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The Search for Diagnostic Markers in Sepsis
Many Miles Yet to Go

Join bedside rounds in any ICU around the world, and within a few minutes, you are nearly guaranteed to hear a vigorous discussion on whether or not a particular patient has sepsis. Despite the many advances in medicine and medical technology over the past decades, early and accurate identification of many of the syndromes we treat most commonly in the ICU—for example, sepsis and acute lung injury—remains a challenge, even for skilled and experienced clinicians.

In this regard, cardiologists and oncologists are well ahead of intensivists, with reasonably accurate diagnostic biomarkers for some of their most commonly treated conditions (troponin for acute myocardial infarction, brain natriuretic peptide for congestive heart failure, and prostate-specific antigen for prostate cancer). Intensivists are naturally at some disadvantage due to the heterogenous pathophysiology of the syndromes we encounter, but the potential value of biomarker-guided diagnosis for sepsis is high. Much as early intervention is critical for the treatment of myocardial infarction, there is clear evidence that early treatment of sepsis with appropriate fluid management and antibiotics has major beneficial effects on clinical outcomes (1). Likewise, ever-increasing rates of antibiotic resistance dictate that antibiotics be rapidly discontinued in critically ill patients who prove not to be infected. Thus, despite the challenges, the search for accurate early diagnostic markers for sepsis should continue.

The statistical requirements for an accurate diagnostic biomarker are high, and as such have been difficult to meet. Many markers that have strong associations with the outcome or disease of interest nevertheless fail to discriminate accurately between

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diseased and nondiseased individuals, as a result of overlap in the values of the marker in these two populations (2). Add in the pathophysiologic heterogeneity of critical illness syndromes, the necessary reliance on consensus criteria rather than objective pathologic findings as the gold standard, and the clinical need for rapid turnaround of test results, and it becomes clear why it has been difficult to identify an ideal marker for diagnosing sepsis.

In this issue of the *Journal*, Gibot and colleagues (pp. 65–71) dive into this challenging arena with their study of the diagnostic utility of three biological markers—procalcitonin, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and the neutrophil CD64 index—in two cohorts of critically ill patients (3). Each of these markers was selected on the basis of prior research suggesting diagnostic utility in discriminating septic from nonseptic patients. Procalcitonin, a peptide precursor of the calcium-regulating hormone calcitonin, is perhaps the most widely used diagnostic marker for sepsis, with an area under the curve reported in a recent metaanalysis of 0.78 (4). TREM-1 is a cell-surface molecule up-regulated on neutrophils and monocytes in the setting of bacterial and fungal infection; plasma levels of the soluble form of TREM-1 have been reported in some studies to have diagnostic utility for severe sepsis, though reports of its accuracy vary widely (5, 6). Similarly, the neutrophil CD64 index measures the relative level of expression of the Fc-γ receptor, a measure of neutrophil activation; in some reports, it has shown moderate to high sensitivity and specificity for diagnosing infection (7, 8).

To evaluate the diagnostic utility of these three markers, Gibot and colleagues obtained plasma samples within 12 hours of admission on 300 critically ill patients from a single center cohort in France. The diagnosis of sepsis was established by two-intensivist review of each patient's hospitalization and defined by consensus definitions. Levels of all three biomarkers were significantly higher in patients with sepsis than in patients without sepsis. Further, all three markers individually demonstrated excellent discrimination, with areas under the curve of 0.73–0.95.

The authors then combined the three markers into what they termed a Bioscore, in which subjects received one point for each of the three biomarkers whose value exceeded a threshold determined from this initial 300-patient cohort. That the Bioscore performed well in the cohort from which it was derived was to be expected; however, the authors also validated the Bioscore in a separate cohort of 79 patients enrolled at a different medical center, and with slightly different clinical characteristics from the first cohort. Again, they observed outstanding performance for the three biomarkers individually and for the combined Bioscore (area under the curve of 0.95). Remarkably, the performance of the biological markers was so strong as to render nonsignificant the contributions of traditional clinical markers like white blood cell count, the use of vasopressors, and severity of illness scores.

Given these compelling data, then, should the Bioscore be considered for use in clinical practice? Not just yet. Although the Bioscore may prove its clinical utility over time, several important issues need to be addressed first. First and foremost, the performance of the Bioscore must be validated by independent investigators in additional cohorts of critically ill patients. Although Gibot and colleagues are to be commended for including a validation cohort in their report, the diagnostic performance of these three markers in this report markedly exceeds the performance that has been reported by other investigators for the same markers (4–6). For example, one report found that the area under the curve for sTREM-1 for the diagnosis of sepsis was as low as 0.62 (9), whereas another reported a sensitivity of only 63% for the neutrophil CD64 index (10). Also, future evaluation of the Bioscore should focus primarily on patients in whom infection is clinically suspected, rather than on unselected cohorts of critically ill subjects. In this report, Gibot and colleagues found that the Bioscore performed equally well in the subset of patients for whom there was a low clinical index of suspicion for infection, a puzzling finding that suggests that the clinical suspicion of infection was not particularly accurate. Thus, external confirmation of the diagnostic value of the Bioscore in the appropriate patient populations is needed, including prospective testing of the proposed cut-off values identified in this study and evaluation of the biomarkers' performance stratified by the severity of sepsis.

