Procalcitonin in special patient populations: Guidance for antimicrobial therapy

Susan E. Smith, PharmD, BCPS, BCCCP, Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Athens, GA

Justin Muir, PharmD, BCCCP, Department of Pharmacy, NewYork-Presbyterian Hospital, Columbia University Irving Medical Center, New York, NY

Julie Kalabalik-Hoganson, PharmD, BCPS, BCCCP, Fairleigh Dickinson University School of Pharmacy and Health Sciences, Florham Park, NJ

Purpose. Procalcitonin (PCT) is an endogenous hormone that increases reliably in response to bacterial infection, and measurement of serum PCT levels is recommended to help guide antimicrobial therapy. The utility of PCT assessment in special patient populations (eg, patients with renal dysfunction, cardiac compromise, or immunocompromised states and those undergoing acute care surgery) is less clear. The evidence for PCT-guided antimicrobial therapy in special populations is reviewed.

Summary. In the presence of bacterial infection, nonneuroendocrine PCT is produced in response to bacterial toxins and inflammatory cytokines, resulting in markedly elevated levels of serum PCT. Cytokine induction in nonbacterial inflammatory processes activated by acute care surgery may alter the interpretation of PCT levels. The reliability of PCT assessment has also been questioned in patients with renal dysfunction, cardiac compromise, or immunosuppression. In many special populations, serum PCT may be elevated at baseline and increase further in the presence of infection; thus, higher thresholds for diagnosing infection or de-escalating therapy should be considered, although the optimal threshold to use in a specific population is unclear. Procalcitonin-guided antimicrobial therapy may be recommended in certain clinical situations.

Conclusion. Procalcitonin may be a reliable marker of infection even in special populations with baseline elevations in serum PCT. However, due to unclear threshold values and the limited inclusion of special populations in relevant clinical trials, PCT levels should be considered along with clinical criteria, and antibiotics should never be initiated or withheld based on PCT values alone. Procalcitonin measurement may have a role in guiding de-escalation of antibiotic therapy in special populations; however, the clinician should be aware of disease states and concomitant therapies that may affect interpretation of results.

Keywords: cardiology; immunosuppression; procalcitonin; renal insufficiency; trauma; surgical procedures, operative

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Procalcitonin (PCT) is an endogenous hormone that is produced by a neuroendocrine pathway in healthy individuals. It is the precursor to calcitonin, which is involved in the regulation of calcium and phosphate homeostasis (Figure 1).[1-4] Under normal physiologic conditions, expression of PCT by the calcitonin 1 (CALC-1) gene in thyroid C-cells is induced by several stimuli. Nearly all of the PCT produced in thyroid C-cells is enzymatically cleaved to calcitonin prior to secretion into the circulation. Thus, extremely low levels of PCT (<0.02 ng/mL) are detected in healthy individuals.

In contrast, PCT levels up to 1,000 ng/mL have been documented in the context of bacterial infections.[3] In animal studies, PCT was found almost exclusively in thyroid tissue in healthy animals. In animals with a bacterial infection, however, PCT was recovered from all tissues examined, including white blood cells, adipocytes, and the spleen, kidneys, pancreas, colon, and

Address correspondence to Dr. Smith (susan.smith@uga.edu).

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brain.[5] These nonendocrine tissues lack the enzymatic pathway to cleave PCT to calcitonin. Thus, PCT is released into the circulation, resulting in elevated levels. This nonneuroendocine PCT is genetically identical to PCT but is produced through 2 nonneuroendocrine pathways: (1) a direct pathway induced by lipopolysaccharide or other bacterial toxins and (2) an indirect pathway induced by inflammatory cytokines such as interleukin-1 β, interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) (Figure 1).[2,3]

After a host is exposed to bacteria, PCT levels increase quickly over 3 to 6 hours, peak at 6 to 13.5 hours, and have a half-life of 22 to 36 hours.[3,4,6,7] Other biomarkers such as IL-6 and TNF-α increase faster than PCT but return to baseline in as little as 6 to 8 hours, limiting their utility for tracking resolution of infection.[6] Use of C-reactive protein as a biomarker of infection is similarly limited by its slower increase and faster recovery relative to PCT, as well as its lack of specificity to bacterial infections. As a result, PCT can be used as a reliable marker of some bacterial infections, with a potential role in tracking clinical resolution and de-escalation of antimicrobials.[8] Procalcitonin has also been investigated as a diagnostic tool for bacterial infection, with conflicting results.[9] When used as a screening assessment for suspected sepsis, PCT levels of <0.5 ng/mL are associated with a low risk of progression to sepsis, and levels of >2 ng/mL are associated with a high risk of progression to sepsis or septic shock.[10]

Procalcitonin has been investigated in a number of different populations and infectious conditions. Respiratory tract infections represent the primary target of many randomized controlled trials (RCTs) in this area, ranging from studies in primary care settings and emergency departments to studies in general inpatient wards and intensive care units (ICUs). Procalcitonin has gained recognition as a reliable biomarker, and multiple clinical practice guidelines, including those of the Surviving Sepsis Campaign, recommend its use to help guide antimicrobial therapy.[11,12] Use of PCT-guided algorithms has been associated with reductions in antimicrobial initiation and duration and with patient outcomes similar to or improved relative to outcomes without PCT use.[13]

