | **our practice, we often or sometimes administer a dilute concentration of the**
19 | **initial vasoactive medication through a peripheral vein if central venous**
20 | **access is not readily accessible.**
21 |
22 |

23 | **Remarks: It is reasonable to begin vasoactive infusions after 40-60 mL/kg of fluid**
24 | **resuscitation if the patient continues to have evidence of abnormal perfusion, or**
25 | **sooner if fluid overload develops or other concerns for fluid administration are**
26 | **present. Either epinephrine or norepinephrine may be administered through a**
27 | **peripheral vein (or intraosseous, if in place) if central venous access is not**
28 | **readily accessible. Dopamine may be substituted as the first-line vasoactive**
29 | **infusion, administered either peripherally or centrally, if epinephrine or**
30 | **norepinephrine is not readily available.**
31 |
32 |

33 | ***Rationale:*** Epinephrine and norepinephrine both have vasopressor and inotropic
34 | effects, are widely used, and are effective in treating children with fluid-refractory septic
35 | shock. No studies directly compare epinephrine with norepinephrine. However,
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4 | epinephrine has been compared to dopamine in two RCTs in children with fluid-
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6 | refractory septic shock ([224, 225](#))(~~219, 220~~). Across both studies, epinephrine was
7 |
8 | associated with a lower risk of mortality (RR 0.63, 95% CI 0.40, 0.99) and more organ
9 |
10 | failure-free days among survivors by day 28 (MD 4 more days, 95% CI 2.0 to 6.0)
11 |
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14 | **(Supplemental Table 10, Supplemental Figure 4).**

15 |
16 | Norepinephrine has not been studied in children with septic shock, but in a
17 |
18 | randomized trial of norepinephrine versus saline in sedated, mechanically ventilated
19 |
20 | children, mortality was not different between groups~~lower with norepinephrine~~ (RR 0.50
21 |
22 | 95% CI 0.10-2.43, Supplemental Table 11a) but the norepinephrine group showed
23 |
24 | higher urine output (p=0.016) and improved blood pressure (p=0.04) suggesting
25 |
26 | improved perfusion relative to saline ([226](#))(~~221~~). Evidence from adult trials
27 |
28 | (Supplemental Table 11b) shows a lower mortality rate (RR, 0.93 95% CI 0.86-1.00)
29 |
30 | and lower incidence of arrhythmias (RR 0.48 95% CI 0.40-0.58] with norepinephrine
31 |
32 | than with dopamine, and no difference in mortality with epinephrine than with
33 |
34 | norepinephrine (RR, 0.96 95% CI 0.77-1.21) ([227](#))(~~222~~).

35 |
36 | Evidence is insufficient to recommend either epinephrine or norepinephrine as
37 |
38 | the initial vasoactive agent for children with fluid-refractory septic shock. In a survey of
39 |
40 | our panel members, an equal number used epinephrine and norepinephrine as the first-
41 |
42 | line vasoactive medication with a general preference for epinephrine to treat myocardial
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44 | dysfunction and low cardiac output and for norepinephrine to increase systemic
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46 | vascular resistance. It therefore seems reasonable to use either epinephrine or
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48 | norepinephrine as the initial vasoactive agent, with the choice made based on individual
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50 | patient physiology, clinician preference, and local system factors. Once cardiac
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4 | ultrasound/echocardiography or other advanced monitoring is available, selection of
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6 | vasoactive therapy should be driven by individual patient physiology.
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9 | No pediatric data identify when shock becomes “fluid-refractory” and, thus, to
10 | guide when to start vasoactive infusions. However, excessive fluid resuscitation can
11 | lead to fluid overload, which has been associated with increased mortality in critically ill
12 | children [\(228\)](#)~~(223)~~. A trial comparing a fluid-sparing strategy with early initiation of
13 | vasoactive medications compared to a fluid-liberal resuscitation strategy is currently
14 | ongoing (SQUEEZE trial, Clinical Trials.gov NCT03080038). Until further data are
15 | available, we consider it reasonable to begin vasoactive infusions after 40-60 mL/kg of
16 | fluid resuscitation if the patient continues to have evidence of abnormal perfusion.
17 |

18 | Additional fluid resuscitation may be concurrently administered if the patient
19 | demonstrates physiologic improvement following each fluid bolus and without signs of
20 | fluid overload.
21 |

22 | All vasoactive agents, including norepinephrine, may be initiated through
23 | peripheral venous (or intraosseous, if in place) access if central venous access is not
24 | readily available to avoid delays in therapy [\(229, 230\)](#)~~(224, 225)~~. However, central
25 | venous access should be obtained as soon as reasonably practicable. In our practice,
26 | 82% of panel members reported at least sometimes administering the initial vasoactive
27 | infusion peripherally if central venous or intraosseous access was not readily available,
28 | particularly in the emergency department or other non-PICU settings. Most panelists
29 | preferred epinephrine or dopamine to norepinephrine if peripheral infusion was needed.
30 | Although epinephrine or norepinephrine is the preferred first-line medication, dopamine
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4 | may be substituted as the first-line vasoactive infusion, administered either peripherally
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6 | or centrally, if neither epinephrine nor norepinephrine is readily available.
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11 | **32. We suggest either adding vasopressin or further titrating catecholamines in**
12 | **children with septic shock who require high-dose catecholamines (weak**
13 | **recommendation, low quality of evidence).**
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18 | **Remarks: No consensus was achieved on the optimal threshold for initiating**
19 | **vasopressin. Therefore, this decision should be made according to individual**
20 | **clinician preference.**
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24 | **Rationale:** Vasopressin-receptor agonists (vasopressin or terlipressin) have been
25 |
26 | studied in three RCTs in children ([Supplemental Table 12](#)). Vasopressin was
27 |
28 | compared with saline in one study in children with vasodilatory shock ([231](#))(~~[226](#)~~) and in
29 |
30 | one study of children with severe lung disease ([232](#))(~~[227](#)~~). Terlipressin was compared
31 |
32 | with usual care in children with septic shock ([233](#))(~~[228](#)~~). The mortality rate (RR, 1.14
33 |
34 | [0.80-1.62]) and ischemic events (RR, 1.56; 95% CI, 0.41-5.91) were higher
35 |
36 | vasopressin/terlipressin. There were fewer vasoactive-free days with vasopressin
37 |
38 | (median 25.2d in AVP (IQR 0.0-28.3), median 27.5d in control (IQR 23.1-28.9). In six
39 |
40 | RCTs in adults, renal replacement therapy was required less often with vasopressin
41 |
42 | (RR, 0.74 95% CI 0.51-1.08) ([234](#))(~~[229](#)~~). Weighing the benefit of avoiding renal
43 |
44 | replacement therapy against the potential harm from ischemic events and the non-
45 |
46 | significant difference in mortality, we suggest that vasopressin may be added or
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48 | catecholamines may be further titrated in children on high doses of catecholamines.
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4 | **33. We were unable to issue a recommendation about adding an inodilator in**
5 | **children with septic shock and cardiac dysfunction despite other vasoactive**
6 | **agents. However, in our practice, we sometimes use inodilators in children**
7 | **with septic shock and evidence of persistent hypoperfusion and cardiac**
8 | **dysfunction despite other vasoactive agents.**
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15 | **Rationale:** There are no RCTs of inodilators (including milrinone, dobutamine, or
16 | levosimendan) in children with septic shock with persistent hypoperfusion and cardiac
17 | dysfunction. A report of two children described improvement in cardiac output with
18 | addition of inodilators [\(235\)](#)~~(230)~~. A case series of 10 children with meningococcal
19 | septic shock treated with milrinone described improved core-to-peripheral temperature
20 | gradient, with stable blood pressure and no change in acidosis [\(236\)](#)~~(231)~~. These data
21 | were not sufficient to formulate a recommendation. However, in our practice, 77% of
22 | panel members reported at least sometimes using inodilators in children with septic
23 | shock who had evidence of persistent hypoperfusion and cardiac dysfunction despite
24 | other vasoactive agents, typically in a PICU with advanced hemodynamic monitoring
25 | available.
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42 | **G. VENTILATION**

43 | **34. We were unable to issue a recommendation about whether to intubate**
44 | **children with fluid-refractory, catecholamine-resistant septic shock.**
45 | **However, in our practice, we commonly intubate children with fluid-**
46 | **refractory, catecholamine-resistant septic shock without respiratory failure.**
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56 | **Rationale:** There are no RCTs and/or observational studies of children receiving early
57 | intubation for refractory shock without respiratory failure compared to delayed or no
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4 | intubation for the same condition, nor is there suitable indirect evidence to substantiate
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6 | a formal recommendation. However, it is well understood that a high metabolic demand
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8 | from refractory shock typically indicated by progressive lactic acidemia and end-organ
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10 | dysfunction can be, at least in part, mitigated by early invasive mechanical ventilation
11 |
12 | even without clinical symptoms of acute pulmonary edema or respiratory failure ([237-](#)
13 |
14 | [239](#))([236-238](#)). Moreover, chest radiograph findings can “lag” behind clinical
15 |
16 | deterioration ([240, 241](#))([239, 240](#)) such that patients with refractory shock and a
17 |
18 | “negative” chest radiograph may still progress toward more overt acute respiratory
19 |
20 | distress syndrome (ARDS). Lung ultrasound may provide an alternative tool to chest
21 |
22 | radiograph in detecting lung pathology, but its utility to identify which sepsis patients
23 |
24 | may benefit from early mechanical ventilation is not yet clear([242-245](#))([241-244](#)). For
25 |
26 | these reasons, 48% of panel members often or always and 35% sometimes intubate
27 |
28 | children with fluid-refractory, catecholamine-resistant septic shock even in the absence
29 |
30 | of clear respiratory failure, while 17% rarely or never do so. Of note, when intubating,
31 |
32 | caution should be exercised to avoid worsening hypotension or precipitating cardiac
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34 | arrest as medications used for inducing anesthesia at the time of tracheal intubation,
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36 | along with conversion from spontaneous breathing to use of positive pressure
37 |
38 | ventilation, may result in a transient deterioration in patient hemodynamics. The panel
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40 | does recognize that in some settings, invasive mechanical ventilation may not be
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42 | available or feasible—or may even be detrimental. In these instances, transport of the
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44 | patient to a higher level of care can be life-saving.
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4 | **35. We suggest not to use etomidate when intubating children with septic**
5 | **shock or other sepsis-associated organ dysfunction (weak**
6 | **recommendation, low quality of evidence).**
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11 | **Rationale:** Etomidate is a short-acting intravenous anesthetic agent that has been
12 | used for inducing anesthesia and sedation for tracheal intubation in patients with
13 | unstable hemodynamics. However, concerns regarding the drug's effect on adrenal
14 | function have been raised in adult studies. No RCTs exist in critically ill children with or
15 | without sepsis comparing etomidate to another anesthesia/sedative regimen. Two
16 | observational studies included children. One study from 1984 [\(246\)](#)~~(245)~~ enrolled
17 | acutely injured adults and children (44 intubated with etomidate versus 90 intubated
18 | with a benzodiazepine and opioid). A more recent study [\(247\)](#)~~(246)~~ enrolled children
19 | with meningococcal sepsis or septic shock with 23 intubated with etomidate as
20 | compared to 37 intubated with any other combination of sedatives. While caution must
21 | be taken given the small sample size, each of these studies reported higher mortality
22 | after use of etomidate (pooled OR 4.51, 95% CI 1.82, 11.16) **(Supplemental Table**
23 | **813)**. In addition, den Brinker et al [\(247\)](#)~~(246)~~ reported a significant association of
24 | etomidate with adrenal insufficiency, with cortisol to adrenocorticotropin hormone
25 | (ACTH) ratios decreasing by 83% after etomidate exposure. Indirect evidence is
26 | available from 4 RCTs in adults [\(248-251\)](#)~~(247-250)~~. In the largest of these trials, Jabre
27 | et al [\(251\)](#)~~(250)~~ compared 234 critically ill adults intubated with etomidate to 235
28 | intubated with an alternative medication regimen and found higher adrenal insufficiency
29 | in the etomidate group (OR 1.79, 95% CI 1.37, 2.36). Pooled odds of all 4 adult studies
30 | was 1.89 (95% CI 1.47, 2.44) with all studies suggesting significantly increased risk of
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4 adrenal insufficiency after etomidate administration. Importantly, this effect was seen
5 even after 1 dose of etomidate. Unfortunately, there is no conclusive evidence to
6 recommend an optimal alternative induction agent to etomidate, though ketamine and
7 fentanyl are routinely available and can offer favorable hemodynamic profiles in the
8 setting of shock.
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19 **36. We suggest a trial of non-invasive mechanical ventilation (over invasive**
20 **mechanical ventilation) in children with sepsis-induced pediatric ARDS**
21 **(PARDS) without a clear indication for intubation and who are responding to**
22 **initial resuscitation (weak recommendation, very low quality of evidence)**
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28 **Remarks: When non-invasive mechanical ventilation is initiated, clinicians should**
29 **carefully and frequently re-evaluate the patient's condition.**
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33 **Rationale:** Non-invasive mechanical ventilation with continuous positive airway
34 pressure ventilation (CPAP) or bi-level positive airway pressure ventilation (BiPAP) may
35 allow for decreased work of breathing and improved oxygenation in the face of sepsis-
36 induced PARDS. Therefore, it is possible to avoid intubation in sepsis patients who are
37 identified early with mild PARDS physiology and no evidence of advancing end-organ
38 dysfunction. However, no RCTs in either critically ill children or children with sepsis-
39 induced PARDS compare the effect of non-invasive ventilation to invasive mechanical
40 ventilation on clinical outcomes. Observational studies have tested whether non-
41 invasive mechanical ventilation could mitigate the need for invasive mechanical
42 ventilation but none specifically focused on children with sepsis [\(252-258\)](#)~~(251-257)~~. We
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4 | non-invasive mechanical ventilation with mortality in a general PICU population ([254](#),
5 | [256, 259](#))(~~[253, 255, 258](#)~~). Using unadjusted estimates pooled from the data across all 3
6 |
7 | studies, we found non-invasive ventilation to be associated with a decreased risk of
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9 | death (RR 0.21, 95% CI 0.09, 0.47) (**Supplemental Figure 35**). One additional RCT in
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11 | immunocompromised children with acute respiratory dysfunction did not find that early
12 |
13 | non-invasive ventilation reduced intubation compared to standard care, but the trial was
14 |
15 | small (42 participants) due to low consent and overall slow recruitment and the direct
16 |
17 | relevance to children with sepsis-induced PARDS without a clear indication for
18 |
19 | intubation and who are responding to initial resuscitation was not clear ([260](#))(~~[259](#)~~).
20 |
21 | Thus, it is reasonable to try non-invasive mechanical ventilation in children with sepsis-
22 |
23 | induced PARDS who do not have a clear indication for intubation. However, non-
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25 | invasive ventilation should be reserved for children with sepsis who are responding to
26 |
27 | initial resuscitation, do not have evidence for ongoing or worsening end-organ
28 |
29 | dysfunction, and in whom close monitoring and frequent re-evaluation can be ensured
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31 | ([255, 257, 261](#))(~~[254, 256, 260](#)~~). This recommendation for children with sepsis-induced
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33 | PARDS aligns with the 2015 PALICC ([262](#))(~~[261](#)~~) and 2017 Pediatric Mechanical
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35 | Ventilation Consensus Conference (PEMVECC)([263](#))(~~[262](#)~~) guidelines.
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48 | **37. We suggest using high positive end-expiratory pressure (PEEP) in children**
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50 | **with sepsis-induced PARDS (weak recommendation, very low quality of**
51 |
52 | **evidence)**
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55 | **Remarks: The exact level of high PEEP has not been tested or determined in**
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57 | **PARDS patients. Some RCTs and observational studies in PARDS have used and**
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4 | **advocated for use of the ARDS-network PEEP to fractional inspired oxygen (FiO₂)**
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6 | **grid though adverse hemodynamic effects of high PEEP may be more prominent**
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8 | **in children with septic shock.**
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11 | **Rationale:** PEEP helps to prevent alveolar collapse, restore end-expiratory lung
12 | volume, and improve mean airway pressures, all of which help to improve adequate
13 | oxygenation in PARDS patients and minimize unnecessary use of high FiO₂. Adult
14 | ARDS patients have been successfully managed with judicious and strict application of
15 | a PEEP/FiO₂ grid, initially implemented in the ARDS-network ARMA trial [\(264\)](#)~~(263)~~.
16 | This grid has been applied in children with PARDS enrolled in RCTs [\(265\)](#)~~(264)~~, but a
17 | pediatric-specific PEEP/FiO₂ grid has not been determined or validated. In 2017, a
18 | multi-center observational study by the Collaborative Pediatric Critical Care Research
19 | Network reported that pediatric critical care clinicians almost uniformly limit PEEP to 10
20 | cm H₂O irrespective of oxygenation and FiO₂ [\(266\)](#)~~(265)~~. This is in contrast to the
21 | PEMVECC [\(263\)](#)~~(262)~~ and PALICC (24) recommendations for use of PEEP in excess of
22 | 15 cm H₂O for severe PARDS patients. Our panel reviewed several observational
23 | studies of PARDS patients, all published since 2007, each including 12-30% sepsis-
24 | induced PARDS [\(266-278\)](#)~~(265-277)~~. The largest, a multicenter study by Khemani et al
25 | [\(278\)](#)~~(277)~~, evaluated 1,134 PARDS patients of whom 26% were managed with lower
26 | PEEP relative to ARDSnet protocol and experienced greater mortality than those
27 | managed in accordance with a higher PEEP strategy as recommended by the ARDSnet
28 | PEEP/FiO₂ grid **[\(Supplemental Table 14\)](#)**. After adjustment for relevant co-morbidities,
29 | pediatric patients managed with a PEEP strategy at or above that recommended by the
30 | ARDSnet low PEEP/FiO₂ grid had a decreased odds of death compared to children
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4 managed with PEEP lower than that recommended by the ARDSnet low PEEP/FiO₂
5 grid (adjusted OR 0.50, 95% CI 0.31-0.81).
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9 The panel concluded that PEEP levels >10 cm H₂O may be necessary with
10 progressive hypoxemia, with the precise amount of “high” PEEP carefully titrated for
11 each individual while attending to the potential adverse hemodynamic effects of
12 increasing intrathoracic pressure in children with septic shock. Therefore, although the
13 optimal approach to setting PEEP has not yet been determined in children with PARDS,
14 carefully increasing PEEP for children with sepsis-induced PARDS who require FiO₂
15 exceeding 60% and/or exhibit ongoing hypoxemia is reasonable, rather than continuing
16 to manage such children with a low- or moderate- PEEP strategy of ≤10 cm H₂O.
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31 **38. We cannot suggest for or against the use of recruitment maneuvers in**
32 **children with sepsis-induced PARDS and refractory hypoxemia.**
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35 **Remarks: If a recruitment maneuver is considered, the use of a stepwise,**
36 **incremental and decremental PEEP titration maneuver is preferred over sustained**
37 **inflation techniques that have not been optimized through direct testing in**
38 **PARDS patients. All PARDS patients must be carefully monitored for tolerance of**
39 **the maneuver.**
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48 **Rationale:** ARDS is characterized by decreased lung compliance, risk for atelectasis,
49 and increased intrapulmonary shunt. Recruitment maneuvers have been used in both
50 children and adults temporarily to increase transpulmonary pressure to recruit lung units
51 with the goal of improving both oxygenation and ventilation. Most recruitment
52 maneuvers include either sustained inflation or a step-wise incremental or decremental
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4 | PEEP titration methodology. However, many clinicians and researchers remain
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6 | concerned that the optimal strategy for lung recruitment has not been determined and
7 |
8 | injudicious implementation of recruitment maneuvers can result in hemodynamic
9 |
10 | compromise [\(279\)](#)~~(278)~~, hypercarbia [\(280\)](#)~~(279)~~, and/or ventilator-induced lung injury
11 |
12 | [\(281\)](#)~~(280)~~. PEMVECC did not recommend use of recruitment maneuvers in children,
13 |
14 | citing an overall lack of evidence in this area [\(263\)](#)~~(262)~~. In contrast, the 2015 PALICC
15 |
16 | provided a weak recommendation in favor of recruitment maneuvers with prioritization
17 |
18 | of a slow stepwise incremental and decremental PEEP method (24).
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23 | Two observational studies are potentially informative about use of recruitment
24 |
25 | maneuvers in children with sepsis-induced PARDS [\(268, 269\)](#)~~(269, 270)~~.

