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Review Article

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Clinical Utility of Procalcitonin on Antibiotic Stewardship: A Narrative Review

Jong Hun Kim

Division of Infectious Diseases, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea

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Corresponding Author:
Jong Hun Kim, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea.
Tel: +82-31-780-5029
Fax: +82-31-780-5583
Email: smonti1976@hotmail.com

ORCID iDs
Jong Hun Kim
https://orcid.org/0000-0001-6703-5804

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ABSTRACT

Procalcitonin (PCT) was discovered as a useful marker for bacterial infection. Following its discovery, there have been a substantial number of clinical studies conducted to evaluate the presence of bacterial infections, and to guide antibiotic treatment by the stratified levels of PCT. Clinical evidence suggests that antibiotic treatment by PCT-guided antibiotic stewardship has been associated with a reduction in antibiotic usage without an increase in adverse outcomes. The use of PCT was approved by the Food and Drug Administration in the United States of America in 2017 to guide antibiotic treatment in sepsis and lower respiratory tract infections (LRTIs). In Korea, the use of PCT for sepsis and for pneumonia was approved in 2015 and 2022, respectively. This review will discuss the clinical utility of PCT on antibiotic stewardship in the management of sepsis and LRTIs including pneumonia.

Keywords: Procalcitonin; Antimicrobial stewardship; Sepsis; Respiratory tract infection; Pneumonia

BACKGROUND AND CHARACTERISTICS OF PROCALCITONIN

Procalcitonin (PCT) is an intracellular precursor of calcitonin which is a polypeptide consisting of 116 amino acids. Under normal circumstances, PCT is mainly produced from the parafollicular C cells of the thyroid, and PCT is subsequently further broken down to form calcitonin. Thus, the level of PCT is low in the serum (≤0.1 ng/mL) in healthy individuals [1, 2]. However, the level of PCT in patients with medullary thyroid carcinoma and small lung carcinoma was known to be elevated due to the production of PCT in the thyroid and pulmonary neuroendocrine cells [1, 2]. Furthermore, the first description of elevated levels of PCT in patients with bacterial infections was described in 1993 [3]. The higher levels of PCT in patients with severe bacterial infections than those of PCT in patients with mild bacterial or viral infections were noted [3]. The rise of PCT in severe bacterial infections is thought to be due to the additional production of PCT from several other body tissues (liver, kidney, spleen, adipose tissue, pancreas, etc) besides the thyroid in response to inflammatory cytokines such as IL-2, IL-6, TNF-α, etc, and bacterial endotoxins [4-6]. Of note, the PCT-producing calcitonin 1 (CALC-1) gene is known to be up-regulated by various inflammatory

cytokines, except for interferon-γ, which decreases the expression of CALC-1 [7, 8]. Thus, a lower level of PCT is found in viral infections [7, 8].

Traditional inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) have limited specificity for bacterial infections [9] as these inflammatory markers can be elevated in association with various infections and non-infectious inflammatory disorders. However, PCT is well known for its favorable sensitivity and specificity for bacterial infections. The level of PCT becomes elevated within 4 - 6 hours following bacterial infection, reaching its peak between 12 - 24 hours, with a half-life of 24 hours [8]. In comparison, CRP begins to increase after 12 - 24 hours and reaches its peak after 2 - 3 days following bacterial infection with a half-life of 19 hours [10]. This kinetics of rising PCT levels after bacterial infections can offer diagnostic advantages over CRP for its more rapid induction. The degree of elevation of PCT levels has been correlated with the severity of bacterial infections. Median PCT levels (ng/ml) on admission were reported to be significantly increased depending on the severity of critical illness as 0.6 for acute systemic inflammatory response syndrome (SIRS), 3.5 for sepsis, 6.2 for severe sepsis, and 21.3 for septic shock (P <0.001) [11]. For pneumonia, median PCT levels were also reported to be significantly increased with increasing severity as shown from a study conducted among patients with community-acquired pneumonia (CAP) [12]. Production of PCT has not been significantly impaired in immunocompromised conditions. Several studies showed that the levels of PCT could be employed as one of the useful markers for predicting bacteremia in patients with febrile neutropenia [13, 14], for predicting in-hospital mortality in patients with human immunodeficiency virus [15], and for diagnosing of infectious complications in recipients of solid organ transplantation or hematopoietic stem cell transplantation [16, 17]. Another notable feature of PCT is its favorable correlation with response to antibiotic treatment. PCT levels were significantly decreased after the resolution of the bacterial infections and persistently elevated levels of PCT were found with the worsened bacterial infections [13].