Consequently, in 2017 the US Food and Drug Administration approved the expanded use of a PCT assay (Vidas Brahms PCT, bioMérieux, Durham, NC) to guide the initiation and discontinuation of antibiotics for suspected lower respiratory tract infections and the discontinuation of antibiotics in patients with sepsis.[14] The manufacturer's labeling includes antibiotic recommendations based on PCT level and clinical stability. For example, in patients with sepsis it is recommended to discontinue antibiotics if the PCT level is less than 0.5 ng/mL or has decreased at least 80% from baseline; in patients with lower respiratory tract infections without sepsis, it is recommended to discontinue antibiotics if the PCT level is less than 0.25 ng/mL.

KEY POINTS

- In special populations, including patients with renal insufficiency, cardiac compromise, or immunosuppression and those undergoing acute care surgery, serum procalcitonin may be elevated at baseline and increase further in the presence of infection.
- In those populations, assessment for procalcitonin threshold values may be useful in combination with clinical criteria for diagnosing infection.
- Procalcitonin may have a role in guiding de-escalation of antibiotic therapy in special populations; however, the effect of disease states and concomitant therapies on procalcitonin values should be considered.

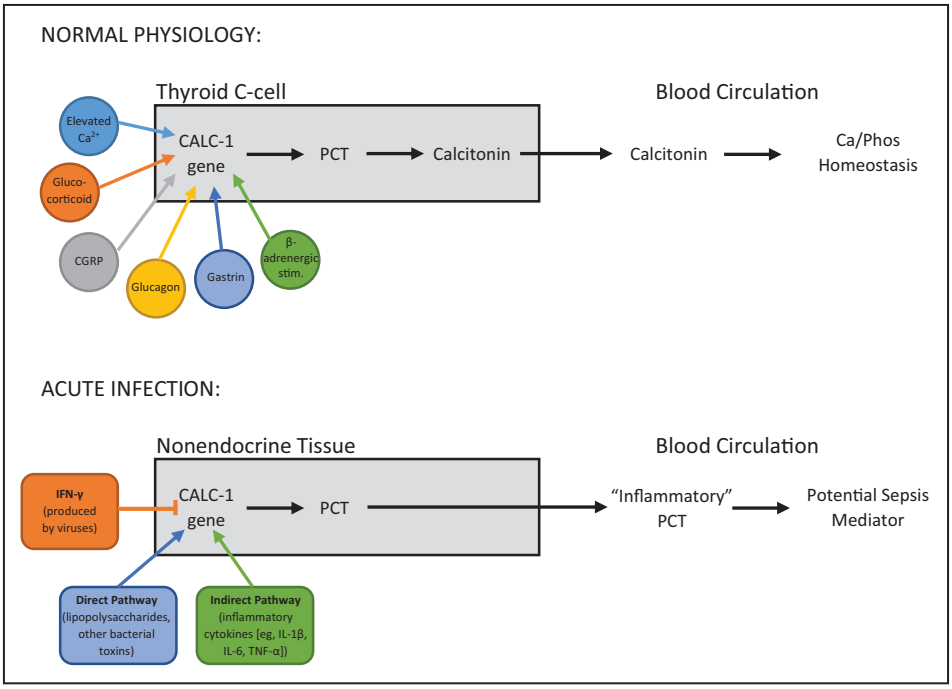
Procalcitonin in special populations

The utility of PCT for guiding antimicrobial therapy may be limited in certain populations. The indirect pathway for nonneuroendocrine PCT production is thought to be driven by cytokines (Figure 1). Cytokine induction is present in nonbacterial inflammatory processes such as trauma, burns, and major surgery, and PCT levels may be altered as a result. The reliability of PCT has also been questioned in other populations, including patients with renal dysfunction or immunosuppression. Large, prospective studies evaluating PCT monitoring often exclude patients with specific infections that require prolonged antibiotic courses, patients with severe immunosuppression, and patients receiving high doses of corticosteroids or other immunosuppressing medications, as well as patients who are pregnant, have short ICU stays, have a low chance of survival, are undergoing cardiac surgery, or have trauma or heat stroke.[15,16] Extrapolation to excluded patient populations is challenging, and subgroups who make up a very low proportion of included patients may not have experienced the same outcomes as the entire population. Here we review the literature relating to PCT for guiding antimicrobial therapy in special patient populations, namely those with renal dysfunction, cardiac compromise, and immunocompromised states and those undergoing acute care surgery. These specific populations were chosen by consensus of the authors based on prevalence in critical care practice and the quantity and quality of published literature.

