International Consensus Criteria for Pediatric Sepsis and Septic Shock
The Phoenix Pediatric Sepsis Criteria

Luregn J Schlapbach*, MD, PhD1,2; R Scott Watson*, MD, MPH3,4 *(corresponding)*; Lauren R. Sorce*, PhD, RN, CPNP-AC/PC5,6; Andrew C. Argent*, MD, MBBCh, MMed 7,8; Kusum Menon, MD9,10; Mark W. Hall, MD11, 12; Samuel Akech, MBChB, MMED13; David J. Albers, PhD14,15; Elizabeth R. Alpern, MD, MSCE16; Fran Balamuth MD, PhD, MSCE17,18; Melania Bembea, MD, PhD19; Paolo Biban, MD20; Enitan D Carrol, MBChB, MD21; Kathleen Chiotos, MD22,23; Mohammod Jobayer Chisti, MBBS, MMed, PhD24; Peter E. DeWitt, PhD25; Idris Evans, MD, MSc26,27; Cláudio Flauzino de Oliveira, MD, PhD28,29; Christopher M. Horvat, MD, MHA26;27; David Inwald MB, PhD30; Paul Ishimine, MD31; Juan Camilo Jaramillo-Bustamante, MD32,33; Michael Levin, MD, PhD34,35; Rakesh Lodha, MD36; Blake Martin, MD37,38; Simon Nadel, MBBS39,40; Satoshi Nakagawa, MD41; Mark J Peters, PhD42,43; Adrienne G. Randolph, MD, MS44,45; Suchitra Ranjit, MD46; Margaret A. Rebull, MA37; Seth Russell, MS37; Halden F. Scott, MD, MSCS47,48; Daniela Carla de Souza, MD, PHD29,49,50; Pierre Tissieres, MD, DSc51; Scott L. Weiss, MD52,53; Matthew O Wiens, PharmD, PhD54,44; James L. Wynn, MD56; Niranjan Kissoon, MD57; Jerry J. Zimmerman, MD, PhD3,4; L. Nelson Sanchez-Pinto**, MD, MBI5,58; Tellen D. Bennett**, MD, MS14,59 *on behalf of the Society of Critical Care Medicine Pediatric Sepsis Definition Task Force (eTable)*

**Equally contributed*

***Equally contributed*

1 Department of Intensive Care and Neonatology, and Children`s Research Center, University Children`s Hospital Zurich, University of Zurich, Zurich, Switzerland
2 Child Health Research Centre, The University of Queensland, Brisbane, Australia
3 Department of Pediatrics, University of Washington; Seattle
4 Center for Child Health, Behavior, and Development and Pediatric Critical Care, Seattle Children's; Seattle, Washington, USA
5 Ann & Robert H. Lurie Children's Hospital, Chicago, USA
6 Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, USA
7 Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, Cape Town, South Africa
8 University of Cape Town, Cape Town, South Africa
9 Department of Pediatrics, Children's Hospital of Eastern Ontario, Ontario, Canada
10 University of Ottawa, Ontario, Canada
11 Division of Critical Care Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA
12 The Ohio State University College of Medicine, Columbus, Ohio, USA
13 Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme, Nairobi, Kenya
14 Departments of Biomedical Informatics, Bioengineering, Biostatistics and Informatics, University of Colorado School of Medicine; Aurora, CO, USA
15 Department of Biomedical Informatics, Columbia University, New York, NY, USA
16 Division of Emergency Medicine, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

17 Department of Pediatrics, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania, USA
18 Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
19 Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
20 Pediatric Intensive Care Unit, Verona University Hospital, Verona, Italy
21 University of Liverpool, Department of Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, Liverpool, United Kingdom
22 Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA
23 Divisions of Critical Care Medicine and Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
24 ICU, Dhaka Hospital, International Centre for Diarroeal Disease Research, Dhaka, Bangladesh
25 Departments of Biomedical Informatics, University of Colorado School of Medicine, Aurora, CO, USA
26 Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
27 The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, Pittsburgh, Pennsylvania, USA
28 AMIB - Associação de Medicina Intensiva Brasileira, São Paulo, Brazil
29 LASI – Latin American Institute of Sepsis, São Paulo, Brazil
30 Paediatric Intensive Care, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
31 Departments of Emergency Medicine and Pediatrics, University of California, San Diego School of Medicine, La Jolla, California, USA
32 PICU General Hospital General de Medellín "Luz Castro de Gutiérrez" and Hospital Pablo Tobón Uribe, Medellín, Colombia
33 Red Colaborativa Pediátrica de Latinoamérica (LARed Network)
34 Section of Paediatric Infectious Diseases, Department of Infectious Diseases, Imperial College London; London, UK
35 Department of Paediatrics, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
36 Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India
37 Departments of Pediatrics (Critical Care Medicine) and Biomedical Informatics and Pediatrics (Critical Care Medicine), University of Colorado School of Medicine; Aurora, CO, USA
38 Pediatric Intensive Care Unit, Children's Hospital Colorado, Aurora, CO, USA
39 Paediatric Intensive Care, St Mary's Hospital, London, United Kingdom
40 Imperial College London, London, United Kingdom
41 Critical Care Medicine, National Center for Child Health and Development, Tokyo, Japan
42 University College London Great Ormond St Institute of Child Health, London, United Kingdom
43 NIHR Biomedical Research Centre London, London, United Kingdom
44 Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, MA, USA
45 Departments of Anaesthesia and Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

46 Pediatric Intensive Care Unit, Apollo Children's Hospital, Chennai, India
47 Department of Pediatrics ,(Section of Pediatric Emergency Medicine), University of Colorado School of Medicine, Aurora, Colorado, USA
48 Emergency Department, Children's Hospital Colorado, Aurora, Colorado, USA
49 Department of Pediatrics (PICU), Hospital Universitario, of the University of São Paulo, São Paulo, Brazil
50 Department of Pediatrics (PICU), Hospital Sírio Libanês, São Paulo, Brazil
51 Pediatric Intensive Care, AP-HP Paris Saclay University, Bicêtre Hospital, Le Kremlin-Bicêtre, France
52 Division of Critical Care, Department of Pediatrics, Nemours Children's Health, Wilmington, Delaware, USA
53 Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, USA
54 Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, Canada
55 Institute for Global Health, BC Children's Hospital, Vancouver, Canada and Walimu, Uganda
56 Department of Pediatrics, University of Florida, Gainesville Florida, USA
57 Department of Pediatrics, University of British Columbia, Vancouver, Canada
58 Department of Pediatrics (Critical Care) and Preventive Medicine (Health & Biomedical Informatics), Northwestern University Feinberg School of Medicine; Chicago, IL, USA
59 Pediatric Intensive Care Unit, Children's Hospital Colorado, Aurora, CO, USA

Word count: ~~3090~~

Key words: Sepsis; septic shock; critical illness; critical care; infection; organ dysfunction

Correspondence:
R. Scott Watson, MD, MPH
4800 Sand Point Way NE
M/S FA.2.112
Seattle, WA 98105
Scott.Watson@seattlechildrens.org
Voice: 206-987-5391

Revision date: December 31~~22~~, 2023

Key Points

Question: How should children with suspected infection at higher risk of mortality, indicative of sepsis, be identified?