26 | **(Supplemental Table 4015.)** First, Boriosi et al [\(282\)](#)~~(281)~~ enrolled 21 children with
27 |
28 | lung injury, of whom 66% had sepsis, and used incremental PEEP recruitment
29 |
30 | maneuvers. Patients experienced improved oxygenation as measured by both the
31 |
32 | partial pressure of oxygen in arterial blood to FiO₂ ratio (PaO₂/FiO₂ or P/F) and alveolar-
33 |
34 | to-arterial oxygen (A-a O₂) gradient for the 4 hours after recruitment. Second, Duff et al
35 |
36 | [\(283\)](#)~~(282)~~ enrolled 32 children and used the sustained inflation technique, which also
37 |
38 | resulted in improved oxygenation for the ensuing 6 hours. However, neither study tested
39 |
40 | the association of recruitment maneuvers with clinical outcomes, such as ventilator days
41 |
42 | or mortality. Consequently, despite the potential for benefit for some patients coupled
43 |
44 | with the possibility of harm [\(284, 285\)](#)~~(283, 284)~~, insufficient data do not allow us to
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46 | recommend either for or against recruitment maneuvers in sepsis-induced PARDS
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48 | patients at this time.
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4 | **39. We suggest a trial of prone positioning in children with sepsis and severe**
5 | **PARDS (weak recommendation, low quality of evidence)**
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9 | **Remarks: Research trials in adults with ARDS and children with PARDS have**
10 | **emphasized prone positioning for at least 12 hours per day, as tolerated.**
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13 | **Rationale:** Prone positioning almost uniformly improves oxygenation in adults with
14 | ARDS and children with PARDS. While the exact mechanisms continue to be
15 | elucidated, prone position has been shown to recruit areas of collapsed, de-recruited
16 | lung with resultant improved elastance, decreased lung stress and strain, and improved
17 | functional residual capacity [\(286\)](#)~~(285)~~. Given that pulmonary perfusion is thought to be
18 | consistent both dorsally and ventrally, an improvement in lung aeration can be met with
19 | continued perfusion, thereby reducing ventilation-perfusion mismatching [\(287\)](#)~~(286)~~.
20 | Most recent RCTs in adults support use of prone positioning as a potentially life-saving
21 | management strategy [\(Supplemental Table 16\)](#), especially in those meeting severe
22 | ARDS criteria (i.e., P/F <150 mmHg) [\(288\)](#)~~(287)~~. This benefit is seen particularly in
23 | patients who are positioned for prolonged periods of time, most commonly reported as
24 | 12-20 hours per day. Two pediatric RCTs tested the use of prone positioning in PARDS
25 | patients [\(265, 289\)](#)~~(264, 288)~~. Pooled analyses of these two studies yielded a RR of
26 | 0.99 (95% CI 0.36, 2.69) for mortality in prone positioning as compared to supine
27 | positioning for this patient population [\(Supplemental Table 16, Figure 6\)](#). Importantly,
28 | no serious adverse events were reported in these trials, although the prone positioning
29 | methodology was protocolized in each with particular attention to avoid accidental
30 | endotracheal extubation and pressure injury. PALICC (24) did not recommend routine
31 | use of prone positioning in PARDS patients but suggested its consideration in severe
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4 | PARDS. The panel noted that the National Institutes of Health (NIH) has approved and
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6 | funded an international RCT of prone positioning in severe PARDS (ClinicalTrials.gov
7 |
8 | identifier NCT02902055).
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14 | **40. We recommend against the routine use of inhaled nitric oxide (iNO) in all**
15 |
16 | **children with sepsis-induced PARDS (strong recommendation, low quality of**
17 |
18 | **evidence).**

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21 | **41. We suggest using iNO as a rescue therapy in children with sepsis-induced**
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23 | **PARDS and refractory hypoxemia after other oxygenation strategies have**
24 |
25 | **been optimized (weak recommendation, moderate quality of evidence)**

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27 |
28 | ***Rationale:*** The presumptive mechanism of sepsis-induced PARDS involves alveolar
29 | epithelial injury, vascular endothelial injury, and activation of inflammatory, fibrosis, and
30 | coagulation cascades. As such, PARDS is not a disease process primarily of pulmonary
31 | arterial hypertension, the therapeutic target of iNO therapy, and so is not recommended
32 | for routine use in children with sepsis-associated PARDS. Nonetheless, many PARDS
33 | patients have co-morbidities that include risk for pulmonary hypertension (e.g., chronic
34 | lung disease after prematurity, congenital heart disease after repair or palliation) or
35 | clinical features, such as acidemia and hypoxemia, that ~~Further, many manifestations~~
36 | ~~of PARDS, especially severe PARDS, will increase endogenous pulmonary arterial~~
37 | ~~pressures, including acidosis and hypoxemia, thus increasing shunt fraction.~~ Thus,
38 | inhaled nitric oxide therapy may be considered in children with documented pulmonary
39 | hypertension or severe right ventricular dysfunction (241, 290). ~~Inhaled nitric oxide~~
40 | ~~therapy (REF).~~ Such use of iNO in sepsis must be balanced against its lack of
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4 ~~availability or high cost in many areas of the world and, that is not available in many~~
5 ~~parts of the world and, in others, is extremely costly. In the US, FDA approval for iNO~~
6 ~~treatment is restricted to use in patients with primary pulmonary hypertension. Finally,~~
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11 once in place, iNO use carries a potential patient safety consideration as inadvertent
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13
14 and abrupt discontinuation of the therapy can result in a rapid and potentially life-
15
16 threatening rebound pulmonary hypertensive crisis.
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18
19 Several small RCTs ~~(291-293)(289-291)~~ and observational studies have
20
21 described significant improvement in oxygenation after iNO therapy ~~(294)(292)~~. Many,
22
23 but not all, of these studies include patients with sepsis ~~(292, 293, 295-298)(290, 291,~~
24
25 ~~293-296)~~, and few analyze longer term, clinically relevant outcomes such as mortality. A
26
27 2016 Cochrane review indicated no mortality benefit from iNO administration (RR 0.78,
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29 95% CI 0.51, 1.18) in 3RCTs ~~(299)(297)~~. Our analysis of two recent observational
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31 studies, one conducted in children on ECMO and another in children with severe
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33 PARDS, respectively, suggest possible increased mortality risk ~~(296, 298)(294, 296)~~,
34
35 whereas one RCT of 55 PARDS patients indicated improved duration of mechanical
36
37 ventilation in PARDS survivors ~~(293)(291)~~ (**Supplemental Table 17, Supplemental**
38
39 **Figure 4-7-Table 12**). Taken together, these data do not support *routine* use of iNO in
40
41 all children with sepsis-induced PARDS but do raise the potential for benefit as an
42
43 emergency rescue therapy for severe, sepsis-induced PARDS with refractory
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45 hypoxemia after other oxygenation strategies have been optimized. Emergency rescue
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47 use of iNO may allow time to realize benefit from other therapies, such as lung
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49 recruitment, or provide a bridge to ECMO or another intervention. However, when iNO
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51 is used, we agree with the PALICC recommendation that “assessment of benefit must
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4 | be undertaken promptly and serially to minimize toxicity and to eliminate continued use
5 | without established effect” (24). These recommendations align with the 2004 guidelines
6 | for use of iNO therapy in neonates and children issued by the European Society for
7 | Pediatric and Neonatal Intensive Care [\(300\)](#)~~(298)~~, PALICC guidelines (24), and a 2017
8 | Cochrane review [\(294\)](#)~~(292)~~ as no relevant change in evidence has become available.
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19 | **42. We were unable to issue a recommendation to use high-frequency**
20 | **oscillatory ventilation (HFOV) versus conventional ventilation in children with**
21 | **sepsis-induced PARDS. However, in our practice, there is no preference to**
22 | **use or not use HFOV in patients with severe PARDS and refractory hypoxia.**
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28 | **Rationale:** HFOV provides a sustained mean airway pressure with superimposed high
29 | frequency, pendelluft-type, oscillatory breaths that may improve oxygenation in patients
30 | with moderate-to-severe lung disease while minimizing barotrauma, volutrauma, and
31 | atelectrauma. However, the most efficacious timing of application, optimal settings, and
32 | ideal population of patients likely to benefit have not been well established. HFOV may
33 | be difficult to apply effectively in centers with little experience, and is not universally
34 | available. Despite these practical limitations, both PALICC (24) and PEMVECC
35 | [\(263\)](#)~~(262)~~ endorsed cautionary use of HFOV as an alternative type therapy in patients
36 | with severe PARDS. In our panel, clinicians who use versus those who do not use
37 | HFOV in patients with severe PARDS and refractory hypoxia were nearly evenly
38 | distributed.
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54 | Application of HFOV in adult ARDS patients has yielded concerning results due to a
55 | potentially increased mortality observed in the adult OSCILLATE RCT [\(301\)](#)~~(299)~~ and a
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4 | neutral result in the adult OSCAR RCT [\(302\)](#)~~(300)~~. Pediatric data include 2
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6 | observational studies with a non-HFOV control group and 3 randomized trials. In the
7 |
8 | two observational studies, oxygenation improved with HFOV relative to conventional
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10 | ventilation but there was a non-significant trend toward increased mortality (Guo et al:
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12 | 34.6% versus 22.7%, adjusted OR 2.74, 95% CI 0.52, 14.6; Bateman et al: 25% versus
13 |
14 | 17%, adjusted OR 1.28, 95% CI 0.92, 1.79)[\(303, 304\)](#)~~(301, 302)~~. Among three small
15 |
16 | RCTs, however, a trend toward reduced mortality in those managed with HFOV was
17 |
18 | observed (pooled RR 0.77, 95% CI 0.43, 1.36)[\(305-307\)](#)~~(303-305)~~. A large, multi-
19 |
20 | center, international RCT of HFOV compared to conventional mechanical ventilation in
21 |
22 | severe PARDS patients, including children with and without sepsis, is underway and will
23 |
24 | seek to address many of these issues ([www.clinicaltrials.gov/ NCT02902055](http://www.clinicaltrials.gov/NCT02902055)).
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33 | **43. We suggest using neuromuscular blockade in children with sepsis and**
34 | **severe PARDS (weak recommendation, very low quality of evidence)**
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36 | **Remarks: The exact duration of neuromuscular blockade to use in severe PARDS**
37 | **patients has not been determined to date. Most of the adult RCT data and**
38 | **pediatric observational data support treatment for 24-48 hours after ARDS onset.**
39 |
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41 | **Rationale:** Indirect evidence from 3 adult RCTs [\(308-310\)](#)~~(306-308)~~ found that early
42 |
43 | use of neuromuscular blocking agents (NMBAs) for up to 48 hours in adults with severe
44 |
45 | ARDS, defined as PaO₂/FiO₂ ratio <150 mmHg, improved 90-day survival and
46 |
47 | shortened duration of mechanical ventilation without increasing muscle weakness. In a
48 |
49 | multi-center double-blind RCT [\(310\)](#)~~(308)~~, 340 patients with early severe ARDS,
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51 | meeting criteria within 48 hours, were randomized to receive either cisatracurium
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4 | besylate or placebo once adequately sedated. After adjustment for baseline PaO₂/FiO₂,
5 |
6 | plateau pressure, and the Simplified Acute Physiology Score, the cisatracurium group
7 |
8 | had a hazard ratio for death at 90 days of 0.68 (95% CI 0.48, 0.98) compared to the
9 |
10 | placebo group. Early use of NMBA was also associated with decreased organ system
11 |
12 | dysfunction, less air leak, and a decreased pro-inflammatory response [\(311\)](#)~~(309)~~.
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15 | These findings remained consistent when combined with earlier smaller studies from
16 |
17 | the same group of investigators in a meta-analysis. However, a more recent adult trial of
18 |
19 | early neuromuscular blockade in those with moderate to severe ARDS was stopped for
20 |
21 | futility at the second interim analysis (enrollment of 1006 patients) with a 90-day
22 |
23 | mortality difference of 42.5% in the intervention limb versus 42.8% in the control limb. In
24 |
25 | this study, the intervention group received continuous cisatracurium and deep sedation
26 |
27 | for 48 hours compared to the control arm that received lighter sedation targets
28 |
29 | (Richmond Agitation Scale of 0 to -1). Both limbs received low tidal volume ventilation
30 |
31 | with high PEEP strategy. Notably, only 13.8% of patients enrolled in ROSE had non-
32 |
33 | pulmonary sepsis as a primary diagnosis.
34 |
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36 |
37 | In pediatrics, there are no prospective data regarding the use of NMBA in
38 |
39 | PARDS (with or without sepsis), although there is an ongoing pediatric trial in the
40 |
41 | Netherlands (Clinical Trials.Gov NCT02902055). In one large retrospective study of 317
42 |
43 | children with PARDS, of whom 23% experienced sepsis-induced PARDS [\(312\)](#)~~(340)~~,
44 |
45 | mortality was lower in those children treated with neuromuscular blockade (8.8% versus
46 |
47 | 17.7%). However, duration of mechanical ventilation was longer in the treatment group
48 |
49 | and proportion with neuromuscular weakness was not assessed (**Supplemental Table**
50 |
51 | **[4318](#)**).
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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 [\(314\)](#)~~(324)~~ 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

