Sepsis Biomarkers
Value and Limitations

Use of biomarkers has flourished in many fields of medicine, and there is no doubt they will have an increasingly important role to play in patient management in the future.

Sepsis biomarkers have three principal applications. First, they can be used to rule out infection. It is often believed that these markers can help identify the presence of infection, but this is not their real value. Indeed, no sepsis biomarker can be entirely specific for infection, because similar pathways can be activated in the absence of an infection; for example, in situations such as trauma or surgery (1). It is rather the negative predictive value, suggesting absence of infection, that can be most useful, encouraging the physician to withhold antibiotics or to discontinue them sooner rather than later. This use of biomarkers has been demonstrated in many studies during the last 10 years, from the initial landmark study by Christ-Crain and colleagues, showing that the use of procalcitonin (PCT) levels could reduce antibiotic therapy in suspected lower tract infections (2), to the more recent analysis of the Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections (ProHOSP) study, which showed that PCT use could decrease antibiotic prescription in patients with heart failure presenting to an emergency department (3). Importantly, and in the same context (that biomarkers can be useful to rule out, rather than rule in, infection), a sepsis marker should not be used to escalate antibiotic therapy; this approach has been shown to be associated with increased organ failure (4).

Second, sepsis biomarkers are also markers of disease severity, which is information that can be useful in patient triage, and especially when making decisions about possible intensive care unit admission (5). PCT is a particularly good severity marker in sepsis, with levels well related to mortality rates (6).

Third, repeated measurements can be helpful to evaluate a patient's clinical course and, therefore, suggest a need for treatment review if levels are not decreasing. A substantial decline in sepsis markers can be used to encourage earlier discontinuation of antibiotic therapy (7, 8).

Could this latter application be used to create simple algorithms to guide patient management? In this issue of the *Journal*, Shehabi and colleagues (pp. 1102–1110) temper our enthusiasm about this possibility (9). In a fairly large study of almost 400 patients enrolled in 11 Australian intensive care units, use of an algorithm that included a PCT cutoff value of 0.1 ng/ml for stopping antibiotics did not influence the total duration of antibiotic therapy.

The study was well-designed and conducted, so the quality of the data is not in question. Why, then, did this approach, based on a sound underlying principle, not work? Were the negative results perhaps related to the chosen cutoff value? Would another threshold have resulted in more positive findings? This proposition is far from established. This study may simply just represent another failure of a simple protocol to influence outcomes, particularly when the standard level of care is already good, as was probably the case in these Australian centers.

Should we, therefore, write off PCT measurements? Of course not. It is, in fact, reassuring to see that PCT levels were higher in patients with positive than in those with negative cultures, and that the time course of PCT levels was strongly associated with outcome. Hence, these blood tests make sense. The study, rather, reminds us of the complexity of the problem. The underlying concept is valid, in that the duration of antibiotic therapy should not be identical in all patients, not only because the virulence of the microorganism and the site of infection will influence response to antibiotics but also because the host immune response may vary among patients; this is precisely why monitoring a marker of the patient's response can be important. However, the decision to stop antibiotic therapy should be based on a composite of bacteriological information, source of infection, duration of antibiotic therapy, clinical evolution (including fever and organ function), and the time course of biomarker levels. Within the complex framework of sepsis, attempting to influence our strategies using a specific cutoff value of a single biomarker is unlikely to be effective; the key message is that a sepsis biomarker should never be used alone to dictate patient management.

Among the more than 170 sepsis markers that have been proposed (10), PCT is one of the best, and it is certainly the most widely studied, but there is nothing magic about it, and it is definitely not perfect. Combining information collected from several biomarkers may be more useful (11), and adding circulating biomarker levels to information about the cellular response (12) and the degree of cell activation (13) may be a valuable future approach to help optimize our anti-infective strategies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Narrowing in on Early Cystic Fibrosis Lung Disease

Cystic fibrosis (CF) lung disease is characterized by chronic infection and inflammation of the airways, bronchiectasis, and progressive lung function decline (1). Although the widespread implementation of newborn screening programs for CF enables diagnosis during the first weeks of life, detecting the onset of lung disease in infants and young children remains challenging (2). Overt respiratory symptoms among children with CF are minimal, and monitoring techniques used in older patients, such as spirometry and sputum cultures, are not directly translatable to younger patients. During the last several years, the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) study has transformed our understanding of early CF lung disease. The AREST CF study enrolls infants diagnosed with CF by newborn screening and is following them longitudinally, with annual infant lung function testing (until age 2–3 years), bronchoalveolar lavage (BAL), and chest computed tomography; the first participants have now been followed for more than a decade. Through this structured protocol, the AREST CF investigators have provided vital insight into just how early CF disease pathogenesis begins. The AREST CF study was the first to show that radiographic evidence of lung disease, specifically bronchiectasis and air trapping, is present in infancy (3, 4) and, once identified, tends to persist or progress (5). In a landmark study, Sly and colleagues found that neutrophil elastase detected in BAL fluid at 3 months was associated with an increased risk for bronchiectasis at 12 and 36 months (6). The AREST CF study also demonstrated that infant lung function measures are already abnormal by 6 months (7), and that isolation of specific microbes from BAL fluid is associated with both lower lung function (8) and more rapid spirometric decline in the first 2 years of life (9). Despite these advances in detection of early disease, current therapeutic options for infants and young children remain comparatively limited.

In this issue of the *Journal*, Ramsey and colleagues (pp. 1111–1116) extend their follow-up of the AREST CF cohort, providing the first depiction of the natural history of CF lung disease from diagnosis by newborn screening into school age (10). The investigators recorded lung function results from 56 school-aged children with CF who underwent early BAL, lung function testing, and computed tomography scanning during the first 2 years of life. A small comparison group of 18 healthy children also had spirometry performed in infancy and at school age. Children with CF had, on average, 8% lower $FEV_{0.75}$ (equivalent to FEV_1 in older patients) than healthy control patients. Early life factors (before 2 years) were examined to identify factors that predicted lower lung function in school age among the patients with CF. Isolation from BAL fluid of pathogens frequently associated with CF (labeled "pro-inflammatory pathogens" and including *Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae*, and *Aspergillus*) and free neutrophil elastase were associated with lower $FEV_{0.75}$ in univariate analyses. In a multivariate analysis, only the detection of abundant pathogens ("infection") remained significantly associated with school age lung function, suggesting infection is the major driver of airway inflammation and damage. Thus, early airway infection appears to have an important and lasting effect on obstructive lung disease. Although other investigators have demonstrated the persistence of abnormal lung function from infancy to preschool or early school age (11–13), this is the first study to demonstrate that lower airway pro-inflammatory pathogens during infancy are associated with this persistent lung function deficit.

Importantly, the investigators found no association of respiratory symptoms during the first 2 years with lower lung function in early childhood, emphasizing the clinically silent nature of early lung damage. The lack of observed association of respiratory hospitalization days in the first 2 years with early childhood lung function contrasts with the report of Byrnes and colleagues (14), who found that early-life pulmonary exacerbations were associated with lower lung function at age 5 years in the Australasian Cystic Fibrosis Bronchoalveolar Lavage Study cohort (15). This discrepancy is likely a result of different study populations and definitions of pulmonary exacerbations. Interestingly, in the current study, treatment with prophylactic antistaphylococcal antibiotics during the first 2 years of life was associated with higher school age lung function in univariate, but not multivariate, analyses; in addition, the treated infants did not have lower rates of infection or inflammation during infancy. Thus, the mechanism by which antibiotic prophylaxis might improve lung function is unclear, and in this observational study, the detected effect may