Auron M, Seymann GB. Utility of Procalcitonin in Clinical Practice. *Brown Hospital Medicine*. 2023;2(3).
doi:10.56305/001c.81280

Brief Reviews

Utility of Procalcitonin in Clinical Practice

Moises Auron, MD, FAAP, FACP, SFHM[1,2], Gregory B Seymann, MD[3]

[1] Department of Hospital Medicine, Cleveland Clinic,
[2] Department of Medicine and Pediatrics, Cleveland Clinic Lerner College of Medicine,
[3] Division of Hospital Medicine, Department of Medicine, University of California San Diego Medical Center

Journal of Brown Hospital Medicine
Vol. 2, Issue 3, 2023

Article Information

Keywords: procalcitonin, infections, antibiotic use, antibiotics

https://doi.org/10.56305/001c.81280

Submitted: May 24, 2023 EST

Accepted: June 19, 2023 EST

Abstract

The rise of multi-resistant infections and complications associated with the overuse of antibiotics has led to the implementation of antibiotic stewardship strategies as a marker of patient safety and quality. Using biomarkers that can accurately predict the presence or absence of bacterial infection, thus signaling the need for antibiotic use, or supporting appropriate and safe discontinuation, has become an increasingly relevant strategy for antibiotic stewardship. Evidence supporting procalcitonin for antimicrobial stewardship has focused mostly on lower respiratory tract infections and sepsis. This review discusses the most relevant evidence to support the use of procalcitonin in clinical practice.

CLINICAL CASE

A 50-year-old man is admitted to the Emergency Department during the winter with complaints of 1 week of worsening pleuritic chest pain, dyspnea, and dry cough. He had upper respiratory infection (URI) symptoms a week before admission, which have since resolved. He is a non-smoker and has no occupational exposure to inhaled particles. On admission, he has a temperature of 38.3°C, respiratory rate of 26, and SpO2 of 96% on room air; the rest of his vital signs were normal. On exam, lungs had vesicular sounds with no rales or wheezing, but a few inspiratory crackles were heard on the posterior infrascapular area bilaterally. A chest X-Ray shows streaky infiltrates of unclear significance, possibly representing atelectasis. Lab work showed WBC of 12,000/uL, CRP 4.0 mg/dL with normal electrolytes and renal function. Treatment for community-acquired pneumonia with levofloxacin was initiated, as well as vancomycin for possible post-viral methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The admitting hospitalist considers that the current clinical scenario may be related to a viral illness and orders serum procalcitonin to help guide antibiotic decision-making. The patient is admitted to the hospital, given sepsis and tachypnea.

INTRODUCTION

In the past decades, the rise of resistant pathogens, heavily associated with antibiotic overutilization, has led to increased attention to antibiotic stewardship as a marker of patient safety and quality.[1] According to the Centers for Disease Control (CDC), it is estimated that up to 50% of antibiotic orders are inappropriate or entirely unnecessary.[2] Antibiotic overuse is a driver of multidrug-resistant organisms and increasing rates of *Clostridium difficile* infection.[3] Even when the clinical presentation suggests an infection, the distinction between bacterial and viral etiologies can complicate antibiotic use decisions. A diagnostic test to enhance physicians' ability to target patients most likely to benefit from antibiotics could be a useful tool to combat the complications of antibiotic overuse. Procalcitonin (PCT) has been approved by the FDA since 2017 to guide antibiotic treatment in sepsis and lower respiratory tract infections.[4]

WHAT IS PROCALCITONIN?

Procalcitonin (PCT) is produced in the thyroidal C-cells as a prohormone which is processed intracellularly and secreted in response to serum calcium levels as calcitonin. In systemic bacterial infections, production, and secretion of intact procalcitonin occur in other organs (liver, adipose tissue, etc.) triggered by cytokines (interleukin 2, tumor necrosis factor-α, interleukin 6, etc.) as well as bacterial endotoxins. Conversely, cytokines present in acute viral illness, such as interferon-γ, suppress procalcitonin release.[4,5] This dichotomy presents an opportunity to use procalcitonin to differentiate bacterial from nonbacterial etiologies in systemic infections and SIRS/sepsis syndromes.