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4 | under-appreciated in critically ill patients, but ~~can~~ contribute to worse outcomes
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6 | [\(322\)](#)~~(329)~~.

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9 | At least one pediatric [\(323\)](#)~~(330)~~ and several adult [\(324\)](#)~~(331)~~ interventional trials
10 | examining adjunctive corticosteroids for septic shock have concluded that this drug
11 | class hastens resolution of shock. Of the four adult, high-quality contemporary RCTs,
12 | two reported a ~~benefit in terms of~~ mortality reduction and two did not [\(325-329\)](#)~~(332-~~
13 | [336\)](#). A recent meta-analysis of 42 RCTs including 9,969 adults and 225 children
14 | ~~(overall mean age 49.5 years)~~ with sepsis found that corticosteroids possibly result in a
15 | small reduction in short-term mortality (RR 0.93, 95% CI 0.84, 1.03), long-term mortality
16 | (0.94, 95% CI 0.89, 1.00), faster resolution of shock, and shorter LOS, while also
17 | possibly increasing the risk of neuromuscular weakness (RR 1.21, 95% CI 1.01, 1.52)
18 | [\(330\)](#)~~(337)~~. Despite a weak recommendation to treat sepsis with hydrocortisone based
19 | on the findings noted in the overall meta-analysis [\(331\)](#)~~(338)~~, ~~the no improvements in~~
20 | ~~mortality were reported in any of the published pediatric RCTs, and the~~ pediatric studies
21 | enrolled ~~a combined~~ small numbers of subjects, reported inconsistent conclusions, ~~and~~
22 | had methodologic limitations, ~~and did not demonstrate an overall mortality reduction~~
23 | [\(323, 332-334\)](#)~~(330, 339-341)~~ (Supplemental Table [1519](#)).

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

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4 stay among 193 children who received and 284 who did not receive open-labeled
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6 corticosteroids database facilitated examination of the role of adjunctive corticosteroids
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8 on outcomes in pediatric septic shock (336)(343). Despite the post hoc analysis, Age,
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10 sex, PRISM-III scores, baseline number of dysfunctional organs, and baseline Pediatric
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12 Overall Performance Category scores did not differ between corticosteroid-treated and
13
14 corticosteroid non-treated groups. In this trial designed to examine the potential benefit
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16 of adjunctive activated protein C in pediatric sepsis, 193 subjects received adjunctive
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18 corticosteroids (mostly for septic shock) and 284 did not. Age, sex, PRISM-III scores,
19
20 baseline number of dysfunctional organs, and baseline Pediatric Overall Performance
21
22 Category scores did not differ between corticosteroid treated and corticosteroid non-
23
24 treated groups. Outcomes of mortality, duration of mechanical ventilation and
25
26 vasoactive-inotropic support, and PICU stay did not differ between the two groups.
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34 Several pediatric and adult ~~retrospective and prospective~~ studies have attempted
35
36 to use random cortisol and/or cosyntropin-stimulated cortisol serum concentrations to
37
38 identify which patients with septic shock would may benefit from hydrocortisone therapy,
39
40 but reliable cutoffs have not yet to be been clearly identified. ~~Many issues have been~~
41
42 ~~raised with regard to assessment of adrenal adequacy in this setting,~~
43
44 ~~including~~ Challenges relate to variability in: 1) the cortisol assay itself; 2) cortisol
45
46 metabolism (11-beta-hydroxysteroid dehydrogenase) during sepsis; 3) corticosteroid-
47
48 binding globulin concentrations; and 4) multiple tissue (e.g., elastase, anti-glucocorticoid
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50 compounds) and cellular (e.g., glucocorticoid receptor) factors. Therefore, use of
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52 random cortisol or stimulation tests to guide corticosteroid prescription in children with
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54 septic shock cannot be recommended as this time. However, for ~~in~~ any patient ~~where~~
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4 ~~the clinician is concerned about the presence of~~ with a clinical concern for primary
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6 adrenal insufficiency (e.g., a patient with significant and unexplained hypoglycemia,
7
8 hyponatremia, and/or hyperkalemia), a high-dose cosyntropin-stimulation test should be
9
10 performed. Interpretation should focus on the baseline serum ACTH concentration
11
12 (above normal indicating primary adrenal insufficiency) and the 60-minute stimulated
13
14 serum cortisol concentration (<18 µg/dL indicating primary adrenal insufficiency)
15
16 (340)(347).

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21 In summary, no high-quality investigations currently support or refute the routine
22
23 use of adjunctive corticosteroids for pediatric septic shock or other sepsis-associated
24
25 organ dysfunction. At the time of this publication, an RCT is in progress to examine the
26
27 potential risks and benefits of adjunctive hydrocortisone for fluid and vasoactive-
28
29 inotropic recalcitrant septic shock in children. However, this uncertainty does not apply
30
31 to ~~for~~ children presenting with septic shock or other sepsis-associated organ dysfunction
32
33 who also have acute or chronic corticosteroid exposure, hypothalamic-pituitary-adrenal
34
35 axis disorders, congenital adrenal hyperplasia or other corticosteroid-related
36
37 endocrinopathies, and or have recently been treated ~~treatment~~ with ketoconazole or
38
39 etomidate, there is no disagreement that for whom prescription of stress-dose
40
41 hydrocortisone is indicated, with or without evaluation of the adrenal axis (341)(348).
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51 I. ENDOCRINE AND METABOLIC

52
53 **46. We recommend against insulin therapy to maintain a blood glucose target**
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55 **at or below 140 mg/dL (7.8 mmol/L) (strong recommendation, moderate**
56
57 **quality of evidence).**
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4 | **47. We were unable to issue a recommendation regarding what blood glucose**
5 | **range to target for children with septic shock or other sepsis-associated**
6 | **organ dysfunction. However, in our practice, there was consensus to target**
7 | **blood glucose levels below 180 mg/dL (10 mmol/L) but there was not**
8 | **consensus about the lower limit of the target range.**
9 |

10 | **Rationale:** While hyperglycemia has been associated with poor outcomes in numerous
11 | studies of critically ill children and adults, three prospective multicenter randomized
12 | clinical trials of glucose control to a low target range (including 50-80, 70-100, 72-126,
13 | 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
14 | clinical benefit in children [\(342-344\)](#)~~(377-379)~~ **[\(Supplemental Table 20\)](#)**. One single-
15 | center RCT did show substantial mortality benefit, but there was a high rate of severe
16 | hypoglycemia and the higher target range cohort had substantially higher blood glucose
17 | levels than those used in the other multicenter RCTs [\(345\)](#)~~(380)~~. A trial involving
18 | children with burn injuries, a unique PICU population, demonstrated no mortality benefit,
19 | but did find a significant reduction in morbidity [\(346\)](#)~~(384)~~. Notably, all trials included
20 | sepsis patients but none targeted them exclusively. Meta-analyses of all published
21 | prospective trials in children have shown no clinical benefits overall, but showed a
22 | substantially higher risk of hypoglycemia when using insulin therapy to maintain a
23 | glucose target below 140 mg/dL (7.8mmol/L) [\(347, 348\)](#)~~(382, 383)~~. Even brief episodes
24 | of severe hypoglycemia during septic shock in children may be a risk factor for poor
25 | long-term developmental outcomes [\(349-352\)](#)~~(384-387)~~.

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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

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4 mg/dL (7.8-10.0 mmol/L) is extremely low. There are, however, no direct comparisons
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7 | between treatment to <180 mg/dL (10.0 mmol/L) and no treatment. Therefore, evidence
8 |
9 | cannot definitively guide this therapeutic target. However, given that the guidelines for
10 |
11 | adults recommend an upper limit of 180 mg/dL (10 mmol/L) and given the lack of harm
12 |
13 | demonstrated in the pediatric trials with those targets, treating children with septic shock
14 |
15 | or other sepsis-associated organ dysfunction with intravenous insulin with a goal upper
16 |
17 | blood glucose target of 180 mg/dL (10 mmol/L) is reasonable. The lower target, i.e., the
18 |
19 | glucose concentration below which insulin infusion should be discontinued, has also not
20 |
21 | been specifically studied, but is reasonable to set at 140-150 mg/dL (7.8-8.3 mmol/L),
22 |
23 | based on similar principles. In a survey of our panel members, 32.5% always or often
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25 | and 17.5% sometimes target glucose levels between 140 and 180 mg/dL. Regardless of
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27 | the glucose target, the overriding goal during insulin therapy should be avoidance of
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29 | hypoglycemia.
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38 | **48. We were unable to issue a recommendation as to whether to target normal**
39 | **blood calcium levels in children with septic shock or sepsis-associated**
40 | **organ dysfunction. However, in our practice, we often target normal**
41 | **calcium levels for children with septic shock requiring vasoactive infusion**
42 | **support.**
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50 | **Rationale:** Calcium has an essential role in nearly all cellular processes, including
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52 | myocardial contractility and vasomotor tone. As such, intracellular and circulating levels
53 |
54 | of calcium are tightly regulated. During septic shock, derangements in calcium
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56 | regulation frequently occur in critically ill adults and children. However, a systematic
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4 | review of adult literature found no evidence to support treating hypocalcemia of critical
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6 | illness [\(353\)](#)~~(420)~~. Calcium supplementation may actually worsen organ dysfunction and
7 |
8 | is correlated with adverse outcomes in critically ill adult patients receiving PN
9 |
10 | [\(354\)](#)~~(421)~~. Although the prevalence of hypocalcemia in critically ill children has been
11 |
12 | reported to be up to 75% and is associated with organ dysfunction [\(355\)](#)~~(422)~~, no
13 |
14 | studies in children with septic shock have investigated the effect of calcium
15 |
16 | supplementation to treat hypocalcemia. However, in our practice, 65% of panel
17 |
18 | members always or often and 20% sometimes target normal calcium levels with
19 |
20 | parenteral calcium administration in children with septic shock requiring vasoactive
21 |
22 | infusion support. Only 15% of panel members rarely or never target normal calcium
23 |
24 | levels.
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34 | **49. We suggest against the routine use of levothyroxine in children with septic**
35 |
36 | **shock and other sepsis-associated organ dysfunction in a sick euthyroid**
37 |
38 | **state (weak recommendation, low quality of evidence).**
39 |

40 | **Rationale:** Critically ill children, similar to adults, develop low tri-iodothyronine (T3) and
41 |
42 | low normal thyroxine (T4) concentrations without the compensatory rise in thyroid
43 |
44 | stimulating hormone (TSH) that is typical of the “sick euthyroid” state or
45 |
46 | hypothyroxinemia of non-thyroidal illness [\(356\)](#)~~(423)~~. The decrease in T3 is due both to
47 |
48 | increased thyroid hormone turnover and to decreased de-iodination of T4 to T3, with
49 |
50 | redirection of T4 metabolism toward higher levels of biologically inactive reverse T3.
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52 | The magnitude of the drop in T3 within the first 24 hours of illness reflects the severity of
53 |
54 | illness [\(357\)](#)~~(424)~~. Although of theoretical benefit, few trials of thyroid hormone
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4 | replacement have been conducted in critically ill children and none in children with
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6 | sepsis. Two prospective RCTs in children undergoing cardiac surgery (without sepsis)
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8 | showed no difference in mortality, vasoactive days, or PICU LOS [\(358, 359\)](#)~~(425, 426)~~.
9 |
10 | One open-label study in premature neonates also showed no difference in clinical
11 |
12 | outcomes [\(360\)](#)~~(427)~~. Taken together, there are no direct data to inform a
13 |
14 | recommendation for children with sepsis, and no indirect data from other critically ill
15 |
16 | children to support a recommendation for the routine use of levothyroxine in children
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18 | with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid
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20 | state.
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28 | **50. We suggest either antipyretic therapy or a permissive approach to fever in**
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30 | **children with septic shock or other sepsis-associated organ dysfunction**
31 |
32 | **(weak recommendation, moderate quality of evidence).**
33 |