Renal dysfunction

With normal renal function, nearly one-third of plasma PCT is eliminated renally.[17] Additionally, the plasma elimination rate of PCT is weakly correlated with renal function. In one study of critically ill patients, PCT

Figure 1: Procalcitonin (PCT) regulation during physiologic and pathophysiologic conditions. Under physiologic conditions, expression of PCT by the calcitonin 1 (CALC-1) gene in thyroid C-cells is induced by several stimuli, including elevated calcium levels, glucocorticoid, calcitonin gene–related peptide (CGRP), glucagon, gastrin, and β-adrenergic stimulation. Procalcitonin is enzymatically cleaved to calcitonin prior to secretion from thyroid C-cells into the systemic circulation. During acute bacterial infection, PCT production is stimulated in nonneuroendocrine tissues by both direct and indirect pathways. These tissues lack the enzymatic activity to cleave PCT to calcitonin; thus PCT is released into the circulation, resulting in elevated levels. During viral infections, however, interferon-γ (IFN-γ) inhibits the expression of the CALC-1 gene. Thus, serum PCT levels are not found to be elevated during acute viral infections. IL-1β indicates interleukin-1 β; IL-6, interleukin-6; TNF-α, tumor necrosis factor α.



kinetics were compared in patients with normal renal function (defined as a creatinine clearance of ≥98 mL/min in men and ≥95 mL/min in women) and those with severe renal dysfunction (defined as a creatinine clearance of <30 mL/min). Procalcitonin half-life was not significantly different between the groups (28.9 and 33.1 hours, respectively; $P = 0.262$).[18] In a subsequent larger study, however, urinary elimination of PCT was significantly reduced in patients with severe renal dysfunction relative to those with normal renal function (median half-life, 30.0 vs 44.7 hours, $P = 0.0003$) and was weakly correlated with creatinine clearance ($R = 0.24$, $P = 0.036$).[17] Although PCT elimination is predominantly nonrenal, the renal component of elimination plays a significant role in patients with renal dysfunction, which is demonstrated by the higher PCT levels observed in patients with chronic kidney disease (CKD).[19-23] Additionally, PCT has a moderate molecular weight (~13 kDa) and is removed by renal replacement therapy (RRT) to differing degrees based on specific RRT modalities and settings.[20,24] Thus, special consideration must be given when assessing PCT levels in patients with varying degrees and types of renal dysfunction.

Chronic kidney disease. The association between CKD and elevations in PCT levels has been reported inconsistently.[20,25,26] In the absence of infection, baseline PCT concentrations in patients with CKD may vary based on the degree of renal impairment, with baseline levels founds to be 0.1 ng/mL in patients with less advanced CKD compared to 1.82 ng/mL in patients with stage 5 CKD prior to initiation of hemodialysis (HD).[20,26] It is hypothesized that PCT is elevated in patients with CKD due to an increased presence of proinflammatory metabolites that stimulate the indirect nonneuroendocrine pathway of PCT production.[19] Despite variations in baseline PCT values in patients with CKD, PCT concentrations increase significantly during acute bacterial infection.[26] Thus, PCT assessment is recommended in combination with clinical criteria for ruling in bacterial infection in patients with varying degrees of CKD.[21,25-27] If PCT is used during routine care in this way, it is recommended to obtain baseline PCT values for each patient due to large interpatient variability in PCT levels based on renal function, inflammatory processes, and other factors.

Acute kidney injury. The diagnostic utility of PCT for detecting bacterial infection in patients with acute

kidney injury (AKI) has been questioned.[28] Others have found the diagnostic accuracy of PCT to be at least as good in patients with AKI as in patients without AKI; however, the cutoff values were increased in patients with AKI.[29] In a retrospective study of 393 patients with varying degrees of AKI, PCT was significantly higher in septic patients than in nonseptic patients for each AKI category. The baseline PCT increased with increasing degrees of renal dysfunction, as did the optimal cutoff value for diagnosing sepsis.[30]

Additionally, PCT appears to be associated with disease severity during AKI. Nakamura et al[30] found PCT levels to increase significantly with increasing severity of sepsis. Others have found PCT to be significantly associated with APACHE II scoring in patients with AKI.[29] Since PCT elimination is thought to occur partially through nonrenal mechanisms, sepsis severity may be at least partially responsible for the rising levels of PCT in septic patients with AKI.[30] This hypothesis is supported by several other investigations using PCT as a predictive marker for sepsis-induced AKI in patients with infection.[31-33]

Renal replacement therapy. Procalcitonin levels are higher before HD, before peritoneal dialysis (PD), and before initiation of continuous renal replacement therapy (CRRT) and are cleared to varying degrees by each mechanism of RRT.[19] Patients on chronic RRT may have chronic systemic inflammation associated with uremia or stimulated by incompatibility of the biomaterial of the dialysis procedures.[27] In patients who have end-stage renal disease (ESRD) but no infection, baseline PCT levels are often above the standard cutoff of 0.5 ng/mL. In a meta-analysis of data on 803 patients who were receiving PD or HD or had renal insufficiency and were treated for infection in ambulatory care, inpatient, or ICU settings, PCT assessment was demonstrated to have diagnostic accuracy similar to its accuracy in patients without renal dysfunction, with sensitivity and specificity of 73% and 88%, respectively.[27] As in other types of renal dysfunction, PCT concentrations in patients with ESRD are higher at baseline and increase reliably with infection, suggesting a higher cutoff value for diagnosing acute bacterial infection in patients with ESRD.[34]