Findings: Using an international survey, systematic review, analysis of >3 million pediatric healthcare encounters, and consensus process, new criteria for sepsis and septic shock in children were developed. Pediatric sepsis in children with suspected infection <18 years of age was ~~defined~~identified by ≥2 points in the novel Phoenix Sepsis Score, including dysfunction of the respiratory, cardiovascular, coagulation, and/or neurologic systems; and septic shock ~~w~~as ~~defined as~~ sepsis with ≥1 cardiovascular point in the Phoenix Sepsis Score.

Meaning: The new criteria for pediatric sepsis and septic shock are globally applicable.

Abstract

Importance: Sepsis is a leading cause of death among children worldwide. Current pediatric-specific criteria for sepsis were published in 2005 based on expert opinion. In 2016, Sepsis-3 defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, but it excluded children.

Objective: To update and evaluate criteria for sepsis and septic shock in children.

Evidence Review: The Society of Critical Care Medicine (SCCM) convened a task force of 35 pediatric experts in critical care, emergency medicine, infectious diseases, general pediatrics, nursing, public health, and neonatology from 6 continents. Using evidence from an international survey, systematic review and meta-analysis, and a new organ dysfunction score developed based on ~~analysis of~~ >3 million electronic health record encounters from 10 sites on 4 continents, a modified Delphi consensus process was employed to develop criteria (endorsed by XX societies listed in the Acknowledgements).

Findings: Based on survey data, most pediatric providers used "sepsis" to refer to infection with life-threatening organ dysfunction, which differed from prior pediatric sepsis criteria that used systemic inflammatory response syndrome (SIRS) criteria, which have poor predictive properties, and included the redundant term, "severe sepsis". The SCCM task force recommends that sepsis in children is ~~defined~~identified by ~~as~~ a Phoenix Sepsis Score ≥2 points in children with suspected infection, which indicates potentially life-threatening dysfunction of the respiratory, cardiovascular, coagulation, and/or neurologic systems. Children with a Phoenix Sepsis Score ≥2 points had in-hospital mortality of 7.1% in higher resource settings and 28.5% in lower resource settings, more than 8 times that of children with suspected infection not meeting these criteria. Mortality was higher in children who had organ dysfunction in 1 of 4 organ systems (respiratory, cardiovascular, coagulation, and/or

neurologic) that was not the primary site of infection. Septic shock was defined as children with sepsis who had cardiovascular dysfunction, indicated by ~~and~~ ≥1 cardiovascular point in the Phoenix Sepsis Score, which included severe hypotension for age, blood lactate >5 mmol/L, or need for vasoactive medication. Children with septic shock had an in-hospital mortality rate of 10.8% and 33.5% in higher and lower resource settings, respectively.

Conclusions and relevance: The Phoenix Pediatric Sepsis Criteria for sepsis and septic shock in children were~~as~~ derived and validated by the international SCCM Pediatric Sepsis Definition Task Force using a large international database and survey, systematic review and meta-analysis, and modified Delphi consensus approach. A Phoenix Pediatric Sepsis Score of ≥2 identified potentially life-threatening organ dysfunction in children <18 years of age with infection, and its use has the potential to improve clinical care, epidemiological assessment, and research in pediatric sepsis and septic shock around the world.

In 2017, an estimated 25 million children experienced sepsis worldwide, leading to over 3 million deaths.[1] Many pediatric survivors of sepsis have ongoing physical, cognitive, emotional, and psychological sequelae, which may have long-term effects on them and their families.[2-4] The ~~burden~~ risk of developing sepsis during the early years of life exceeds that of any other age group, with the most disproportionate effect among children in lower resource settings.[5] The World Health Organization resolution on sepsis called for dedicated efforts to improve diagnosis, prevention, and management of sepsis, all of which require use of criteria that accurately identify those with infection who are at high risk of adverse outcomes and death.[6,7] However, such criteria are lacking for children.

The most recent operational criteria specific to pediatric sepsis were published in 2005 by the International Pediatric Sepsis Consensus Conference (IPSCC) and have been widely incorporated in clinical, research, quality improvement, and policy efforts.[8,9] Similar to criteria for adult sepsis at the time (Sepsis-2),[10] the IPSCC criteria were based on expert opinion and characterized sepsis as suspected or confirmed infection in the presence of the systemic inflammatory response syndrome (SIRS). Severe sepsis was defined as sepsis with cardiovascular or respiratory organ dysfunction or dysfunction of ≥2 other organ systems. Septic shock was defined as sepsis with hypotension, need for ~~inotropes~~vasoactive medications, or evidence of impaired perfusion despite resuscitation with ≥40 mL/kg intravenous fluid boluses.

In 2016, the Third International Consensus Conference for Sepsis and Septic Shock (Sepsis-3) revised criteria for sepsis and septic shock in adults used data from nearly 150,000 patients with suspected infection in the U.S. and Germany.[11] The Sepsis-3 definition differentiated sepsis from uncomplicated infection by the presence of life-threatening organ dysfunction caused by a dysregulated host response to infection and ~~defined~~identified sepsis ~~as~~ using an

increase in the Sequential Organ Failure Assessment (SOFA) score by ≥2 points in patients with suspected infection.[12] Septic shock was ~~defined~~identified ~~as~~ in ~~sepsis~~ septic patients with vasopressor use to maintain mean arterial blood pressure ≥65 mm Hg and serum lactate level >2 mmol/L in the absence of hypovolemia.[13] These criteria were not developed with pediatric data nor validated or broadly adapted for children.

Sepsis in children has important differences from that in adults, including age-specific variability of vital signs, developmental age-dependent immune function, and differences in pediatric-specific comorbidities, epidemiology, and outcomes.[14-17] Due to the high morbidity and mortality caused by sepsis in children worldwide, sepsis criteria should be derived and validated specifically for diagnosis in children.

Limitations of current criteria for sepsis in children

The IPSCC criteria for pediatric sepsis include many children with mild illness severity, and recent literature supports that SIRS criteria do not reliably identify children with infection at risk for poor outcomes.[18,19] Furthermore, studies have reported discrepancies in how the criteria are applied clinically, which limit~~ing~~ accurate characterization of sepsis disease burden.[20] Finally, the global applicability of IPSCC criteria for populations in lower resource settings, where disease burden remains greatest, has not been rigorously evaluated.[21-23]

Insights from the process of developing and validating Sepsis-3 in adults and subsequent validation studies provided guidance to inform the revision of pediatric sepsis criteria.[24,25] Sepsis criteria for children should be based on robust, readily available data from diverse clinical settings. Sepsis-3 used the pre-existing SOFA score, but the sensitivity and positive predictive value of pediatric organ dysfunction scores[26-29] for children with infection, are unclear.[30] In addition, while sepsis research ~~in adults~~ has focused on patients requiring intensive care, 80% of pediatric patients with sepsis initially present to emergency

department (ED) or regular inpatient care settings. Therefore, data spanning the entire hospital care continuum should be considered in pediatric patients with sepsis.[31]

The process of developing and validating new criteria for sepsis in children

This manuscript followed the Guidelines on Modifying the Definition of Diseases[32]. A task force was assembled in 2019 by the Society of Critical Care Medicine (SCCM) to update criteria for pediatric sepsis (eTable 1). A diverse panel in terms of discipline, gender, and healthcare setting was considered essential. Pediatric experts in intensive care, emergency medicine, infectious diseases, general pediatrics, informatics, nursing, neonatology, and research were approached based on their expertise and experience in sepsis, ensuring that healthcare settings with different resources and geography on 6 continents were represented. The task force included 35 nurse and physician experts from Australia, Bangladesh, Brazil, Canada, France, India, Italy, Japan, Switzerland, South Africa, United Kingdom, and the United States.