In addition, understanding the dynamics of PCT as an acute phase reactant with faster kinetics than erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) permits its appropriate clinical application.[6] Levels of PCT rise within 3 – 6 hours of infection, so patients

Table 1. Procalcitonin False Positives*

Physiologic Stress	• Newborns (<48-72 hours; after 72 interpret levels as usual) • Massive stress (severe trauma, surgery, cardiac shock, burns) • Prolonged, severe cardiogenic shock or organ perfusion abnormalities
Non-bacterial cytokine activation	• Some forms of vasculitis and acute graft vs. host disease • Malaria and some fungal infections • Chronic renal disease (approximate 2x increase in baseline levels)
Dysregulated procalcitonin production	• Treatment with agents which stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, interleukin-2, granulocyte transfusion) • Paraneoplastic syndromes due to medullary thyroid and small cell lung cancer

*Adapted from ref. 4, 5 and 6.

presenting early in the disease course may have falsely low levels. PCT levels correlate with the severity of illness and should fall within 2 - 3 days of initiating appropriate therapy; thus, this is a reasonable time frame for a repeat assay in stabilizing patients and may be a candidate for early antibiotic cessation. Studies support stopping antibiotics in stable patients once the PCT level falls below 0.25 μ/L for lower respiratory tract infections, 0.5 μg/L for sepsis, or decreases by at least 80% from the peak.[7] Persistent elevation despite treatment suggests inadequate antibiotic therapy or source control and is predictive of excess mortality.

SPECIAL SITUATIONS: FALSE POSITIVE PCT ASSAYS

Most drivers of false positive PCT levels are rare and easily identifiable (**Table 1**).[4] However, similar to serum cardiac troponin I, patients with chronic kidney disease may have delayed PCT clearance; hence baseline levels may be about double the normal range. Studies suggest that patients on hemodialysis may have a PCT level >= 0.5 despite the absence of infection, with a range of 0.25 - 1.0 ng/mL. In one study, mean levels in patients with CKD not yet on dialysis were 1.82 +/- 0.39 ng/mL in uninfected patients. If a baseline is known, monitoring the rise and fall of PCT levels remains clinically helpful in this population.[5,8]

CLINICAL APPLICATION: LOWER RESPIRATORY TRACT INFECTIONS

Lower respiratory tract infections (LRTI) are common; however, the primary symptoms of cough and dyspnea can be caused by many noninfectious conditions like reactive airway disease, chemical pneumonitis from aspiration, allergies, heart failure, as well as viral infections, none of which require antibiotic therapy.

Multiple studies have demonstrated that procalcitonin can be safely used to guide antibiotic prescribing in patients with lower respiratory tract infections (LRTI), including community-acquired pneumonia (CAP) as well as ventilator-associated pneumonia (VAP). The first large multicenter randomized controlled trial to address the topic was the Swiss PROHOSP study.[9] Investigators randomized 1359 patients hospitalized with LRTI to PCT-guided or guideline-based antimicrobial therapy; the LRTI were community-acquired pneumonia, acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and acute bronchitis. After an initial PCT level was measured, antibiotic prescribing in the PCT arm of the study followed a prespecified protocol; specifically, clinicians were discouraged from prescribing antibiotics in patients with PCT levels < 0.25 μg/L (**Table 2**). For patients who were particularly ill or unstable at admission, the protocol allowed clinicians to prescribe antibiotics despite a low PCT level, contingent on repeat measurement and reassessment of the antibiotic decision within 24 hours. Clinicians caring for patients in the control arm were presented with condition-specific clinical practice guidelines to reinforce antibiotic choices. In both arms, the final decision on antibiotic treatment was at the attending physician's discretion. The investigators reported no difference in the combined outcome of death, intensive care unit (ICU) admission, or complications in the ensuing 30 days, but antibiotic use was significantly reduced. Mean antibiotic exposure dropped from 8.7 to 5.7 days, a reduction of 35%, with the most significant decrease among patients with chronic obstructive pulmonary disease (COPD) and acute bronchitis. Antibiotic-related adverse effects fell by 8.2%. Strengths of the study included a very high rate of protocol compliance (90%) by the treating clinicians.

