

# The Role of Procalcitonin in Respiratory Infections

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**Abstract** Accurate diagnosis, risk stratification, and decisions about the need for and optimal duration of antibiotic therapy are cornerstones of the management of patients with respiratory infections. A growing body of evidence supports the use of procalcitonin, a marker of bacterial infection, in addition to conventional clinical parameters to improve diagnostic and prognostic assessment in patients with suspicion of respiratory infections. In addition, several randomized controlled trials indicate that procalcitonin may be used for clinical decision making about initiation and optimal duration of antibiotic therapy. For patients with respiratory infections, procalcitonin-guided antibiotic therapy resulted in less antibiotic use without any apparent adverse patient outcome. For other infections outcome studies are currently lacking. This review summarizes the results of recent investigations of procalcitonin in respiratory infections to provide physicians an overview of the utility and limitations of procalcitonin when used for bedside decision making.

**Keywords** Procalcitonin · Respiratory infection · Antibiotic stewardship · Biomarker

## Introduction

Despite recent advances in diagnostic and therapeutic measures, mortality and morbidity associated with respiratory infections remains unacceptably high [1]. Recent studies

indicate that early and adequate antibiotic treatment is highly effective in reducing disease burden in patients with bacterial community-acquired pneumonia (CAP) [2]. However, identifying which patients with respiratory symptoms benefit from antibiotics is a recurrent challenge in both inpatient and outpatient settings. Blood and sputum cultures are seen as the gold standard for identifying bacterial pathogens, but they are difficult to obtain, take days to turn positive, and may not reveal the causative organism [3, 4]. In the absence of a timely and reliable gold standard, clinicians often treat patients empirically with antibiotics, either due to patient demand, as in the outpatient setting, or due to clinicians' concern about the severity of illness, as in the emergency department or intensive care setting. The resultant overuse of antibiotics is costly, contributes to the growing problem of antibiotic resistance and exposes patients to the risk of side effects [5, 6]. Therefore, the accurate identification of which patients truly need antibiotics would benefit not only the patients by protecting them from unnecessary medications and side effects, but also society by decreasing selection pressure for drug resistance.

In recent years procalcitonin (PCT) has emerged as a promising marker for bacterial infection, with potential both for identifying which patients need antibiotics and for deciding how long to continue antibiotics once started. First identified in 1975 in a patient with pancreatitis [7], PCT has several features that argue for its use in clinical practice. First, in human cell culture models its level increases rapidly in response to LPS or IL-1 $\beta$ , common mediators of bacterial sepsis, but does not increase in response to interferon- $\gamma$ , a common cytokine in viral infections [8]. In addition, unlike markers such as the erythrocyte sedimentation rate or C-reactive protein, it is unaffected by steroid administration [9, 10]. In a recent study of over a dozen biomarkers in patients with either bacterial or viral infections, PCT emerged as the marker with the highest sensitivity and specificity for bacterial infection [11•]. These

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characteristics have prompted studies of PCT in various clinical settings, from CAP to malaria to febrile neutropenia [12]. Numerous reviews and meta-analyses of PCT exist [12–14, 15, 16–20, 21]; the aim of the current review is to focus on recent developments in the use of PCT for antibiotic management, diagnosis, and prognosis of respiratory illnesses. The principle clinical settings discussed are: patients presenting from the community with suspicion of a lower respiratory tract infection (i.e. pneumonia or bronchitis); chronic obstructive pulmonary disease (COPD) flare; and the intensive care setting, including ventilator-associated pneumonia (VAP), aspiration pneumonia, and sepsis with and without a pulmonary focus (Table 1).

