International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*

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Objective: **Although general definitions of the sepsis continuum have been published for adults, no such work has been done for the pediatric population. Physiologic and laboratory variables used to define the systemic inflammatory response syndrome (SIRS) and organ dysfunction require modification for the developmental stages of children. An international panel of 20 experts in sepsis and clinical research from five countries (Canada, France, Netherlands, United Kingdom, and United States) was convened to modify the published adult consensus definitions of infection, sepsis, severe sepsis, septic shock, and organ dysfunction for children.**

Design: **Consensus conference.**

Methods: **This document describes the issues surrounding consensus on four major questions addressed at the meeting: a) How should the pediatric age groups affected by sepsis be delineated? b) What are the specific definitions of pediatric SIRS, infection, sepsis, severe sepsis, and septic shock? c) What are the specific definitions of pediatric organ failure and the validity of pediatric organ failure scores? d) What are the appropriate study populations and study end points required to successfully conduct clinical trials in pediatric sepsis? Five subgroups first met separately and then together to evaluate the following areas: signs and symptoms of sepsis, cell markers, cytokines, microbiological data, and coagulation variables. All conference participants approved the final draft of the proceedings of the meeting.**

Results: **Conference attendees modified the current criteria used to define SIRS and sepsis in adults to incorporate pediatric physiologic variables appropriate for the following subcategories of children: newborn, neonate, infant, child, and adolescent. In addition, the SIRS definition was modified so that either criteria for fever or white blood count had to be met. We also defined various organ dysfunction categories, severe sepsis, and septic shock specifically for children. Although no firm conclusion was made regarding a single appropriate study end point, a novel nonmortality end point, organ failure-free days, was considered optimal for pediatric clinical trials given the relatively low incidence of mortality in pediatric sepsis compared with adult populations.**

Conclusion: **We modified the adult SIRS criteria for children. In addition, we revised definitions of severe sepsis and septic shock for the pediatric population. Our goal is for these first-generation pediatric definitions and criteria to facilitate the performance of successful clinical studies in children with sepsis. (Pediatr Crit Care Med 2005; 6:2–8)**

KEY WORDS: sepsis; pediatric; consensus; child; critical care; intensive care; organ dysfunction; systemic inflammatory response syndrome

Based on the 1992 Consensus Conference on definitions for sepsis and organ failure, severe sepsis was defined in adult patients as sepsis associated with at least one acute organ dysfunction (1). This definition was upheld in the recent 2001 Consensus Conference (2). With the exception of certain pediatric-specific diagnostic criteria for sepsis introduced in the 2001 Consensus Conference report, little guidance or consensus exists in the literature for the definition of pediatric systemic inflammatory response (SIRS) with infection, more generally termed pediatric sepsis.

Sepsis remains a major cause of morbidity and mortality among children (3–6). Sepsis-associated mortality in children decreased from 97% in 1966 (7) to 9% among infants in the early 1990s (8). A recent population-based study by Watson and colleagues (9) of U.S. children with severe sepsis (bacterial or fungal infection with at least one acute organ dysfunction) reported >42,000 cases in 1995 with a mortality rate of 10.3%. Although this represents a significant improvement over the past few decades, severe sepsis remains one of the leading causes of death in children, with >4,300 deaths annually (7% of all deaths among children) and estimated annual total costs of $1.97 billion (9).

Both the United States Food and Drug Administration and the U.S. Congress have recently emphasized the importance of testing biomedical therapeutics in children (10). As novel sepsis therapeutics continue to be developed, they will be increasingly evaluated in children. Thus, there is a need for a consensus definition of the pediatric sepsis continuum including SIRS, infection, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) to aid in standardization of observational studies and evaluation of therapeutic interventions in clinical trials.

In an effort to address this need, a group of international experts in the fields of adult and pediatric severe sepsis and clinical research gathered in 2002. A panel was chosen that consisted of published pediatric critical care physicians and physicians and scientists with clinical

***See also p. 83.**

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Sponsored, in part, by an unrestricted educational grant from Eli Lilly and Company.

