Invited Commentary

Labeling Sepsis: Many Square Pegs into Countless Round Roles

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In the 2000 years since Homer and Hippocrates described *sepo* as, literally, rotting flesh, medicine has come to understand an incredible amount about the biology and pathophysiology of sepsis. Yet, the most recent definition of sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" remains unsatisfyingly vague.[1] This is not meant as criticism, but rather as a recognition that sepsis is more a medical construct than a single discrete entity, borne of heterogeneous causes with numerous pathobiological mechanisms that converge on a recognizable spectrum of common clinical signs and symptoms. Indeed, many of what are currently deliberated in the literature as "sepsis sub-phenotypes" will 1 day emerge as distinct diagnoses with identifiable causes, mechanisms, and treatments.[2,3] Until such time, there remains an incredible value in using the term sepsis to evoke a shared mental model that a patient is likely infected, organ systems are failing, and death is an immediate concern. Calling out sepsis establishes urgency to implement a series of life-saving therapies. However, problems with diagnostic imprecision and inclusion of multiple phenotypes under the moniker of "sepsis" become readily apparent when trying to quantify these efforts to measure epidemiology, conduct research, or benchmark quality of care for sepsis.

In this issue of *Pediatric Quality and Safety*, Dr. Ramgopal and colleagues evaluate numerical estimates and acuity of episodes of pediatric sepsis in United States emergency departments (EDs) generated by using 3 sets of criteria.[4] Their primary aim was to compare children with sepsis defined by a modification of the Children's Hospital Association's Improving Pediatric Sepsis Outcomes (IPSO) criteria with billing codes either explicit for sepsis or indicative of a combination of infection and organ dysfunction. Multiple prior studies have used and compared the 2 billing code strategies to identify episodes of pediatric sepsis from within administrative data.[5–9] The novelty of these new data is the application of the modified IPSO criteria to identify pediatric sepsis episodes using national survey, rather than electronic health record (EHR) data. The IPSO criteria were originally developed as a pragmatic set of clinical actions commonly used to diagnose or treat sepsis that could be operationalized from the EHR for large-scale data abstraction in a multicenter quality improvement initiative.[10] Notably, the objective of these QI criteria was to identify clinician intent to treat for sepsis rather than confirm that sepsis was present. A prior study demonstrated reasonable reliability and validity of the IPSO sepsis criteria for "sustainable case ascertainment and quality measurement," though cautioned against their use for epidemiologic studies of confirmed sepsis.[10]

Dr. Ramgopal and colleagues modified the IPSO sepsis criteria to align with data elements available in the National Hospital Ambulatory Medical Care Survey, a cross-sectional probability sample survey of visits to US EDs. Without access to EHR data, their approach required several modifications to the original IPSO sepsis criteria, including substituting systemic inflammatory response syndrome criteria instead of more comprehensive sepsis screening processes, equating *any* fluid administration to multiple fluid bolues, and only including treatment administered in an ED setting. They then reported 2 key findings. First, the modified IPSO sepsis criteria identified 4 times more ED episodes of pediatric sepsis than the explicit billing codes and 2 times more than combination billing codes. Not surprisingly, patient demographics, symptoms, diagnostic studies, treatments, and ED

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disposition differed between the groups (although patient overlap between groups precluded statistical tests of comparison). Second, the modified IPSO criteria had the highest proportion with tachycardia, tachypnea, blood culture, antibiotic use, and intravenous fluids, leading the authors to conclude that the group identified by modified IPSO sepsis criteria had higher acuity than the combination billing code criteria [despite a much higher rate of hypotension (3% versus 79%) with combination billing codes], but less acuity than the explicit sepsis billing code criteria [which had a higher rate of hospital admission (63% versus 84%)].

It is not surprising that these 3 criteria identified overlapping, yet distinct, groups of children labeled as "sepsis" with divergent demographics and treatment. Several prior studies have reported similar findings when pediatric sepsis episodes are identified using different sets of criteria.[5,6,11,12] Although the original IPSO sepsis definition achieved an 80% overlap with hospital-based sepsis-registries,[10] further work is needed to compare the modified IPSO sepsis criteria to a reference definition to truly understand its utility to identify episodes of pediatric sepsis. It is also difficult to evaluate the authors' acuity conclusion for several reasons. First, patient characteristics were based on only 97–244 individuals per group, leading to unreliable estimates with wide confidence intervals. Second, there appears a discrepancy between proportions with tachycardia and hypotension within groups, with 79% hypotension in the combination billing codes despite only 17% with tachycardia and the lowest rate of admission in this group. Third, there were no outcomes reported to compare across the 3 criteria to further support conclusions of differential acuity.

Despite these challenges, we agree with the authors' statement that there are "challenges in generating estimates of pediatric sepsis using combinations of administrative and clinical data." This is especially relevant when relying exclusively on initial clinician behavior rather than on objective measures of organ dysfunction or persistent need for therapy, as is true with both the original and modified IPSO sepsis criteria. Such an approach risks "rewarding" unnecessary treatment by defining sepsis solely by claiming to treat it and missing true cases in which the clinician failed to treat. For these reasons, we support a pediatric sepsis surveillance definition that uses more objective clinical data available within the EHR to indicate a high probability of confirmed infection concurrent with life-threatening (ie, at least moderate) organ dysfunction.[13] Our group has developed such a definition,[14] though we acknowledge its need for external validation and comparison with other identification strategies, such as the 3 criteria used by Dr. Ramgopal and colleagues. Hopefully, increased availability and access to EHR-based datasets will minimize the need to rely on less granular datasets for epidemiologic surveillance.

Hippocrates relied on the clinical presentation of rotting flesh to diagnose sepsis. While sepsis is now recognized far earlier, our continued reliance on a set of nonspecific clinical and laboratory criteria that are broadly and inconsistently applied creates square pegs of various sizes. Not surprisingly, attempts to then fit this heterogeneous group of square pegs into a myriad of round holes (ie, disparate sepsis criteria) yields overlapping, but distinct groups of patients all labeled as "sepsis." Perhaps the most important lesson to take from the study by Dr. Ramgopal and colleagues is the need to continue to refine and disentangle the very concept of sepsis.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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