With PCT's moderate molecular weight, the effect of CRRT on plasma PCT concentrations may not be apparent. Multiple studies have confirmed that PCT is removed by CRRT primarily by convection, with additional removal by adsorption during the first hours of therapy.[24,35] Some investigators concluded that PCT is a useful diagnostic marker in septic patients requiring CRRT due to minimal PCT removal during conventional CRRT with a low ultrafiltration rate.[24,36,37] Others have demonstrated 50% removal of PCT by continuous venovenous hemodiafiltration with a high cutoff membrane.[38] Ultimately, it seems that PCT removal is dependent on specific CRRT parameters, including mode, membrane size, and effluent rate.

While some contend that PCT can be used for initiating antibiotic therapy in patients with renal dysfunction, the optimal cutoff value is unclear and likely varies based on the degree of renal impairment (Table 1). Nonrenal mechanisms account for about two-thirds of PCT elimination; thus, downtrending PCT values could theoretically be used to guide discontinuation of therapy in patients with renal dysfunction not requiring RRT. Declines in PCT levels, however, will be slower and based on the degree of renal impairment. Removal of PCT by RRT complicates the picture, and PCT should likely not be used independently to guide duration of therapy in this population.

Cardiac compromise

Cardiac arrest. Several studies evaluating PCT levels to predict neurological outcomes in cardiac arrest suggest that high PCT levels after resuscitation are common and are associated with poor outcomes. Procalcitonin levels are highest on the first day following hypothermia and gradually decrease, regardless of the presence of infection.[39] In a subcohort analysis of the FINNRESUSCI study, PCT levels had good predictive value for hemodynamic instability over 48 hours and for poor outcomes at 12 months in patients with out-of-hospital cardiac arrest.[40] Several studies have confirmed this correlation between elevated PCT levels and mortality and poor neurological outcomes.[41-48] In one study, PCT sensitivity and specificity in predicting neurological outcome in patients who survived at least 24 hours after cardiopulmonary resuscitation (CPR) were 94.7% and 50%, respectively.[44] PCT levels was significantly higher in patients who had CPR durations of 10 minutes or longer.

While PCT is elevated following cardiac arrest, it is further elevated in the presence of infection. In one study, PCT levels were elevated in patients with return of spontaneous circulation (ROSC) who had ventilator-associated pneumonia (VAP) compared to those without VAP (6 ng/mL vs 0.5 ng/mL, $P < 0.001$). Procalcitonin had a sensitivity of 100% and specificity of 75% for detecting VAP in the first 7 days following ROSC.[49] Another study demonstrated that PCT levels may be elevated due to acute inflammation in the absence of infection.[50]

Cardiogenic shock. PCT levels may be elevated in the setting of cardiogenic shock without infection.[51,52] In one study, PCT levels were higher in patients with cardiogenic shock than in healthy controls but were lower than in patients with septic shock. Patients with cardiogenic shock who had multiorgan failure had higher PCT levels than patients without organ failure. This study demonstrated that patients with cardiogenic shock who have multiorgan failure may have high PCT concentrations in the absence of infection.[53] In patients with cardiogenic shock undergoing extracorporeal membrane oxygenation (ECMO), a PCT level greater than 10 ng/mL in the first week of ECMO was associated with mortality, and higher PCT levels were associated with higher mortality.[54]