A three-pronged approach (eMethods 1) was used to develop the new criteria, including 1) a global survey of 2835 clinicians,[33] 2) a systematic review and meta-analysis (eMethods 3),[34,35] and 3) a data-driven derivation and validation study,[36] which culminated in a modified Delphi consensus process by the entire task force. At each step, the task force included data from lower and higher resource settings and considered the ~~unique and shared~~ challenges related to limited resources ~~and needs related to resource context~~ (eMethods 2). The global survey and systematic review informed the design of the derivation and validation study, the results of which were used in the consensus process to arrive at the final criteria for pediatric sepsis. During the consensus process, results of analyses were presented to the members of the task force for review, discussion, and voting using REDCap surveys. Consensus was defined as >80% agreement of >80% of the task force members for any given question. If

this threshold was not reached, further discussion (and data analysis where necessary) ensued, followed by additional rounds of voting until consensus was reached (eMethods 4). Preterm neonates (less than 37 weeks gestation at birth) and newborns who remained hospitalized after birth were excluded due to challenges with defining organ dysfunction in babies born prematurely and because of the unique context of perinatally acquired infections.[37,38]

The global survey highlighted concern about inconsistent availability of diagnostic tests and therapeutic tools across settings and a need for new criteria applicable to clinical care, benchmarking, quality improvement, epidemiology, and research.[33] The survey also confirmed the preferred use of the term "sepsis" by pediatric clinicians to refer to~~identify~~ children with infection-associated organ dysfunction rather than with infection-associated SIRS, indicating widespread adoption of the Sepsis-3 conceptual framework.

The systematic review and meta-analysis examined the association of individual clinical and laboratory criteria with the development of sepsis or increased risk for adverse outcomes, including organ dysfunction scores.[34] This confirmed the choice of using validated measures of organ dysfunction for the development of sepsis and septic shock criteria for children.

An international, multicenter electronic health record database was developed using data from health systems in 6 higher resource sites (all in the US) and 4 lower resource sites in Bangladesh, China, Colombia and Kenya. This database included >3 million hospital encounters of patients aged <18 years across various hospital locations (e.g., emergency department, regular inpatient care area, ICU), excluding birth hospitalizations and children with post-conceptional age <37 weeks.[36] Data from each encounter were available from presentation through discharge or death~~,~~ and were divided into derivation and validation datasets, stratified by resource setting (higher vs. lower). The Sepsis-3 conceptual definitions of sepsis as life-threatening organ dysfunction caused by infection and septic shock as sepsis

leading to cardiovascular dysfunction,[12] broadly acceptable in a global survey of clinicians and researchers caring for children,[33] were used as starting points by the task force.

The organ-specific subscores of 8 existing pediatric organ dysfunction scores[26-29] were calculated using data from the first 24 hours of presentation to the hospital and compared to ascertain those best discriminating in-hospital mortality (including in the emergency department) among children with suspected infection, defined as those receiving systemic antimicrobials and undergoing microbiological testing. The best-performing subscores were used as inputs in stacked regression models to determine their association with in-hospital mortality.[36] When subscores performed similarly, the task force voted to determine which to include in the final models.

The final model, which incorporated levels of dysfunction for 4 organ systems (cardiovascular, respiratory, neurological, and coagulation), had comparable performance to a score generated from an 8-organ system model that also included renal, hepatic, endocrine, and immunological dysfunction (Phoenix-8 score[36]). The final 4-organ system model was supported by the task force based on performance and parsimony~~,~~ and was translated into an integer-based score, the Phoenix Sepsis Score, (Table) to optimize utility. Thresholds in the score for sepsis and septic shock were set through the consensus process involving the entire task force, based on sensitivity and positive predictive value. Once completed, the recommendations were circulated to endorsing societies.

Results/recommendations

Criteria to identify children with sepsis

Sepsis in children was ~~defined~~identified using~~by~~ the Phoenix Pediatric Sepsis Criteria, which was ≥2 points in the ~~novel~~ Phoenix Sepsis Score, indicating potentially life-threatening organ

Commented [LS1]: Why highlighted?

Commented [SW2R1]: To make sure we use capital letters in a consistent manner with the data paper - Nelson said they only capitalized Phoenix for this term

dysfunction of the respiratory, cardiovascular, coagulation, and/or neurologic systems in children with suspected or confirmed infection (see Table, Box 1, eTable 2 and eTable 3). Children with suspected infection in the first 24 hours of presentation had in-hospital mortality of 0.7% (1,049/144,379) in higher resource settings and 3.6% (1,016/28,605) in lower resource settings. Among these children, a Phoenix Sepsis Score ≥2 in the first 24 hours of presentation occurred in 7.1% (10,243/144,379) in higher resource settings and 5.4% (1,549/28,605) in lower resource settings and identified children at a higher risk of death (in-hospital mortality 7.1% [726/10,243] in higher resource settings and 28.5% [441/1,549] in lower resource settings). The threshold of Phoenix Sepsis Score ≥2 points had higher positive predictive value and higher or comparable sensitivity for in-hospital mortality in children with confirmed or suspected infection in the first 24 hours when compared with the IPSCC definition of sepsis (i.e., SIRS with suspected or confirmed infection) and severe sepsis (i.e., IPSCC sepsis with IPSCC-based organ dysfunction criteria) in the main analysis and in multiple sensitivity analyses.[36]

Criteria to identify children with septic shock

Pediatric septic shock was ~~defined~~indicated by ~~as~~ sepsis and ≥1 point in the cardiovascular component of the Phoenix Sepsis Score (i.e., severe hypotension for age, blood lactate >5 mmol/L, or receipt of vasoactive medication). Because vasoactive medications may not be available in some clinical settings,[39] this approach allowed the identification of septic shock in the absence of such resources. The prevalence of septic shock among children with sepsis was 53.7% (5,502/10,243) in higher resource settings and 81.3% (1,260/1,549) in lower resource settings and was associated with in-hospital mortality of 10.8% (593/5,502) and 33.5% (422/1,260), respectively.