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35 | **Rationale:** Fever is a complex physiologic response associated with sepsis, and it
36 |
37 | remains unclear whether fever is a beneficial [\(361\)](#)~~(428)~~ or a harmful [\(362\)](#)~~(429)~~
38 |
39 | response to infection. Potential benefits include inhibiting the growth of some pathogens
40 |
41 | and increased neutrophil production and lymphocyte proliferation. Conversely, fever is
42 |
43 | associated with an increased metabolic rate (which may or may not have detrimental
44 |
45 | effects in patients with sepsis) and may impair some components of immune function.
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47 | Fever can also make patients uncomfortable [\(363\)](#)~~(430)~~. Thus, the putative benefits of
48 |
49 | maintaining normothermia by treating fever are unclear.
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54 | No direct evidence for or against the use of antipyretics in febrile children with
55 |
56 | sepsis-associated organ dysfunction exists. Rather, the panel had to consider indirect
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4 data extrapolated from studies in adults. One systematic review of adult patients studied
5 the use of antipyretics and physical cooling methods included 8 RCTs (1507 patients)
6 and 8 observational studies (17,432 patients) [\(364\)](#)~~(431)~~. This study had 28-day
7 mortality as the primary outcome, with additional outcomes of early mortality (i.e., death
8 on or prior to day 14), frequency of acquisition of hospital-acquired infection, frequency
9 of shock reversal, and mean changes in body temperature, heart rate, and minute
10 ventilation. No difference was noted in 28-day mortality. Effects on early mortality
11 differed between the randomized (favored reduced mortality with antipyretic therapy)
12 and observational (favored increased mortality with antipyretic therapy) studies. While
13 antipyretic therapy successfully decreased body temperature, there was no effect on
14 heart rate, minute ventilation, shock reversal, or acquisition of nosocomial infections.
15 This study did not assess outcome measures of patient comfort. Based on available
16 data, we are not able to recommend the optimal approach to fever in children with
17 sepsis. However, it is reasonable to provide antipyretic therapy to optimize patient
18 comfort, to reduce metabolic demand under certain clinical scenarios (e.g., refractory
19 shock, pulmonary hypertension), and to reduce extreme body temperatures.
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48 **J. NUTRITION**