Table 1. Recommendations for Procalcitonin Use in Special Populations

Clinical Condition	Effect on PCT	Recommendation(s)[a]	PCT Threshold	Level of Evidence
Chronic kidney disease	• Inconsistent increase in PCT reported • Proposed hypothesis: proinflammatory metabolites stimulate nonneuroendocrine pathway of PCT production	• Consider a higher PCT threshold for ruling in bacterial infection	• >0.85-1.5 ng/mL[24,25]	• Single-center, prospective, observational studies[24,25]
Acute kidney injury	• Inconsistent increase in PCT reported • PCT levels also associated with disease severity in patients with AKI	• Consider a higher PCT threshold for ruling in bacterial infection	• >0.42-2 ng/mL[28,29] • 7.13 ng/mL with failure per RIFLE criteria[29]	• Retrospective, observational studies[28,29]
Chronic RRT (HD or PD)	• Baseline PCT levels higher in ESRD but increase reliably with infection • PCT levels high prior to each HD or PD session and PCT cleared to varying degrees	• Consider a higher PCT threshold for ruling in bacterial infection • Measure PCT level prior to HD	• >1.5 ng/mL in detecting severe infection or sepsis[20]	• Single-center, prospective, observational study[20]; meta-analysis[26]
Continuous RRT	• PCT removed by convection (primarily) and adsorption • Effect on plasma PCT levels is limited with conventional modes of CRRT • Significant PCT clearance with high-cutoff CRRT membranes	• Must be aware of specific CRRT parameters to assess potential impact on PCT utility • With conventional CRRT, PCT may remain a useful diagnostic marker	• No specific threshold recommended[23,35-37]	• Single-center, prospective, observational studies[23,35-37]
Cardiac arrest	• PCT is higher in cardiac arrest; PCT correlates to survival and neurological outcomes	• Consider measuring PCT for predicting survival and neurological outcomes	• 0.291-1.36 µg/L for 12-month outcome[39] • 0.5 ng/mL for poor outcomes[41] • 0.05 ng/mL for mortality[43] • 1 ng/mL for ventilator-associated pneumonia[48] and neurological outcome[42]	• Subcohort analysis of prospective, observational multicenter study[39] • Retrospective study[42,43] • Prospective observational study[41,48]
Cardiogenic shock	• Elevated PCT is associated with infection, sepsis, and mortality	• Consider measuring PCT to predict infection, sepsis, and mortality	• ≥2 ng/mL for infection[50] • >10 ng/mL for sepsis[52] • >10 ng/mL for mortality in patients receiving ECMO[53]	• Prospective observational[50] • Retrospective[52, 53]
Cardiac surgery	• Elevated PCT is associated with infection and postoperative complications	• Consider measuring PCT to predict infection and postoperative complications	• 1-9.4 ng/mL for infection[54,55,57,60,66,67] • 2.95-5 ng/mL for complications[56,58]	• Retrospective[54] • Prospective observational[55-58,66,67] • Systematic review[60]
Heart failure	• Elevated PCT is associated with death, rehospitalization, and infection	• Consider measuring PCT to predict death, rehospitalization, and infection	• ≥0.2 ng/mL for death and rehospitalization[71] • 0.086-0.657 ng/mL for infection[75]	• Multicenter randomized, double-blind placebo controlled[71] • Retrospective[75]

Table 1. Continued

Clinical Condition	Effect on PCT	Recommendation(s)[a]	PCT Threshold	Level of Evidence
Surgery	• Elevated PCT is associated with infection and mortality • PCT-guided antibiotic therapy led to shorter duration of antibiotic therapy and reduced antibiotic costs without increase in negative outcomes	• Consider measuring PCT to predict infection and mortality • Consider using PCT-guided antibiotic therapy	• >1.5 ng/mL for postoperative infection[55] • 1.44 ng/mL for mortality; 0.75 ng/mL for morbidity and mortality[77] • PCT-guided antibiotic treatment resulted in shorter length of treatment and reduced costs without increase in negative outcomes[78]	• Prospective observational[55] • Retrospective[77] • Prospective randomized[78]
Burns	• Elevated PCT is associated with infection and sepsis	• Consider measuring PCT to predict infection and sepsis	• Variable (0.5-3 ng/mL) for sepsis and infection[79,81,82,84,85-89,91] • 5.12 ng/mL for bloodstream infection[90]	• Retrospective observational[79,81,90] • Small, prospective observational[82-86,91] • Meta-analyses[88,89]
Trauma	• Elevated PCT is associated with sepsis, complications, and poor outcomes	• Consider using PCT as a marker for infection, sepsis, and risk for complications	• 0.1-0.2029 ng/mL for sepsis and infection[103,104] • 1-2 ng/mL for complications and poor outcomes[96,98] • >5 ng/mL for increased mortality[95] • 0.6-5 ng/mL[107]	• Retrospective[95] • Prospective observational[96, 98,103,104] • Meta-analysis[107]
Hematologic malignancy	• PCT level not expected to be significantly affected by malignancy • Elevations with engraftment syndrome and GVHD after HSCT, T cell–directed therapies	• Avoid using PCT for management of antimicrobials if a confounding condition/medication is present • Consider using along with clinical criteria to facilitate antimicrobial discontinuation during febrile neutropenia	• >0.5 ng/mL for bacterial infection in febrile neutropenia[115] • >2 ng/mL for risk of severe sepsis or septic shock[117]	• Prospective observational studies and meta-analysis[115] • Single-center randomized controlled trial[120]
Solid tumors	• Elevations with medullary thyroid cancer, small cell lung cancer	• Avoid using PCT for management of antimicrobials if a confounding oncologic condition is present • Consider using along with clinical criteria to facilitate antimicrobial discontinuation during febrile neutropenia	• >0.5 ng/mL for bacterial infection in febrile neutropenia[115]	• Prospective observational studies and meta-analysis[115]
Solid organ transplantation	• Elevations with T cell–directed therapies	• Avoid using PCT early after receipt of alemtuzumab or antithymocyte globulin • Consider using along with clinical criteria to facilitate antimicrobial discontinuation in the setting of suspected infection	• Variable cutoffs for bacterial infection (0.14-8.18 ng/mL)[119]	• Prospective observational studies and meta-analysis[119]

Abbreviations: AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ESRD, end-stage renal disease; GVHD, graft-versus-host disease; HD, hemodialysis; HSCT, hematopoietic stem cell transplant; PCT, procalcitonin; PD, peritoneal dialysis; RIFLE, risk, injury, failure, loss of kidney function, end-stage kidney disease; RCT, randomized controlled trial; RRT, renal replacement therapy.
[a]All recommendations are based on the literature cited in this review. In many cases, the available evidence consists of small and/or observational studies. The reader should be aware of the level of evidence in support of these recommendations and should apply the recommendations accordingly.