Organ dysfunction remote from the primary site of infection

Children meeting Phoenix Pediatric Sepsis Criteria included those with organ dysfunction limited to the primary infected organ (e.g., isolated respiratory dysfunction in a child with pneumonia), and those with Phoenix Sepsis scores that indicated organ dysfunction remote from the primary site of infection (e.g. respiratory dysfunction in a child with meningitis). However, children with sepsis and organ dysfunction remote from the primary site of infection, which includes patients with septic shock and multi-organ dysfunction, represent an important, distinct subset of children with sepsis (eFigures 1 and 2). Children with sepsis and remote organ dysfunction had higher mortality (8.0% [700/8,728] vs 32.3% [427/1,320] in higher and lower resource settings, respectively) and represented 85.2% (8,728/10,243) vs 85.2% (1,320/1,549) of children with sepsis in higher and lower resource settings, respectively. In contrast, children with a Phoenix Sepsis Score ≥2 who had organ dysfunction limited to the primary site of infection had a mortality of 1.7% vs 6.1% in higher and lower resource settings, respectively.

Discussion

Main findings

The ~~new~~ Phoenix Pediatric Sepsis Criteria for pediatric sepsis and septic shock, developed with an international survey, a systematic review, analyses of >3 million pediatric encounters, and a modified Delphi consensus process, were designed to reliably identify children with sepsis for the purpose of clinical care, benchmarking, quality improvement, epidemiology, and research in pediatric sepsis. The methodology used to develop the criteria leveraged knowledge gained by the Sepsis-3 process while incorporating novel elements, utilizing a globally diverse task force and relying on data from diverse healthcare systems. ~~The results demonstrate that~~ SIRS should no longer be used to diagnose sepsis in children, and, as any

life-threatening condition is severe, the term severe sepsis is redundant. The Phoenix Pediatric Sepsis criteria were intended to be globally applicable and were named in reference to the symbolic meaning of the phoenix and Phoenix, Arizona, ~~the place~~ where the criteria were presented ~~during~~ at the 2024 SCCM Congress.

Considerations for use of the Phoenix Pediatric Sepsis Criteria

In recent years, many health care institutions caring for adults have implemented SOFA-based extraction procedures in their electronic health care records to identify patients with sepsis, improve sepsis care, and facilitate more accurate coding and billing.[40] The Phoenix Sepsis Score could achieve the same goals for children across diverse settings. ~~Of note, use of the score may affect estimates of the prevalence of sepsis in children depending on care practices and resource availability, particularly related to laboratory evaluation of children with suspected infection.~~

Considerations for organ dysfunctions not included in the Phoenix Sepsis Score

The Phoenix Sepsis Score incorporated sepsis-defining organ dysfunction associated with increased risk of death. Although this score only included 4 organ systems, the model was ~~had excellent~~ sensitive with good positive predictive value when compared with the more complex Phoenix-8 score ~~performance and good content and construct validity~~. The task force prioritized parsimony, performance, and feasibility across different resource~~d~~ settings and thus limited the number of organ systems used to differentiate sepsis and septic shock from infection without sepsis. Although the 4 organs in the Phoenix Sepsis Score are most commonly involved in sepsis, this does not diminish the crucial importance of other organ dysfunction, such as kidney failure[41]. ~~in clinical care and research in terms of qualifying the severity of sepsis, identifying children at risk of long-term morbidity, and defining specific subgroups that may require particular attention.~~ Clinicians and researchers can identify and

classify additional organ dysfunctions (e.g. kidney or hepatic dysfunction), with the Phoenix-8 score.[36]

Considerations for lower resource settings

The Phoenix Pediatric Sepsis Criteria accurately identified sepsis~~proved robust~~ in datasets from lower resource settings,[36] which should facilitate international dissemination and data collection for future studies. The restriction to 4 organ systems reduces requirements for laboratory investigation and data collection. While serum lactate was included in the Phoenix Pediatric Sepsis score and may not available in some settings, the modeling and global survey provide rationale for its inclusion as an essential test whenever possible, even in lower resource settings.[22] The task force acknowledges that organ support such as mechanical ventilation or vasoactive medications may not be available in some lower resource settings, in which case other score items such as a low SaO_2/FiO_2 ratio or low mean arterial blood pressure can be used. In addition, the availability of coagulation parameters may be limited in areas of the world with fewer resources ~~that~~than ~~the many of~~ the sites included in this study, however there is enough redundancy in the score that it still performs well when coagulation parameters are not reported.

Considerations for identification of children at risk of sepsis

The Phoenix Criteria for sepsis and septic shock were intended to ~~define~~identify life-threatening organ dysfunction due to infection in children. They were not designed for screening or early identification of children with suspected sepsis. Thus, it is imperative to continue to develop sepsis screening and early warning tools to correctly identify patients at higher risk of developing sepsis, in both outpatient and inpatient settings, which may lead to early interventions that could decrease the morbidity and mortality associated with pediatric

sepsis. The development of such tools is a future goal of the Pediatric Sepsis Definition Task Force.[42]

Considerations for quality improvement and antimicrobial stewardship

The Phoenix Criteria have the potential to advance pediatric sepsis quality improvement initiatives,[43] although not all patients meeting these criteria will have bacterial infections (e.g., those with viral infections such as adenovirus or dengue). ~~Appropriate process and balancing measures~~ Efforts to enhance antimicrobial stewardship ~~efforts should therefore be~~ integrated into quality improvement work should therefore include both measures of timely antibiotic administration as well as their appropriateness.[44,45]

Implications of organ dysfunction remote from the site of infection and development towards phenotype-based sepsis criteria

After considerable discussion and debate, the task force defined sepsis as infection-associated organ dysfunction regardless of the site of infection. However, in terms of pathophysiology and management, patients with isolated organ dysfunction due to local infection-related tissue damage likely differ from those with organ dysfunction remote from the site of infection, e.g., those who have shock and/or multi-organ dysfunction~~,~~ and a substantially higher mortality[46]. Children with this systemic form of sepsis may harbor distinct targets for translational and clinical research to understand its evolution and optimal treatment ~~, as well as care pathway development, to understand its development and optimal treatment~~.[46] Given the heterogeneity of sepsis, studies should be designed to incorporate phenotype-based criteria ~~that is~~ reflective of individual biology and which may identify patient subgroups that are more likely to benefit from specific therapeutic interventions.[47-49]

Limitations

First, the Phoenix Pediatric Sepsis Criteria inherently represent a simplification of the complex biological processes leading to sepsis in children and the heterogeneity of the condition in terms of host, pathogen, and contextual factors. Second, identification of "infection" by proxy markers such as ~~XX~~ microbiological testing and ~~YY~~ antibiotics is affected by resource availability and local practice. Third, similar to Sepsis-3, we have not attempted to characterize specific markers of dysregulated host response, nor have we validated findings on datasets of higher biological resolution such as those including multi-omics data. Fourth, the data from higher resource settings were derived exclusively from children's hospitals in the US, so they may not be representative of or generalizable to children in other higher resource countries. Fifth, death as a primary endpoint in children with infection, while pragmatic, does not account for infection-associated morbidity, and does not include the long-term effects on children and their families. Sixth, the 24-hour presentation window used in the development of the criteria excluded children who developed sepsis as a result of healthcare-associated infections~~, and, conversely, may be wide given the sometimes fulminant nature of pediatric sepsis~~.[50] Seventh, the temporal sequence of infection followed by organ dysfunction and death does not prove causality, and ~~the criteria~~ dynamic measures of physiology may reflect deteriorating patients more accurately than static/single time point assessments used in the criteria.~~were based on static features rather than dynamic features incorporating change over time~~. Eighth, the new criteria incorporated treatments delivered in response to sepsis (e.g., vasoactive medications) and may not have accounted for other therapies (e.g., sedation) that could have influenced organ dysfunction. Ninth, preterm neonates and term newborns who were hospitalized directly after birth were excluded from this study, so these pediatric sepsis criteria do not apply to those patients.