DOI: 10.1097/01.PCC.0000149131.72248.E6

research experience in pediatric sepsis including pediatric health outcomes, past U.S. Food and Drug Administration pediatric advisory panel experience, and members of past successful consensus conferences on adult severe sepsis. The panel met with the goal of agreeing on definitions and criteria for the components of the sepsis continuum that could consistently be applied in the pediatric population. In addition, the consensus conference panel discussed potential end points for clinical studies in pediatric sepsis. The ultimate objective of the conference was to prospectively develop the conceptual framework and practical guidelines for the design, conduct, and analysis of large, multiple-center international therapeutic trials aimed at improving the outcome of children with sepsis.

METHODS

The conference was held in February 2002 in San Antonio, Texas, and included 20 participants from Canada, France, the Netherlands, the United Kingdom, and the United States. During the conference the following was reviewed by all participants: the first adult consensus conference on sepsis (1, 2), current available definitions of pediatric SIRS and sepsis (9, 10), organ dysfunction scoring systems used in adults (11–14) and pediatrics (15–18), a review of the bactericidal/permeability-increasing protein ($rBPI_{21}$) phase III trials in meningococcemia (19, 20), and a review of the Food and Drug Administration guidance for pediatric trials (21).

The conference panel addressed four main questions:

1. How should the pediatric age groups affected by sepsis be delineated?
2. What are the specific definitions of pediatric SIRS, infection, sepsis, severe sepsis, and septic shock?
3. What are the specific definitions of pediatric organ failure and the validity of pediatric organ failure scores?
4. What are the appropriate study populations and study end points for conduct of clinical trials in pediatric sepsis?

The group was split into two breakout sessions with designated discussion leaders to address the first three questions and bring forward their recommendations to the combined group. An overall recommendation was then formed by majority opinion. The facilitated discussion on recommendations for conduct of pediatric sepsis trials was conducted with the whole group. All conference participants reviewed and approved the final document. The final document was circulated to the Pediatric Section of the Society of Critical Care Medicine, the American College of Critical Care Medicine, and the Section on Critical Care of the American Academy of Pediatrics for comment before submission for publication.

RESULTS

How Should the Pediatric Age Groups Affected by Sepsis Be Delineated?

The clinical variables used to define SIRS and organ dysfunction are greatly affected by the normal physiologic changes that occur as children age (22–26). Therefore, definitions of the sepsis continuum in children rely on age-specific norms of vital sign and laboratory data. We propose six clinically and physiologically meaningful age groups for age-specific vital sign and laboratory variables to meet SIRS criteria (Table 1): newborn, neonate, infant, toddler and preschool, school-aged child, adolescent, and young adult. In the table, newborns are a separate age group from 0 to 7 days of life. Premature infants were not included as their care occurs primarily in neonatal intensive care units. These age groups were determined by a combination of age-specific risks for invasive infections, age-specific antibiotic treatment recommendations, and developmental cardiorespiratory physiologic changes (22–29). When we use the term "children" in this document, we refer collectively to all of these age groups.

What Are the Specific Definitions of Pediatric SIRS, Infection, Sepsis, Severe Sepsis, and Septic Shock?

SIRS was proposed by the American College of Chest Physicians and Society of Critical Care Medicine to describe the nonspecific inflammatory process occurring in adults after trauma, infection, burns, pancreatitis, and other diseases (1). Sepsis was defined as SIRS associated with infection (1). The SIRS criteria were developed for use in adults and therefore contain a number of clinical signs and laboratory values specific to adults. A number of modifications of these criteria for a pediatric population can be found in the literature (20, 30–36).

Table 1. Pediatric age groups for severe sepsis definitions

Newborn	0 days to 1 wk
Neonate	1 wk to 1 mo
Infant	1 mo to 1 yr
Toddler and preschool	2–5 yrs
School age child	6–12 yrs
Adolescent and young adult	13 to <18 yrs

One of the most recent pediatric modifications of the Bone et al. (1) definitions were those used in an open-label trial of drotrecogin alfa (activated), or recombinant human activated protein C, for severe sepsis in children (37). These criteria were used as a basis for discussion and the proposed pediatric definitions.

