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International Consensus Criteria for Pediatric Sepsis and Septic Shock

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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, the Third International Consensus Definitions for Sepsis and Septic Shock (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 more than 3 million electronic health record encounters from 10 sites on 4 continents, a modified Delphi consensus process was employed to develop criteria.

FINDINGS Based on survey data, most pediatric clinicians 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 be identified by a Phoenix Sepsis Score of at least 2 points in children with suspected infection, which indicates potentially life-threatening dysfunction of the respiratory, cardiovascular, coagulation, and/or neurological systems. Children with a Phoenix Sepsis Score of at least 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 at least 1 of 4—respiratory, cardiovascular, coagulation, and/or neurological—organ systems that was not the primary site of infection. *Septic shock* was defined as children with sepsis who had cardiovascular dysfunction, indicated by at least 1 cardiovascular point in the Phoenix Sepsis Score, which included severe hypotension for age, blood lactate exceeding 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 sepsis criteria for sepsis and septic shock in children 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 Sepsis Score of at least 2 identified potentially life-threatening organ dysfunction in children younger than 18 years 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.

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Supplemental content

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In 2017, an estimated 25 million children experienced sepsis worldwide, leading to more than 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 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 criteria specific to pediatric sepsis were published in 2005 by the International Pediatric Sepsis Consensus Conference (IPSCC) and have been widely incorporated in clinical practice, research, quality improvement, and policy efforts.[8,9] Similar to criteria for adult sepsis at the time—the 2001 Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society, and Surgical Infection Society International Sepsis Definitions Consensus Conference (Sepsis-2)[10]—which developed a second recommendation, 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 at least 2 other organ systems. *Septic shock* was defined as sepsis with hypotension, need for vasoactive medications, or evidence of impaired perfusion despite resuscitation with 40 mL/kg or more of 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 using data from nearly 150 000 patients with suspected infection in the US 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 identified sepsis using an increase in the Sequential Organ Failure Assessment (SOFA) score by at least 2 points in patients with suspected infection.[12] Septic shock was identified in patients with sepsis with vasopressor use to maintain mean arterial blood pressure of 65 mm Hg or higher and serum lactate level more than 2 mmol/L (18.02 mg/dL) 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 the SIRS criteria do not reliably identify children with infection at risk of poor outcomes.[18,19] Furthermore, studies have reported discrepancies in how the criteria are applied clinically, which limit 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 preexisting 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, although sepsis research has focused on patients requiring intensive care, 80% of pediatric patients with sepsis initially present to emergency department or regular inpatient care settings. Therefore, data spanning the entire hospital care continuum should be considered in pediatric patients with sepsis.[31]

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, and analysis of more than 3 million pediatric health care encounters, and consensus process, new criteria for sepsis and septic shock in children were developed. Pediatric sepsis in children (<18 years) with suspected infection was identified by at least 2 points in the novel Phoenix Sepsis Score, including dysfunction of the respiratory, cardiovascular, coagulation, and/or neurological systems; and septic shock as sepsis with at least 1 cardiovascular point in the Phoenix Sepsis Score.

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

The Process of Developing and Validating New Criteria for Sepsis in Children

This article follows the Guidelines on Modifying the Definition of Diseases.[32] A task force was assembled in 2019 by the SCCM to update criteria for pediatric sepsis (eTable 1 in Supplement 1). A diverse panel in terms of discipline, gender, and health care 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 health care 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 3-pronged approach (eMethods 1 in Supplement 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 in Supplement 1),[34,35] and (3) a data-driven derivation and validation study,[36] which culminated in

Table. The Phoenix Sepsis Score[a]

Variables	0 Points	1 Point	2 Points	3 Points
Respiratory, 0-3 points				
	Pao_2:FIo_2 ≥400 or Spo_2:FIo_2 ≥292[b]	Pao_2:FIo_2 <400 on any respiratory support or Spo_2:FIo_2 <292 on any respiratory support[b,c]	Pao_2:FIo_2 100-200 and IMV or Spo_2:FIo_2 148-220 and IMV[b]	Pao_2:FIo_2<100 and IMV or Spo_2:FIo_2 <148 and IMV[b]
Cardiovascular, 0-6 points				
		1 Point each (up to 3)	2 Points each (up to 6)	
	No vasoactive medications[d]	1 Vasoactive medication[d]	≥2 Vasoactive medications[d]	
	Lactate <5 mmol/L[e]	Lactate 5-10.9 mmol/L[e]	Lactate ≥11 mmol/L[e]	
Age based[f]				
	Mean arterial pressure, mm Hg[g]			
<1 mo	>30	17-30	<17	
1 to 11 mo	>38	25-38	<25	
1 to <2 y	>43	31-43	<31	
2 to <5 y	>44	32-44	<32	
5 to <12 y	>48	36-48	<36	
12 to 17 y	>51	38-51	<38	
Coagulation (0-2 points)[h]				
		1 Point each (maximum 2 points)		
	Platelets ≥100 × 10^3/μL	Platelets <100 × 10^3/μL		
	International normalized ratio ≤1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
Neurological (0-2 points)[i]				
	Glasgow Coma Scale score >10; pupils reactive[j]	Glasgow Coma Scale score ≤10[j]	Fixed pupils bilaterally	
Phoenix sepsis criteria				
Sepsis	Suspected infection and Phoenix Sepsis Score ≥2 points			
Septic shock	Sepsis with ≥1 cardiovascular point(s)			

