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Making Sepsis Molecular: Is There Enough Time for New Tests?

Sepsis occurs in more than 1.7 million patients annually (1) and may account for more than one in two to three hospital deaths (2). A principal treatment for sepsis is timely, appropriate antibiotic therapy as recommended by international practice guidelines and multiple professional societies (3). Recent studies show that timely administration of antibiotics in sepsis is associated with a significant reduction in risk-adjusted in-hospital mortality, particularly for individuals in shock (4). Yet, amid the enthusiasm to broadly administer antimicrobial therapy as fast as possible, there are important caveats. Antibiotics are unnecessary when no bacterial infection (e.g., viral infection) is present or when sepsis itself is misdiagnosed. In such cases, fast-paced antibiotic administration could result in distracting the clinician from other acute conditions, expansion of antimicrobial resistance, or even avoidable adverse drug reactions. As such, there is an imperative to make the diagnosis of sepsis early and correctly, and distinguish sepsis from other conditions presenting in a similar fashion.

For almost 25 years, clinicians have used the systemic inflammatory response syndrome (SIRS) criteria, a measure of the clinical expression of the host response to inflammation, as a marker of sepsis (5). The presence of two or more SIRS criteria were included as sepsis criteria in a consensus statement by the American College of Chest Physicians and Society of Critical Care Medicine in 1992 (6), and remain a key step in the diagnosis of sepsis in international guidelines and both state and national policy mandates. However, SIRS criteria have been criticized for being overly sensitive and may be present in as many as two out of three patients in the ICU, many without infection (7). Criteria such as tachycardia and tachypnea could result from a number of conditions, including pancreatitis, acute respiratory distress syndrome, and traumatic injury.

To make the diagnosis of sepsis, physicians rely on their clinical acumen. Yet, studies of case vignettes reveal wide subjectivity and lack of agreement among ICU clinicians, particularly when asked to identify

infection in patients with shock (8). Blood procalcitonin, a peptide that typically is elevated in bacterial rather than viral infections, also tends to correlate with the severity of infection. Yet, in a large observational cohort of more than 100 hospitals, procalcitonin was variably measured in sepsis and not associated with improved clinical outcomes (9). Another approach could leverage gene expression from microarray or next-generation sequencing. And despite promising discovery work in public and private cohorts (10), the generalizability of this method to the larger and more variable populations at risk for sepsis needs to be established (11).

In this issue of the *Journal*, Miller and colleagues (pp. 903–913) explore the role of molecular diagnostics in distinguishing sterile inflammation from sepsis in the ICU (12). The authors evaluated the SeptiCytE LAB, a U.S. Food and Drug Administration–cleared four-gene host response assay, in a prospective cohort at seven sites in the United States and an additional validation site in the Netherlands to determine its performance. The SeptiCytE LAB is a real-time qRT-PCR assay that quantitates the relative expression levels of four genes (*CEACAM4*, *LAMP1*, *PLAC8*, and *PLA2G7*) with a turnaround time of approximately 6 hours. The proposed test generates a score in four groups (e.g., bands), and uses a binary cutoff of 3.1 to classify patients as having a high or low risk of sepsis. In the absence of a gold-standard diagnosis of sepsis across cohorts, the authors used a three-member adjudication panel to determine whether there was partial agreement (two agreed), unanimous agreement (three agreed), or indeterminate agreement about whether sepsis was present.

The authors found that the SeptiCytE LAB and subsequent SeptiScore values were markedly higher among sepsis patients compared with those with sterile inflammation (area under the receiver operating characteristic curve, range 0.82–0.89). The discrimination of the SeptiCytE LAB improved the classification of sepsis versus sterile inflammation beyond more easily measured clinical classifiers such as procalcitonin and the total number of SIRS criteria within 24 hours of ICU admission. These results were robust to variations in demographics, race, geography, and strategies to handle missing data.

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There are several limitations to this approach to the diagnosis of sepsis, most of which are acknowledged by the authors. First, patients were enrolled at various times during their ICU course, and some had already received antibiotic therapy up to 24 hours before sampling. The timing of sampling in the trajectory of the patients' sepsis episode and antibiotic treatment could impact the discrimination of the SeptiCyte LAB. Second, the reported performance characteristics were limited to only those patients with SIRS, excluding the more than one in eight who may be septic without SIRS features (13). Third, the test performance was lowest in pneumonia, the most common cause of sepsis (14). Finally, although the patient sample was diverse, the sample size of the study was modest.

The work by Miller and colleagues raises some important questions. First, should tests such as the SeptiCyte LAB inform new diagnostic criteria for sepsis? The recent Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) excluded molecular tests from any proposed criteria, citing pragmatism and a lack of evidence (15). Second, should bedside clinicians routinely use the SeptiCyte LAB to determine whether a sick patient with signs of inflammation is septic? And if so, should antibiotics be withheld until definitive results are available? Given current mandates for early antibiotics (16), the answer to the latter is most certainly no, and the potential for routine use may hinge exclusively on the time required to obtain a result. What if the SeptiScore result is less than 3.1—should antibiotics be stopped? Almost certainly not, if there are not several other clinical indicators prompting such an action. Finally, what would be the optimal clinical moment(s) to test the SeptiCyte LAB? These data were derived from an ICU cohort, but the majority of potential sepsis cases are evaluated during prehospital care and in the emergency department (15). In these forward clinical settings, at-risk patients with SIRS criteria have not yet been treated with antibiotics, and the diagnosis of sepsis is not always overt. Further evaluations of the SeptiCyte LAB could include a closer examination of its use in these emergency situations to better determine its practical application and clinical utility. ■

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