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Web Exclusive. Annals for Hospitalists Inpatient Notes: A Critical Look at Procalcitonin Testing in Pneumonia

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Antibiotic misuse for acute respiratory conditions is widespread, including in the acute care setting. Qualitative research suggests that much of this misuse can be attributed to diagnostic uncertainty (1). In the context of suspected pneumonia, uncertainty often stems from concerns about atypical presentations (for example, older adults), unreliable performance of chest radiography and the possibility of overlapping diagnoses. Uncertainty about the presence of a bacterial infection may influence providers to initiate empirical antibiotics "just in case" to avoid potential adverse outcomes related to delayed treatment. The importance of this problem is further underscored by the fact that viral infections are more common than bacterial infections among inpatients who meet the clinical criteria for pneumonia (2). Clearly, better tools and strategies are needed to address stewardship in this population.

Procalcitonin (PCT) is a serum biomarker that increases in response to bacterial infections and is inhibited by virus-associated cytokines. This unique property has generated tremendous interest in PCT as a solution to antibiotic prescribing dilemmas in patients with suspected acute respiratory tract infections. In 2017, the U.S. Food and Drug Administration approved an expanded indication for PCT "to help health care providers determine if antibiotic treatment should be started or stopped in patients with lower respiratory tract infections." This approval was informed by a Cochrane meta-analysis, which demonstrated that a PCT-guided approach reduced antibiotic initiation and duration without adversely affecting safety across various settings and acute respiratory diagnoses (3).

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Despite the new indication and supporting evidence, the optimal use of PCT in patients with suspected or confirmed pneumonia remains an area of significant controversy. The results of recent U.S.-based trials have been mixed, raising concerns about the real-world effectiveness of PCT. In addition, the 2019 joint guideline on community-acquired pneumonia (CAP) from the American Thoracic Society and Infectious Diseases Society of America recommends against the use of PCT testing to guide initiation of empirical antibiotic therapy for radiologically confirmed pneumonia (strong recommendation, moderate evidence) (4). This recommendation is supported by a study of 1735 patients admitted with CAP who had comprehensive pathogen identification procedures, including PCT testing, as part of the Centers for Disease Control and Prevention EPIC (Etiology of Pneumonia in the Community) study. In this cohort, viral and bacterial pathogens were identified in 24% and 14% of cases, respectively. Although PCT concentrations were significantly higher in the bacterial infection group, the negative predictive value of a PCT value of less than 0.1 ng/mL was 82.4% (95% CI, 71.2% to 86.9%). In other words, approximately 1 in 5 patients with microbiologically confirmed bacterial CAP had a negative PCT test result (2).

Although the prospect of failing to initiate antibiotics in nearly 20% of patients with bacterial CAP is unacceptable, several features of the analysis warrant further consideration. First, despite extremely comprehensive efforts, a pathogen was not identified in nearly 2 out of 3 cases. The cited negative predictive value applies only to patients with microbiologically confirmed bacterial CAP and may not be generalizable to the broader population of patients hospitalized for pneumonia. For instance, when cases with unknown causes were included, the negative predictive value of PCT increased to 93.9% (CI, 91.9% to 95.5%). Second, this analysis included only a single PCT measurement, whereas other protocols have used repeated testing as a means to reduce false-negative results related to the time required for upregulation of PCT in response to a bacterial challenge. Finally, 22% of this cohort were patients admitted to intensive care (2). There is no rationale for withholding antibiotics in critically ill patients with suspected pneumonia, and these patients were excluded from nearly all previous PCT trials.

In light of these considerations, how should hospitalists incorporate PCT as an antibiotic stewardship tool? First, it is critical to recognize that PCT should not be viewed as a standalone test. Instead, PCT should be applied as a tool to complement traditional clinical and diagnostic assessment using Bayesian principles. This is especially important given the known diagnostic performance limitations of clinical signs and symptoms and chest radiographs. We recommend a selective, rather than universal, application of PCT for patients admitted with suspected CAP. For stable patients with low pretest probability of bacterial pneumonia (for example, ambiguous chest radiograph or a likely alternative diagnosis) and a favorable comorbidity profile, a negative PCT test result can be used as an objective metric to guide the withholding of antibiotic therapy. A follow-up test within 12 hours may be useful in this scenario to ensure that there is no delayed increase in the PCT value. In contrast, we do not believe that PCT should be used to guide decisions on antibiotic initiation when pretest probability for bacterial CAP is moderate or greater, in high-risk patient populations (for example, immunocompromised), or in those with severe disease (for example, pneumonia severity index ≥IV or sepsis criteria).

In addition to its role at the time of admission, serial PCT testing has been shown to safely reduce the duration of antibiotic therapy in patients with CAP (3). The most common approach is to discontinue antibiotic treatment when PCT decreases by 80% or more from its peak. The magnitude of antibiotic exposure duration reduction identified in the Cochrane meta-analysis was 2.43 days (5.7 vs. 8.1 days [CI, −2.71 to −2.15 days]; $P < 0.001$) (3). However, the American Thoracic Society and Infectious Diseases Society of America guideline on CAP recommends only 5 days of antibiotic therapy for patients with adequate clinical response (for example, 48 hours afebrile, no oxygen requirement, and stable vitals) (4). Because most patients with CAP will respond and be discharged before hospital day 5, routine use of PCT to guide the discontinuation of antibiotic treatment is unlikely to provide clinically meaningful benefits. Given that adverse outcomes can occur in relation to excess durations of antibiotics for CAP, we suggest that stewardship efforts focus on encouraging adherence to 5-day treatment guidelines instead of PCT-based protocols (5).

In conclusion, PCT is a unique but imperfect diagnostic test. Although it is likely that future biomarkers and host response assays will surpass the performance of PCT, for now, PCT remains the best antibiotic stewardship tool available for lower respiratory infections. Procalcitonin should be reserved for antibiotic initiation guidance in stable, low-risk patients with low pretest probability for pneumonia. In this patient population, a negative PCT result may allow clinicians to safely withhold antibiotics.

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