Where Do We Go From Here?

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(See the major article by Branche et al on pages 1692–700.)

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Since 2004, European investigators have published at least 14 clinical trials that support the measurement of serum procalcitonin (PCT) levels in patients with respiratory tract infections [1–3]. The results consistently show that elevated serum PCT levels are encountered in patients with a clinical syndrome of bacterial pneumonia and that low levels correlated with a picture of viral pneumonia or noninfectious causes of pulmonary infiltrates. In a Cochrane review, European colleagues systematically reviewed studies of PCT-guided treatment algorithms that suggest whether to start or stop empirical antibiotic therapy in patients with 1 or 2 low initial PCT values [4]. The authors concluded that PCT-guided therapy was not associated with an increase in mortality or clinical failures. Further, they called for non-European studies to confirm the published results [4].

A valid concern with the published trials is the paucity of data that associate the microbiologic etiology of respiratory tract infections with PCT levels. One exception is a modestly sized retrospective study of children in German emergency departments, wherein low PCT levels reliably distinguished between documented viral and bacterial respiratory tract infections [5].

Data generated by investigators at the University of Rochester in this issue of The Journal of Infectious Diseases are pertinent to the topic [6]. The Rochester studies by Branche et al are based on 3 assumptions: (1) traditional cultures of sputum and blood specimens, plus probing urine samples for the antigens of Streptococcus pneumoniae and Legionella species, do not identify the role of viral pathogens; (2) measurement of serum PCT levels would assist in separating viral from bacterial invasive infections and in clarifying whether an identified bacteria was invading or colonizing; and (3) the combination of aggressive attempts at pathogen detection and PCT levels would enhance antibiotic stewardship.

In an earlier study by the Rochester investigators, with extensive testing for viral, bacterial, and atypical pathogens, a microbiologic diagnosis was made in 76 of 134 patients (56%) with acute exacerbations of chronic obstructive pulmonary disease (COPD) [7]. That study documented a high frequency of pathogenic viruses, either alone, in 26 of 76 patients, or in combination with bacterial pathogens, in 21 of 76 patients. PCT levels were low with pure viral infection, but PCT levels rose in patients with mixed viral and bacterial infections or only bacterial infections.

With this foundation, plus the ability to diagnose an increased number of respiratory virus targets via multiplex polymerase chain reaction (PCR) platforms, the Rochester group reasoned that it was possible, within 2–3 hours of admission (or study enrollment), to inform physicians whether a pathogenic virus was present or absent. In addition, the study intervention provided physicians with the patient’s serum PCT concentration. It was postulated that the combination of pathogen identification and PCT levels would remove most of the uncertainties among physicians that prevent withholding or de-escalating antibiotic therapy in patients with viral lower respiratory tract infections [8].

Branche et al randomly assigned patients with lower respiratory tract infections, most of which involved acute exacerbations of COPD, to receive either standard care or treatment based on algorithms involving findings from a combination of multiplex viral PCR platforms and serum PCT levels [6]. A viral etiology was found in 63 of the 150 patients in the intervention group, with an associated low PCT level in 49. The duration of antibiotic therapy was shortened by 2 days in these patients ($P = .002$). Further, fewer days of antibiotic therapy were seen in virus-positive patients with low PCT levels. It is encouraging that fewer patients from this latter group were discharged receiving antibiotics.

As in many previous PCT studies, there were no adverse consequences as a result of following the intervention PCT algorithm. In short, the current study
data address a major criticism of the European PCT trials and demonstrate the positive potential of combining rapid, sensitive, and broad molecular diagnostic tests with properly interpreted, easily accessible, serum PCT levels.

With this perspective, where do we go from here? First, Branche et al included lower respiratory tract infections but purposely tried to exclude patients with pneumonia. Hence, there is a need to replicate the study in a large number of patients hospitalized with community-acquired pneumonia.

Second, future studies should further optimize microbial diagnostic assays. Multiplex viral PCR platforms should be expanded to include DNA probes for S. pneumoniae, Staphylococcus aureus, Legionella species, selected aerobic gram-negative bacilli, and, perhaps, antibiotic resistance genes. We should ensure that PCR diagnostic assays are performed and PCT serum levels measured within 2 hours of specimen collection in rapid-response laboratories 24 hours a day, 7 days a week. We should also form an active stewardship team that includes pharmacists and infectious diseases physicians to ensure that the results of the assays described above influence antibiotic management. The goal is communication with the pertinent physician provider by a stewardship team member within a few minutes or hours of the availability of PCT and microbial diagnostic results. Early discussions increase the impact of the data on patient management. The logistics of this approach are daunting but need to be addressed.

Third, physicians must be educated about the current understanding of PCT biology. To begin with, we should know that the gene encoding PCT is not activated by pure viral infections and that the negative predictive value of a normal PCT finding for a bacterial infection is well over 90% [5, 9]. We should also appreciate that an elevated PCT level can occur in patients with pure viral respiratory infections, owing to the influence of comorbid conditions that may independently increase PCT levels (eg, a patient with human metapneumovirus pneumonia and catheter-induced urinary tract infection). Finally, we must be aware that increased serum PCT levels appear to be a sensitive indicator of impaired perfusion of the mucosa of the gastrointestinal tract. For example, elevated PCT levels are detectable after aorto-coronary bypass surgery, in patients with cardiogenic shock, and in patients with intestinal ischemia. Current data support the hypothesis that the increases in PCT concentration are due to translocation of gut bacteria [10–12]. Hence, elevated PCT levels in patients with pneumonia who are also profoundly hypotensive do not help discriminate viral from bacterial infections.

Fourth, we should encourage investigations of several additional factors. Specifically, it would be valuable to know whether PCR quantitation will help clinicians decide whether a predetected viral pathogen is colonizing or invading [13]. Knowledge of variations in PCT levels associated with various pathogens would also be useful. Preliminary data suggest that PCT levels may be higher with infection caused by gram-negative bacilli versus gram-positive cocci [14, 15]. There may be differences among viral pathogens, as well, and there are precious few data on fungal pathogens. Finally, detection of biomarkers that are more sensitive and specific than PCT would be beneficial. Perhaps host-based gene expression signatures will prove more useful than PCT levels [16, 17].

One prioritized goal of the White House’s National Action Plan for Combating Antibiotic-Resistant Bacteria is the establishment of effective antibiotic stewardship programs to reduce the overuse of empirical antibiotics [18]. Treatment of respiratory tract infections is a prime example of such overuse. The tools to fix this—rapid, sensitive, and specific pathogen detection, coupled with a biomarker indicating the presence or absence of bacterial invasion—are now available. With drug-resistant bacteria causing an estimated 2 million illnesses and approximately 23 000 deaths per year in the United States alone, the time for comprehensive study, validation, and implementation is now.

Note

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