Abbreviations: FEU, fibrinogen equivalent units; IMV, invasive mechanical ventilation; INR, international normalized ratio of prothrombin time; MAP, mean arterial pressure; Pao_2:FIo_2, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; Spo_2, oxygen saturation measured by pulse oximetry (only Spo_2 of ≤97%).

SI conversion factor: To convert lactate from mmol/L to mg/dL, divide by 0.111.

[a] The score may be calculated in the absence of some variables (eg, 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, neonates whose postconceptional age is younger than 37 weeks, or those 18 years of age or older.

[b] Spo_2:FIo_2 ratio is only calculated if Spo_2 is 97% or less.

[c] The respiratory dysfunction of 1 point can be assessed in any patient receiving oxygen, high-flow, noninvasive positive pressure, or IMV respiratory support, and includes a Pao_2:FIo_2 ratio of less than 200 and a Spo_2:FIo_2 ratio of less than 220 in children who are not receiving IMV. For children receiving IMV with a Pao_2:FIo_2 less than 200 and Spo_2:FIo_2 less than 220, see criteria for 2 and 3 points.

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

[e] Lactate reference range is 0.5 to 2.2 mmol/L. Lactate can be arterial or venous.

[f] Age is not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, children whose postconceptional age is younger than 37 weeks, or those 18 years or older.

[g] Use measured MAP preferentially (invasive arterial if available or noninvasive oscillometric), and if measured MAP is not available, a calculated MAP (1/3 × systolic + 2/3 × diastolic) may be used as an alternative.

[h] Coagulation variable reference ranges: platelets, 150 to 450 × 10^3/μL; D-dimer, <0.5 mg/L FEU; fibrinogen, 180 to 410 mg/dL. The INR reference range is based on the local reference prothrombin time.

[i] The neurological dysfunction subscore was pragmatically validated in both sedated and nonsedated patients, and those receiving or not receiving IMV support.

[j] The Glasgow Coma Scale score measures level of consciousness based on verbal, eye, and motor response (range, 3-15, with a higher score indicating better neurological function).

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 challenges related to limited resources (eMethods 2 in Supplement 1). 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 vote using REDCap surveys. Consensus was defined as more than 80% agreement of more than 80% of the task force members for any given question. If this

Box 1. Key Concepts for Pediatric Sepsis

- Pediatric sepsis criteria apply to children younger than 18 years but are not applicable to newborns or neonates whose postconceptional age is younger than 37 weeks.
- The former criteria based on systemic inflammatory response syndrome should not be used to diagnose sepsis in children.
- The former term *severe sepsis* should no longer be used because 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 2 points. The new Phoenix Sepsis Score is a composite 4-organ system model including criteria for cardiovascular, respiratory, neurological, and coagulation dysfunction.
- Septic shock is a subset of sepsis in patients with manifested 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 among 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.

threshold was not reached, further discussion (and data analysis where necessary) ensued, followed by additional rounds of voting until consensus was reached (eMethods 4 in Supplement 1). Preterm neonates (<37 weeks' gestation at birth) and newborns who remained hospitalized after birth were excluded due to challenges with defining organ dysfunction in neonates 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 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 of 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 more than 3 million hospital encounters of patients younger than 18 years across various hospital locations (eg, emergency department, regular inpatient care area, intensive care unit), excluding birth hospitalizations and children whose postconceptional age was younger than 37 weeks.[36] Data from each encounter were available from presentation through discharge or death and were divided into derivation and validation data sets, 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 were compared to ascertain those that were best able to discriminate 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.