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51 **51. We were unable to issue a recommendation regarding early**
52 **hypocaloric/trophic enteral feeding followed by slow increase to full enteral**
53 **feeding versus early full enteral feeding in children with septic shock or**
54 **sepsis-associated organ dysfunction without contraindications to enteral**
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4 | **feeding. However, in our practice, there is a preference to commence early**
5 | **enteral nutrition within 48 hours of admission in children with septic shock**
6 | **or sepsis-associated organ dysfunction who have no contraindications to**
7 | **enteral nutrition and to increase enteral nutrition in a stepwise fashion until**
8 | **nutritional goals are met.**
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15 | **Rationale:** No studies examine the enteral nutrition advancement strategy in children
16 | with septic shock or other sepsis-associated organ dysfunction. Indirect evidence from a
17 | small RCT in critically ill children examines early (6-24 hour) versus late enteral nutrition
18 | (>24 hour) in, respectively, 57 and 52 children [\(365\)](#)~~(349)~~. Early enteral feeding had no
19 | effect on duration of PICU stay, but a trend toward better survival in the early feeding
20 | group (30% in early feeding versus 48% in late feeding, p=0.07) was shown. There is
21 | also indirect evidence from the EDEN trial in adults [\(366\)](#)~~(350)~~ in which 200 patients
22 | were randomized to receive either trophic or full enteral feeding for the first 6 days. This
23 | study demonstrated no difference in number of ventilator-free days, mortality at 60 days,
24 | or infectious complications, but trophic enteral feeding was associated with less
25 | gastrointestinal intolerance. Because neither of these studies was conclusive nor
26 | directly studied children with septic shock or other sepsis-associated organ dysfunction,
27 | no evidence-based recommendation could be made by the panel. However, in critically
28 | ill children, a stepwise approach to increasing enteral feeds has been shown to reduce
29 | time needed to reach nutritional goals [\(367-370\)](#)~~(351-354)~~. In our practice, 60% of panel
30 | members always or often and 20% sometimes commence early enteral feeding within
31 | 48 hours of admission in children with septic shock or sepsis-associated organ
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4 | dysfunction who have no contraindications to enteral nutrition, while 20% of panel
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6 | members rarely or never pursue this practice.
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11 | **52. We suggest not withholding enteral feeding solely on the basis of**
12 | **vasoactive-inotropic medication administration (weak recommendation, low**
13 | **quality of evidence).**
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18 | **Remarks: Enteral feeding is not contraindicated in children with septic shock**
19 | **after adequate hemodynamic resuscitation who no longer require escalating**
20 | **doses of vasoactive agents or in whom weaning of vasoactive agents has started.**
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24 | **Rationale:** We reviewed indirect evidence from three observational studies (two
25 | retrospective and one prospective) in post-operative/cardiac pediatric populations.
26 | These studies reported that enteral feeding was tolerated in patients on non-
27 | escalating/weaning doses of vasoactive agents without increased adverse effects or
28 | gastrointestinal complications [\(371-373\)](#)~~(355-357)~~. In another study of 339 critically ill
29 | children, there was no association between enteral feeding and the development of
30 | severe gastrointestinal outcomes such as vomiting, diarrhea, abdominal distension,
31 | bleeding, necrotizing enterocolitis, or perforation [\(371\)](#)~~(355)~~. However, in the report, the
32 | decision to start enteral nutrition may have been biased by the clinical condition of the
33 | patient. In a retrospective study of 52 critically ill children, the use of vasoactive
34 | medications was not associated with an increase in feeding intolerance or
35 | gastrointestinal complications [\(372\)](#)~~(356)~~. In a prospective observational study of
36 | critically ill children who received post-pyloric feeding, 44/65 (67.7%) of patients with
37 | shock and 284/461 (61.6%) of patients without shock received enteral nutrition within 48
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4 | hours. Although gastrointestinal complications were more common in children admitted
5 |
6 | with shock, no association between the incidence of digestive tract complications and
7 |
8 | early (first 48 hours) or late administration of post-pyloric enteral nutrition was reported
9 |
10 | [\(373\)](#)~~(357)~~. Based on these studies which, while providing indirect evidence, all
11 |
12 | consistently found that enteral feeding was not associated with harm, we recommend
13 |
14 | not to withhold enteral nutrition solely because vasoactive-inotropic medications are
15 |
16 | being used. Current evidence supports starting enteral nutrition in hemodynamically
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18 | stable patients who are no longer requiring fluid resuscitation or escalating doses of
19 |
20 | vasoactive agents.
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30 | **53. We suggest enteral nutrition as the preferred method of feeding and that**
31 | **parenteral nutrition may be withheld in the first 7 days of PICU admission in**
32 | **children with septic shock or other sepsis-associated organ dysfunction**
33 | **(weak recommendation, moderate quality of evidence).**
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38 | **Rationale:** No studies have been published on this specific issue of nutrition in children
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40 | with septic shock or other sepsis-associated organ dysfunction. However, in a general
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42 | cohort of 1440 critically ill children enrolled in the international multicenter RCT of
43 |
44 | pediatric early versus late PN in critical illness [\(374\)](#)~~(358)~~, withholding parenteral
45 |
46 | nutrition during the first week in PICU when enteral nutrition was less than 80% of
47 |
48 | prescribed goal was clinically superior to providing supplemental parental nutrition
49 |
50 | within 24 hours of admission [\(375\)](#)~~(359)~~. Secondary analyses of the PEPaNIC trial
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52 | showed that withholding PN was also beneficial in term neonates and children who
53 |
54 | were undernourished at admission [\(376, 377\)](#)~~(360, 364)~~, though withholding parenteral
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4 | nutrition in term neonates was also associated with increased risk of severe
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6 | hypoglycemia [\(376\)](#)~~(369)~~. A long-term follow-up 2 years after PICU admission showed
7 |
8 | that withholding parenteral nutrition for 1 week did not affect survival, anthropometrics,
9 |
10 | or health status, but did improve certain domains of neurocognitive development
11 |
12 | [\(378\)](#)~~(362)~~. Although the results of the PEPaNIC trial corroborated the findings from
13 |
14 | adult RCTs, the optimal timing of parenteral nutrition in the critically ill child with sepsis
15 |
16 | is still not clear [\(374, 379-381\)](#)~~(358, 363-365)~~. Our recommendation is based on one
17 |
18 | trial and therefore, the evidence to withhold PN in the first 7 days of PICU admission is
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20 | of moderate certainty and must be explored further using pragmatic timing for PN in the
21 |
22 | first week, particularly in severely malnourished patients and neonates.
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31 | **54. We suggest against supplementation with specialized lipid emulsions in**
32 | **children with septic shock or other sepsis-associated organ dysfunction**
33 | **(weak recommendation, very low quality of evidence).**
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36 | **Rationale:** In two RCTs evaluating immunomodulatory formulas, including lipid
37 |
38 | emulsions, in critically ill children, outcomes were not significantly different [\(382,](#)
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40 | [383\)](#)~~(366, 367)~~. One RCT was terminated during interim analysis because of unlikely
41 |
42 | benefit in the intervention arm [\(383\)](#)~~(367)~~. In another small RCT, use of enteral feeding
43 |
44 | supplemented with or without omega-3 fatty acids in 120 critically ill children with sepsis
45 |
46 | was investigated [\(384\)](#)~~(368)~~. Univariate analyses showed a significant difference in
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48 | inflammatory mediators and reduction in PICU LOS, but these outcome benefits were
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50 | not evident in the multivariable analyses. Taken together, although promising,
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4 insufficient evidence is available to support routine supplementation in pediatric sepsis
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7 with specialized lipid emulsions.
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11 **55. We suggest against the routine measurements of gastric residual volumes**
12 **(GRV) in children with septic shock or other sepsis-associated organ**
13 **dysfunction (weak recommendation, low quality of evidence).**
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19 **Rationale:** Although routine measurement of GRV is a relatively common practice in
20 PICUs, there is no direct evidence in pediatric sepsis. In a two-center observational
21 cohort study of critically ill children admitted with a variety of diagnoses, one center
22 reported routine use of GRV monitoring while the other center did not practice GRV
23 measurements [\(385\)](#)~~(369)~~. The center that advanced enteral nutrition without routine
24 measurements of GRV did not have an increase in the incidence of vomiting, ventilator
25 acquired pneumonia, or necrotizing enterocolitis in comparison with the other PICU
26 [\(Supplemental Table 21\)](#). Although there are likely some children for whom measuring
27 GRV would likely be useful (e.g., gastroparesis, omphalocele, gastroschisis), no
28 evidence supports routine measurements in all patients at this time and, if measured,
29 GRV is not sufficient to diagnose EN intolerance.
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48 **56. We suggest administering enteral feeds through a gastric tube, rather than**
49 **a post-pyloric feeding tube, to children with septic shock or other sepsis-**
50 **associated organ dysfunction who have no contraindications to enteral**
51 **feeding (weak recommendation, low quality of evidence)**
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4 | **Rationale:** In 3 small RCTs, gastric versus post-pyloric enteral feeding were compared
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6 | in mechanically-ventilated children with a variety of diagnoses [\(386-388\)](#)~~(370-372)~~. The
7 |
8 | outcomes reported included lower caloric achievement with gastric feeding and delayed
9 |
10 | start of enteral feeding with post-pyloric feeding [\(386, 387\)](#)~~(370, 371)~~. No significant
11 |
12 | difference was found in the incidence of ventilator-associated pneumonia between
13 |
14 | gastric and post-pyloric feeding [\(388\)](#)~~(372)~~. On the basis of these studies, there is no
15 |
16 | clear evidence that post-pyloric feeding is beneficial and there is concern for potential
17 |
18 | harm through delayed optimization of enteral nutrition. Therefore, we suggest that
19 |
20 | feeding with a gastric tube is physiologic and, based on current evidence, the preferred
21 |
22 | method for enteral nutrition. Post-pyloric feeding may be considered in patients in whom
23 |
24 | gastric feeding is either contraindicated (e.g., high-risk for aspiration) or was not
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26 | tolerated/advanced, and as a result, nutritional goals were unable to be met.
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36 | **57. We suggest against the routine use of prokinetic agents for the treatment**
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38 | **of feeding intolerance in children with septic shock or other sepsis-**
39 |
40 | **associated organ dysfunction (weak recommendation, low quality of**
41 |
42 | **evidence).**
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45 | **Rationale:** Prokinetic agents, such as metoclopramide and erythromycin, are often
46 |
47 | used in the PICU in an effort to reduce feeding intolerance [\(389\)](#)~~(373)~~. Indirect evidence
48 |
49 | for this question was provided from the only pediatric randomized control trial, which
50 |
51 | was a combined intervention of enteral zinc, selenium, glutamine, and intravenous
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53 | metoclopramide. In critically ill children, this combined intervention failed to reduce the
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55 | development of sepsis or incidence of hospital-acquired infection in immunocompetent
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4 | children, although the intervention including metoclopramide did reduce the rate of
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6 | hospital-acquired infection and sepsis in immunocompromised children. However, the
7 |
8 | application of this study to children who already have sepsis is not clear. Prokinetic
9 |
10 | agents are also not without risk as they have been associated with prolongation of the
11 |
12 | QT interval and ventricular arrhythmias [\(390-392\)](#)~~(374-376)~~. Further investigation is
13 |
14 | needed to determine if prokinetic agents are beneficial in patients with sepsis,
15 |
16 | particularly in immunocompromised children.
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23 | **58. We suggest against the use of selenium in children with septic shock or**
24 | **other sepsis-associated organ dysfunction (weak recommendation, low**
25 | **quality of evidence).**
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30 | **Rationale:** Although clinical research examining the use of selenium among critically ill
31 |
32 | neonates and adults has been done [\(Supplemental Table 22\)](#), there no data regarding
33 |
34 | selenium supplementation as potential adjunctive therapy for pediatric sepsis. Selenium
35 |
36 | plays a key role as a cofactor for glutathione peroxidase, iodothyronine deiodinase, and
37 |
38 | thioredoxin [\(393\)](#)~~(388)~~; accordingly, selenium deficiency could affect thyroid metabolism
39 |
40 | and the response to oxidative stress during critical illness. Moreover, low serum
41 |
42 | selenium concentrations are common in critical illness [\(394, 395\)](#)~~(389, 390)~~ and
43 |
44 | infection [\(396\)](#)~~(394)~~, and have been associated with measures of oxidative stress in
45 |
46 | neonates [\(397\)](#)~~(392)~~ and adults [\(398\)](#)~~(393)~~.
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53 | A systematic review of investigations examining selenium supplementation in
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55 | preterm neonates reported improved outcomes, including reduction in occurrence of
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57 | sepsis [\(399\)](#)~~(394)~~. Similarly, a published systematic review and meta-analysis of the
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4 | effect of parenteral selenium supplementation in critically ill adult sepsis patients
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7 | concluded that this intervention reduced risk of mortality [\(400\)](#)~~(395)~~, but when the meta-
8 |
9 | analysis was updated to include the results of a more recent RCT, there was no
10 |
11 | difference in mortality in those treated with or without selenium supplementation (50). In
12 |
13 | an interventional trial examining the potential benefit of zinc, selenium, glutamine, and
14 |
15 | metoclopramide administration to critically ill children, there was no reduction in the
16 |
17 | primary outcome measure, namely, time until the first episode of nosocomial
18 |
19 | infection/sepsis [\(383\)](#)~~(367)~~. Based on lack of interventional trials examining selenium
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21 | supplementation in the setting of pediatric sepsis and sepsis-associated organ
22 |
23 | dysfunction, we suggest against its use as a weak recommendation.
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31 | **59. We suggest against the use of glutamine supplementation in children with**
32 | **septic shock or other sepsis-associated organ dysfunction (weak**
33 | **recommendation, low quality of evidence).**
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36 | **Rationale:** During catabolic stress, the human body is unable to produce adequate
37 |
38 | quantities of glutamine and, therefore, its essential role as a fuel source for enterocytes
39 |
40 | and immune cells is diminished. Over the past two decades, several investigations of
41 |
42 | glutamine administration alone and in various combinations with other nutritional
43 |
44 | supplements have been conducted in critically ill populations [\(383, 401-407\)](#)~~(367, 396-~~
45 |
46 | [402\)](#), including those with sepsis [\(402, 408-410\)](#)~~(397, 403-405)~~. Contemporary studies
47 |
48 | have not found glutamine in any form (enteral or parenteral) and/or in combination with
49 |
50 | other nutritional elements to significantly improve morbidity or mortality in critically ill
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52 | infants, children, and adults, including those with sepsis [\(411-413\)](#) **[\(Supplemental](#)**
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4 | **Table 23**(~~406-408~~). However, single element studies administering only glutamine to
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6 | children with sepsis and septic shock are scarce. An RCT by Jordan et al (~~404~~)(~~399~~)
7 |
8 | randomized children (49 control; 49 interventional) with sepsis and septic shock for the
9 |
10 | purpose of examining oxidative stress and inflammatory response. This investigation
11 |
12 | supports earlier studies in broader populations finding no differences in PICU ($p=0.062$)
13 |
14 | or hospital LOS ($p= 0.09$) or hospital mortality ($p=0.31$). Two other studies of glutamine
15 |
16 | administration in combination with other elements to children with septic shock and
17 |
18 | critical illness are available (~~383, 402~~)(~~367, 397~~). The RCT by Briassoulis et al
19 |
20 | (~~402~~)(~~397~~) examined children with septic shock receiving glutamine in combination with
21 |
22 | arginine, antioxidants, and omega-3 fatty acids. Although the main outcome of change
23 |
24 | in cytokines showed some promise, no difference was noted between groups for
25 |
26 | hospital survival (80% versus 87%) or LOS (10.4 ± 2.2 versus 11.4 ± 2.5 days) (~~45~~)(~~15~~).
27 |
28 | Carcillo et al (~~383~~)(~~367~~) randomized 283 subjects from 8 PICUs to a control group
29 |
30 | receiving whey protein formula or an intervention group receiving formula with zinc,
31 |
32 | selenium, glutamine and IV metoclopramide supplementation. There was no difference
33 |
34 | between hospital-acquired infections and clinical sepsis per 100 days ($p=0.81$), PICU
35 |
36 | LOS ($p= 0.16$), or 28-day mortality (8/139 [5.8%] versus 15/145 [10.3%]). Subjects from
37 |
38 | this trial were also categorized by immune status with the suggestion that immune
39 |
40 | status may play a role in the effectiveness of nutritional supplemental, including
41 |
42 | glutamine (~~414~~)(~~409~~). However, no direct evidence regarding glutamine
43 |
44 | supplementation in children with sepsis exists; hence, we suggest against the use of
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46 | glutamine therapy in children with septic shock or other sepsis-associated organ
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48 | dysfunction until further data become available.
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7 | **60. We suggest against the use of arginine in the treatment of children with**
8 | **septic shock or other sepsis-associated organ dysfunction (weak**
9 | **recommendation, very low quality of evidence).**
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12 | **Rationale:** Reduced availability of arginine in sepsis may lead to decreased
13 |
14 | endogenous nitric oxide synthesis, loss of microcirculatory regulation, and altered
15 |
16 | immune response [\(415-417\)](#)~~(410-412)~~. In the only pediatric RCT of arginine
17 |
18 | supplementation in children with sepsis [\(418\)](#)~~(413)~~, ten children received infusions of
19 |
20 | arginine and had enhanced arginine oxidation and increased nitric oxide levels, but no
21 |
22 | clinical outcomes were reported. In indirect data from adult studies, RCTs of L-arginine
23 |
24 | supplementation have been small and have reported both positive and negative effects
25 |
26 | on mortality [\(419-423\)](#)~~(414-418)~~. One trial in septic adults found decreased
27 |
28 | mortality~~(421)~~~~(416)~~, but other studies found no benefit or increased mortality in adults
29 |
30 | with sepsis~~(419, 422, 423)~~~~(414, 417, 418)~~. Some authors found improvement in
31 |
32 | secondary outcomes in patients with sepsis, such as reduced infectious complications
33 |
34 | and shorter LOS, but the relevance of these findings and their applicability to children
35 |
36 | with sepsis in the face of potential harm is unclear. Hence, in the absence of evidence
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38 | of demonstrated benefit, we suggest against the use of arginine therapy in children with
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40 | sepsis-associated organ dysfunction until further data become available.
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53 | **61. We suggest against using zinc supplementation in children with septic**
54 | **shock and other sepsis-associated organ dysfunction (weak**
55 | **recommendation, very low quality of evidence).**
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4 **Rationale:** Alterations in zinc homeostasis and associations between zinc levels and
5
6 outcomes have been reported in the critically ill. Benefits of zinc supplementation have
7
8 been shown in some forms of infectious illnesses. However, no trials of zinc
9
10 supplementation in children with sepsis have been conducted. One RCT in critically ill
11
12 children comparing daily supplementation with zinc, selenium, glutamine, and
13
14 metoclopramide versus whey protein was stopped during interim analysis due to futility
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16 [\(383\)](#)~~(367)~~. Based on conflicting studies in the adult literature, routine supplementation
17
18 of zinc is not recommended in nutritional guidelines for critically ill adults [\(424\)](#)~~(419)~~.
19
20 Future RCTs examining the optimal timing and dose of zinc in children with sepsis and
21
22 septic shock and its impact on immune response and clinical outcomes might help
23
24 answer this question.
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34 **62. We suggest against the use of ascorbic acid (vitamin C) in the treatment of**
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36 **children with septic shock or other sepsis-associated organ dysfunction**
37
38 **(weak recommendation, very low quality of evidence).**
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41 **Rationale:** Ascorbic acid (vitamin C) has multiple physiologic functions. Most
42
43 importantly in the setting of sepsis, vitamin C is an antioxidant and neutralizes reactive
44
45 oxygen and nitrogen radicals, inhibits activation of pro-inflammatory cytokines,
46
47 increases endogenous vasopressor synthesis, and inhibits bacterial replication [\(425-](#)
48
49 [427\)](#)~~(432-434)~~. Adults with sepsis frequently have very low levels of vitamin C. In one
50
51 study, 88% of adults with septic shock had hypovitaminosis C [\(428\)](#)~~(435)~~. Small studies
52
53 in adults suggest that treatment of septic patients with vitamin C may improve organ
54
55 dysfunction [\(429\)](#)~~(436)~~ and reduce mortality [\(430\)](#)~~(437)~~. Vitamin C has also been used
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4 | as a component of combination therapy, typically with thiamine and corticosteroids, in
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6 | adults with sepsis [\(431\)](#)~~(438)~~. One study compared such treatment in 47 adult patients
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8 | with sepsis to historical control patients [\(432\)](#)~~(439)~~. Treatment was associated with
9 |
10 | decreased hospital mortality (OR 0.13, 95% CI 0.04, 0.48), shorter duration of
11 |
12 | vasopressor therapy, and improved organ dysfunction scores [\(Supplemental Table](#)
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14 | [24](#)).
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19 | Currently, there are no data on the use of vitamin C in critically ill children or in
20 |
21 | pediatric sepsis. The prevalence of low vitamin C levels in septic children is unknown,
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23 | and no studies have investigated the effect of vitamin C supplementation, either alone
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25 | or in combination with other agents, in the treatment of pediatric sepsis.
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31 | **63. We suggest against the use of thiamine to treat children with sepsis-**
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33 | **associated organ dysfunction (weak recommendation, low quality of**
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35 | **evidence).**
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38 | **Rationale:** Thiamine is a crucial factor in cellular metabolism. In its active form,
39 |
40 | thiamine pyrophosphate (TPP) is an essential coenzyme used to generate energy
41 |
42 | (ATP) from glucose. The human body does not produce thiamine and, with a short half-
43 |
44 | life and small body stores, thiamine deficiency can develop within days of critical illness
45 |
46 | and inadequate nutrition, resulting in impaired oxidative and carbohydrate metabolism.
47 |
48 | Low blood concentrations of thiamine have been reported on admission of critically ill
49 |
50 | children and adults with sepsis and septic shock [\(433-435\)](#)~~(440-442)~~. A study examining
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52 | thiamine deficiency in children admitted to the PICU showed that low blood thiamine
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54 | concentration in those with severe sepsis or septic shock was associated with mortality
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4 | (OR 8.40, 95% CI 1.38, 51.0)(434)(441). In an RCT of 88 adults with septic shock
5 |
6 | **(Supplemental Table 25)**, there were no differences between treatment with thiamine
7 |
8 | versus placebo for the primary outcome of change in lactate levels or the secondary
9 |
10 | outcomes of mortality, shock reversal, and LOS (433)(440). However, on *post hoc*
11 |
12 | analysis, thiamine treatment in the subgroup with thiamine deficiency on admission was
13 |
14 | associated with lower lactate level within 24 hours and lower mortality (p=0.047).
15 |
16 | However, more evidence is needed to recommend whether thiamine supplementation
17 |
18 | should be used to treat children with septic shock or other sepsis-associated organ
19 |
20 | dysfunction. Also, it may be important for this evidence to be considered in the context
21 |
22 | of thiamine status at PICU admission.
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30 | **64. We suggest against the acute repletion of vitamin D deficiency (VDD) for**
31 | **treatment of septic shock or other sepsis-associated organ dysfunction**
32 | **(weak recommendation, very low quality of evidence).**
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36 | **Rationale:** A systematic review and meta-analysis of 17 studies including 2,783
37 |
38 | patients showed that approximately half of critically ill children have VDD (25-hydroxy
39 |
40 | vitamin D [25(OH)D] level < 50 nmol/L or <20 ng/mL) at PICU admission (190). Further,
41 |
42 | VDD was associated with higher illness severity, multiple organ dysfunction, and
43 |
44 | mortality across these studies. Six of these studies focused on or separately analyzed
45 |
46 | children with sepsis (436-440)(443-447). Three studies reported a greater need for
47 |
48 | vasoactive agents in VDD children (436-438)(443-445), although mortality across these
49 |
50 | six studies was not associated with VDD (436-440)(443-447) **(Supplemental Table 26)**.
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56 | Vitamin D levels are lowered by fluid resuscitation, which can confound the
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58 | association with illness severity and disease complications (437)(444). In addition, free
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4 or bioavailable 1,25(OH)₂D is the active form which is influenced by the level of vitamin
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6 D binding protein (VDBP) and a patient's VDBP genotype, which was not estimated or
7
8 measured in prior studies [\(441\)\(448\)](#). Although vitamin D levels are a potentially
9
10 modifiable risk factor via supplementation, a meta-analysis of rapid normalization of
11
12 vitamin D levels concluded that it is best achieved using loading therapy that takes into
13
14 account disease status, determines baseline vitamin D level, and considers patient
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16 weight [\(442-444\)\(449-451\)](#). A loading dose >300,000 IU should be avoided outside of
17
18 RCTs evaluating risk and benefit.
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24 Hypervitaminosis D is associated with hypercalcemia and other severe
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26 complications [\(445\)\(452\)](#) and vitamin D overdoses can be fatal [\(446\)\(453\)](#). No current
27
28 data support that rapid acute correction of VDD is an effective treatment in septic shock
29
30 or improves outcomes of septic children. Further, measurement of 25(OH)₂D levels is
31
32 not currently a standard component of sepsis care and methods of accurately
33
34 measuring bioavailable vitamin D are not yet widely validated. However, if VDD is
35
36 diagnosed, repletion should occur as a usual part of general holistic pediatric care
37
38 according to recommended guidelines independently of the presence of sepsis
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43 [\(447\)\(454\)](#).
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48 **K. ADJUNCTIVE THERAPIES BLOOD PRODUCTS**

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51 **65. We suggest against transfusion of red blood cells if the blood hemoglobin**
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53 **concentration is ≥ 7 g/dL in hemodynamically stabilized children with septic**
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55 **shock or other sepsis-associated organ dysfunction (weak**
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57 **recommendation, low quality of evidence).**
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4 **Remarks: According to the 2018 Transfusion and Anemia Expertise Initiative**
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6 **(TAXI) guidelines, for the purposes of red blood cell transfusion,**
7
8 **“hemodynamically stabilized” is defined as a mean arterial blood pressure higher**
9
10 **than 2 standard deviations below normal for age and no increase in vasoactive**
11 **medications for at least 2 hours.**
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16 **66. We cannot make a recommendation regarding hemoglobin transfusion**
17 **thresholds for critically ill children with unstable septic shock.**
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21 **Rationale:** The only study evaluating specific red blood cell (RBC) transfusion
22 thresholds in children with sepsis is a *post hoc* subgroup analysis of the Transfusion
23 Requirements in the Pediatric Intensive Care Unit (TRIPICU) study [\(448\)\(455\)](#)
24 **(Supplemental Table 27)**. This study included 137 stabilized critically ill children (MAP
25 >2 standard deviations below normal for age and cardiovascular support not increased
26 for at least 2 hours before enrollment) with sepsis, with a hemoglobin \leq 9.5 g/dL within 7
27 days after PICU admission. Patients were randomized to receive RBCs if hemoglobin
28 decreased to either <7.0 g/dL (restrictive group) or 9.5 g/dL (liberal group). No
29 differences were found between the restrictive versus liberal group in the primary
30 endpoint of new or progressive multiple organ dysfunction syndrome (18.8% versus
31 19.1%) or mortality ($p=0.44$). These results are similar to those from primary analysis of
32 the TRIPICU study [\(449\)\(456\)](#), as well as in adults [\(450\)\(457\)](#). Our suggestion against
33 transfusion if hemoglobin is >7 g/dL in hemodynamically-stable children with sepsis
34 parallels the TAXI recommendations [\(451\)\(458\)](#).
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55 Insufficient data are available to guide red blood cell transfusion therapy in
56 children with unstable septic shock. Two pediatric RCTs did demonstrate decreased
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4 | mortality when red blood transfusion to goal hemoglobin ≥ 10 (hematocrit $>30\%$) was
5 | included as part of an early goal-directed therapy algorithm targeting ScvO₂, but the
6 | impact of each individual component, including red blood transfusion, is unclear [\(212,](#)
7 | [452\)](#)~~(187, 459)~~. In critically ill adults, the Transfusion Requirements in Septic Shock
8 | (TRISS) trial randomized 998 subjects with septic shock to either a transfusion
9 | threshold hemoglobin of 7 g/dL or 9 g/dL [\(453\)](#)~~(460)~~. At randomization, all patients had
10 | hypotension (mean arterial pressure <70 mmHg) and/or were being treated with
11 | vasopressors. Ninety-day mortality showed no differences (relative risk, 0.94; 95%CI
12 | 0.78-1.09), suggesting that a restrictive transfusion strategy in hemodynamically
13 | unstable septic adults was safe. **(Supplemental Table [4727](#).)** The SSC recommends
14 | that RBC transfusion in adults occur only when hemoglobin concentration decreases to
15 | <7.0 g/dL in the absence of extenuating circumstances, such as myocardial ischemia,
16 | severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of
17 | evidence)[\(50\)](#). This adult recommendation is also valid for hemodynamically unstable
18 | patients.