The consensus definition for SIRS in children is listed in Table 2. The differences from the adult definition are in bold. Although Bone et al.'s (1) basic recommendations for the definition of SIRS are applicable to the pediatric population, tachycardia and tachypnea are common presenting symptoms of many pediatric disease processes. Therefore, the major difference in the definition of SIRS between adults and children is that the diagnosis of pediatric SIRS requires that temperature or leukocyte abnormalities be present (i.e., SIRS should not be diagnosed if a pediatric patient exhibits only elevated heart and respiratory rates). In addition, numeric values for each criterion need to be modified to account for the different physiology of children. Finally, bradycardia may be a sign of SIRS in the newborn age group but not in older children (in whom it is a near-terminal event). Table 3 gives the age-specific cutoffs for each criterion. These values were chosen after careful review of the medical literature and the cited references. As no evidence-based values for abnormal vital signs and laboratory values were found, the values cited are based on expert opinion from the cited references.

Children with core temperatures of ≥38°C may be considered to have fever (38, 39). However, a temperature of ≥38.5°C improves specificity and reflects clinical intensive care unit practice. A core temperature by either rectal, bladder, oral, or central catheter probe is required. Temperatures taken via the tympanic, toe, or axillary route are not

Table 2. Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock

SIRS[a]

The presence of at least two of the following four criteria, **one of which must be abnormal temperature or leukocyte count:**

- Core[b] temperature of >38.5°C or <36°C.
- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period **OR for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.**
- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Table 4.

Septic shock

Sepsis **and cardiovascular organ dysfunction as defined in Table 4.**

Modifications from the adult definitions are highlighted in boldface.

[a]See Table 3 for age-specific ranges for physiologic and laboratory variables; [b]core temperature must be measured by rectal, bladder, oral, or central catheter probe.

Table 3. Age-specific vital signs and laboratory variables (lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th and upper values for heart rate, respiration rate, or leukocyte count for the 95th percentile)

	Heart Rate, Beats/Min[b,c]				
Age Group[a]	Tachycardia	Bradycardia	Respiratory Rate, Breaths/Min[d]	Leukocyte Count, Leukocytes × 10^3/mm^3[b,c]	Systolic Blood Pressure, mm Hg[b,c,e,f]
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 yr	>180	<90	>34	>17.5 or <5	<100
2–5 yrs	>140	NA	>22	>15.5 or <6	<94
6–12 yrs	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 yrs	>110	NA	>14	>11 or <4.5	<117

NA, not applicable.

[a]Modified from Ref. 24; [b]modified from Ref. 25; [c]modified from Ref. 22; [d]modified from Ref. 55; [e]Ref. 26; [f]Ref. 56.

sufficiently accurate. Fever may also be documented by a reliable source at home if within 4 hrs of presentation to the hospital or physician's office. Fever may be due to overbundling in small infants (38). If overbundling is suspected, the child should be unbundled and the temperature retaken in 15–30 mins (37). Hypothermia (i.e., <36°C) may also indicate serious infection, especially in infants (38, 40, 41).

Biochemical markers of inflammation may one day prove to be more objective and reliable than physiologic variables. Elevated sedimentation rate, C reactive protein, base deficit, interleukin-6, and procalcitonin levels have been reported as potential biochemical markers of SIRS (42–51). However, although some markers are sensitive they lack specificity, and no biochemical markers have been confirmed to be robust enough to add to the general definition at this time.

The conference panel accepted the original infection criteria specified by Bone et al. (1) as well as the original definition of sepsis (SIRS associated with a suspected or proven infection). Infection could be of bacterial, viral, fungal, or rickettsial origin. Although a bacterial infection may often be confirmed by culture or other methods, other pathogens may not be positively confirmed. Examples of clinical findings indicating an infection include petechiae and purpura in the setting of hemodynamic instability; fever, cough, and hypoxemia in the setting of leukocytosis and pulmonary infiltrates; or distended tympanitic abdomen with fever and leukocytosis associated with a perforated bowel.

The definition of severe sepsis is sepsis plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or two or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic). Organ dysfunction definitions are modified for children and defined in Table 4.

The definition of septic shock remains problematic. As children often will maintain their blood pressure until they are severely ill (26), there is no requirement for systemic hypotension to make the diagnosis of septic shock as there is in adults. Shock may occur long before hypotension occurs in children. Carcillo et

Table 4. Organ dysfunction criteria

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr

- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age[a]

OR

- Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

- Two of the following
  Unexplained metabolic acidosis: base deficit >5.0 mEq/L
  Increased arterial lactate >2 times upper limit of normal
  Oliguria: urine output <0.5 mL/kg/hr
  Prolonged capillary refill: >5 secs
  Core to peripheral temperature gap >3°C

Respiratory[b]