Conclusion

The Phoenix Pediatric Sepsis Criteria for sepsis and septic shock in children ~~was~~ were derived and validated by the international SCCM Pediatric Sepsis Definition Task Force using a large international database and survey, systematic review and meta-analysis, and modified Delphi consensus approach. A Phoenix Pediatric Sepsis Score of ≥2 identified potentially life-threatening organ dysfunction in children <18 years of age with infection and its use has the potential to improve clinical care, epidemiological assessment, and research in pediatric sepsis and septic shock around the world.

Acknowledgements

The authors would like to thank Kathy Vermoch, Lori Harmon, and Lynn Retford at the Society of Critical Care Medicine for their invaluable assistance throughout this project.

The authors would like to thank Rebeca Mozun, University Children`s Hospital Zurich, Switzerland, for help with creating the Figures.

The authors would also like to thank Clifford S. Deutschman, MS, MD and Derek C. Angus, MD, MPH for their ~~providing~~ invaluable guidance in developing and conducting the work of the task force.

Endorsing societies: *To be populated after acceptance*

Author contributions:

Concept and design: The project plan for the Pediatric Sepsis Definition Taskforce was drafted by LJS, RSW, LRS, ACA, JJZ, and NK. The plan for the data analyses was designed by TDB and LNS-P. The plan for the Delphi process was designed by KM.

Acquisition, analysis, or interpretation of data: TDB and LNS-P led data acquisition and analysis including the building of the harmonized international database used to develop and validate the new criteria. FB, MB, TDB, MJC, IE, CMH, JCJ-B, LNS-P, RSW, and SLW curated data at contributing sites, performed data quality checks, and contributed to data harmonization. TDB and LNS-P led a team including DJA, PED, BM, MNR, and SR who conducted the harmonization and analysis of the data, including the Delphi process results, with clinical and scientific contributions by RSW, LJS, HS, SLW, FB, and ERA, and KM. All Taskforce members contributed to weekly Delphi rounds focusing on the interpretation of the data.

Drafting of the manuscript: LJS and RSW wrote the first draft of the manuscript with contributions from LRS, ACA, KM, TDB, and LNS-P.

Critical review of the manuscript for important intellectual content: All authors contributed to the work of the Taskforce and the Delphi process, provided revisions to the manuscript, and reviewed and approved the final version.

Obtained Funding: JJZ, NK, LJS, and RSW obtained funding for the work through the Society of Critical Care Medicine. TDB, LNS-P, RSW, LJS, HFS, SLW, FB, and ERA obtained NIH funding.

Administrative, technical, or material support: LJS, RSW, ACA, LRS served as co-chairs, and co-vice chairs of the Taskforce and together with SCCM staff were responsible for the organization, minute taking, and conduct of the work.

Pediatric Sepsis Definition Task Force Group Information: See eTable 1.

Conflict of Interest Statements:

Enitan D Carrol has provided scientific advisory board expertise to Thermofisher, Biofire and bioMerieux, but not received any personal fees. All funding paid directly to her employing institution.

Kathleen Chiotos receives grant funding (to her institution) from the Centers for Disease Control and Prevention, and within the past 24 months from the Agency for Healthcare Research and Quality. She received funding for conference travel from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America.

Mark Hall receives consultant fees paid from Abbvie for service on a Data Safety Monitoring Board, licensing income from Kiadis for a product unrelated to sepsis, and study drug free of charge for two clinical trials for which he is the Principal Investigator from Partner Therapeutics and Sobi.

Adrienne G. Randolph is Chair of the International Sepsis Forum, which receives funding from industry sponsors. She has provided advisory expertise to Volition on diagnostics related to sepsis with compensation for travel. She receives royalties from UpToDate for editorial duties related to pediatric sepsis.

Lauren R. Sorce is an elected member of the Executive Committee and serves as President-elect of the Society of Critical Care Medicine (SCCM) 2023-2024 and President 2024-2025. The research presented is that of the author and does not represent SCCM.

Luregn Schlapbach received support from the NOMIS foundation.

Daniela Carla de Souza is the current President of the Latin American Sepsis Institute (ILAS) 2022-2023 and served as Vice-President 2020-2021.

Pierre Tissieres has provided scientific advisory board expertise for Thermofisher, Baxter, Sanofi, Paion, and have served as President of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) 2019-2021 and past-President 2021-2023.

Jerry Zimmerman receives research funding from Immunexpress, Seattle, WA and textbook royalties from Elsevier Publishing.

Funding sources: This work was supported by the Society of Critical Care Medicine and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grant number R01HD105939 to TDB and LNS-P. LJS received support from the

NOMIS foundation. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor decision to submit the manuscript for publication

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. Jan 18 2020;395(10219):200-211. doi:10.1016/S0140-6736(19)32989-7

2. Zimmerman JJ, Banks R, Berg RA, et al. Critical Illness Factors Associated With Long-Term Mortality and Health-Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock. *Crit Care Med*. Mar 2020;48(3):319-328. doi:10.1097/CCM.0000000000004122

3. Carlton EF, Gebremariam A, Maddux AB, et al. New and Progressive Medical Conditions After Pediatric Sepsis Hospitalization Requiring Critical Care. *JAMA Pediatrics*. 2022:e223554. doi:10.1001/jamapediatrics.2022.3554

4. Carlton EF, Barbaro RP, Iwashyna TJ, Prescott HC. Cost of Pediatric Severe Sepsis Hospitalizations. *JAMA Pediatr*. Oct 1 2019;173(10):986-987. doi:10.1001/jamapediatrics.2019.2570

5. Souza DC, Jaramillo-Bustamante JC, Céspedes-Lesczinsky M, et al. Challenges and health-care priorities for reducing the burden of paediatric sepsis in Latin America: a call to action. *Lancet Child Adolesc Health*. Feb 2022;6(2):129-136. doi:10.1016/s2352-4642(21)00341-2

6. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med*. Aug 3 2017;377(5):414-417. doi:10.1056/NEJMp1707170

7. Kissoon N, Reinhart K, Daniels R, Machado MFR, Schachter RD, Finfer S. Sepsis in Children: Global Implications of the World Health Assembly Resolution on Sepsis. *Pediatr Crit Care Med*. Dec 2017;18(12):e625-e627. doi:10.1097/PCC.0000000000001340

8. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. Jan 2005;6(1):2-8. doi:10.1097/01.PCC.0000149131.72248.E6

9. Gebara BM. Values for systolic blood pressure. *Pediatr Crit Care Med*. Jul 2005;6(4):500; author reply 500-1.

10. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Consensus Development Conference Review. *Crit Care Med*. Apr 2003;31(4):1250-6. doi:10.1097/01.CCM.0000050454.01978.3B

11. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. Feb 23 2016;315(8):762-74. doi:10.1001/jama.2016.0288

12. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. Feb 23 2016;315(8):801-10. doi:10.1001/jama.2016.0287

13. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. Feb 23 2016;315(8):775-87. doi:10.1001/jama.2016.0289

14. Schlapbach LJ, Straney L, Alexander J, et al. Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. *Lancet Infect Dis*. Jan 2015;15(1):46-54. doi:10.1016/S1473-3099(14)71003-5

15. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med*. Mar 1 2003;167(5):695-701. doi:10.1164/rccm.200207-682OC

16. de Souza DC, Goncalves Martin J, Soares Lanziotti V, et al. The epidemiology of sepsis in paediatric intensive care units in Brazil (the Sepsis PREvalence Assessment Database in Pediatric population, SPREAD PED): an observational study. *Lancet Child Adolesc Health*. Dec 2021;5(12):873-881. doi:10.1016/S2352-4642(21)00286-8

17. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med*. May 15 2015;191(10):1147-57. doi:10.1164/rccm.201412-2323OC

18. Scott HF, Deakyne SJ, Woods JM, Bajaj L. The prevalence and diagnostic utility of systemic inflammatory response syndrome vital signs in a pediatric emergency department. *Acad Emerg Med*. Apr 2015;22(4):381-9. doi:10.1111/acem.12610

19. Schlapbach LJ, Straney L, Bellomo R, MacLaren G, Pilcher D. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. *Intensive Care Med*. Feb 2018;44(2):179-188. doi:10.1007/s00134-017-5021-8

20. Weiss SL, Fitzgerald JC, Maffei FA, et al. Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Crit Care*. Sep 16 2015;19:325. doi:10.1186/s13054-015-1055-x

21. Wiens MO, Larson CP, Kumbakumba E, et al. Application of Sepsis Definitions to Pediatric Patients Admitted With Suspected Infections in Uganda. *Pediatr Crit Care Med*. May 2016;17(5):400-5. doi:10.1097/PCC.0000000000000708

22. Carrol ED, Ranjit S, Menon K, et al. Operationalizing Appropriate Sepsis Definitions in Children Worldwide: Considerations for the Pediatric Sepsis Definition Taskforce. *Pediatr Crit Care Med*. Apr 25 2023;doi:10.1097/pcc.0000000000003263

23. Sankar J, Dhochak N, Kumar K, Singh M, Sankar MJ, Lodha R. Comparison of International Pediatric Sepsis Consensus Conference Versus Sepsis-3 Definitions for Children Presenting With Septic Shock to a Tertiary Care Center in India: A Retrospective Study. *Pediatr Crit Care Med*. Mar 2019;20(3):e122-e129. doi:10.1097/PCC.0000000000001864

24. Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA*. Jan 17 2017;317(3):290-300. doi:10.1001/jama.2016.20328

25. Machado FR, Nsutebu E, AbDulaziz S, et al. Sepsis 3 from the perspective of clinicians and quality improvement initiatives. *Journal of critical care*. Aug 2017;40:315-317. doi:10.1016/j.jcrc.2017.04.037

26. Schlapbach LJ, Weiss SL, Bembea MM, et al. Scoring Systems for Organ Dysfunction and Multiple Organ Dysfunction: The PODIUM Consensus Conference. *Pediatrics*. Jan 1 2022;149(Supplement_1):S23-s31. doi:10.1542/peds.2021-052888D

27. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med*. Jul 2013;41(7):1761-73. doi:10.1097/CCM.0b013e31828a2bbd

28. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. *JAMA pediatrics*. 2017;171(10):e172352. doi:10.1001/jamapediatrics.2017.2352

29. Bembea MM, Agus M, Akcan-Arikan A, et al. Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Contemporary Organ Dysfunction Criteria: Executive Summary. *Pediatrics*. Jan 1 2022;149(Supplement_1):S1-s12. doi:10.1542/peds.2021-052888B

30. Schlapbach LJ, Goertz S, Hagenbuch N, et al. Organ Dysfunction in Children With Blood Culture-Proven Sepsis: Comparative Performance of Four Scores in a National Cohort Study. *Pediatr Crit Care Med*. Oct 25 2023;doi:10.1097/PCC.0000000000003388

31. Balamuth F, Scott HF, Weiss SL, et al. Validation of the Pediatric Sequential Organ Failure Assessment Score and Evaluation of Third International Consensus Definitions for Sepsis and Septic Shock Definitions in the Pediatric Emergency Department. *JAMA Pediatrics*. 2022;doi:10.1001/jamapediatrics.2022.1301

32. Doust J, Vandvik PO, Qaseem A, et al. Guidance for Modifying the Definition of Diseases: A Checklist. *JAMA Intern Med*. Jul 1 2017;177(7):1020-1025. doi:10.1001/jamainternmed.2017.1302

33. Morin L, Hall M, de Souza D, et al. The Current and Future State of Pediatric Sepsis Definitions: An International Survey. *Pediatrics*. May 25 2022;149(6)doi:10.1542/peds.2021-052565

34. Menon K, Schlapbach LJ, Akech S, et al. Criteria for Pediatric Sepsis-A Systematic Review and Meta-Analysis by the Pediatric Sepsis Definition Taskforce. *Crit Care Med*. Jan 1 2022;50(1):21-36. doi:10.1097/CCM.0000000000005294

35. Menon K, Schlapbach LJ, Akech S, et al. Pediatric Sepsis Definition-A Systematic Review Protocol by the Pediatric Sepsis Definition Taskforce. *Crit Care Explor*. Jun 2020;2(6):e0123. doi:10.1097/cce.0000000000000123

36. Sanchez-Pinto LN, Bennett TD, Dewitt PE, al. e. Development and Validation of the Phoenix Criteria for Pediatric Sepsis and Septic Shock *manuscript under review*. 2023;

37. Molloy EJ, Wynn JL, Bliss J, et al. Neonatal sepsis: need for consensus definition, collaboration and core outcomes. *Pediatr Res*. Jul 2020;88(1):2-4. doi:10.1038/s41390-020-0850-5

38. Wynn JL. Defining neonatal sepsis. *Curr Opin Pediatr*. Apr 2016;28(2):135-40. doi:10.1097/MOP.0000000000000315

39. Evans IVR, Phillips GS, Alpern ER, et al. Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. *JAMA*. Jul 24 2018;320(4):358-367. doi:10.1001/jama.2018.9071