One of the first studies addressing patients with VAP was a multicenter randomized controlled trial of 100 patients; 50 were allocated to conventional therapy and 50 to a protocol of PCT-guided treatment; the recommendation according to PCT levels was: <0.25 μg/L suggested the absence of VAP and discontinuation of antibiotics was strongly encouraged; 0.25 and 0.5 μg/L or a decrease ≥80% compared with baseline suggested low

Table 2. Procalcitonin-guided antibiotic algorithm for lower respiratory tract infection (PROHOSP)*

Procalcitonin Level (μg/L)	Likelihood of bacterial infection	Antibiotic treatment
<0.1	Absent	Strongly discouraged
0.1-0.25	Unlikely	Discouraged
0.25-0.5	Possible	Encouraged
>0.5	Present	Strongly encouraged

*Adapted from Ref. 7.
For patients with sepsis/septic shock, antibiotic cessation is recommended once the procalcitonin level falls below 0.5 μg/L. (adapted from Ref. 7).

likelihood of bacterial infection and discontinuation of antibiotics was encouraged; ≥0.5 μg/L or decrease <80% compared with baseline suggested unresolved bacterial infection. The duration of antibiotic therapy was decreased by 27% in the procalcitonin group (p = 0.038) and, at 28 days, had a higher rate of antibiotic discontinuation compared with patients receiving conventional therapy (HR 1.6, 95% CI 1.02–2.71; P = 0.043).[10] A single-center 5 year prospective study of 157 patients with VAP in which 48.4% were treated according to PCT-guided protocol and compared with conventional treatment, demonstrated a longer duration of antibiotic therapy in the conventional treatment arm compared with the PCT-guided protocol (9.5 vs. 8.0 days; p= 0.02); the rates of unfavorable outcomes (death or relapse of VAP) were similar (46.9% vs. 51.3%; p = .69).[11] A systematic review of all available studies of procalcitonin-guided therapy for LRTI was published in 2018 and included 26 randomized controlled trials encompassing 6708 patients in 12 countries. Findings confirmed an overall reduction of 2.4 days in antibiotic exposure, 6% in antibiotic-related adverse effects, and, importantly, a 17% relative risk reduction in 30-day mortality.[12]

Among the many positive studies on PCT-guided antibiotic therapy, one notable outlier is the 2018 PROACT study, which included > 1650 patients with suspected LRTI presenting to 14 different US hospitals.[13] Despite the design, unlike most other trials, the investigators could not demonstrate a reduction in antibiotic exposure, leading them to conclude that PCT guidance may not be useful for antibiotic stewardship. Low compliance rates with the study protocol and the inclusion of a significantly healthier study population hampered the generalizability of these findings. Compared to the 90% compliance rate in PROHOSP, protocol compliance in PROACT was 63%. Almost 40% of the patients included in PROACT had asthma exacerbations, which are generally not treated with antibiotics; additionally, almost all patients had low baseline PCT levels (91% of PCT values were < 0.25). Rather than indicating a failure of PCT, the study's findings underscore the fact that the utility of any lab test is limited unless applied in an appropriate diagnostic setting.

CLINICAL APPLICATION: SEPSIS

Sepsis is a life-threatening multi-organ dysfunction associated with infection with an associated increase in mortality. Its early identification and treatment aiming for a consequent decrease in associated mortality has been the target of nationwide quality improvement efforts.[14] The role of biomarkers in sepsis is promising as it can allow more accurate identification of the patients that warrant an earlier intervention by either implementing new antimicrobial treatment or escalating the current antimicrobial regimen.[15]

The benefits of PCT-guided therapy have been demonstrated among severely ill patients. A randomized multicenter trial of 266 patients with sepsis (using Sepsis-3 definitions) due to lower respiratory tract infections, acute pyelonephritis, or primary bloodstream infection compared standard care to PCT-guided therapy in which the criteria to stop antibiotics was a decrease of > 80% in PCT levels or any PCT<0.5 mg/L at day 5 or later.[16] In the PCT-guided group, there was a decrease in the rate of infection-associated adverse events (HR 0.45; 95% CI, 0.20–0.98; p = 0.045); 28-day mortality (HR 0.51; 95% CI, 0.29–0.89; p = 0.02); and median length of antibiotic therapy 5 (range, 5–7) versus 10 (range, 7–15) days (p<0.001). The cost of hospitalization was also reduced in the PCT arm.[7]

An extensive systematic review and meta-analysis of 5000 critically ill patients found that PCT-guided antibiotic discontinuation was associated with decreased mortality (RR 0.89; 95% CI, 0.83-0.97).[17] A meta-analysis including 523 patients with bacteremia noted a mean reduction in antibiotic exposure of 2.86 days, without excess mortality.[18] A third meta-analysis of 4482 critically ill patients admitted to the ICU with sepsis demonstrated a reduction in antibiotic exposure and mortality.