### Procalcitonin to Guide Antibiotic Treatment of Respiratory Infections

A promising role for PCT is the antibiotic management of respiratory infections; that is, determining which patients with nonspecific symptoms of a lower respiratory tract infection (cough, fever, etc.) should receive antibiotics and for how long. Since PCT levels increase with bacterial infection and decrease upon recovery, PCT can be used as a biomarker to guide antibiotic therapy in individual patients. Using a highly-sensitive PCT immuno-assay with a sensitivity of 0.06 ng/mL, antibiotic stewardship algorithms based on PCT values have been successfully implemented [21, 22, 23, 24, 25, 26, 27, 28, 29]. The salient PCT levels used in most PCT-guided therapy algorithms were 0.1, 0.25, and 0.5 ng/mL, with protocols adapted to the severity of illness and the clinical setting

(Fig. 1) [21]. Measured at the time of presentation these levels were used to guide the initiation of antibiotics; measured serially they indicate when it is safe to stop antibiotics. In outpatients and patients with moderate severity illness in the emergency department, PCT levels <0.1 ng/mL indicated that antibiotics were strongly discouraged; antibiotics were discouraged for levels <0.25 ng/mL, encouraged for levels >0.25 ng/mL, and strongly encouraged for levels >0.5 ng/mL. For reference, the PCT level in healthy people is less than 0.03 ng/mL while the level in a patient with a bacterial infection is at least one order of magnitude higher, sometimes a thousand-fold higher [30]. For higher severity patients in the intensive care unit the protocols were adapted so that a PCT level <0.5 ng/mL indicated that levels were back to “normal” and antibiotic therapy could be discontinued. Importantly, protocols for lower acuity patients used PCT to decide upon initiation and duration of antibiotic treatment; in higher acuity patients the focus was on the duration of therapy, to avoid the risk of withholding antibiotics in a potentially septic patient [2, 21].

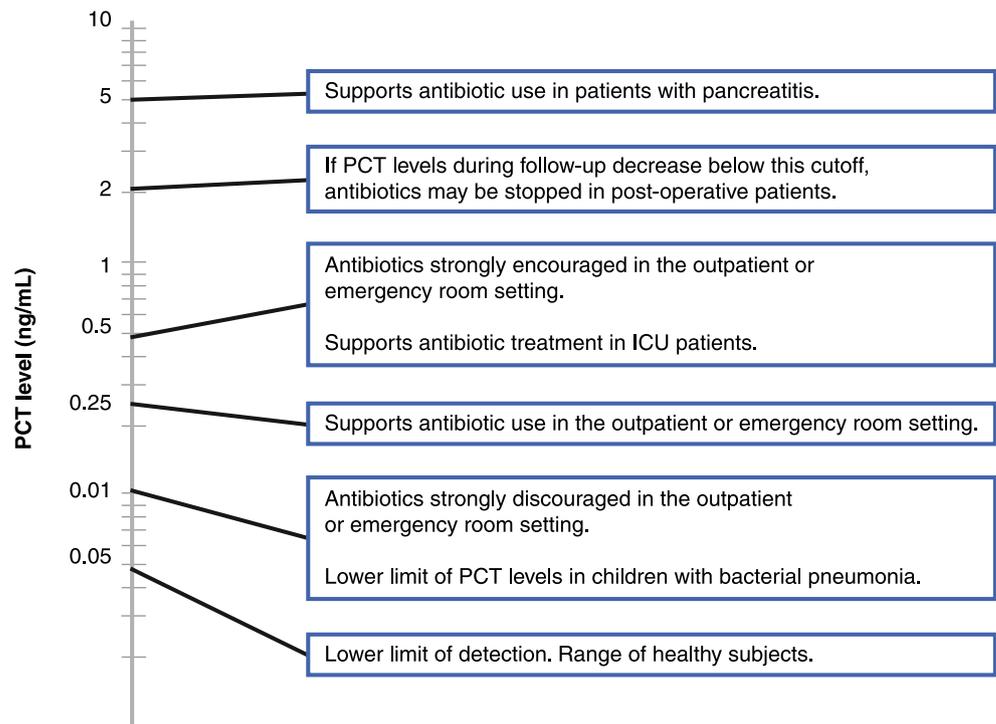
### Antibiotic Management of Community Acquired Pneumonia and Bronchitis

Several randomized controlled trials (RCTs) have investigated PCT-based protocols to guide decisions about initiation and/or duration of antibiotic therapy in patients presenting from the community with symptoms of a lower respiratory tract infection. In these studies the benefit and harm were measured by clinical outcomes, assuming that if the patient recovered without antibiotics there was no relevant