40. Sahni NR, Carrus B. Artificial Intelligence in U.S. Health Care Delivery. *New England Journal of Medicine*. 2023;389(4):348-358. doi:10.1056/NEJMra2204673

41. Starr MC, Banks R, Reeder RW, et al. Severe Acute Kidney Injury Is Associated With Increased Risk of Death and New Morbidity After Pediatric Septic Shock. *Pediatr Crit Care Med*. Sep 2020;21(9):e686-e695. doi:10.1097/pcc.0000000000002418

42. Jimenez-Zambrano A, Ritger C, Rebull M, et al. Clinical decision support tools for paediatric sepsis in resource-poor settings: an international qualitative study. *BMJ open*. Oct 24 2023;13(10):e074458. doi:10.1136/bmjopen-2023-074458

43. Prescott HC, Posa PJ, Dantes R. The Centers for Disease Control and Prevention's Hospital Sepsis Program Core Elements. *JAMA*. 2023;doi:10.1001/jama.2023.16693

44. Klompas M, Rhee C, Singer M. The Importance of Shifting Sepsis Quality Measures From Processes to Outcomes. *JAMA*. 2023;doi:10.1001/jama.2023.0340

45. Schlapbach LJ, Weiss SL, Wolf J. Reducing Collateral Damage From Mandates for Time to Antibiotics in Pediatric Sepsis-Primum Non Nocere. *JAMA Pediatr*. May 1 2019;173(5):409-410. doi:10.1001/jamapediatrics.2019.0174

46. Weiss SL, Carcillo JA, Leclerc F, et al. Refining the Pediatric Multiple Organ Dysfunction Syndrome. *Pediatrics*. Jan 1 2022;149(Supplement_1):S13-s22. doi:10.1542/peds.2021-052888C

47. Komorowski M, Green A, Tatham KC, Seymour C, Antcliffe D. Sepsis biomarkers and diagnostic tools with a focus on machine learning. *eBioMedicine*. 2022;86doi:10.1016/j.ebiom.2022.104394

48. Sanchez-Pinto LN, Stroup EK, Pendergrast T, Pinto N, Luo Y. Derivation and Validation of Novel Phenotypes of Multiple Organ Dysfunction Syndrome in Critically Ill Children. *JAMA Netw Open*. Aug 3 2020;3(8):e209271. doi:10.1001/jamanetworkopen.2020.9271

49. Seymour CW, Kennedy JN, Wang S, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA*. May 28 2019;321(20):2003-2017. doi:10.1001/jama.2019.5791

50. Schlapbach LJ, MacLaren G, Festa M, et al. Prediction of pediatric sepsis mortality within 1 h of intensive care admission. *Intensive Care Med*. Aug 2017;43(8):1085-1096. doi:10.1007/s00134-017-4701-8

Table. The Phoenix Sepsis Score.

	0 points	1 point	2 points	3 points
Respiratory (0-3 points)	P/F ≥400 or S/F[1] ≥292	P/F <400 on any respiratory support[2] or S/F[1] <292 on any respiratory support	P/F 100-200 and IMV or S/F[1] 148-220 and IMV	P/F <100 and IMV or S/F[1] <148 and IMV
Cardiovascular (0-6 points)	• No vasoactive medications[3] • Lactate[4] <5 mmol/L Age-based • MAP[5] (mmHg) <1 month >30 1 to 11 months >38 1 to <2 years >43 2 to <5 years >44 5 to <12 years >48 12 to 17 years >51	1 point each (up to 3) for: • 1 vasoactive medication[3] • Lactate[4] 5-10.9 mmol/L • MAP[5] (mmHg) 17-30 25-38 31-43 32-44 36-48 38-51	2 points each (up to 6) for: • ≥2 vasoactive medications[3] • Lactate[4] ≥11 mmol/L • MAP[5] (mmHg) <17 <25 <31 <32 <36 <38	
Coagulation[6] (0-2 points)	• Platelets ≥100 K/µL • INR[7] ≤1.3 • D-Dimer ≤2 mg/L FEU • Fibrinogen ≥100 mg/dL	1 point each (max. 2 points) for: • Platelets <100 K/µL • INR[7] >1.3 • D-Dimer >2 mg/L FEU • Fibrinogen <100 mg/dL		
Neurologic[8] (0-2 points)	• GCS[9] >10 • Pupils reactive	GCS[9] ≤10	Fixed pupils bilaterally	

Phoenix Pediatric Sepsis Criteria
• **Sepsis**: Suspected infection and Phoenix Sepsis Score ≥2 points • **Septic shock**: Sepsis with ≥1 cardiovascular point(s)

P/F, PaO_2/FiO_2 ratio; *S/F*, SpO_2/FiO_2 ratio (only SpO_2 of 97% or less); *IMV*, invasive mechanical ventilation; *MAP*, mean arterial pressure; *INR*, international normalized ratio of prothrombin time; *GCS*, Glasgow coma scale score.

Notes for use: The score may be calculated in the absence of some variables (e.g., even if lactate level is not measured and vasoactive medications are not used, a cardiovascular score can still be ascertained using blood pressure). It is expected that laboratory tests and other measurements will be obtained at the discretion of the medical team based on clinical judgment. Unmeasured variables contribute no points to the score. Ages are not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, children with post-conceptional age <37 weeks, or those 18 years of age or older.

[1]S/F ratio is only calculated if SpO_2 is 97% or less.

[2]The respiratory dysfunction of 1 point can be assessed in any patient on oxygen, high flow, non-invasive positive pressure, or IMV respiratory support, and includes P/F <200 and S/F <220 in children who are not on IMV.

[3]Vasoactive medications include any dose of epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and/or vasopressin (for shock).

[4]Lactate reference range is 0.5-2.2 mmol/L.

[5]~~S/F ratio is only calculated if SpO_2 is 97% or less.~~ Use measured MAP preferentially (invasive arterial if available or non-invasive oscillometric), and if measured MAP is not available, a calculated MAP (1/3*systolic + 2/3*diastolic) may be used as an alternative. Lactate can be arterial or venous.

[6]~~Lactate reference range is 0.5-2.2 mmol/L. Vasoactive medications include any dose of epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and/or vasopressin (for shock).~~ The coagulation variables reference ranges are: platelets 150-450 K/µL; D-Dimer <0.5 mg/L FEU; Fibrinogen 180-410 mg/dL.

[7]The INR reference range is based on the local reference prothrombin time.

[8]The neurologic dysfunction subscore was pragmatically validated in both sedated and non-sedated patients, and those on and off IMV support.