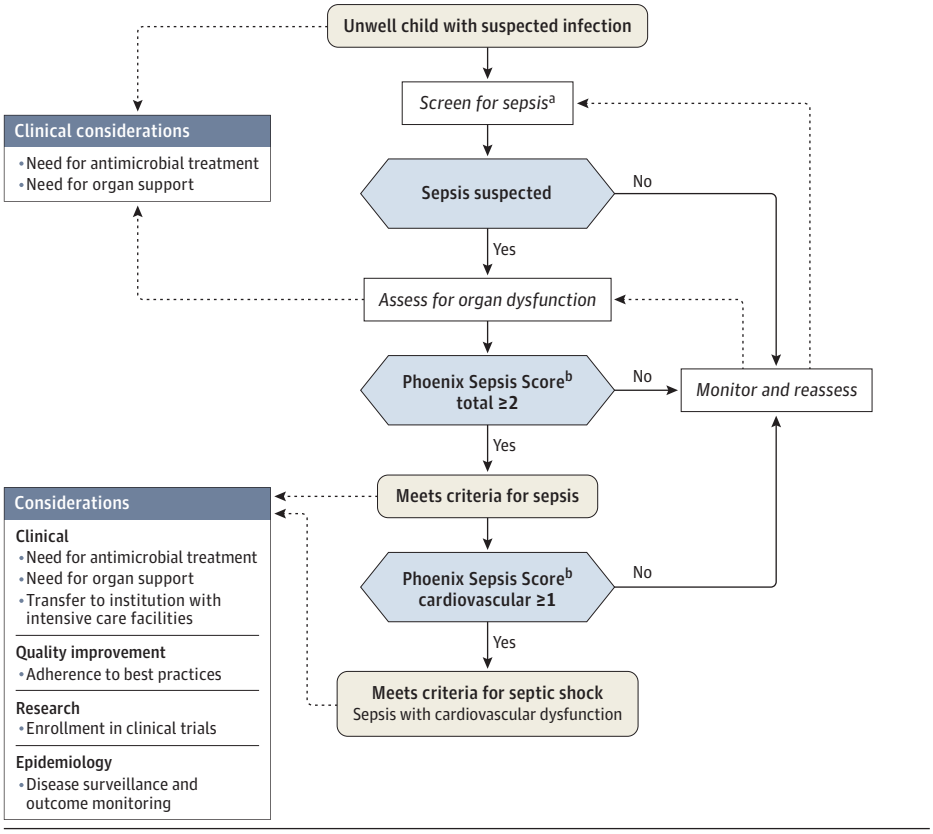
The final model, which incorporated levels of dysfunction for 4—cardiovascular, respiratory, neurological, and coagulation—organ systems, had comparable performance with a score generated from an 8-organ system model that also included renal, hepatic, endocrine, and immunological dysfunction (Phoenix-8 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

Criteria to Identify Children With Sepsis

Sepsis in children was identified using the Phoenix sepsis criteria, which was 2 or more points in the Phoenix Sepsis Score, indicating potentially life-threatening organ dysfunction of the respiratory, cardiovascular, coagulation, and/or neurological systems in children with suspected or confirmed infection (Table, **Box 1**, and eTables 2 and 3 in Supplement 1). Children with suspected infection in the first 24 hours of presentation had in-hospital mortality of 0.7% (1049 of 144 379) in higher-resource settings and 3.6% (1016 of 28 605) in lower-resource settings. Among these children, a Phoenix Sepsis Score of at least 2 in the first 24 hours of presentation occurred in 7.1% (10 243 of 144 379) in higher-resource settings and 5.4% (1549 of 28 605) in lower-resource settings and identified children at a higher risk of death (in-hospital mortality of 7.1% [726 of 10 243] in higher-resource settings and 28.5% [441 of 1549] in lower-resource settings; eFigure 2 in Supplement 1). The threshold of Phoenix Sepsis Score of at least 2 points had higher positive predictive value and higher or comparable sensitivity

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 the Table).

[a] 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, which must be rigorously evaluated in different populations and contexts. The Phoenix Sepsis Score is not intended for early screening or recognition of possible sepsis and management before organ dysfunction is overt.

[b] Please refer to the Table for the Phoenix Sepsis Score.

for in-hospital mortality in children with confirmed or suspected infection in the first 24 hours when compared with the IPSCC definition of sepsis (ie, SIRS with suspected or confirmed infection) and severe sepsis (ie, 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 identified in children with sepsis by at least 1 point in the cardiovascular component of the Phoenix Sepsis Score (ie, severe hypotension for age, blood lactate >5 mmol/L, or receipt of vasoactive medication; **Figure**). 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% (5502 of 10 243) in higher-resource settings and 81.3% (1260 of 1549) in lower-resource settings and was associated with in-hospital mortality of 10.8% (593 of 5502) and 33.5% (422 of 1260), respectively.