There are several limitations for the use of PCT. False positives causing elevated levels of PCT can occur in various conditions, such as cardiogenic shock, trauma, surgery, burns, cerebral hemorrhage, and pancreatitis [18-23]. Certain diseases such as severe liver disease, medullary thyroid cancer, and Kawasaki disease may raise PCT levels [24-26]. Of note, chronic kidney disease (CKD) patients are known to have higher baseline PCT levels when compared to those without CKD [25]. Although PCT levels can increase in response to bacterial infections in CKD patients, the rate of rising PCT levels may be slower in CKD patients [27]. Immunomodulatory agents including T cell antibodies and alemtuzumab [28] can also raise PCT levels. In contrast, false negatives of PCT levels can occur in localized infections such as uncomplicated cellulitis, and tonsillitis [29, 30]. Also, if PCT is checked prematurely in the process of infection, false negative PCT levels can occur [31] given its kinetics [8]. Other caveats of PCT may include its lower level elevations in atypical infections than those observed in typical bacterial infections. Several studies showed that levels of PCT elevations by atypical bacterial infections such as *Legionella* spp., *Mycoplasma* spp., and *Chlamydia* spp. were lower than those caused by typical bacterial infections [32, 33]. Similar trends of lower level elevations of PCT in the infections caused by less common atypical pathogens including *Candida* spp., *Aspergillus* spp., *Plasmodium* spp., *Pneumocystis jirovecii*, and *Mycobacterium tuberculosis* were also observed [34-37].

Despite certain limitations associated with PCT, its favorable sensitivity and specificity for bacterial infection along with the appropriate kinetics for acute phase test have led to a

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number of clinical studies. This narrative review will discuss the clinical utility of PCT on antibiotic stewardship in the management of sepsis and lower respiratory tract infections (LRTIs) including pneumonia.