[9]The GCS measures level of consciousness based on verbal, eye, and motor response and ranges from 3 to 15, with a higher score indicating better neurological function. ~~Ages are not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, children with post-conceptional age <37 weeks, or those 18 years of age or older.~~

372

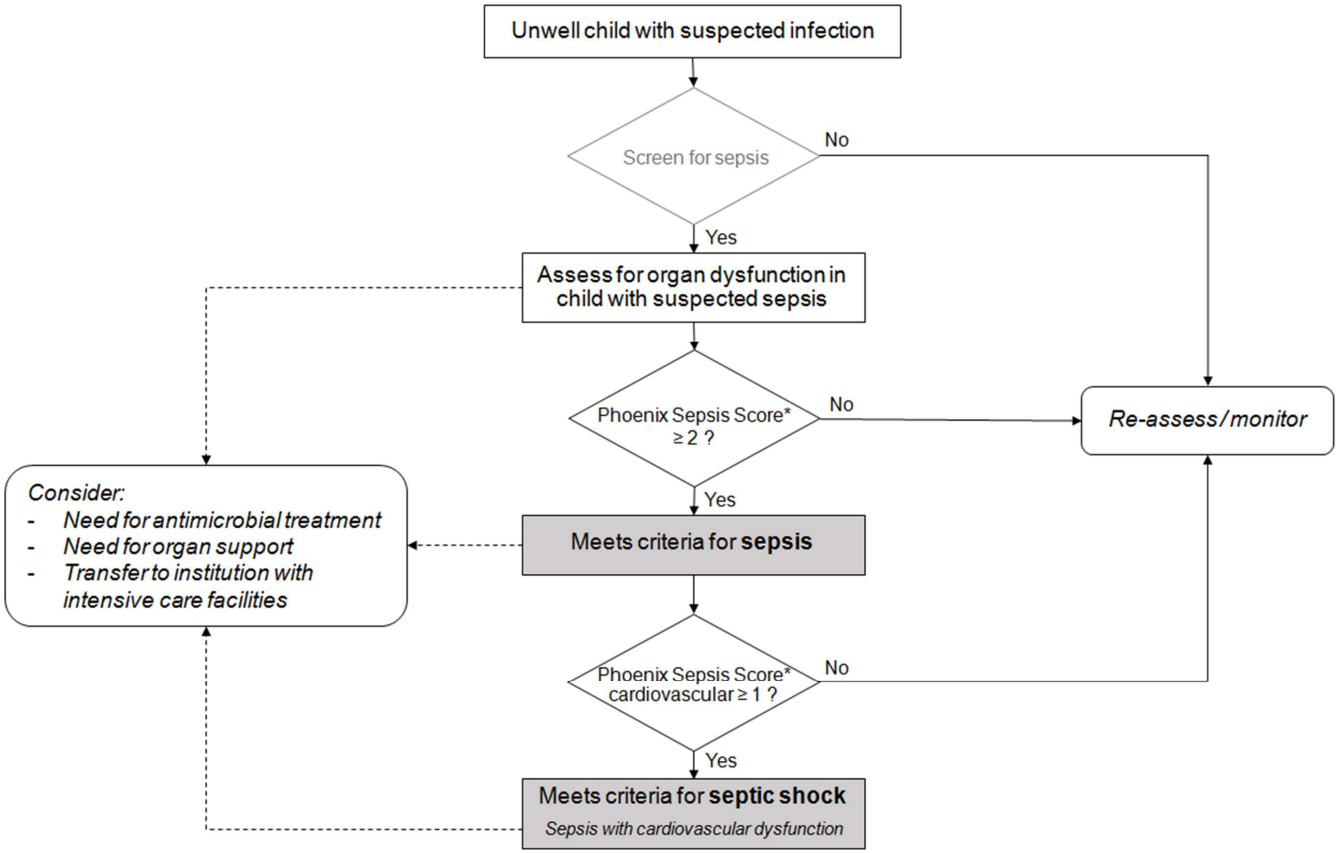
Box 1. Key Concepts for pediatric sepsis.

- Pediatric sepsis criteria apply to children <18 years of age but are not applicable to newborns or babies with post-conceptional age <37 weeks.
- The former criteria based on systemic inflammatory response syndrome (SIRS) should not be used to diagnose sepsis in children.
- The former term "severe sepsis" should no longer be used, as sepsis is life-threatening organ dysfunction associated with infection, and is thus indicative of a severe disease state.
- Life-threatening organ dysfunction in children with suspected or confirmed infection can be identified in settings with different resources as a Phoenix Sepsis Score of at least two points. The new Phoenix Sepsis Score is a composite four-organ system model including criteria for cardiovascular, respiratory, neurological, coagulation dysfunction.
- Septic shock is a subset of sepsis where patients manifest cardiovascular dysfunction, which is associated with higher mortality. Septic shock can be operationalized by a cardiovascular subscore of at least 1 point of the Phoenix Sepsis Score in children with sepsis.
- Children with sepsis who manifest organ dysfunction remote from the site of infection have a higher risk of death, suggesting life-threatening systemic processes.
- These criteria may facilitate harmonized data collection on epidemiology of disease globally and may serve to support clinical care, quality improvement, benchmarking, and research to improve outcomes for children with sepsis.

Box 2. Future directions and considerations for research.

- Timely and accurate recognition of sepsis requires data-driven screening tools with reasonable precision and high sensitivity, which are adaptable to different healthcare settings. While the Phoenix Pediatric Sepsis Criteria performed well across over 3 million pediatric encounters in different settings, future independent validation (especially in lower resource, remote, and mixed healthcare settings) is warranted.
- Work is also required to ensure such tools perform robustly across age groups and for patients with chronic conditions such as technology dependance, congenital conditions, or severe malnutrition.
- The unique developmental context of sepsis in preterm infants, as well as that of perinatal infections, combined with difficulties in robust operationalization of organ dysfunction for this vulnerable patient group, necessitates efforts to validate sepsis and septic shock criteria for preterm infants.
- Children with sepsis who manifest organ dysfunction remote from the site of infection, including patients with septic shock and those with sepsis-associated multi-organ dysfunction, should be targeted by future trials.
- Improved understanding of types of host response to infection associated with organ dysfunction, for example through multi-omics studies and harvesting of large EHR datasets, is a prerequisite to decipher biological manifestations of dysregulated host response(s) in sepsis, which then can inform the design of personalized approaches to sepsis in children.
- The global challenges related to antimicrobial resistance demand investment to test efficacy and effectiveness of novel clinical and molecular markers which can reliably discriminate children evaluated for sepsis necessitating targeted antimicrobial therapy.

Figure. Proposed diagnostic flow to characterize patients using the new criteria for sepsis and septic shock in children. Sepsis diagnosis is operationalized as 2 points or more on the Phoenix Sepsis Score, and septic shock as sepsis with cardiovascular dysfunction (see Table). Institutionally available procedures to identify deteriorating patients with infection should be followed for screening. There is a need for data-driven tools to screen children at risk of development of sepsis.


Unwell child with suspected infection
Screen for sepsis
No
Yes
Assess for organ dysfunction in child with suspected sepsis
Phoenix Sepsis Score* ≥ 2 ?
No
Re-assess/monitor
Yes
Consider:
- Need for antimicrobial treatment
- Need for organ support
- Transfer to institution with intensive care facilities
Meets criteria for sepsis
Phoenix Sepsis Score* cardiovascular ≥ 1 ?
No
Yes
Meets criteria for septic shock
Sepsis with cardiovascular dysfunction