- Pa_{O_2}/F_{IO_2} <300 in absence of cyanotic heart disease or preexisting lung disease

OR

- Pa_{CO_2} >65 torr or 20 mm Hg over baseline Pa_{CO_2}

OR

- Proven need[c] or >50% F_{IO_2} to maintain saturation ≥92%

OR

- Need for nonelective invasive or noninvasive mechanical ventilation[d]

Neurologic

- Glasgow Coma Score ≤11 (57)

OR

- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

Hematologic

- Platelet count <80,000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)

OR

- International normalized ratio >2

Renal

- Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn)

OR

- ALT 2 times upper limit of normal for age

BP, blood pressure; ALT, alanine transaminase.

[a]See Table 2; [b]acute respiratory distress syndrome must include a Pa_{O_2}/F_{IO_2} ratio ≤200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure (Refs. 58 and 59). Acute lung injury is defined identically except the Pa_{O_2}/F_{IO_2} ratio must be ≤300 mm Hg; [c]proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; [d]in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

al. (52) defined septic shock in pediatric patients as tachycardia (which may be absent in the hypothermic patient) with signs of decreased perfusion including decreased peripheral pulses compared with central pulses, altered alertness, flash capillary refill or capillary refill >2 secs, mottled or cool extremities, or decreased urine output. Hypotension is a sign of late and decompensated shock in children and, although not needed for the definition, is confirmatory of shock state if present in a child with suspected or proven infection (52). Although there are distinct clinical presentations and classifications of shock in children (e.g., warm and cold shock; fluid refractory and catecholamine resistant), conference participants did not believe that this level of differentiation was required for the purposes of this consensus statement. As many of the pediatric shock criteria described by the ACCM Guidelines (52) are incorporated into the definition of cardiovascular organ dysfunction (Table 4), septic shock is defined as sepsis in the presence of cardiovascular dysfunction (i.e., severe sepsis with cardiovascular dysfunction).

What Are the Specific Definitions of Pediatric Organ Dysfunction and the Validity of Pediatric Organ Dysfunction Scores?

The criteria to define pediatric organ dysfunction and scoring systems to quantify pediatric organ dysfunction were reviewed. The primary goal was to identify a reproducible assessment of organ dysfunction that allows for tracking of changes in organ function, both improvement and deterioration, as a potential end point in clinical trials of therapeutic agents. Although adult organ dysfunction criteria have been applied to various pediatric populations, they lack sufficient evidence of validity in children to be considered for widespread use.

Several scoring systems for measuring pediatric MODS have been described in the literature. These include the Multiple Organ System Failure score (15), the Pediatric Multiple Organ Dysfunction Score (16), the Pediatric Logistic Organ Dysfunction score (17), and the Pediatric-MODS (18). Only the Pediatric Logistic Organ Dysfunction score has been validated in a multiple-center study (17). Thus, the panel chose not to advocate for use of a single MODS score but rather developed criteria for organ dysfunction (Table 4) based on those used in the Pediatric Logistic Organ Dysfunction, Pediatric-MODS, and Multiple Organ System Failure scores as well as the criteria used in the open-label recombinant human activated protein C study. Criteria were chosen based on a balance of specificity, sensitivity, and widespread availability of the laboratory tests.

For the purposes of enrolling children with severe sepsis in clinical trials of therapeutic agents, the panel specified that the two most important organ dysfunctions, cardiovascular and respiratory (requiring mechanical ventilator support for respiratory failure), must be present. Other organ dysfunctions should be monitored during clinical studies. Organ dysfunction-free days may be potentially quite useful as a primary end point, but this needs to be confirmed and we need to evaluate how this metric will perform at predicting long-term, clinically meaningful outcome. In addition, a pediatric MODS scoring system should be used for additional documentation of organ dysfunction.

What Are the Appropriate Study Populations and Study End Points for Conduct of Clinical Trials in Pediatric Sepsis?

Appropriate study populations in pediatric sepsis should be representative of age-based risk groups for specific severe infections. In addition, special groups, such as the immunocompromised host, should be considered. In general, infants <2 months are at risk for sepsis with organisms such as Group B streptococcus, *Escherichia coli*, *Listeria*, and herpes simplex virus. Children older than 1–2 months are at risk for community-acquired organisms (e.g., infection caused by invasive *Streptococcus pneumonia* or *Neisseria meningitidis* (53). Children with underlying disease, including immunocompromised patients, make up a much larger proportion of the population with severe sepsis than in adults (9). Both congenital and acquired immunodeficiency states need to be considered. Studies specifically designed to address these populations should be considered for evaluations of new anti-infective, anti-inflammatory, or antisepsis drugs.