**Table 1** Strength of evidence for different clinical settings and applications focusing on respiratory infections

Clinical Setting	Application			
	Diagnosis	Antibiotic Initiation	Antibiotic Course	Prognosis
CAP	PCT may help to identify bacteremic CAP and type of pathogen [41–43]	Low PCT may help to rule out severe CAP in need of antibiotics [22, 23, 24, 25, 26]	Evidence strongly favors use [23, 26, 27, 28]	Initial PCT correlates with prognosis, but does not add much to existing severity scores for mortality [51–55, 57, 58, 59, 60].
COPD	Evidence not conclusive [85]	Evidence favors use [23, 26, 34–36]	Evidence favors use [23, 26, 34–36]	Evidence not conclusive [61]
VAP	Evidence not conclusive [45, 46]	PCT may rather be used for guiding duration [29]	Evidence favors use [29]	PCT correlates with prognosis, but does not add to existing severity scores [63, 64, 65, 66, 67]
Critically ill patients	Sepsis diagnosis is improved with PCT testing	Antibiotics should not be delayed in this population	Evidence favors use, [29, 86, 87] but further evidence is needed to demonstrate safety	Repeated measurements may be the preferred strategy [86, 87]
Bacterial super-infection of influenza	Some evidence for use [48, 49, 50]	Low PCT may help to early identify influenza CAP in need of anti-viral therapy [48, 49, 50]	No evidence	No evidence

**Fig. 1** Levels of procalcitonin and their significance



bacterial illness in need of antibiotic therapy. These RCTs have shown that using PCT to guide antibiotic use results in less antibiotic use without increasing rates of adverse events [22, 23•, 24•, 25•, 26]. These studies were conducted in emergency rooms (ERs), hospitals, and outpatient clinics. For example, in a multicenter RCT of patients presenting with symptoms of a lower respiratory tract infection to emergency departments in Switzerland, a PCT-based algorithm led to less antibiotic exposure (5.7 days in the PCT group vs. 8.7 days in the control group), fewer side effects (19.8% vs. 28.1%), and no increase in adverse outcomes (15.4% vs. 18.9%) [23•]. Most of the patients included in above study and other ER studies were admitted to the hospital and the studies were conducted in the European health care system, so until this year there was less data on patients evaluated in the ER but treated as outpatients. The most recent study, by Long et al., fills this gap. They demonstrated that a PCT-guided algorithm decreased antibiotic use among patients with community acquired pneumonia (CAP) presenting to an emergency room in Shanghai (5 days of antibiotics in the PCT group vs. 7 days in the control group); all patients in this trial were treated as outpatients [25•]. A PCT-guided antibiotic protocol was also successful for patients presenting with acute respiratory tract infections in a primary care setting [22, 24•]. Though an observational study suggested that outpatients, even those with pneumonia, generally had lower PCT values compared to hospitalized patients [31], two RCTs showed that using PCT to guide therapy in these patients can reduce antibiotic use markedly with similar time to recovery and without increasing adverse outcomes [22, 24•].

After the decision to initiate antibiotic therapy in a patient with symptoms of a respiratory infection comes the decision about optimal duration of therapy. Though there are some recommendations about how long to continue antibiotic therapy for patients with pneumonia due to specific pathogens (i.e. *Legionella*) or bronchitis, these guidelines are rather empiric and based on little efficacy data [32]. Christ-Crain et al. (2006) found that using serial PCT levels (at 4, 6, and 8 days after antibiotic initiation) to determine when to stop antibiotics for CAP led to a 55% reduction in antibiotic duration in the PCT-guided group without any change in patient outcome [28]. These results were confirmed in a large multicenter trial in Switzerland (PCT measured on days 3, 5, and 7) [23•], as well as a smaller trial in Denmark (single PCT measurement early in the hospital stay) [26]. In 2011, Saeed et al. broadened these results to patients with any suspected infection. Although the study was not randomized, they found that using PCT levels to indicate when to withhold antibiotics led to a 17% reduction in antibiotic use without apparent harm for patients [27•]. These findings have tantalizing applications for antimicrobial stewardship as well as control of healthcare costs.