Despite a relatively small decrease in antibiotic duration of 1.19 days, the investigators found an 11% reduction in 30-day mortality rates (p = 0.03) in the PCT-guided group.[19] A more recent meta-analysis of 12 studies with a total of 4292 patients in the ICU with sepsis, found that a PCT-guided strategy was associated with decreased duration of antimicrobial therapy (−1.98 days (95% CI: −2.76, −1.21); p = 0.00001) with no increase in mortality at 28 days (RR 0.89; 95% CI, 0.79; 0.99); p = 0.04).[20]

A new trial is ongoing in the United Kingdom (PRONTO), aimed to evaluate the implementation of sepsis treatment pathways in the emergency department, comparing the use of early warning score alone and enhanced with PCT. The endpoints are the initiation of intravenous antibiotics at 3 hours (superiority comparison) and 28-day mortality (non-inferiority comparison).[21]

CLINICAL APPLICATIONS: ACUTE EXACERBATION OF COPD AND ACUTE BRONCHITIS

The use of antibiotics, especially macrolides, in AECOPD does not necessarily target the treatment of bacterial infection per se but rather has immunomodulatory and airway anti-inflammatory properties and is associated with enhanced outcomes, including decreased mortality.[22,23] Circulating levels of PCT correlate with the degree of invasiveness of infection in respiratory illness, and could help to refine the clinical indication for antibiotic therapy in AECOPD.[24]

Several randomized controlled trials (RCT) and meta-analyses have demonstrated the impact of PCT use in decreasing antibiotic usage in AECOPD. In an RCT of 208 patients, the use of PCT was associated with decreased antibiotic prescription by 30% ($p < 0.0001$) in the index exacerbation exposure; it was associated with a sustained decrease in antibiotic exposure at six months (RR, 0.76; 95% CI, 0.64 to 0.92; $p=0.004$).[25] A RCT of 194 patients with AECOPD and PCT < 0.1 ng/mL (95 patients in the antibiotic group and 96 patients in the control group) demonstrated no significant difference in the treatment success rate ($p=0.732$) or secondary outcome.[26] A RCT of 120 patients with AECOPD in which 62 were treated according to a PCT-guided algorithm and 58 according to the local guidelines demonstrated that the PCT-guided group had a decreased median duration of antibiotic exposure (3.5 days vs. 8.5 days; $p=0.02$); PCT-guided protocol was also associated with a decreased number of patients using antibiotics for ≥5 days (41.9% vs. 67.2%; $p=0.01$). There were no differences in outcomes (death, rehospitalization, or intensive care unit admission) within 28 days.[27]

A meta-analysis of 4 RCTs (N = 679 patients with AECOPD) by Lin et al., demonstrated that PCT-guided treatment, when compared to standard treatment, was associated with decreased antibiotic use (OR 0.26, 95% CI 0.14-0.50, $p<0.0001$) in comparison to standard treatment without increasing clinical failure or mortality.[28] Mathioudakis et al. demonstrated in a meta-analysis of eight trials (N = 1062 patients with AECOPD) that PCT-guided treatment was associated with reduced antibiotic prescription (RR 0.56, 95% CI 0.43-0.73; $p<0.0001$) with no significant difference in clinical outcomes (treatment failure, duration of hospitalization, exacerbation rate or mortality); however, the authors emphasized the limitations of the study (low to moderate quality of evidence, small sample and methodological limitations) and recommended further evaluation through use of RCT.[29]

A series of cross-sectional and longitudinal multivariable analyses of the Premier claim database with > 200,000 patients hospitalized with AECOPD comparing two periods (2009-2011 and 2013-2014) demonstrated that hospitals that adopted PCT-guided protocols had no significant differences in the rate of antibiotic treatment or duration of therapy compared with those that did not.[30] The findings of the latter study need to be taken with the caution of time (already ten years ago), as well as due to the complexities associated with individual clinical-decision making, clinical variability of COPD, and patient comorbidities.[31]

Given methodological differences among studies and the clinical variability in the severity of illness found in patients with AECOPD, in addition to the benefits of antibiotic therapy in this population independent of their anti-bacterial effects, most sources find limited application for procalcitonin in this population. In addition, given that AECOPD is generally felt to be a localized rather than a systemic infection, it is less likely to impact PCT levels.

