EDITORIAL

Are septic children really just “septic little adults”?

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The third international consensus definitions for sepsis and septic shock (Sepsis-3) have profoundly influenced how we identify patients with sepsis [1]. The Sepsis-3 Task Force defined sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection” and eliminated the term “severe sepsis”. To operationalize this definition, datasets containing > 6 million patient records were interrogated to identify clinical criteria that discriminated patients with simple infection from those with outcomes consistent with sepsis [2]. The Task Force found that, relative to two or more systemic inflammatory response syndrome (SIRS) criteria, a sequential organ failure assessment (SOFA) score ≥ 2 more accurately predicted mortality and/or an intensive care unit (ICU) stay ≥ 3 days. Logic dictates that the new definitions should apply to both adults and children if a uniform, age-independent pathobiologic process underlies sepsis/septic shock. However, age certainly modifies the clinical manifestations of sepsis [3, 4], and the Sepsis-3 Task Force indicated that the new criteria must be validated in children. To date, the pediatric community has relied on recommendations from the 2005 International Pediatric Sepsis Consensus Conference, describing a spectrum of increasing clinical severity—SIRS, sepsis, severe sepsis, septic shock [5]. Can these recommendations be reconciled with the clinical criteria that operationalize Sepsis-3?

In this issue of *Intensive Care Medicine* (ICM), Schlapbach and colleagues used area under the receiver operator characteristic (AUROC) curve analysis to compare

the ability of SIRS, an age-adapted variant of SOFA (pediatric or pSOFA), and the Pediatric Logistic Organ Dysfunction (PELOD)-2 score [6] to discriminate hospital mortality or ICU length of stay ≥ 3 days from among 2594 children admitted to ICUs in Australia and New Zealand [7]. Importantly, they also compared infection + pSOFA/PELOD-2 score ≥ 2 to 2005 “severe sepsis”, defined as SIRS + infection + either cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or ≥ 2 other organ system dysfunctions [5]. The investigators found that both pSOFA and PELOD-2 had better overall predictive validity as measured by the AUROC than SIRS and 2005 “severe sepsis” for the chosen outcomes. However, when analyzed using the numerical cut-point recommended by Sepsis-3, the adjusted AUROCs for mortality were 0.74 and 0.73 for pSOFA ≥ 2 and PELOD-2 ≥ 2 , respectively, while the AUROC for 2005 “severe sepsis” was similar at 0.71. Use of PELOD-2 ≥ 8 generated the highest adjusted AUROC at 0.81. The composite outcome of mortality and/or ICU length of stay ≥ 3 days yielded similar results.

Similar to Sepsis-3 in adults, Schlapbach et al. have provided strong evidence that SIRS is not necessary to identify pediatric sepsis. This finding is important because use of SIRS to identify sepsis may be problematic; for example, most febrile children with bronchiolitis currently qualify as septic despite an exceedingly low risk for mortality. Furthermore, the use of SIRS to discriminate between low and high illness severity in acute pediatric disease is not supported by recent data [8]. Schlapbach et al. have convincingly demonstrated that organ dysfunction—not SIRS—is the key element that identifies septic children at risk for poor outcome from within a cohort of acutely infected children. Thus, either pSOFA or PELOD-2 [or, in adults, SOFA or the Logistic Organ Dysfunction Score (LODS)] may be used (without SIRS) as a clinical proxy of organ dysfunction.

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That said, the use of a pSOFA or PELOD-2 threshold of two points may not be the optimal approach. In Sepsis-3, the choice of SOFA ≥ 2 was data-driven; it outperformed SOFA ≥ 1 while use of SOFA ≥ 3 provided only marginal improvement [2]. Schlappach et al. demonstrated that PELOD-2 ≥ 8 best discriminated for both mortality and the composite outcome, while data on alternative pSOFA cut-points were not provided. This finding mirrors a prior study by Leclerc et al. who also reported that PELOD-2 ≥ 8 best discriminated mortality in children with suspected infection [9]. Schlappach et al. reasoned that higher pSOFA/PELOD-2 thresholds would select for patients with multiple organ dysfunction syndrome but exclude children with single or more subtle organ dysfunction. This reasoning may be correct, but it requires validation with data.