19 |
20 | However, in the absence of pediatric data, we are not able to provide a
21 | recommendation for critically ill children with unstable septic shock.

22 |
23 | **67. We suggest against prophylactic platelet transfusion based solely on**
24 | **platelet levels in non-bleeding children with septic shock or other sepsis-**
25 | **associated organ dysfunction and thrombocytopenia (weak**
26 | **recommendation, very low quality of evidence).**

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4 | **Rationale:** One observational study demonstrated an association between the
5 |
6 | administration of platelet transfusions to critically ill children and worse clinical outcomes
7 |
8 | **(Supplemental Table 28)**, including longer ICU LOS, progressive organ dysfunction,
9 |
10 | and increased mortality [\(454\)](#)~~(461)~~. Indirect evidence can be found in an RCT of 660
11 |
12 | infants born at less than 34 weeks gestational age, the majority of whom were treated
13 |
14 | for sepsis, that compared a platelet transfusion threshold of 50,000 /mm³ (high
15 |
16 | threshold) with 25,000 /mm³ (low threshold)[\(455\)](#)~~(462)~~. More infants in the high- versus
17 |
18 | low-threshold group received at least one platelet transfusion (90% vs 53%). More
19 |
20 | adverse events, including new major bleeding or death, were also seen in the high
21 |
22 | threshold group (OR 1.57, 95% CI 1.06, 2.32).
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28 | Although existing evidence does not support a platelet threshold at which
29 |
30 | transfusion is absolutely indicated, the risk of spontaneous bleeding may be greater at
31 |
32 | lower platelet counts, e.g., <10-20,000 /mm³. In addition, some populations of
33 |
34 | thrombocytopenic critically ill children may have a relatively high risk of bleeding, such
35 |
36 | as those with oncological diagnoses or those receiving ECMO. Because the threshold
37 |
38 | at which the benefits of platelet transfusion outweigh the risks is unknown, clinical
39 |
40 | judgment based on patient risk factors for bleeding in addition to the measured platelet
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42 | level must be exercised carefully.
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50 | **68. We suggest against prophylactic plasma transfusion in non-bleeding**
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52 | **children with septic shock or other sepsis-associated organ dysfunction**
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54 | **and coagulation abnormalities (weak recommendation, very low quality of**
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56 | **evidence).**
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4 **Remarks: Prophylactic plasma transfusion refers to situations in which there is**
5 **an abnormality in laboratory coagulation testing but no active bleeding.**
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9 **Rationale:** No direct data exist to inform a recommendation about plasma transfusion in
10 pediatric sepsis. One RCT evaluates prophylactic plasma transfusion in critically ill
11 children without sepsis. Pieters et al randomized 81 children <2 years of age requiring
12 primary repair of craniosynostosis to receive plasma using either a prophylactic (in
13 absence of bleeding) or reactive (when the patient was bleeding) strategy [\(456\)](#)~~(463)~~.
14
15 The prophylactic plasma transfusion group received a significantly higher volume of
16 plasma compared to the reactive group (29.7 mL/kg versus 16.1 mL/kg, $p < 0.001$).
17
18 Despite an improvement in coagulation values in the prophylactic group, there was no
19 difference in PRBC transfusion requirements or blood loss between the two groups.
20
21 **(Supplemental Table 4929)** Additionally, a meta-analysis published in 2012 that
22 included 80 RCTs (mostly in adults) concluded that there was no consistent evidence
23 for benefit of prophylactic plasma transfusion across a range of indications that were
24 evaluated [\(457\)](#)~~(464)~~. Observational studies in critically ill children have shown that
25 plasma transfusions are associated with worse clinical outcomes [\(458, 459\)](#)~~(465, 466)~~.
26
27 Furthermore, plasma transfusion frequently fails to correct abnormal coagulation tests in
28 critically ill adults and children [\(459, 460\)](#)~~(466, 467)~~. We therefore suggest against
29 prophylactic plasma transfusions for children with septic shock and other sepsis-
30 associated organ dysfunction who are not bleeding.
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53 However, some specific patient populations might benefit from prophylactic
54 plasma transfusions, such as patients with worsening coagulation tests at high risk for
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4 | disseminated intravascular coagulopathy (DIC), children with comorbid cancer, or
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6 | children with sepsis on extracorporeal life support (ECLS).
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11 | **L. PLASMA EXCHANGE, RENAL REPLACEMENT, AND EXTRACORPOREAL**
12 |
13 | **SUPPORT**
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16 | **69. We suggest against using plasma exchange in children with septic shock**
17 | **or other sepsis-associated organ dysfunction without thrombocytopenia-**
18 | **associated multiple organ failure (TAMOF) (weak recommendation, very low**
19 | **quality of evidence)**
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24 | **70. We cannot suggest for or against the use of plasma exchange in children**
25 | **with septic shock or other sepsis-associated organ dysfunction with**
26 | **TAMOF.**
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33 | **Rationale:** Therapeutic plasma exchange (PLEX) for septic shock or sepsis-associated
34 | organ dysfunction ~~is one of the techniques of blood purification, aiming~~ aims to
35 | normalize the plasma milieu of a systemically inflamed septic patient. Currently, no
36 | large RCTs ~~have~~ evaluated PLEX in pediatric septic shock or sepsis-associated organ
37 | dysfunction. Rimmer et al. performed a meta-analysis that included 4 ~~small~~ RCTs
38 | evaluating PLEX in adults (n=128) and pediatric (n=66) patients with sepsis and septic
39 | shock. PLEX was associated with reduced mortality in adults (RR 0.63, 95% CI 0.42,
40 | 0.96), but not in children (RR 0.96, 95% CI 0.28, 3.38) ~~(461)(468)~~. ~~However, b~~Because
41 | of the heterogeneity of the patient population, inclusion criteria, technical modalities of
42 | PLEX (filtration versus centrifugation), and types of replacement fluid (plasma versus
43 | albumin) in these 4 studies ~~as well as the costs and potential risks, it is difficult to make~~
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4 ~~a definitive conclusion~~ PLEX cannot be routinely recommended as this time
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6 **(Supplemental Table 2030)**. ~~Currently, using the existing evidenced-based literature on~~
7 ~~the use of PLEX in “Sepsis with multi-organ failure,”~~ Similarly, the American Society for
8 Apheresis recommended that the for Apheresis gives a category III recommendation,
9 which is “O” optimum role of apheresis therapy is not established” in sepsis with multi-
10 organ failure. Decision making should be individualized (462)(469).

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19 In pediatrics, ~~three proof-of-concept studies on the use of PLEX in a specific~~
20 ~~inflammation phenotype of sepsis-induced multiple organ failure named TAMOF exist~~
21 ~~(470-472). Clinically, TAMOF is an inflammatory phenotype of sepsis-induced multiple~~
22 ~~organ dysfunction in children that can be identified clinically by patients develop new-~~
23 ~~onset thrombocytopenia in the setting of and evolving multiple organ failed dysfunction~~
24 ~~(463, 464)(REF). Autopsies performed on patients who died with TAMOF revealed~~
25 ~~disseminated microvascular thromboses in various organs (463)(472). These patients~~
26 ~~had~~ deficient activity of a disintegrin and metalloproteinase with thrombospondin type
27 1 motif (ADAMTS-13), elevated von Willebrand factor (VWF) activity ~~ies~~, and the
28 presence of ultra-large plasma VWF (463, 465)(472, 473). Thrombocytopenia in these
29 patients results from widespread platelet aggregation and thrombotic microangiopathy
30 caused, in part, by deficient proteolysis of ultra-large VWF and large plasma VWF.
31 ADAMTS-13 functions to cleave VWF at a specific site to regulate VWF’s multimeric
32 size and adhesive properties Decreased activity of ADAMTS-13 leads to high circulating
33 levels of ultra-large VWF that induce widespread platelet activation and thrombotic
34 microangiopathy. that cause platelet aggregation. A number of inflammatory mediators
35 are elevated in sepsis that can inhibit or proteolytically inactivate ADAMTS-13 including

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4 interleukin (IL)-6, granulocyte elastase, plasmin, thrombin, plasma free hemoglobin,
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6 shigatoxins, and immunoglobulin (Ig)G auto-antibody (466-471)(474-479). ~~In a primate~~
7
8 ~~model, direct ADAMTS-13 inhibition by monoclonal antibodies results in disseminated~~
9
10 ~~microvascular thromboses and organ injuries in the kidney, heart, and brain(219).~~