Cardiac surgery. Results of several studies suggest that PCT is increased following cardiac surgery and that further elevations may predict infection or postoperative complications at various cutoff values.[55-60] In a systematic review, PCT levels increased after uncomplicated cardiac surgery, with levels peaking within 24 hours of surgery. PCT levels were further elevated in patients with sepsis, postoperative complications, poor outcomes, and organ dysfunction or failure.[61] In patients undergoing coronary artery bypass grafting or valve replacement requiring cardiopulmonary bypass (CPB), patients with PCT levels of >2 ng/mL on day 1 or 2 experienced more postoperative abnormalities.[62] Significantly elevated PCT levels following cardiac surgery have also been observed in patients with perioperative myocardial infarction and in patients with multiple organ dysfunction syndrome.[63,64] The association between PCT elevation and infection following cardiac surgery is less clear. In one study, significant increases in PCT were observed in patients undergoing CPB who had systemic inflammatory response syndrome (SIRS), as compared to those without SIRS, but PCT did not have predictive value for detecting sepsis after CPB.[65] Similarly, Chakravarthy et al[66] did not identify a correlation between elevated PCT and postoperative infection in adult cardiac surgery patients. On the other hand, another study demonstrated that PCT was significantly higher in CPB recipients with infection than in patients without infection.[67] Procalcitonin has been proposed as a diagnostic marker for VAP in cardiac surgery patients, with a cutoff value of 5 ng/mL (sensitivity of 91%, specificity of 71%).[68]

The role of PCT in predicting adverse renal outcomes following cardiac surgery has been explored. In 122 cardiac surgery patients, PCT measured on the second postoperative day was found to have good predictive value for adverse renal outcomes.[69,70] One study of cardiac surgery patients demonstrated higher postoperative PCT levels in patients with AKI. Interestingly, in patients with serum creatinine of ≥2 mg/L, PCT levels were similar in infected and noninfected patients; however, when serum creatinine was less than 2 mg/L, PCT was higher in patients with infection, suggesting that an elevated PCT level may not indicate infection in post–cardiac surgery patients with AKI and high creatinine levels.[28]

Heart failure. Patients with heart failure (HF) often have elevated PCT levels in the absence of infection, a finding that has been associated with poor outcomes. In a study of 261 patients with acute HF but no active infection, PCT elevation was associated with significantly greater risks of death, all-cause rehospitalization, and acute HF rehospitalization.[71] In a study of 1,781 patients from the PROTECT trial, higher PCT levels were associated with increased 30-day all-cause mortality.[72] In patients with acute decompensated HF without infection, PCT had good predictive value for all-cause death and hospitalization at day 90 (area under the curve [AUC], 0.67). Patients with consistently high PCT or an increase in PCT in the first 72 hours after being hospitalized had the worst outcomes.[73] The PCT level differentiated between patients with HF and healthy controls with sensitivity of 88.9% and specificity of 100%.[74]

A meta-analysis focused on the prognostic and diagnostic value of PCT in patients with suspected HF revealed that patients with HF and concomitant infections have higher PCT levels than patients with HF alone.[75] Wang and colleagues[76] found that patients with HF had higher PCT levels than controls and that patients with bacterial infection and HF had higher PCT levels than patients with infection but not HF. As HF severity increased, the positive predictive value of PCT decreased. Schuetz and colleagues[77] performed a secondary analysis of the ProHOSP trial to determine if antibiotic stewardship with a PCT algorithm would improve outcomes in 233 patients with HF presenting with possible respiratory infection. In patients with low initial PCT levels (<0.25 ng/mL), patients in the PCT guidance group experienced a lower adverse outcome rate (4% vs 20%; $P = 0.01$) and fewer antibiotic exposure days (mean [SD], 3.7 [4.0] vs 6.5 [4.4]; $P < 0.01$). In the group with an initial PCT of ≥0.25 ng/mL, patients in the PCT group also had significantly less antibiotic exposure, with no difference in adverse outcomes. This study suggested that using a PCT-based approach to excluding infection and guiding antibiotic use in patients with HF who have respiratory symptoms may decrease antibiotic exposure.