It is also not clear that use of either pSOFA or PELOD-2 at the ≥ 2 cut-point offers substantial benefit over 2005 “severe sepsis”. In the study being discussed, the three sets of criteria performed similarly. Interestingly, Shankar-Hari et al. recently compared Sepsis-2 (“severe

sepsis”) and Sepsis-3 (“sepsis”) criteria in a large dataset of adult patients and found substantial (> 90%) overlap [10]. However, when compared to Sepsis-2, Sepsis-3 criteria provided significantly better predictive validity for septic shock, a comparison that Schlappach et al. did not address. A recent study by Matics and Sanchez-Pinto that used a similarly derived pSOFA was able to demonstrate strong predictive validity for Sepsis-3 criteria in children, with mortality of 12.1 and 32.3% for sepsis and septic shock, respectively, but did not compare these outcomes to 2005 criteria [11]. Thus, while existing data suggest that use of validated proxies for organ dysfunction improves predictive validity relative to the 2005 “severe sepsis” criteria, the application of pSOFA and PELOD-2 to additional datasets is necessary to identify the “best” approach to operationalize the clinical criteria for sepsis and septic shock in children.

This last comment segues into our final point. As the well-conducted study by Schlappach et al. demonstrates, Sepsis-3 criteria must be appropriately modified before they can be applied to children (Table 1).

Table 1 Existing and proposed new terminology, definitions, and clinical criteria for pediatric sepsis

	2005 IPSCC [5]	Potential “Pediatric Sepsis-3”
Approach	Expert consensus opinion	Expert opinion (definition) and data-driven (clinical criteria)
Terms	SIRS Sepsis Severe sepsis Septic shock	Sepsis Septic shock
Definition		
Sepsis	SIRS associated with infection	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Severe sepsis	Sepsis plus cardiovascular dysfunction or ARDS or ≥ 2 organ system dysfunctions	N/A
Septic shock	Severe sepsis with cardiovascular dysfunction	Subset of sepsis where underlying cardiovascular and cellular/metabolic abnormalities are associated with increased mortality
Clinical criteria (in addition to infection)		
Sepsis	≥ 2 SIRS criteria ^{a,b}	A combination of easily measured clinical variables that have either construct validity or predictive validity for an outcome consistent with sepsis (e.g., mortality or prolonged ICU LOS) ^c
Severe sepsis	Cardiovascular dysfunction or ARDS or ≥ 2 organ system dysfunctions	N/A
Septic shock	Severe sepsis with cardiovascular dysfunction	Sepsis with decreased perfusion or hypotension requiring vasoactive support $\pm$ hyperlactatemia ^{d,e}

N/A not application, SIRS systemic inflammatory response syndrome, ARDS acute respiratory distress syndrome

^a At least one abnormality in temperature or leukocyte count is required; elevated heart rate and respiratory alone are not sufficient to diagnose pediatric SIRS

^b Equivalent to infection with systemic signs of inflammation in pediatric sepsis-3

^c Leading considerations include the Pediatric Logistic Organ Dysfunction (PELOD)-2 score or newly constructed and validated function such as pediatric sequential organ failure assessment (pSOFA); optimal thresholds to be determined using a data-driven approach

^d Clinical criteria for shock should likely include measures of both decreased perfusion or hypotension. The most appropriate measure of “decreased perfusion” should be based on easily applied criteria that have an evidenced-based association with outcome

^e In adults, the mortality associated with the combination of hypotension and lactate ≥ 2 was statistically significantly higher than the mortality associated with either criterion alone [1]. A data-driven approach is required to determine if the same is true in children

The importance of that necessity must be emphasized. The term “sepsis” is a catch-all phrase representing an amalgam of disorders that present differently and that have different risks and outcomes. Age (young or old) directly modifies the very pathobiological responses that produce sepsis from infection. So too do sex, race, economic status, comorbidities and responses to therapy. Perhaps the key lesson to be derived from the work of Schlapbach et al. is that optimizing recognition and treatment will eventually require that we characterize sepsis “subtypes” much as we differentiate cancers on the basis of origin, biology, and genetics. Recognizing that septic children are not just “septic little adults” may be the ideal place to start.

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Compliance with ethical standards

Conflicts of interest

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