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14 Three studies have examined the utility of PLEX in children with sepsis and
15
16 TAMOF (463, 472, 473)(REF). In the most recent ~~pediatric TAMOF registry and largest~~
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18 ~~study (n=81), Fortenberry et al. reported the largest prospective observational cohort~~
19
20 ~~study (n=81) on the use of PLEX for TAMOF. These investigators found that PLEX was~~
21
22 associated with lower 28-day mortality by multivariate analysis (aRR 0.45, 95% CI 0.23,
23
24 0.90) and by propensity score weighting (aRR, 0.46, 95% CI 0.22, 0.97) (472)(REF). In
25
26 ~~a second study, Sevketoglu et al reported a a~~ retrospective cohort study from the
27
28 Turkish TAMOF Network (n=42), ~~that~~ PLEX was associated with lower 28-day mortality
29
30 compared to the no PLEX group (27% versus 70%; p=0.004) ((473) (REF207). In ~~at the~~
31
32 third study, Nguyen et al ~~reported the first description of pediatric TAMOF (n=28) and a~~
33
34 ~~pilot study of PLEX for TAMOF (n=10). randomized 10 children to either PLEX or~~
35
36 ~~standard therapy (463)(REF).~~ The 5 patients who received PLEX had restoration of
37
38 ADAMTS-13 activity and greater survival (5/5) survived compared to ~~only 1 of 5 in the~~
39
40 ~~non-PLEX group standard therapy (1/5, p<0.05) (208).~~ Taken together, these data
41
42 support there is a biologic rationale for the use of plausibility in using PLEX for in
43
44 TAMOF. ~~TAMOF appears to be a specific inflammatory phenotype of sepsis-induced~~
45
46 ~~multiple organ failure and PLEX is thought to i.e., the removal of~~ pathologic ultra-large
47
48 VWF and ADAMTS-13 inhibitors and ~~replenish~~ restoration of ADAMTS-13 activity. ~~Theis~~
49
50 approach of using PLEX is similar to ~~that used for~~ the rationale for using PLEX in
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4 | thrombotic thrombocytopenic purpura [\(474\)](#)~~(480)~~. ~~Hence, further studies and RCTs are~~
5 | ~~needed.~~ While the panel acknowledges a potential benefit for PLEX and encourages an
6 | RCT to better define the utility of PLEX in children with sepsis and TAMOF, a
7 | recommendation could not be made based on existing data.
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15 | **71. We suggest using renal replacement therapy to prevent or treat fluid**
16 | **overload in children with septic shock or other sepsis-associated organ**
17 | **dysfunction who are unresponsive to fluid restriction and diuretic therapy**
18 | **(weak recommendation, very low quality of evidence).**
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24 | ***Rationale:*** Renal replacement therapy is increasingly being used in PICUs for renal
25 | and non-renal conditions. The rationale for renal replacement therapy in septic shock
26 | includes impending or established fluid overload following initial resuscitation or for
27 | cytokine removal, reversal of coagulopathy, to buffer lactic acidosis, to address AKI, or
28 | a combination of these factors. Continuous renal replacement therapy (CRRT) may be
29 | useful for treating established fluid overload or to prevent further fluid overload while
30 | allowing liberal volume administration for nutrition, antimicrobials, and other
31 | medications, sedation, and transfusions. In addition, certain techniques of continuous
32 | blood purification may help to regulate systemic inflammation and promote kidney
33 | recovery [\(475\)](#)~~(481)~~. Fluid overload has been shown to cause increased morbidity and
34 | mortality in various intensive care settings and there is documented favorable
35 | association of CRRT in fluid overload [\(476\)](#)~~(482)~~.
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54 | However, no high-quality studies in critically ill children with sepsis exist to
55 | directly determine whether RRT is definitively beneficial compared to diuretics and/or
56 | fluid restriction. Most of the data come from adult studies where outcomes have varied
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4 from mortality to ICU length of stay and ventilator- and vasoactive-free days. One study
5 addressed the timing of CRRT initiation in 27 children with sepsis and multiple organ
6 dysfunction, demonstrating that CRRT was associated with survival when started within
7 48 hours of admission compared to those started on CRRT after 48 hours of admission
8 (61% versus 33%, $p < 0.001$). However, timing of CRRT initiation was at the discretion of
9 the treating team, raising concern for confounding between groups, and all patients in
10 both groups experienced normalization of kidney function [\(477\)](#)~~(483)~~ **(Supplemental**
11 **Table 2431)**.
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24 The possible benefits of CRRT must also be weighed against potential risks,
25 including the need for an invasive catheter, costs, limited availability in some centers,
26 the need for clinician and nursing-specialist expertise, and the challenge of optimal
27 timing (e.g., following resuscitation for fluid removal or earlier for acute cytokine
28 clearance). Therefore, as the initial treatment strategy, we judge that fluid restriction and
29 use of diuretics are reasonable in the presence of impending or established fluid
30 overload with CRRT reserved as a second-line option to prevent or treat fluid overload
31 in children with septic shock or other sepsis-associated organ dysfunction who are
32 unresponsive to fluid restriction and diuretic therapy.
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48 **72. We suggest against high-volume hemofiltration over standard**
49 **hemofiltration in children with septic shock or other sepsis-associated**
50 **organ dysfunction who are treated with renal replacement therapy (weak**
51 **recommendation, low quality of evidence).**
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4 **Rationale:** High-volume hemofiltration (HVHF) for critically ill patients with septic shock
5 and AKI is an appealing strategy for maintaining acid–base and fluid homeostasis, or for
6 having a potential immunomodulatory effect in sepsis by removal of toxins and other
7 inflammatory mediators, especially cytokines that contribute to organ injury and
8 dysfunction.
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16 In adults, use of higher CRRT flux rates (>35 mL/kg/hr filtration-dialysis), while
17 initially encouraging, has not shown overall mortality benefit in subsequent RCTs and
18 meta-analysis. A 2017 Cochrane review found no significant benefit in mortality, severity
19 of organ dysfunction, LOS, or adverse effects with HVHF versus standard hemofiltration
20 rates in critically ill adults [\(478\)](#)~~(484)~~. Notably, the results of this meta-analysis show that
21 very few studies have been conducted to investigate the use of HVHF in critically ill
22 patients with septic shock (four studies totaling 201 participants).
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33 In a study involving 155 pediatric patients with severe sepsis, HVHF treatment
34 did not significantly reduce 28-day mortality compared to standard volume CRRT.
35 Moreover, there were no significant reductions in plasma levels of inflammatory
36 mediators or in improving hemodynamic variables for HVHF. However, the incidence of
37 hyperglycemia was significantly higher in HVHF group than in CVVH group [\(479\)](#)~~(485)~~
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46 **(Supplemental Table [2232](#))**.
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50 **73. We suggest using veno-venous extracorporeal membrane oxygenation**
51 **(ECMO) in children with sepsis-induced PARDS and refractory hypoxia**
52 **(weak recommendation, very low quality of evidence)**
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4 | **Rationale:** ECMO was introduced more than 40 years ago to support patients with
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6 | reversible but severe cardiovascular and/or respiratory failure refractory to conventional
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8 | medical therapy. As such, children with life-threatening sepsis-induced ARDS are often
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10 | considered as candidates for ECMO rescue [\(480\)](#)~~(311)~~, and PALICC endorsed ECMO
11 |
12 | for the treatment of refractory hypoxia (24). The use of ECMO in pediatric sepsis has
13 |
14 | increased over the past decade [\(481, 482\)](#)~~(312, 313)~~; whether this has improved
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16 | survival remains to be determined [\(483\)](#)~~(314)~~. To date, no RCT examining the effect of
17 |
18 | ECMO on outcome in pediatric sepsis has been published. In the absence of such data,
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20 | using propensity score matching, Barbaro et al [\(484\)](#)~~(315)~~ reported that children with
21 |
22 | severe PARDS enrolled in the RESTORE trial had similar mortality rates when
23 |
24 | supported with ECMO (15/61, 25%) as compared with those who were not (18/61,
25 |
26 | 30%)[\(485\)](#)~~(316)~~ (**Supplemental Table 1433**). Research is underway to determine
27 |
28 | optimal pre-ECMO candidacy [\(486\)](#)~~(317)~~ as measures of renal, hepatic, neurologic, and
29 |
30 | hematologic dysfunction, and particularly the presence of blood stream infections, seem
31 |
32 | to discriminate mortality risk better than traditional pediatric severity of illness scores
33 |
34 | such as Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM), and
35 |
36 | Pediatric Logistic Organ Dysfunction (PELOD). Clearly, ECMO is not available
37 |
38 | worldwide, and transfer of highly unstable patients to higher levels of care that offer the
39 |
40 | therapy can carry substantial risk. However, adult and pediatric data suggest a potential
41 |
42 | association with improved mortality, particularly if transfer is to high volume ECMO
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44 | centers [\(487, 488\)](#)~~(318, 319)~~.
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4 | **74. We suggest using veno-arterial (VA) ECMO as a rescue therapy in children**
5 | **with septic shock only if refractory to all other treatments (weak**
6 | **recommendation, very low quality of evidence).**
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11 | **Rationale:** Several anecdotal reports of use of VA ECMO in the management of
12 | refractory septic shock in children exist. (The role of veno-venous [VV] ECMO for
13 | oxygenation/ventilation failure is addressed in the Ventilation section.) More recent
14 | reports suggest that VA ECMO may be associated with better survival than
15 | conventional therapy, and strategies to maximize flow rates to reverse shock and
16 | multiple organ dysfunction may play an important role [\(489, 490\)](#)~~(232, 233)~~. However,
17 | considerable concern surrounds the risks of this highly invasive therapy, such as
18 | hemorrhage and thromboembolic events.
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21 | The most recent and largest report of VA-ECMO in 44 pediatric patients with
22 | refractory septic shock secondary to bacterial, viral, or fungal infection admitted to 7
23 | tertiary PICUs across 5 different countries compared their outcome to 120 children with
24 | refractory septic shock managed by conventional therapy [\(491\)](#)~~(234)~~. Inclusion in the
25 | study required children to meet 3 of 4 criteria for severe septic shock in the first 24
26 | hours of their ICU stay: arterial pH ≤ 7.15 , arterial lactate ≥ 4.0 mmol/L, base excess $\leq -$
27 | 10 mmol/L, and in-hospital cardiac arrest. Patients were excluded if they had cyanotic
28 | congenital heart disease, myocarditis, or an out-of-hospital cardiac arrest. The results
29 | showed no significant difference in survival to hospital discharge (50% in the VA ECMO
30 | cohort versus 40% in the conventional therapy cohort). Survival was significantly higher
31 | in patients who received high ECMO flows (>150 mL/kg/min at 4 hours after institution
32 | of ECMO) compared with children who received standard ECMO flows or no ECMO. ~~†~~
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4 ~~addition, among children who had suffered an in-hospital cardiac arrest, VA ECMO was~~
5
6 ~~associated with a 24% survival advantage (Supplemental Table 734).~~

9 The potential use of VA ECMO for refractory septic shock suggests that the
10 definition of refractory septic shock (RSS) should be standardized across institutions. As
11 yet, no universal definition of refractory septic shock in children exists. One published
12 definition that could be applied is from the European Society of Paediatric and Neonatal
13 Intensive Care (492)(235). The suggested definition for RSS was ~~the association of: (1)~~
14 blood lactate >8 mmol/L or a 1 mmol/L lactate increase after 6 hours of resuscitation;
15 ~~and (2)~~ high vasoactive dependency (vasopressor-inotrope score >200), ~~or ; and (3)~~
16 myocardial dysfunction; defined as the occurrence of a resuscitation-responsive cardiac
17 arrest in PICU or cardiac ultrasound findings with left ventricle ejection fraction <25% or
18 a cardiac index <2.2 L/min/m². ~~This definition encompasses in-hospital cardiac arrest,~~
19 ~~and parameters that are associated with survival on VA-ECMO.~~

38 M. IMMUNOGLOBULINS

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

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

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53 **Rationale:** The proposed rationale for IVIG in severe infections is to boost passive
54 immunity through neutralization of bacterial toxins, promoting opsonization of bacteria,
55 and inhibition of immune cell proliferation and inflammatory mediators. However, IVIG
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4 | has considerable batch-to-batch variability and its true biologic activity is not clear.
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6 | There are no high-quality studies of IVIG in critically ill children with sepsis, and small
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8 | observational studies have reported conflicting results [\(493\)](#)~~(486)~~. An RCT of polyclonal
9 |
10 | IVIG in 100 children with sepsis demonstrated a reduction in mortality (28% versus
11 |
12 | 44%), LOS (6 versus 9 days), and less progression to complications (8% versus
13 |
14 | 32%)[\(494\)](#)~~(487)~~. However, a more recent multicenter trial of polyclonal IVIG in 3,493
15 |
16 | neonates with suspected or proven serious infection found no significant differences in
17 |
18 | mortality or major disability [\(495\)](#)~~(488)~~. Other studies have been carried out with specific
19 |
20 | monoclonal antibodies (e.g., monoclonal antibody against endotoxin in children with
21 |
22 | meningococcal septic shock), but there are no definitive data to support general benefit
23 |
24 | of polyclonal immunoglobulin in neonates or children with septic shock at this time. Data
25 |
26 | from adult patients with septic shock also do not support a routine benefit of IVIG
27 |
28 | [\(496\)](#)~~(489)~~, though administration of IgM- and IgA-enriched polyclonal IVIG has shown
29 |
30 | possible efficacy [\(497\)](#)~~(490)~~. **(Supplemental Table 2335.)**

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32 |
33 | For patients with toxic shock syndrome, especially those with streptococcal
34 |
35 | etiology, polyclonal IVIG may have clinical utility [\(498\)](#)~~(494)~~. Other potential pediatric
36 |
37 | populations that may benefit from IVIG in sepsis are those with necrotizing fasciitis
38 |
39 | (though evidence in adults does not support use [\(499, 500\)](#)~~(492)~~), and those with
40 |
41 | primary humoral immunodeficiencies or immunocompromised with documented low
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43 | immunoglobulin levels.

44 | **N. PROPHYLAXIS**

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4 | **76. We suggest against the routine use of stress ulcer prophylaxis in critically**
5 | **ill children with septic shock or other sepsis-associated organ dysfunction,**
6 | **except for high-risk patients (weak recommendation, very low quality of**
7 | **evidence).**
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10 | **Remarks: Although *routine* stress-ulcer prophylaxis is not recommended, some**
11 | **high-risk patients may benefit from stress ulcer prophylaxis. Studies have**
12 | **supported benefit of stress-ulcer prophylaxis when baseline rate of clinically**
13 | **important bleeding is approximately 13%.**
14 |

15 | ***Rationale:*** Stress ulcer prophylaxis should not be routinely administered to children
16 | with septic shock or other sepsis-associated organ dysfunction, as evidence for benefit
17 | is lacking [\(501\)](#)~~(493)~~ and may increase risk of adverse effects, such as pneumonia or
18 | *Clostridioides difficile* (formerly *Clostridium*) infection [\(502\)](#)~~(494)~~. Rather than routine,
19 | universal administration of stress-ulcer prophylaxis, individual patients should be
20 | assessed for the presence of risk factors of clinically important gastrointestinal bleeding.
21 | These include multiple organ dysfunction [\(503\)](#)~~(495)~~, prolonged mechanical ventilation
22 | (>48 hours), coagulopathy, persistent shock, and treatment with corticosteroids and
23 | non-steroidal anti-inflammatory agents [\(504\)](#)~~(496)~~.
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25 | The risk of GI bleeding is also reduced by mucosal protection introduced by
26 | gastric feeding. Early enteral nutrition could therefore be a viable alternative to
27 | pharmacological stress-ulcer prophylaxis. A meta-analysis of 1836 adult patients
28 | reported that, in the presence of enteral nutrition, pharmacological stress ulcer
29 | prophylaxis did not significantly change the risk of GI bleeding. Notably, in those
30 | patients who received enteral nutrition and were treated with stress ulcer prophylaxis,
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4 | the risk of pneumonia was increased compared to patients on parenteral nutrition (OR
5 | 2.81, 95% CI 1.2, 6.6) [\(505\)](#)~~(497)~~ (**Supplemental Table 2436**).
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11 | **77. We suggest against routine deep vein thrombosis (DVT) prophylaxis**
12 | **(mechanical or pharmacologic) in critically ill children with septic shock or**
13 | **other sepsis-associated organ dysfunction, but potential benefits may**
14 | **outweigh risks and costs in specific populations (weak recommendation,**
15 | **low quality of evidence).**
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23 | **Rationale:** An open-label RCT of low molecular weight heparin to prevent CVC-
24 | associated thrombosis in the PICU was terminated early because of poor recruitment
25 | [\(506\)](#)~~(498)~~. Eleven (14.1%) of 78 patients randomized to reviparin had DVT proven on
26 | venogram versus 10 (12.5%) of 80 controls (OR 1.15, 95% CI 0.42, 3.23). Three
27 | adverse events (major bleed or death) all occurred in the control group and no deaths
28 | occurred because of venous thromboembolism **(Supplemental Table 37)**. A
29 | subsequent systematic review found the quality of evidence to be low and that the
30 | efficacy of low molecular weight heparin in preventing CVC-associated thrombosis is
31 | unknown [\(507\)](#)~~(499)~~. It is important to highlight that these studies were specific to
32 | children with CVCs who may or may not have had sepsis and that they may not apply to
33 | the general thromboembolic risk in children with sepsis.
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36 | While CVCs represent the principal risk factor for DVT in infants [\(508\)](#)~~(500)~~, older
37 | children may have other risk factors. For example, the risk of DVT increases in
38 | adolescence, obesity, cancer, and in those with multiple medical conditions, especially
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4 | renal and cardiac disease ([509, 510](#))(~~501, 502~~). At present, it is unknown whether
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6 | certain high-risk populations of children with sepsis may benefit from DVT prophylaxis.
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10 | **KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES**

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13 | This report from the SSC pediatric guidelines panel covers 5 main topic areas
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15 | (i.e., early recognition and infection, hemodynamics, ventilation, endocrine and
16 |
17 | metabolic therapies, and adjunctive therapies) with a total of 76 recommendations
18 |
19 | arising from 67 PICO questions. On review of these evidence-based analyses, it is clear
20 |
21 | that, for many PICO questions, the literature review failed to identify sufficient data to
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23 | develop strong (or even weak in some instances) recommendations for critically ill
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25 | children with septic shock or other sepsis-associated organ dysfunction. These SSC
26 |
27 | pediatric guidelines, at the same time, also identified gaps that can inform future
28 |
29 | research opportunities. As new research populates the evidence-base, it can then be
30 |
31 | used to develop future iterations of the SSC pediatric guidelines, creating a cycle
32 |
33 | designed to grow the evidence and increase the number of strong recommendations in
34 |
35 | the future. Further clarity is needed from both informative pathophysiology studies as
36 |
37 | well as well-designed RCTs, and the panelists have listed these in the text. The design
38 |
39 | of meaningful and effective future research should be informed by the needs identified
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41 | by the collective clinical expertise within the panel.
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51 | Overall, the process of developing the SSC-pediatric guidelines generated at
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53 | least [27-29](#) pathophysiology questions warranting further study and [22-23](#) RCTs (i.e.,
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55 | total of [49-52](#) studies). We presented these questions as research opportunities, but
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57 | have not yet prioritized these opportunities into a formal research agenda (**Table 6**). We
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4 | **envis**ionage that many of the ~~27~~ pathophysiology questions can be taken up by
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6 | individual research groups and we hope that the SSC children’s guidelines document
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8 | will serve as a template of current evidence and how best to fill the gaps in our
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10 | knowledge. In contrast, the necessary RCTs will need a coordinated
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12 | national/international effort and our community will need to prioritize the most
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14 | appropriate studies at different phases of management (i.e., recognition, fluid
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16 | resuscitation, first 48 hours, etc.).
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25 | **Acknowledgments**