CLINICAL APPLICATION: COVID-19

The recent SARS-CoV-2 (COVID-19) pandemic has posed a challenge to the best evidence to support its medical management. There is no established role for empiric antibiotic therapy unless suspicion of concomitant bacterial infections is strong. A retrospective study of 191 patients with COVID-19 in Wuhan, China, found that more than 70% had a PCT < 0.25 ng/mL and no evidence of bacterial infection upon admission.[32] A study of 66 ICU patients with COVID-19 in The Netherlands found that PCT elevation correlated with development of secondary bacterial infection. Furthermore, the analysis of PCT performance demonstrated that PCT < 0.25 μg/L had a negative predictive value of 81%, and a PCT > 1.00 μg/L had a positive predictive value of 93%.[33] An observational retrospective study of 368 patients with COVID-19, demonstrated that withholding antibiotics in patients with a PCT ≤0.25 ng/mL was associated with decreased antibiotic exposure with no adverse impact on mortality.[34] Given the limitations of these small single-center studies performed during the pandemic's peak, more robust studies are needed.

CLINICAL APPLICATION: GENERAL PRACTICE

For acute medical conditions such as CAP and sepsis, there are few clinical situations in which providers would be comfortable withholding empiric antibiotics regardless of initial PCT level. Although some studies support using PCT to guide antibiotic initiation, most guidelines suggest reliance on clinical judgment over biomarkers, especially in patients requiring hospital admission. There are certain situations in which providers may consider using a low PCT value to support withholding antibiotics; examples include patients with respiratory symptoms felt most likely to be due to noninfectious causes (i.e., congestive heart failure, pulmonary fibrosis, advancing lung cancer), patients felt to have acute viral infections without superinfection, or outpatients at low risk of decompensation.

Currently, the most clinically useful role of PCT testing is to guide the duration of antibiotic therapy. Although the literature supports short-course antibiotic therapy in many common acute medical conditions, overprescribing remains prevalent.[35] Although guidelines suggest uncomplicated community-acquired pneumonia (CAP) treatment for no more than 5 – seven days, most patients receive longer courses.[36] A review of >150,000 patients across the United States with uncomplicated CAP documented a mean antibiotic duration of 9.5 days, with close to 70% of patients receiving > 7 days of therapy.[37] A multicenter study of CAP patients hospitalized in Michigan noted similar findings, with a mean 2-day excess duration of therapy or 2526 excess days of treatment per 1000 discharges.[38] Although existing guidelines support short-course therapy, obviating the need for biomarker guidance, clinicians have not reliably adopted this practice. A PCT-guided de-escalation algorithm may reduce therapy duration and shorten unnecessary antibiotic use. This practice applies regardless of pneumonia severity, including VAP and pneumonia with septic shock.[10,11,39]

CLINICAL CASE (CONTINUATION)

The patient was admitted to a regular nursing floor, where a serum procalcitonin was ordered, and its value was 0.23 μg/L. He improved rapidly on the initial antibiotic therapy, and a repeat assay on hospital day 3 was 0.13 μg/L. Given the lack of systemic inflammatory response markers, hemodynamic stability, and clinical improvement, antibiotics were stopped without adverse events. The patient was discharged that afternoon and found to have recovered on a follow-up visit 2 weeks later.

CONCLUSION

Procalcitonin is a unique biomarker that rises rapidly in the presence of systemic bacterial infections and sepsis, falls in response to adequate treatment, and correlates with the severity of illness. In appropriate clinical settings, particularly for patients with LRTI, it can be used as a tool for antibiotic stewardship to support decisions to discontinue antibiotics earlier than may otherwise have occurred with clinical judgment alone. With an understanding of its limitations, clinicians can apply PCT as a tool for more effective prescribing and hopefully help reduce the adverse effects of excess antimicrobial utilization.

TAKE HOME POINTS

- Procalcitonin is a useful marker to identify bacterial infection.
- Procalcitonin can help guide antibiotic stewardship and shorten the duration of antibiotics without increasing the risk of complications.
- Cut-off values of < 0.25 ng/mL have a good negative predictive value to rule out a bacterial infection. In contrast, values> 1 ng/mL are more likely associated with an active bacterial infection.
- Procalcitonin values must be used within the context of careful clinical assessment and judgment.

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DISCLOSURES/CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

Corresponding Author

Moises Auron, MD, FAAP, FACP, SFHM
Professor of Medicine and Pediatrics, Cleveland Clinic Lerner College of Medicine of Case Western Reserve

University
Department of Hospital Medicine, Cleveland Clinic
9500 Euclid Ave, M2 Annex
Cleveland, OH, 44122
Email: auronm@ccf.org

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