Second, as the authors recognize, to be truly useful for clinical practice, an early diagnostic marker for sepsis must have a rapid turnaround time and be widely available. On this point, the Bioscore is not yet ready for prime time. Although point-of-care testing is available for procalcitonin, measurement of sTREM-1 requires an enzyme-linked immunoassay, and the neutrophil CD64 index is measured using flow cytometry. Thus, further development of rapid, easily performed assays for these markers would be required before the Bioscore is ready for testing in the emergency room or the ICU.

Finally, perhaps the most difficult hurdle to clear before the Bioscore should be recommended for clinical practice is whether its use will improve clinical outcomes. To be sure, many biomarkers that we commonly use have not met this criteria—consider, for instance, the white blood cell count; alternatively, whether or not certain biomarkers meet this criteria is hotly debated—for example, the use of prostate-specific antigen as a screening test for prostate cancer (11). However, in the setting of a common, already costly syndrome like sepsis and with ever-increasing attention to the role of health care expenditures and comparative effectiveness, we must consider whether measurement of three separate biomarkers, with the attendant materials and personnel costs, would measurably improve patient-centered outcomes in sepsis. Moreover, the impact of adding biomarker measurements to clinical care is not always predictable or beneficial. For instance, although procalcitonin was initially found to be useful to guide the de-escalation of antibiotic therapy in patients with sepsis (12, 13), measurement of procalcitonin in a recent large randomized controlled trial actually worsened patient outcomes, with higher rates of pulmonary and renal organ failures and longer ICU length of stay in the procalcitonin measurement group (14). Thus, the clinical impact of measuring novel diagnostic markers for sepsis must be carefully considered.

Where do we stand then as a critical care community in our search for diagnostic biomarkers for sepsis? Despite the challenges, we should continue to aggressively search for and test new diagnostic markers, guided by our understanding of the pathogenesis of the syndromes we study and treat. Our colleagues in other disciplines have demonstrated that the development of novel diagnostic biomarkers is not only feasible but potentially clinically important. In the meantime, we must continue to rely primarily on those imperfect but widely used biomarkers we have had for decades—for instance, fever, white blood cell count, plasma lactate, and blood pressure—and our old-fashioned clinical skills to help us determine whether or not a patient has sepsis (15).

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Predicting Disease Progression in Cystic Fibrosis

New Use of an Old Tool

The maximum expiratory flow–volume curve is the methodology that underlies spirometry, the time-honored modality by which pulmonologists/respirologists have tested individuals of all ages for lung health and disease for decades. Although measurements of vital capacity date back to the 19th century (1), it was Hyatt and colleagues in 1958 who first published the first description of the maximum expiratory flow–volume curve (2). Standardization of technique and measurements has been an interest of the American Thoracic Society and European Respiratory Society for decades (3, 4). A PubMed search for articles related to spirometry showed a total of 21,893 such articles published in the medical literature and literally hundreds recorded already in 2012 as of April 20 (5).

Most specialists in pulmonology would be hard-pressed to think of new and creative applications of this tried and true technique for lung function measurement. In fact, Vilozni and colleagues in this issue of the *Journal* (pp. 82–87) have done so (6). They address the important clinical problem of predicting progression of end-stage lung disease in children, adolescents, and young adults with cystic fibrosis (CF). Serial spirometry was available in 93 subjects in a single CF center in Israel at least twice yearly over a several-year period. The authors describe a dynamic phenomenon that they call dysanapsis of the ratio of forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25–75}$) and the forced vital capacity (FVC) itself. It was Green, Mead, and Turner who first applied the term dysanapsis to pulmonary developmental physiology. They described dysanapsis as the dissociation between a measure of lung volume and a measure of airway size (7). They believed that the variability among healthy individuals reflected a relatively loose coupling of lung size and airway size. This concept has rarely been applied to disease.

Vilozni and colleagues evaluated the change in airway function, $FEF_{25–75}$, divided or normalized by FVC over time in a diverse cohort of patients with CF ranging from young children to adults. In their patient population, they determined three distinct patterns of lung function change—a control group (group N) with forced expiratory volume in 1 second (FEV_1) > 80% of predicted values, group B with abnormal lung function who did not progress to end-stage lung disease by the end of the study, and a third group of patients (LT) with initially abnormal lung function who did progress to end-stage lung disease. Groups B and LT were not different by anthropometric data or baseline lung function data at entry into the study. FEV_1/FVC declined at similar rates in all groups. It was the rate of decline in $FEF_{25–75}$/FVC that clearly differentiated group LT from the other groups. The figures in the paper are very impressive, indicating that the findings in this paper are not a matter of "mere statistical significance". Associated significant clinical differences between group LT and group B included the presence of airway reactivity at baseline and a higher incidence of *Mycobacterium abscessus* infection in the LT group. No other infection or specific genotype reached statistical significance.

The authors discuss several interesting clinical implications of their findings. It is unclear to them to and to me how the presence of *M. abscessus* lung infection would accelerate lung deterioration. However, when they partitioned treated *M. abscessus* patients from untreated, there appeared to be an even more accelerated disease advancement in the untreated patients. Because airway reactivity is common over time in CF, the import of the apparent correlation between baseline presence of airway reactivity and accelerated disease progression is also unclear. In addition, there was a trend for patients with distal intestinal obstruction syndrome and CF-related diabetes mellitus to accelerate disease progression. The authors support the need to apply their findings to other centers to confirm or refute these provocative findings.

The authors were restrained in speculating about the anatomic and pathophysiologic implications of $FEF_{25–75}$/FVC dysanapsis for CF lung disease. Although it is an oversimplification to pigeonhole $FEF_{25–75}$ as a "measure of small airways obstruction," the findings