The choice of the most appropriate study end point remains difficult and controversial. The mortality rate in pediatric meningococcemia patients is approximately 10% (20). This precludes powering a pediatric sepsis trial using mortality as a primary end point. For example, at a baseline morality rate of 10%, to detect a relative reduction in the risk of mortality of 25% or greater (alpha = .05, beta = .2, two-tailed) would require 1,979 patients per group or almost 4,000 children with severe sepsis for a two-armed trial. To enroll this high number of children with severe sepsis is infeasible, even across 50 centers, because in the 2- to 4-yr time frame of a clinical trial it requires that each center enroll 20–40 patients per year. An example of this problem was shown in the phase III randomized trial of $rBPI_{21}$ in moderate to severe meningococcemia (19). Despite a sample size of almost 400 subjects with moderate to severe meningococcemia, statistical significance in mortality between groups was not reached, in part due a high mortality on or shortly after enrollment, even though there was evidence for drug effect, including a significant (although *post hoc*) improvement in functional outcome determined by the Pediatric Overall Performance Category Score (54).

Although mortality cannot be the sole end point of pediatric sepsis trials, it is the most important outcome and must be included. The panel discussed the use of composite outcomes such as organ failure-free days or ventilator-free days. These scores incorporate mortality by giving it the worst score (zero free days). The discussions from this meeting did influence the choice of the outcome measure for the current multinational, prospective, randomized controlled trial of recombinant human activated protein C pediatric septic shock (sponsored by Eli Lilly). The primary end point of the EVBP RESOLVE trial is an increase in organ failure-free days with secondary end points including mortality and change in Pediatric Overall Performance Category between before pediatric intensive care unit admission to patient discharge. Long-term outcomes, such as overall level of functioning on 3- or 6-month follow-up, should also be considered in future trials.

Selected biomarkers, such as procalcitonin, D-dimers, interleukin-6, and interleukin-8, may have a role as primary end points in certain trials (42–51). However, such biomarkers have not been shown to predict clinically important outcomes, nor have they been studied in large prospective trials in children. The panel concluded that these biomarkers could be used as pharmacodynamic end points or secondary end points until more data can be compiled concerning their correlation with durable clinical outcomes.

FUTURE DIRECTIONS

The definition of sepsis in children needs further refinement and requires a series of evidence-based consensus conferences in the future. We hope that these definitions will provide a uniform basis for clinicians and researchers to study and diagnose severe sepsis in children. The definitions presented in this document should be considered a "work in progress" that will require continuous refinements and adjustments as our knowledge about pediatric sepsis grows. We fully expect that more objective biological markers of the sepsis process and of organ system failure will be incorporated as they are developed and tested. Until that time, we suggest that these definitions will serve as a common ground for research in pediatric sepsis.

Our goal is for these first-generation pediatric definitions and criteria to facilitate the performance of successful clinical studies in children with sepsis.

ACKNOWLEDGMENTS

Members of the International Consensus Conference Panel included: Gordon Bernard, MD, Vanderbilt University, Nashville, TN. John Bradley, MD, Children's Hospital, San Diego, CA. Richard Brilli, MD, Children's Hospital Medical Center, Cincinnati, OH. Heidi Dalton, MD, Children's National Medical Center, Washington, DC. Saul Faust, MD, Imperial College School of Medicine at St. Mary's, London, UK. Jacques Lacroix, MD, Hopital Sainte-Justine, Montreal, Canada. Francis Leclerc, MD, Hopital Jeanne de Flandre, Lille, France. Michael Levin, PhD, MD, Imperial College School of Medicine at St. Mary's, London, UK. Simon Nadel, MD, St. Mary's Hospital, London, UK. Carl Peck, MD, Georgetown University, Washington, DC. Chris Rubino, Cognigen Corporation, Buffalo, NY. Patrick Scannon, MD, PhD, XOMA Limited, Berkeley, CA. Ann Thompson, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA. Marcel van Deuren, MD, University Hospital Nijmegen Radboud, Netherlands. Ellen Wald, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA.

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