Procalcitonin: The right answer but to which question?

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Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality worldwide. CAP management guidelines recommend empiric antibacterial therapy targeting the most likely bacterial pathogens, but large studies employing extensive microbiologic testing suggest CAP is frequently caused by viral infection alone[1, 2]. Accordingly, the provision of empiric antibacterial therapy for all patients with CAP may subject those without a bacterial infection to the risk of adverse effects without clear benefit. In the broader context of acute respiratory infections (including tracheobronchitis, upper respiratory tract infections, and sinusitis), the burden of bacterial infection is likely lower[3]. Despite a lack of evidence demonstrating clear benefit, acute respiratory tract infections (ARI) remain the most common indication for outpatient antibacterial prescriptions and an important contributor to the epidemic of antibacterial resistance[4]. Diagnostics are urgently needed to rapidly and accurately identify those patients most or least likely to benefit from antibacterial therapy.

Fundamentally, signs and symptoms of ARI manifest either from a direct effect of the invading pathogen or the host's response to that pathogen. For decades, the majority of clinically available diagnostic tests for ARI relied upon pathogen identification. Improvements in culture methods and the explosion of rapid and highly specific assays significantly improved pathogen detection, especially viruses. Despite these advances, a pathogen was identified in less than 40% of patients with CAP enrolled in a high-quality study employing an advanced panel of microbiologic tests[1]. Rates of pathogen detection are even lower in standard clinical practice. In addition to limited sensitivity, pathogen detection-based diagnostics may also be limited by a prolonged time to result, risks and difficulties of obtaining adequate clinical specimens, and the inability to distinguish colonization from infection.

Looking to the host's response to infection may address some of these limitations. Rudimentary measures of host response such as temperature, total white blood cell count, and C-reactive protein are common and readily available; yet lack the ability to accurately distinguish bacterial and viral causes of ARI. Procalcitonin (PCT) may provide additional information based on the premise that levels are higher in cases of bacterial infection and lower in viral infection. An adequate assessment of PCT's ability to reliably distinguish bacterial and viral infections has thus far been limited by inconsistent or incomplete microbiologic testing. Despite this uncertainty, a number of clinical trials demonstrated that PCT-guided algorithms for ARIs reduce antibacterial exposure without increasing rates of disease progression or treatment failure[5]. Notably, the prevalence of viral

infections is so high, that nearly any algorithm utilizing almost any diagnostic test, no matter how poor, could reduce antibacterial exposure without significantly increasing treatment failure rates. However, even in a sicker population (>90% hospitalized, >68% with CAP) where the prevalence of bacterial infection is likely high, a PCT-driven algorithm still safely reduced antibacterial exposure[6]. These and other clinical trials served as the basis for recent FDA clearance of the VIDAS® BRAHMS PCT assay to aide clinicians in making antibiotic decisions for the management of emergency department or hospitalized patients with lower respiratory tract infections [7].

The current study by Self and colleagues attempts to reconcile these two perspectives, host and pathogen. To do so, they measured PCT in a subset of the CDC-EPIC cohort. Patients were subdivided based on microbiology: typical bacterial, atypical bacterial, viral, and unknown. PCT was measured for each group and evaluated for its ability to distinguish microbiological etiologies. Though higher levels of PCT correlated with an increased likelihood of bacterial infection, there was no PCT threshold that reliably distinguished bacterial and viral etiologies. For example, PCT <0.25 ng/mL resulted in recommendations against antibacterial use in previous studies. Indeed, only 4% of patients with PCT <0.25 ng/mL had a typical bacterial infection. However, this constituted 23% of all patients with typical bacterial etiologies. These results prompt the obvious question: If PCT poorly discriminates bacterial and viral etiologies of CAP, then how do PCT-guided antibacterial management algorithms reduce antibiotic exposure without increasing rates of treatment failure? Some of this discrepancy between the host and pathogen perspectives may arise from the Self et al. study design. Specifically, microbiological test results served as the reference standard, which has limitations. Cases of bacterial CAP may be missed by a reference standard that relies on insensitive microbiologic tests or the collection of clinical specimens that could not be readily obtained for all patients (e.g. high-quality sputum cultures). It is possible some patients with viral etiologies, which are more easily detected, indeed had concurrent bacterial CAP but were designated as viral because that was the only identified pathogen. In contrast, a positive bacterial culture from a nonsterile site does not necessary represent infection. Misclassifying bacterial colonization as infection would diminish PCT's discriminating ability. Another consideration is that the impact of prior antibacterial therapy could not be rigorously analyzed in the current study. Previous work suggests PCT levels may fall precipitously with appropriate antibacterial therapy, potentially diminishing the ability to find a useful PCT threshold for bacterial infection. Finally, little is known about the net effects of bacterial and viral coinfection on PCT concentrations. Do proinflammatory cytokines triggered by bacterial infection (e.g., interleukin-6, tumor necrosis factor) promote PCT secretion

more than the inhibitory effects of virus-induced interferon release[8, 9]? These limitations highlight an urgent need in the field of diagnostics development for ARI. A well-defined and comprehensive reference standard is needed, which incorporates clinical observations, appropriate follow-up, and microbiologic testing interpreted in the context of both the overall clinical scenario and operating characteristics of the individual tests.

It is not clear how well PCT would differentiate bacterial from viral etiologies of CAP even if a perfect reference standard was available. CAP, and ARI in general, encompasses a heterogeneous disease process caused by a diverse group of pathogens. Though there are stereotypical host responses associated with certain pathogen classes, the response of individual signaling pathways can vary significantly even for pathogens of the same class. For example, although viral infection induces interferon gamma expression, there is substantial heterogeneity among patients and different viruses[10]. This heterogeneity suggests a broader and unbiased assessment of the host response to infection may prove more reliable. Indeed more comprehensive host response assays using gene expression analysis from peripheral blood samples have shown promise as accurate markers of bacterial and viral infection, as well as noninfectious systemic inflammatory syndromes[11, 12].

Based on the study by Self et al., there is no single PCT threshold that would reliably distinguish bacterial and viral infection. Yet PCT-guided algorithms have been successful. How do we reconcile this difference? A simple answer is that PCT is a poor biomarker, assuming pathogen detection is the appropriate standard. Given the high prevalence of viral infections, even a poorly discriminating biomarker could decrease antibacterial use. Conversely, perhaps pathogen detection strategies are misleading and PCT more reliably reflects the infectious process. The more likely and more complex scenario is that pathogen detection and host response each tells a partial story. For example, detection of a typical bacterial pathogen in a patient with a high PCT value might suggest a severe infection requiring antibacterial treatment. However, identification of the same bacterial pathogen but with a low PCT may indicate a clinically mild infection that resolves without antibacterial therapy. This latter scenario will be addressed in the anticipated LRTI-TRAP study, which will randomize patients with low PCT to either azithromycin or placebo[13].

The question posed by Self et al. is how well does PCT correlate with viral or bacterial etiologies of ARI. The answer is that it does, but not terribly well. However, the more clinically relevant question

is whether PCT (or other host response biomarkers) can be used to guide clinical management. The answer to that question is a more convincing yes. The challenge going forward is learning how to reconcile host and pathogen-based diagnostics to gain a comprehensive understanding of the patient's disease.

Notes

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