Acute care surgery

Surgery. While PCT may be elevated due to inflammation following surgery, increased PCT is associated with sepsis and mortality in surgical patients, as in other populations.[56,78] Furthermore, PCT-guided algorithms have been evaluated for their utility in de-escalating antibiotics in surgical patients. In one study including 27 surgical ICU patients with severe sepsis, a PCT-guided antibiotic algorithm resulted in, on average, 1.7 fewer antibiotic days, a 17.8% reduction in antibiotic costs, and no difference in negative outcomes.[79] Similar findings have been repeated in multiple studies, suggesting that PCT-guided algorithms for managing antibiotic therapy may be effective in the surgical population.

Burns. Patients with burns commonly have elevations in inflammatory biomarkers. Multiple studies have demonstrated the value of PCT for predicting infection, sepsis, and patient outcomes; however, in these studies thresholds for infection varied by source and pathogen.[80-87] Nonsurviving patients with burns were found to have higher PCT levels than survivors.[88] In a meta-analysis, the overall pooled AUC for PCT as a biomarker for sepsis was 0.83 at a cutoff value of 1.47 ng/mL.[89] Another meta-analysis revealed a similar AUC for detecting sepsis, with pooled sensitivity of 0.74 and pooled specificity of 0.88.[90] PCT is also elevated in patients with burns who have bacteremia.[91] In one study of 175 such

patients, PCT levels measured within 48 hours after burn injury correlated significantly with positive blood culture results and mortality rates. The area under the receiver operating characteristic curve for PCT as a predictor of mortality was 0.844. Patients with a PCT level of ≥2 ng/mL had a significantly higher mortality rate than patients with a PCT level of <2 ng/mL.[92] Another study found that PCT correlated with tissue hypoperfusion.[93] In a single-center, prospective, observational study of 46 patients with burns, Lavrentieva and colleagues[94] investigated the effect of a PCT-guided algorithm for antibiotic use. Use of the PCT-guided algorithm resulted in less antibiotic exposure than the standard antibiotic regimen (mean [SD], 10.1 [4] days vs 15.3 [8] days; $P = 0.034$), with no significant differences in mortality, relapse or superinfection, length of ICU or hospital stay, or maximum Sequential Organ Failure Assessment (SOFA) score.

Trauma. Results of several studies indicate that among trauma patients, PCT elevation is associated with sepsis and with complications related to the trauma.[95-104] Ahmed and colleagues[105] found that PCT levels on day 5 correlated with SOFA score and Injury Severity Score in multiple-trauma and major surgery patients. PCT levels were higher in nonsurvivors vs survivors. In patients with traumatic brain injury, a rapid increase in PCT levels was observed 24 hours after extracranial injuries (median increase, 3 ng/mL). In the case of abdominal and extremity trauma, the amount of PCT increase correlated to injury severity.[106] In one study, PCT failed to differentiate between patients with and without VAP.[107] In a meta-analysis of PCT as a diagnostic test for sepsis in adult patients after surgery or trauma, the global odds ratio for diagnosing infection with PCT use was 15.7 (95% confidence interval [CI], 9.1-27.1).[108] Svoboda and colleagues[109] evaluated the role of using PCT levels to guide timing of reinterventions in septic patients after multiple trauma or major surgery. Patients with severe sepsis and a PCT level of >2 ng/mL had their antibiotic regimens and intravascular devices changed. Severe sepsis and a PCT level of ≤2 ng/mL prompted ultrasonography and/or computed tomography, with surgery ordered for patients with localized infection. The control group was treated by standard evaluation and surgeon consultation. There were no significant differences between the PCT group and the control group with regards to hospital mortality, average SOFA score, decline in ICU days, and ventilated days.[109]

Immunosuppressed states

PCT guidance in an immunocompromised population might be helpful in the diagnosis of bacterial infection, in deciding to initiate antibiotics, or to facilitate earlier discontinuation of antibiotics. In general and in contrast to other markers (eg, white blood cell [WBC] count), immunocompromising conditions and medications appear to have little direct effect on suppressing PCT expression (given that PCT is secreted by many tissues in the body), and leukocytes only play a minor role.[5] One study found lower PCT levels in patients with more severe leukopenia (WBC count of $<1 \times 10^9$ cells/L), but this has not been consistently reported.[110,111]

Some conditions and medications that could be present in immunocompromised patients have been associated with significant elevations in PCT in the absence of infection. These conditions include medullary thyroid cancer, small cell lung cancer, engraftment syndrome or acute graft-versus-host disease after hematopoietic stem cell transplantation, and administration of T cell–directed therapies (T-cell antibodies, antithymocyte globulin, alemtuzumab, and IL-2) or granulocyte infusions.[112-115]

A 2015 meta-analysis of 28 observational studies evaluating PCT as a diagnostic tool in adult and pediatric patients with febrile neutropenia as a complication of hematologic malignancy, chemotherapy, or solid organ transplantation found that PCT use had an overall sensitivity of 65% and overall specificity of 88% for documented bacterial infection, with the most common PCT threshold being 0.5 ng/mL.[116] PCT appeared to be more useful to help confirm rather than to rule out bacterial infection. The range of results among the studies varied considerably, with sensitivity ranging from 12% to 94% and specificity ranging from 45% to 100%.