#### Antibiotic Management of COPD Exacerbations

For exacerbation of chronic obstructive pulmonary disease (COPD) it would be extremely helpful to identify which patients would benefit from antibiotics and which would not. Although a recent post-hoc analysis of a RCT comparing doxycycline versus placebo for COPD exacerbation found a clinical response to antibiotics among patients with a low PCT

level [33], results from prospective RCTs using PCT to guide antibiotic therapy are quite promising [34]. In a randomized trial of PCT-guided antibiotic therapy versus conventional treatment (i.e. antibiotics at the discretion of the attending physician) for patients admitted to the hospital with COPD exacerbation, Stolz et al. (2007) found that using PCT to determine whether or not to start antibiotics led to less antibiotic use overall without an increase in adverse outcomes and similar recovery times in lung function [35]. Subsequent RCTs overall including more than 550 COPD patients have confirmed these results [23•, 26, 34, 36].

#### Antibiotic Management in the Intensive Care Setting

PCT also shows promise for guiding antibiotic therapy in a critical care setting. In a randomized trial of 101 patients with ventilator-associated pneumonia (VAP), Stolz et al. (2009) found that using PCT to decide when to de-escalate antibiotics led to an increase in antibiotic-free days without causing an increase in mortality [29•]. Other studies have examined PCT-guided antibiotic use for all critically ill patients with suspected infection, not just respiratory infection. Saeed et al. (2011) found that using PCT to guide therapy in an intensive care unit (ICU) – including initiation, escalation, and discontinuation of antibiotics – led to less antibiotic use, which ultimately meant a lower cost of hospital stays [27•]. A meta-analysis including all ICU trials found that in addition to lower antibiotic consumption, cost can also be reduced without apparent harmful effects [37•]; however, the total number of patients studied is still too small to rule out a slight increased mortality risk from the PCT-guided strategy [15•, 37•]. A recent article urges caution before adopting PCT-guided therapy in the critical care setting, as occasionally patients with positive blood cultures will have low initial PCT levels [38]. Although these results contradict other studies that found increased PCT levels in most patients with bacteremia [39], initial antibiotic therapy should not be delayed in ICU patients with suspicion of infection and PCT should rather be used to guide duration of treatment. Although the available evidence from RCTs supports the use of PCT for de-escalation of antibiotic therapy for patients with infections, the same may not be true for escalation of antibiotic therapy when PCT levels increase, as demonstrated in a recent large sepsis trial [40•]. In this trial from Denmark, PCT-guided antimicrobial escalation in the ICU did not improve survival and did lead to organ-related harm (particularly kidney failure) and prolonged ICU stays.

#### Procalcitonin to Diagnose Respiratory Infections

Separate from the question of when and how long to prescribe antibiotics for patients with symptoms of a respiratory

infection is the question of what specific type of infection a patient has. PCT has a less established role in this area, but potential applications are emerging.

#### Identifying Pathogens in Community Acquired Pneumonia

RCTs have demonstrated the role of PCT in guiding antibiotic use for CAP; other studies have examined its role in identifying which type of bacterial infection a patient has [41–43]. A recent Swiss study found that PCT was significantly higher in patients with CAP plus bacteremia (mostly *S. pneumoniae*) compared to patients with unknown CAP etiology [39]. A PCT cutoff of 0.25 ng/mL would have enabled a reduction of blood cultures by 37% while still identifying 96% of positive blood cultures. A study of German patients with CAP showed that PCT levels were significantly higher among patients with “typical” pneumonia (again, mostly *S. pneumoniae*) compared to patients with either “atypical” (*Mycoplasma*, *Chlamydia*, or *Legionella*) or viral pneumonia [43]. However, there was a large degree of overlap in PCT levels between the groups. This suggests that PCT is helpful in estimating the risk of typical bacterial CAP, but is not specific enough to identify a given pathogen. Similarly, though a retrospective study in Austria found PCT levels significantly higher in patients with *S. pneumoniae* pneumonia compared to patients with *Legionella* pneumonia, the differences were not enough to generate either a sensitive or a specific test for identifying either pathogen [41].

#### PCT for Diagnosis in the Intensive Care Setting

As described above, PCT can be useful in guiding the duration of antibiotic therapy in VAP; however, it appears not to be as useful for the initial diagnosis of VAP. Though a first report found that PCT was helpful in identifying patients with VAP [44], other studies found very poor sensitivity and specificity for VAP [45] or other nosocomial pneumonia in the intensive care setting [46•]. A recent study examined PCT for distinguishing aspiration pneumonitis from aspiration pneumonia in intubated patients; there was no significant difference in PCT levels between patients with culture-positive bronchoalveolar lavage (i.e. aspiration pneumonia) from those with culture-negative lavage [47•]. So far, then, the role for PCT in the diagnosis of nosocomial pneumonias remains unclear.