26 |
27 |
28 | The authors wish to thank Darlene Barkman, MA, and Janna Pogers, PT, MPT,
29 |
30 | NCS, CSRS for their sensitive and insightful comments from the perspective of parents
31 |
32 | of children with sepsis. Their input, particularly related to ranking the importance of
33 |
34 | outcomes to consider through the literature search, provided valuable direction to the
35 |
36 | panel. The authors also wish to thank Rebecca Skidmore and James D. Medd for their
37 |
38 | dedication as they conducted the literature searches for the five panels. Their
39 |
40 | experience and professionalism contributed greatly to the final publication. Finally,
41 |
42 | appreciation is extended to Deborah L. McBride for project management and editorial
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44 | support.
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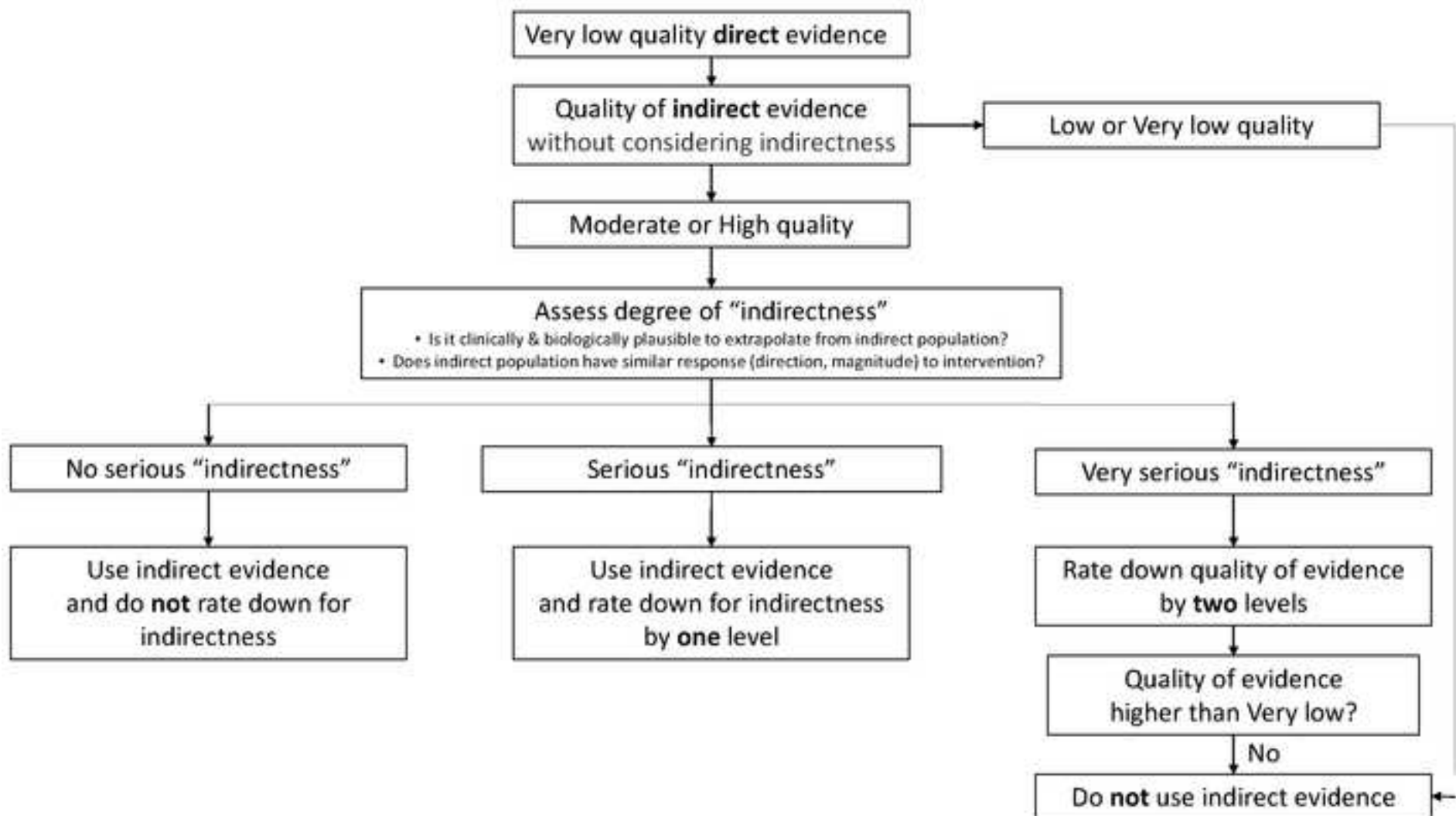


Table 1: Determination of the Quality of Evidence

<p>Underlying methodology</p> <ol style="list-style-type: none">1. High: Systematic reviews, RCTs2. Moderate: Downgraded RCTs or upgraded observational studies3. Low: Well-conducted prospective observational cohort studies4. Very Low: Downgraded observational cohort studies, case-control studies, case series or expert opinion or other evidence <p>Factors that may decrease the strength of evidence</p> <ol style="list-style-type: none">1. Methodologic features of available RCTs suggesting high likelihood of bias2. Inconsistency of results, including problems with subgroup analyses3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)4. Imprecision of results5. High likelihood of reporting bias <p>Factors that may increase the strength of evidence</p> <ol style="list-style-type: none">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

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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 *Staphylococcus aureus*; MDRO, multi-drug resistant organism

Table 5: Normal Ranges for Advanced Monitoring

Parameter	Formula	Normal range	Units
Cardiac index	$CI = CO / \text{body surface area}$	3.5–5.5	L/min/m ²
Stroke index	$SI = CI / \text{heart rate}$	30–60	mL/m ²
Systemic vascular resistance index	$SVRI = 80 \times (MAP - CVP) / CI$	800–1600	dyne-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	<ol style="list-style-type: none"> 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) 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Role of source control (see Rec 15 and 16) 	
D. Fluid Therapy: 1 pathophysiology study and 2 RCTs	<ol style="list-style-type: none"> 1. Features of early recognition of fluid overload (see Rec 17-19) 	<ol style="list-style-type: none"> 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		<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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) 	<ol style="list-style-type: none"> 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		<ol style="list-style-type: none"> 1. Adjunctive corticosteroids for refractory septic shock (see Rec 45)
I. Endocrine and metabolic therapies: 2 pathophysiology studies and 1 RCT	<ol style="list-style-type: none"> 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) 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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) 	<ol style="list-style-type: none"> 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

	<p>3. The prevalence of low serum vitamin C levels in children with septic shock or other sepsis-associated organ dysfunction (see Rec 62)</p>	<p>shock or other sepsis-associated organ dysfunction (see Rec 51, 52, and 53)</p> <p>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)</p> <p>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)</p> <p>5. Vitamin C supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 62)</p> <p>6. Thiamine deficiency, and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 63)</p> <p>7. Vitamin D deficiency and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 64)</p>
<p>K. Blood Products: 2 pathophysiology studies</p>	<p>1. Optimal hemoglobin level in children with septic shock or other sepsis-associated organ dysfunction (see Recs 65 and 66)</p> <p>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)</p>	
<p>L. Plasma Exchange, Renal Replacement, and Extracorporeal Support: 2 pathophysiology studies and 2 RCTs</p>	<p>1. Optimal timing and approach for ECMO in refractory shock (see Rec 74)</p> <p>2. To define optimal pre-ECMO candidacy (see Recs 73 and 74)</p>	<p>1. Plasma exchange in children with septic shock or sepsis-associated organ dysfunction with thrombocytopenia-associated organ failure (see Rec 70)</p> <p>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)</p>

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, and systematic management of sepsis: 4 pathophysiology studies and 2 RCTs	<ol style="list-style-type: none"> 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) 	<ol style="list-style-type: none"> 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: 57 pathophysiology studies	<ol style="list-style-type: none"> 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 4513) 6. The use of procalcitonin as a guide to antimicrobial therapy and relationship to outcome (see Rec 4513) 7. The determinants of optimal duration of antimicrobial therapy (see Rec 4614) 	
C. Source Control: 31 pathophysiology studies	<ol style="list-style-type: none"> 1. The Role of source control (see Rec 4315 and 4416) 	
D. Fluid Therapy: 1 pathophysiology study and 42 RCTs	<ol style="list-style-type: none"> 1. Features of early recognition of fluid overload (see Rec 4817-19) 	<ol style="list-style-type: none"> 1. Clinical markers of cardiac output to guide fluid resuscitation (see Rec 4817-19) 4- Balanced crystalloid versus 0.9% saline (see Rec 21) — Specific hemodynamic targets (>5th versus >50th MAP percentile) (see Rec 19)

		<p>Balanced crystalloid versus 0.9% saline (see Rec 21)</p> <p>2. Lactate-guided resuscitation (see Rec 22)</p>
E. Hemodynamic Monitoring: 12 RCTs		<p>1. Balanced crystalloid versus 0.9% saline (see Rec 24)</p> <p>1. <u>Specific hemodynamic targets (>5th versus >50th MAP percentile) (see Rec 24)</u></p> <p>2. <u>Lactate-guided resuscitation (see Rec 27)</u></p>
F. Vasoactive Medications: 3 pathophysiology studies	<p>1. The choice of first-line vasoactive infusion (see Rec 30<u>29</u>)</p> <p>2. The optimal threshold for using continuous infusion of vasopressin (see Rec 31<u>32</u>)</p> <p>3. The use and effects of inodilators (see Rec 32<u>33</u>)</p>	
G. Ventilation: 5<u>4</u> pathophysiology studies and 5 RCTs	<p>1. Non-invasive modalities to identify the need for early mechanical ventilation (see Rec 36)</p> <p>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)</p> <p>3. The optimal approach to setting PEEP in mechanical ventilation for sepsis-induced PARDS (see Rec 37)</p> <p>4. The use of recruitment maneuvers in mechanical ventilation for sepsis-induced PARDS (see Rec 38)</p>	<p>1. Early- versus delayed-endotracheal intubation for refractory shock without respiratory failure (see Rec 34)</p> <p>2. During mechanical ventilation, low- versus moderate-PEEP strategy for sepsis-induced PARDS (see Rec 37)</p> <p>2.</p> <p><u>3.</u> During mechanical ventilation, prone positioning in sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 39)</p> <p>→</p> <p>4. HFOV versus conventional mechanical ventilation in sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 42)</p> <p>4. 5.</p> <p><u>4-5.</u> NMBA during mechanical ventilation for sepsis-induced severe PARDS (current RCT will need secondary analysis of this subgroup) (see Rec 43)</p>
H. Corticosteroids: 1 RCT	<u>To define optimal pre ECMO candidacy (see Recs 33 and 44)</u>	<p>1. Adjunctive corticosteroids for refractory septic shock (see Recs 45 and 46)</p>

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<p>I. Endocrine and metabolic therapies: 5 pathophysiology studies and 9 RCTs <u>2 pathophysiology studies and 1 RCT</u></p>	<p>1. <u>Lipid solution effects on inflammatory physiology (see Rec 50)</u></p> <p>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)</p> <p>— Hypocalcemia and supplements in children with septic shock or other sepsis-associated organ dysfunction (see Rec 48)</p> <p>1-2.</p>	<p><u>1. Fever management in children with septic shock or other sepsis-associated organ dysfunction (see Rec 50)</u></p> <p>1. Adjunctive corticosteroids for refractory septic shock (see Recs 45 and 46)</p> <p>1. Early versus late enteral nutrition in children with septic shock or other sepsis-associated organ dysfunction (see Recs 47, 48, and 49)</p> <p>1. Bolus versus continuous enteral feeding in children with septic shock or other sepsis-associated organ dysfunction (see Rec 47, 48 and 49)</p> <p>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)</p>
<p>J. Nutrition: 3 pathophysiology studies and 8 RCTs</p>	<p><u>1. Lipid solution effects on inflammatory physiology (see Rec 54)</u></p> <p>— The role of prokinetic agents in immunocompromised children with septic shock or other sepsis-associated organ dysfunction (see Rec 5357)</p> <p>1. <u>Lipid solution effects on inflammatory physiology (see Rec 54)</u></p> <p>2.</p> <p>1.</p> <p>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)</p> <p>3. Hypocalcemia and supplements in children with septic shock or other sepsis-associated organ dysfunction (see Rec 60)</p> <p>2-3. 3. The prevalence of low serum vitamin C levels in children with septic shock or other sepsis-associated organ dysfunction (see Rec 6362)</p>	<p>1. <u>1. Early- versus late- enteral nutrition in children with septic shock or other sepsis-associated organ dysfunction (see Recs 51, 52, and 53)</u></p> <p>2. <u>2. Bolus versus continuous enteral feeding in children with septic shock or other sepsis-associated organ dysfunction (see Rec 51, 52, and 53)</u></p> <p>3. <u>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)</u></p> <p>1-4. 4. Dietary supplements (selenium, glutamine, arginine, zinc) in children with septic shock or other sepsis-associated organ dysfunction (see Recs 5658, 5759, 5860, and 5961)</p>

		<p>2. Fever management in children with septic shock or other sepsis-associated organ dysfunction (see Rec 62)</p> <p>3-5. Vitamin C supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 6362)</p> <p>4-6. Thiamine deficiency, and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 6463)</p> <p>5-7. 8-VDD Vitamin D deficiency; and supplementation in children with septic shock or other sepsis-associated organ dysfunction (see Rec 6564)</p>
K. Blood Products: 2 pathophysiology studies	<ol style="list-style-type: none"> 1. Optimal hemoglobin level in children with septic shock or other sepsis-associated organ dysfunction (see Recs 665 and 676) 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 678) 	
L. Plasma Exchange, Renal Replacement, and Extracorporeal Support: 2 pathophysiology studies and 2 RCTs	<ol style="list-style-type: none"> 1. Optimal timing and approach for extracorporeal membrane oxygenationECMO in refractory shock (see Rec 74) 1-2.2. To define optimal pre-ECMO candidacy (see Recs 73 and 74) 	<ol style="list-style-type: none"> 1. Plasma exchange in children with septic shock or sepsis-associated organ dysfunction with thrombocytopenia-associated organ failure (see Rec 70 and 74) 2. CRRTRenal 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		<ol style="list-style-type: none"> 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 *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

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 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 (ScvO₂).

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 (FiO₂) 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.~~

~~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~~

DB. 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, 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 (ScvO₂).

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~~

EG. 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 (FiO₂) 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~~

DH. 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

EK. 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). 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

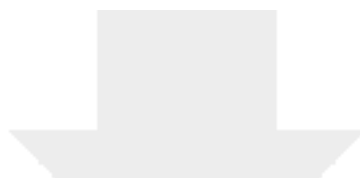


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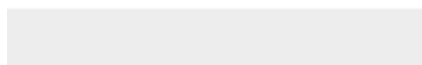
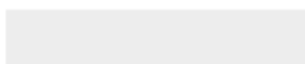




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