As in other populations, higher levels of PCT in immunocompromised patients may predict a risk of complications like sepsis and septic shock.[117] In one cohort of patients with febrile neutropenia, PCT levels offered additional prognostic information by identifying a subset of patients considered to be at low risk for poor outcomes by Multinational Association of Supportive Care in Cancer (MASCC) scoring who still developed bacteremia or septic shock.[118] Elevations in PCT may be associated with mortality as well, though this has not been extensively studied in these populations.[117]

As in populations with hematologic malignancy, a number of studies have investigated the diagnostic utility of PCT in the context of solid organ transplantation. One meta-analysis included 7 studies involving kidney, liver, heart, and/or lung transplant recipients.[119] Using PCT cutoffs ranging from 0.14 to 8.18 ng/mL, sensitivity for documented infection ranged from 72% to 100% (85% overall) and specificity ranged from 70% to 100% (81% overall). The authors concluded that these results were similar to those documented in the published literature for nontransplant populations and that PCT diagnostic value was maintained in patients who had undergone solid organ transplantation.

Few interventional trials have specifically studied PCT use in immunocompromised patients. In the only RCT of a PCT algorithm specifically focused on an immunocompromised population to date, 61 adults with

hematologic malignancy and febrile neutropenia were evaluated.[120] After 72 hours from presentation, patients were randomly assigned to either a PCT or control arm. There were several exclusion criteria, including severe organ dysfunction, ICU admission, and documented infection with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Acinetobacter* species. In the PCT group, antibiotic discontinuation was recommended when patients were afebrile for 2 to 3 days and when PCT levels fell at least 90% from the peak or to less than 0.5 ng/mL for 2 consecutive days. PCT guidance did not modify average antibiotic durations (9 days in the PCT group and 8 days in the control group), and clinical outcomes were similar in the 2 groups. Adherence to the protocol was relatively high (73%), though most antibiotic discontinuations occurred as a result of agreement between the PCT trend and clinical criteria. It is unknown if a more aggressive algorithm or wider inclusion criteria would have impacted the duration of antibiotic therapy or clinical outcomes. Additionally, the exclusion criteria used in the study may limit the potential for application of its findings to many patients who commonly present with febrile neutropenia.

The PRORATA trial included 98 patients (among a total of 630 patients) considered immunosuppressed, defined as having acquired immunodeficiency syndrome or hematological malignancy or receipt of solid organ transplantation, chemotherapy or radiotherapy, immunosuppressive agents, or long-term corticosteroid therapy.[15] In the immunosuppressed subgroup, antibiotic-free days were significantly increased in the PCT-guided arm (13 days vs 9.4 days), as was the case in the whole study population. Mortality was higher in the PCT group (25.5% vs 19.6%), but this difference was not statistically significant. Interpretation of these outcomes is limited due to the reduced statistical power inherent in a subgroup analysis, due to the lack of knowledge about specific immunocompromising states in this group, and because rates of nonadherence to the PCT-guided antibiotic recommendations were not specifically reported for subgroups.

PCT use in clinical practice

In many of the special populations discussed, PCT may be elevated in the absence of infection and elevated even further when infection is present. This observation has led to recommendations of increased PCT thresholds for diagnosing infection. Particularly in critically ill and immunocompromised patients, even a low false-negative rate may be unacceptable. Withholding antimicrobials may lead to increased morbidity and mortality if an infection is actually present. Another major limitation in many of the observational trials is the lack of a standardized and definitive method to reliably diagnose bacterial infection, which may affect both the sensitivity and specificity of the test. Among the few randomized trials that have been conducted in these special populations, it is unknown if negative results were due to the failure of PCT use in a specific population, the failure of the specific algorithm studied, or poor algorithm adherence. If PCT is used in these populations, it should only be done so in conjunction with clinical criteria. Antimicrobials should not be withheld based on PCT alone until further evidence is available.

It is tempting to use PCT to help rule in infections and initiate antibiotics before obvious signs or complications have occurred, but this practice could be particularly troublesome in special populations, in which the optimal PCT threshold is often unclear and elevations are often seen after clinical decline, regardless of infection. In a heterogeneous critically ill population, the PASS trial found that a practice of preemptive initiation or escalation of antimicrobials outside of standard-of-care practice led to increased broad-spectrum antibiotic utilization without improved clinical outcomes.[121] Procalcitonin may still have a role in guiding de-escalation and discontinuation of antibiotic therapy in special populations; however, the clinician should be aware of disease states and concomitant therapies that may affect interpretation of results.

Conclusion

Procalcitonin may be a reliable marker of infection even in special populations with baseline elevations in PCT. However, due to unclear threshold values and the limited inclusion of special populations in clinical trials, PCT should be considered along with clinical criteria, and antibiotics should never be initiated or withheld based on PCT levels alone. Procalcitonin may have a role in guiding de-escalation of antibiotic therapy in special populations; however, the clinician should be aware of disease states and concomitant therapies that may affect interpretation of results.

Disclosures

The authors have declared no potential conflicts of interest.

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