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New Criteria for Pediatric Sepsis: A Phoenix Rising

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ABBREVIATIONS IPSCC, International Pediatric Sepsis Consensus Conference; PODIUM, Pediatric Organ Dysfunction Information Update Mandate; SIRS, systemic inflammatory response syndrome

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Pediatric sepsis is a condition associated with high mortality, ranging from approximately 2% to 8% in high-income settings to 25% in low-resource countries.[1] Remarkably, the definition of pediatric sepsis has been elusive despite its epidemiologic importance. In January 2024, two side-by-side articles in the *Journnal of the American Medical Association*[2,3] (with accompanying editorials[4,5]) proposed new criteria, labeled the "Phoenix" criteria, for defining pediatric sepsis, superseding those recommended by the 2005 International Pediatric Sepsis Consensus Conference (IPSCC)[6] and coming on the heels of the 2022 Pediatric Organ Dysfunction Information Update Mandate (PODIUM).[7,8] Indeed, Phoenix's place can be best appreciated when discussed in the context of these 2 prior initiatives.

The 2005 IPSCC criteria, widely embraced but now somewhat antiquated, assigned the diagnosis of pediatric sepsis to any child with a suspected or documented infection who had at least 2 manifestations of the systemic inflammatory response syndrome (SIRS),[6] which itself is composed of a set of physiologic responses to an infecting pathogen, specifically, alterations in body temperature, heart rate, respiratory rate, and white blood cell count. IPSCC designated sepsis as "severe" if it was associated additionally with abnormalities of at least 1 major organ system, and as "septic shock" if there was significant cardiovascular dysfunction.[6] By the late 2010s, however, the IPSCC criteria were felt to be lacking. Most notably, the criteria had poor specificity; infants presenting with viral bronchiolitis, for example, with fever and elevated respiratory and heart rate, fulfilled IPSCC sepsis criteria, but clearly were not septic in the common medical vernacular. Relatedly, the IPSCC distinction between "sepsis" and "severe sepsis" was confusing because most caregivers consider all sepsis, implying a health- or life-threatening condition needing immediate intervention and stabilization, as severe.

In reality, the conceptualization of sepsis had evolved since the publication of the IPSCC recommendations, diminishing or abandoning SIRS-driven definitions and embracing those based on infection-related aberrations of organ function. Adult sepsis criteria had already accommodated a similar reconceptualization of sepsis through the presentation of the so-called Sepsis-3 criteria published in 2016,[9] which were anchored entirely on worsening organ dysfunction. In recognition that the key factor in pediatric sepsis outcomes similarly was organ dysfunction, the National Institute of Child Health and Human Development sponsored the PODIUM initiative in 2015.[7,8] Eighty-eight experts in pediatric organ dysfunction, as reflected in their recent peer-reviewed research, were convened to determine the most reliable measures of organ dysfunction in children, both in composite,[8] as typically occurs in sepsis, as well as in each organ system separately.[7] To achieve this end, the PODIUM panelists conducted a host of systematic reviews to determine the performance characteristics of previously developed tools. While the PODIUM panelists identified multiple scoring systems that had been proposed over the prior several decades, they concluded that the scores were impossible to unify, their diagnostic performance characteristics were difficult to discern, they frequently were informed by expert opinion rather than the statistical analysis of large datasets, and the data used to develop them were biased heavily toward relatively narrow populations of children studied in wealthy nations.[8] In short, all currently available scores came up wanting. They concluded that contemporary electronic health records from multiple sources and counties could, and should, be used to assist data-driven, rather than largely expert-based, approaches.[8]

Against this background, in the early 2020s the Society of Critical Care Medicine convened a task force, whose membership overlapped with those who had participated in PODIUM, to revisit sepsis criteria in children, and the resulting product was Phoenix. The process by which Phoenix was achieved was a multistepped tour de force developed to address the deficiencies identified by the PODIUM panelists.[2,3] It began with a survey of thousands of caregivers across the globe, which indicated that already most felt the term *pediatric sepsis* should be limited to children with

infection-related organ dysfunction. A simultaneous systematic review of pediatric sepsis studies confirmed that abnormalities in organ function were the principal drivers of mortality. These steps were followed by the accumulation and harmonization of over 3 million electronic medical records from children with suspected infection presenting to emergency departments, inpatient wards, and intensive care units, from both high-income and low-income countries, between 2010 and 2019. This dataset then was used to develop pediatric-specific organ-function assessment tools evaluating the function of 8 organ systems, derived *de novo* or from previously published scores. Sophisticated regression analyses then were conducted to derive a mortality prediction model called the *Phoenix Sepsis Score*, with the discriminatory power of the score validated by using a subset of the data pool. The model subsequently was simplified to include assessments of 4 of the 8 original organ systems, namely, respiratory, cardiovascular, hematologic (specifically assessing coagulation), and neurologic, which rendered the score more parsimonious without affecting its predictive performance. Finally, diagnostic thresholds were established by the project participants using a modified Delphi method, using sensitivity and positive predictive value of mortality to determine the optimal cutoff. The bottom line to this effort was that a Phoenix Sepsis Score ≥2 in the context of proven or suspected infection was proposed as the new criterion for diagnosing pediatric sepsis.