A promising application for the intensive care setting is using PCT to estimate the risk for bacterial super-infection of influenza pneumonia. Three studies, from France, Spain, and Australia, examined PCT in critically ill patients during the 2009 H1N1 influenza pandemic [48•, 49, 50]. All three found that PCT levels were lower in patients with H1N1 alone, while patients with either standard bacterial pneumonia

or with bacterial super-infection of viral pneumonia had elevated PCT levels. Therefore, PCT may be useful in determining which patients with severe influenza need antibiotics in addition to oseltamivir.

### Procalcitonin in Determining Prognosis of Respiratory Infections

Respiratory infections are the leading cause of sepsis and death from infectious diseases in Western countries and health expenditures, in particular for inpatient management, are substantial [1]. Accurate prediction of outcome is a prerequisite for safe decision-making about hospitalization versus outpatient management, and can also help families make decisions for their critically ill loved ones. Several studies have investigated the potential of PCT as a prognostic marker.

#### Procalcitonin for Prognosis in CAP

In patients with CAP, many studies indicate that higher PCT levels correlate with more severe illness and risk of adverse outcome [51–55]. In that vein, a study from the ProHOSP group indicated that PCT levels were useful in predicting which patients with CAP would develop bacteremia [39]. However, few studies have shown that PCT offers prognostic information beyond that of standard measurements of pneumonia severity such as the Pneumonia Severity Index (PSI) or CURB-65 scores [56]. Kruger et al. (2008) found that PCT levels correlated with pneumonia severity and were significantly higher in non-survivors. In addition, PCT improved the prognostic potential of the CRB-65 score [57]. In contrast, Huang et al. (2008) found that PCT level did *not* improve upon CURB-65 or PSI scores for predicting 30-day mortality, except for patients who had high clinical scores yet low PCT levels. In that subgroup, low PCT connoted a mortality risk similar to that of patients with low clinical scores [58]. More recent work indicates that adding PCT to clinical risk scores improves their predictive potential only moderately [59, 60]. A Swiss study, finally, found that initial PCT levels did not improve clinical risk scores for mortality prediction [60]; however, decreasing PCT levels over time correlated with a favorable outcome. In addition, the study found that PCT was more helpful to predict serious adverse events other than mortality (i.e. ICU admission, CAP-related complications). For these outcomes PCT significantly improved clinical risk scores.

#### Procalcitonin for Prognosis in COPD

There are fewer data on the use of PCT in the prognosis of COPD patients. In 116 patients with COPD exacerbations severe enough to require intubation, PCT levels were

associated with increased mortality, even when controlling for clinical severity scores [61]. A recently published study of 318 Spanish patients with COPD found higher PCT levels in patients who died within thirty days of PCT measurement, but no significant relationship between PCT levels and two-year mortality [62]. Further work is needed to determine the use of PCT to indicate prognosis in COPD exacerbation outside the ICU setting.

#### Procalcitonin for Prognosis in VAP

Both Duflo (2002) and Luyt (2005) established that higher levels of PCT were associated with worse outcome in patients with VAP [63, 64]. More recently, Bloos et al. (2011) studied serial PCT levels in 175 ventilated patients with pneumonia, including 61 with VAP, in 10 hospitals in Europe, Canada, and the United States. They found that initial PCT levels were significantly higher in VAP non-survivors than in survivors; PCT levels performed similarly to APACHE II (Acute Physiology And Chronic Health Evaluation) scores in this study [65]. A study of 101 patients with VAP in hospitals in the United States and Switzerland also found that non-survivors had higher levels of PCT at diagnosis. In this study, adding PCT and MR-proANP (mid-regional pro-atrial natriuretic peptide) levels to the SOFA (Sequential Organ Failure Assessment) score improved the AUC for that score from 0.768 to 0.895, though the change did not reach significance ( $p=0.087$ ), probably due to low power [66]. In addition, when Hillas et al. (2010) examined PCT levels on days 1, 4, and 7 of VAP in 45 patients in a Greek intensive care unit they found that, though PCT levels were higher in non-survivors, this difference was not significant when included as part of a multivariate prediction model. That said, an increasing PCT level from day one to day seven of VAP was a significant predictor of mortality in their multivariate model [67]. Overall, while higher PCT levels are associated with an increased risk of death in VAP, it is unclear if PCT contributes significant prognostic information beyond that provided by clinical indices such as APACHE II or SOFA.

