



The Role of Procalcitonin in the Management of Infectious Diseases

Procalcitonin (PCT) is a precursor to the hormone calcitonin and is a serum biomarker of interest in infectious diseases. Many studies have analyzed its utility and role in assisting clinical decision making, especially in conditions that result in inflammation due to a bacterial infection. A systemic inflammatory response from a bacterial infection begins with the release of endotoxins/exotoxins and a response from immune system mediators that release cytokines, such as interleukin- 1β and tumor necrosis factor- α . These cytokines contribute to the development of a fever, the release of stress hormones, such as cortisone and epinephrine, and interleukin-6, which stimulates acute phase reactants, such as C-reactive protein (CRP) and PCT.^{1,2}

C-reactive protein and white blood cell count (WBC) are commonly used clinically as biomarkers that assist in the recognition of the infectious process and may be indicators of disease prognosis, but both lack specificity for bacterial infections. Consequentially, using CRP and WBC as clinical decision aids may result in unnecessary antibiotic therapy, which may result in an increase in drug-related adverse events and antibiotic resistance. A major distinction of PCT is that it has greater specificity than does CRP, because it tends to be elevated primarily as a result of inflammation due to bacterial

infections. Procalcitonin can be used to distinguish bacterial from viral infections because its up-regulation is attenuated by interferon-gamma, a cytokine released in response to viral infections.² Thus, PCT may be a more effective clinical marker for optimizing the diagnosis, monitoring, and treatment in patients with systemic bacterial infections.

PROCALCITONIN AS A MARKER

A study evaluating infectious markers compared the use of PCT, lactate, and CRP as diagnostic tools in patients with septic shock. The results of this study indicated that PCT was the only marker significantly elevated in patients with septic shock that was also normal in patients not in septic shock (14 $\mu\text{g}/\text{mL}$ vs 1 $\mu\text{g}/\text{mL}$, $P = .0003$).³ This and other studies led the FDA to approve PCT use in 2005 as an aid to clinical decision making in the assessment of critically ill patients with sepsis.⁴ Overall, the literature supports the use of PCT as a diagnostic tool in infections requiring antimicrobial therapy within appropriate clinical settings.

Strong evidence exists confirming PCT's role as an aid to clinical decision making in bronchitis, chronic obstructive pulmonary disease exacerbations, pneumonia, and severe sepsis/shock management.² Procalcitonin's kinetic profile makes it a good monitoring tool, because its levels promptly increase within 3 to

6 hours of infection, peak at 12 to 48 hours, and rapidly decline during recovery. Additionally, its levels closely parallel the extent and severity of present inflammation, making it a useful prognostic marker of disease progression and response to antibiotic therapy.^{2,4,5}

Christ-Crain and colleagues studied the outcome of PCT-guided antibiotic algorithms for patients with lower respiratory tract infections (RTIs) presenting to the emergency department. A serum PCT level of 0.25 to 0.5 $\mu\text{g}/\text{L}$ suggested a likely bacterial infection, and physicians were advised to initiate antimicrobial therapy. Serum levels above 0.5 $\mu\text{g}/\text{L}$ were suggestive of a bacterial infection, and initiation of antimicrobial therapy was strongly recommended. The results showed that PCT-guided algorithms significantly reduced the number of antibiotic-treated patients ($n = 99$ [83%] vs $n = 55$ [44%]; $P < .0001$), reduced the duration of antibiotic treatment (12.8 days vs 10.9 days; $P = .03$), and decreased the antibiotic cost per patient (\$202.5 vs \$96.3; $P < .0001$) compared with the standard group ($n = 119$) without a significant difference in mortality.⁶

Sepsis/septic shock is another area in which PCT has been studied. Use of a PCT-guided algorithm in critically ill patients with suspected or documented severe sepsis or septic shock to guide discontinuation of antimicrobial therapy resulted in reduced duration of antibiotic therapy (10 days vs 6 days; $P = .003$) in the PCT group ($n = 31$) compared with

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the standard of care group (n = 37) while maintaining similar mortality and infection recurrence rates between the 2 groups. The PCT algorithm in this study recommended discontinuing antimicrobial therapy when PCT levels had decreased by > 90% from identification of sepsis/septic shock but not prior to 3 or 5 days of therapy, depending on the baseline PCT level.⁷

Systematic reviews of multiple trials have confirmed these representative results. Using a PCT algorithm to withhold or de-escalate antibiotics in patients with suspected bacterial infection leads to a significant reduction in antimicrobial utilization without adversely affecting patient outcome.⁸

Procalcitonin levels should be rechecked 48 to 72 hours after beginning antimicrobial therapy in clinically stable patients with RTIs in order to reevaluate patient need for continued therapy. In patients whose antibiotics are withheld due to low PCT levels, it is recommended to obtain a repeat level 12 to 48 hours after the decision if clinical improvement is not seen.^{6,9-12} Literature suggests that it is reasonable to check PCT levels every 48 to 72 hours in patients with sepsis for considering discontinuation of antibiotic therapy as well as in patients who are not clinically improving and may need to broaden antibiotic therapy.^{7,12}

Limitations of the use of PCT as a clinical biomarker include its inability to be used in immunocompromised patients. In addition, PCT levels are increased in severe, noninfectious inflammatory conditions, such as inhalation injury, pulmonary aspiration, severe burns, pancreatitis, heat stroke, mesenteric infarction, trauma, surgery, and pneumonitis.¹² The presence of low-grade inflammation from a bacterial infection can lead to slightly elevated PCT levels that are difficult

to quantify due to the low sensitivity of current PCT assays.¹³

The level of PCT up-regulation may depend on the infecting pathogen. One study showed that PCT was highly elevated in patients with pneumococcal community-acquired pneumonia (CAP), and another study demonstrated that PCT levels did not increase in CAP due to atypical organisms.^{14,15} Thus, atypical antimicrobial coverage should be continued per current guidelines in patients in whom there is high suspicion of atypical organism-involvement in CAP.

CONCLUSION

Many studies have analyzed the use of PCT as a biomarker for infectious disease diagnosis, monitoring, and treatment. Current evidence supports its use in RTIs and sepsis, although it may be useful in other conditions as well, such as bacteremia and postoperative infections.² Due to its limitations and controversy, PCT should not be used as a sole marker but as an adjunct to a patient's clinical presentation, overall clinical picture, and other biomarkers. ●

Additional Note

An earlier version of this article appeared in the Pharmacy Related Newsletter: The Capsule, of the William S. Middleton Memorial Veterans Hospital.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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