It is worth noting what Phoenix has contributed, what its limitations are, and what it is not. Unquestionably, Phoenix cemented the paradigm shift in the way pediatric sepsis is conceptualized, with the abandonment of SIRS and the embracing of infection-related organ dysfunction as the primary phenomenon defining the presence of sepsis and its severity. That said, Phoenix has some limitations.[4,5] The Phoenix Sepsis Score was developed by using only clinical data collected within the first 24 hours of hospitalization and thus did not accommodate improvement or deterioration despite intervention, nor was it validated for sepsis acquired after admission. Premature infants were excluded, so a mortality prediction model for this important population was not established. Data from resource-limited settings sadly were culled only from a small number of hospitals advanced enough to have electronic medical records, and thus relevance to the large populations of children without access to such facilities remains unknown. The only outcome predicted by the Phoenix Sepsis Score is mortality; important aspects of morbidity were not explored. Finally, it is important to recognize that the Phoenix Sepsis Score is not a sepsis screening or sepsis management tool. The requirement for immediate intervention in the infected child with organ dysfunction is implied by Phoenix, but steps that can be taken to mitigate further organ dysfunction in the patient with evolving sepsis are not addressed. Thus, while the Phoenix criteria may be important for pediatric sepsis "benchmarking, quality assurance, epidemiology, and research," as its developers assert, its practical application to bedside clinical care, a claim also proffered by its developers,[3] is not apparent.

Nonetheless, Phoenix confirmed the importance of research designed to understand the biology of sepsis and its attendant organ dysfunction. Undeniably, sepsis is a syndrome with some common immunologic, hemostatic, endothelial, and pathogen-specific alterations[10,11] that should first be better understood before further clinical definitions are developed. Although improved and more precise characterization are provided by Phoenix, the biological alterations underlying each of these is complex and multifarious. Real-time endotyping of adults and pediatric patients in several clinical research studies holds great promise to further define the individual biologic and maladaptive responses of children.[12–14] For instance, the whole blood response of tumor necrosis factor production after lipopolysaccharide as reported by Hall et al[15] has allowed the definition of an immunoparalysis population, suggesting new restorative boosting therapies. Other groups have adopted new transcriptomic, immunologic, and proteomic approaches to best understand mechanisms underpinning individual patients, all phenomena that are not captured, nor better defined, via the current Phoenix criteria. However, marrying both sophisticated descriptive and mechanistic advanced laboratory tests with the better clinical categorization initiated by the Phoenix criteria can enhance randomized controlled trials and pave a way to targeted deployment of therapies that considers the nuanced biological clinical responses to pathogen and to therapy.

Without a doubt, key challenges that have hindered progress in management of pediatric sepsis have included the difficulty in identifying specific functional immune endotypes. Refining the clinical characteristics over time (not just at admission) will assist in this endeavor and Phoenix represents a first step. Future derivations of the Phoenix criteria must first be validated and include multidimensional machine learning approaches to invariably reach the holy grail for the field in identifying immunomodulatory molecules that effectively restore normal immunity against biologic endotypes. The Phoenix criteria 2.0 and onward should be developed with an eye toward stratifying and reflecting specific pediatric sepsis endotypes and narrowing the "Grand Canyon" that exists between clinical data science research and translationally based biologic understanding of causal dynamic pathways and relevant targets for modulation.

Phoenix isn't perfect, but it is a step in the right direction to understand key parameters of organ dysfunction that are likely driven by differing immune effector changes, alterations at the endothelial-vascular-mitochondria level, and influenced by epigenetic

phenomena. It refines clinical phenotypes and, in the future, can enhance the dynamic nature of sepsis in a fashion that allows better tools to inhibit organ dysfunction. Amidst a previous desert of simplistic definitions of pediatric sepsis relying solely on a suspicion of a bug, the presence of a fast heart or breathing rate, and an increased fever, stands a Phoenix beginning its ascent from antiquity and at the precipice of advanced clinical and biologic endotyping to improve pediatric outcomes. Phoenix is an excellent first step on that journey.

Article Information

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