### Pediatric Populations

One area that deserves further study is the role of PCT in diagnosing bacterial respiratory infections in children. It is difficult to distinguish viral from bacterial pneumonia on radiological or clinical grounds, so — despite the frequency of viral infections in this age-group — children often get empiric antibiotics for respiratory infections. Some observational studies found that PCT levels were higher in children with severe bacterial infection compared to children with viral infection [68, 69], while other studies found no difference

or only a marginal diagnostic advantage [70–76]. In light of these results, PCT's role in diagnosing childhood respiratory infections remains unclear and further evidence is needed.

In terms of managing infections in children, a retrospective analysis suggests that withholding antibiotics from children with PCT levels <0.1 ng/mL would be safe [77]. Also, a RCT of using PCT to guide duration of antibiotics in neonatal sepsis suggested that, as in adults, PCT can reduce antibiotic use without increasing adverse outcomes [78]. Further RCTs of PCT-guided therapy in children are needed.

### Limitations of Procalcitonin

Though mentioned in context above, it is worth reiterating the areas and applications in which PCT has only limited usefulness: PCT may have low sensitivity and/or specificity (i.e. low “signal to background ratio”) to identify VAP or other nosocomial pneumonias, may not add to existing severity markers, and have not yet been adequately studied in pediatric populations to recommend its widespread use in clinical practice. In addition, some conditions produce a high PCT level without infection; any significant tissue injury – burns, mechanical trauma, surgery – will cause an elevated PCT level, as will pancreatitis [30]. This may partly be explained by translocation of bacteria from the intestines in severe conditions. Finally, sometimes patients with strong clinical suspicion of bacterial infection will have low PCT levels, and these patients should receive empiric antibiotic therapy, as no diagnostic test can rule out infection with a 100% accuracy [38]. Thus, no blood test should replace clinical impression and septic patients always warrant early antibiotics.

### Emerging Applications

Given the promise of PCT in bacterial respiratory infections, researchers have explored its use in other areas as well, such as tuberculosis (TB) and febrile neutropenia. For TB, several studies have shown that PCT levels are lower in pulmonary TB than in CAP [79–81]. However, it appears that, as with other respiratory infections, a high PCT level is associated with a poor prognosis in TB [81]. No one has yet studied if PCT has a role in TB treatment. In febrile neutropenia, the stakes are high to identify and treat an infection quickly and appropriately. A study of oncology patients in Sweden found that a PCT level of >0.5 ng/mL had about a 60% sensitivity and 80% specificity for identifying febrile patients whose blood cultures would ultimately turn positive. Increasing the cut-off to 2 ng/mL increased the specificity to 95% [82]. Other studies have found similar results, and monitoring serial PCT levels may prove useful

in anticipating bacteremia among neutropenic patients [83]. That said, a recent brief report out of France suggested that PCT was not helpful in predicting infection in neutropenic patients [84]. Clearly, more studies are needed to determine the role of PCT in oncology patients.

### Conclusions

In conclusion, the current evidence supports a role for PCT in guiding antibiotic therapy for respiratory infections. There is good evidence that using PCT to determine when to prescribe antibiotics to patients presenting from the community with symptoms of a respiratory infection leads to less antibiotic use without affecting clinical outcomes. This concept has also been adapted by the 2012 surviving sepsis guidelines which now suggest the use of low procalcitonin to assist the clinician in the discontinuation of empiric antibiotics when no evidence of infection is found (grade 2C). Generally, the role of PCT as a diagnostic and prognostic marker in the intensive care setting is less well established. It may add to diagnosing bacterial infection in this setting and improves slightly existing prognostic indicators. It's main role may be in determining the course of antibiotics in critically ill patients. Future work will clarify its role in this setting, as well as in pediatric populations and in non-respiratory infections.

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