Organ Dysfunction Remote From the Primary Site of Infection

Children meeting Phoenix sepsis criteria included those with organ dysfunction limited to the primary infected organ (eg, 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 (eg, 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 those with multiorgan dysfunction, represent an important, distinct subset of children with sepsis (eFigures 1 and 2 in Supplement 1). Children with sepsis and remote organ dysfunction had higher mortality (8.0% [700 of 8728] and 32.3% [427 of 1320] in higher- and lower-resource settings, respectively) and represented 85.2% (8728 of 10 243) and 85.2% (1320 of 1549) of children with sepsis in higher- and lower-resource settings, respectively. In contrast, children with a Phoenix Sepsis Score of at least 2 who had organ dysfunction limited to the primary site of infection had a mortality of 1.7% and 6.1% in higher- and lower-resource settings, respectively.

Discussion

The Phoenix criteria for pediatric sepsis and septic shock, developed with an international survey, a systematic review, analyses of more than 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 method used to develop the criteria leveraged knowledge gained by the Sepsis-3 process while incorporating novel elements, using a globally diverse

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 health care settings. Although the Phoenix sepsis criteria performed well across over 3 million pediatric encounters in different settings, future independent validation (especially in lower-resource, remote, and mixed-health care settings) is warranted.
- Work is also required to ensure that such tools perform robustly across age groups and for patients with chronic conditions such as technology dependence, 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 multiorgan dysfunction, should be targeted for future trials.
- Improved understanding of types of host response to infection associated with organ dysfunction, for example through multiomics studies and harvesting of large electronic health record 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 treating sepsis in children.
- The global challenges related to antimicrobial resistance demand investment to test efficacy and effectiveness of novel clinical and molecular markers that can reliably discriminate children evaluated for sepsis necessitating targeted antimicrobial therapy.

task force and relying on data from diverse health care systems. SIRS should no longer be used to diagnose sepsis in children, and because any life-threatening condition is severe, the term *severe sepsis* is redundant. The Phoenix criteria were intended to be globally applicable and were named in reference to the symbolic meaning of the mythological phoenix and the location where the criteria were presented during the 2024 SCCM Congress (Phoenix, Arizona).

Considerations

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.

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 sensitive with good positive predictive value when compared with the more complex Phoenix-8 Score. The task force prioritized parsimony, performance, and feasibility across different resource 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 the assessment and management of other organ dysfunction.[41] Clinicians and researchers can identify and classify additional organ dysfunctions (eg, kidney or hepatic dysfunction), with the Phoenix-8 Score.[36]

Lower-Resource Settings

The Phoenix sepsis criteria accurately identified sepsis in data sets 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. Although serum lactate was included in the Phoenix Sepsis Score and may not be 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 arterial oxygen saturation to fraction of inspired oxygen (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 than the sites included in this study; however, there is enough redundancy in the score that it still performs well in identifying children with sepsis when coagulation parameters are not reported.

Identification of Children at Risk of Sepsis

The Phoenix criteria for sepsis and septic shock were intended to identify life-threatening organ dysfunction due to infection in children. They were not designed for screening children at risk for developing sepsis 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 SCCM Pediatric Sepsis Definition Task Force.[42]

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 (eg, those with viral infections such as adenovirus or dengue). Efforts to enhance antimicrobial stewardship integrated into quality improvement work should therefore include both measures of timely antimicrobial administration as well as its appropriateness.[44,45]

Development Toward 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, eg, those who have shock and/or multiorgan 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.[46] Given the heterogeneity of sepsis, studies should be designed to incorporate phenotype-based criteria reflective of individual biology and that may identify patient subgroups that are more likely to benefit from specific therapeutic interventions.[47-49]

Limitations

First, the Phoenix 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 (**Box 2**). Second, identification of "infection" by proxy markers such as microbiological testing and 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 data sets of higher biological resolution such as those including multiomics 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 end point 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 health care–associated infections.[50] Seventh, the temporal sequence of infection followed by organ dysfunction and death does not prove causality, and dynamic measures of physiology may reflect deteriorating patients more accurately than static or single-time point assessments used in the criteria. Eighth, the new criteria incorporated treatments delivered in response to sepsis (eg, vasoactive medications) and may not have accounted for other therapies (eg, 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.

Conclusions

The Phoenix sepsis criteria for sepsis and septic shock in children 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 Sepsis Score of at least 2 identified potentially life-threatening organ dysfunction in children younger than 18 years 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.

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Author Contributions: Drs Sanchez-Pinto and Bennett had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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