PROCALCITONIN AND LOWER RESPIRATORY TRACT INFECTIONS

The impact of PCT guided antibiotic therapy in LRTIs was examined in many studies and critical evidence was found in randomized trials and systemic review with meta-analyses. In a large multicenter randomized trial (Procalcitonin-guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: the ProHOSP study) conducted in Switzerland involving adult patients in the emergency room with LRTIs [38], PCT guided antibiotic therapy was employed as follows: discouragement of antibiotic therapy for PCT ≤0.25 ng/mL, strong discouragement of antibiotic therapy for PCT <0.1 ng/mL, encouragement of antibiotic therapy for PCT >0.25 ng/mL, and strong encouragement of antibiotic therapy for PCT >0.5 ng/mL. Overrule of PCT guided antibiotic therapy was allowed for critical illness, localized infection such as empyema, *Legionella* infection, immunosuppression, or concomitant other infection than LRTIs requiring antibiotic treatment. Between the control group (n = 688) and PCT guided antibiotic therapy group (n = 671), overall adverse outcomes including death were similar (control group 18.9%, PCT guided group 15.4%). However, the duration of antibiotic therapy was significantly shorter in the PCT guided antibiotic therapy group (control group 8.7 days, PCT guided group 5.7 days). A significant difference was also observed in subgroups of patients with exacerbation of chronic obstructive pulmonary disease (control group 5.1 days, PCT guided group 2.5 days) and patients with CAP (control group 10.7 days, PCT guided group 7.2 days). The authors concluded that PCT guided antibiotic therapy may reduce antibiotic exposure without increased adverse outcomes in LRTIs. The results of other similar randomized controlled trials conducted between 2004 and 2016 were analyzed in a 2017 Cochrane database review [39]. A total of 26 randomized controlled trials with 6708 patients was included in the analysis, which found that PCT guided antibiotic therapy led to a significantly shorter duration of antibiotic therapy (5.7 days *vs.* 8.1 days, P <0.001) with lower 30-day mortality (8.6% *vs.* 10.0%, P = 0.037) in acute respiratory infections. Therefore, the authors concluded that their review and meta-analysis supported the role of PCT in antibiotic stewardship for the management of acute respiratory infections. In addition, the use of PCT for guidance of initiation or discontinuation of antibiotic treatment in the management of lower respiratory tract infections was approved by the United States of America (USA) Food and Drug Administration (FDA) in 2017 based on the analysis of data from the clinical trials [40]. Besides the clinical studies which showed effectiveness and safety of PCT guided antibiotic therapy, there have been studies that reported negative results. The most notable example is a recently conducted large multicenter randomized trial (Procalcitonin Antibiotic Consensus Trial [ProACT]) involving adult patients in the emergency room with LRTIs in the USA [41]. The cut-offs of PCT guidance used were identical to the previous trial (ProHOSP) [38]. Overall adverse outcomes (13.1% *vs.* 11.7%) and antibiotic-days by day 30 (4.3 days *vs.* 4.2 days) were similar between the control group and PCT guided antibiotic therapy group in the ProACT trial [41]. The authors concluded that there was a lack of reduction in antibiotic use associated with PCT guided antibiotic therapy for patients with LRTIs in the emergency room. However, a lower rate of antibiotic use in the control group and clinician adherence to PCT guided antibiotic therapy protocol than those of the previous trial (ProHOSP) [38] were considered as potential reasons for the lack of significance observed in the ProACT trial [41].

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Based on the clinical evidences and aforementioned studies, several clinical guidelines recommend PCT as one of the adjunctive clinical tools that can be used for the management of pneumonia. For CAP, the 2019 Infectious Diseases Society of America (IDSA) guideline [42] recommends initiation of antibiotic therapy for clinically suspected CAP with radiographic confirmation regardless of initial levels of PCT. However, serial measurement of PCT levels may be useful for antibiotic management in clinical situations where the duration of antibiotic therapy for CAP exceeds the average length of recommended duration (5 – 7 days). Similarly, the 2017 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) guideline [43] and the 2016 IDSA guideline for HAP and VAP [44] do not routinely recommend using PCT levels for the guidance of antibiotic therapy in settings where the standard duration of antibiotic therapy is anticipated and employed (7 – 8 days). However, both 2017 ESCMID and 2016 IDSA guidelines [43, 44] for HAP and VAP suggest that in certain clinical conditions that may be difficult for clinicians to evaluate the clinical status of progression or may require a longer duration of antibiotic therapy, serial measurement of PCT levels with clinical assessment can be considered to guide the discontinuation of antibiotic therapy. While development of the revised HAP and VAP guideline is in progress by the Korean Academy of Tuberculosis and Respiratory Diseases, the use of PCT for guidance of discontinuation of antibiotic treatment in the management of pneumonia in Korea was recently approved by the Ministry of Health and Welfare in 2022 based on the potential clinical benefits found from the clinical trials and guidelines [45].

PROCALCITONIN AND SEPSIS

Sepsis continues to contribute to a significant clinical burden as one of the major causes of morbidity and mortality [46]. As antibiotic therapy is a critical component of sepsis management [47], studies regarding optimal antibiotic therapy employing appropriate stewardship have been performed. Among various studies, the impact of PCT guided antibiotic therapy in critically ill patients with sepsis was evaluated in several studies and key evidence was identified in randomized trials and systemic review with meta-analyses. The PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) trial [48] was a multicenter randomized controlled trial conducted in seven intensive care units (ICUs) in France among critically ill patients with suspected sepsis. Pediatric patients, patients with neutropenia, infections requiring a longer duration of antibiotic treatment, and a low chance of survival were excluded from the study. PCT level was measured daily until the course of antibiotic therapy was completed under the guidance of PCT to discontinue the antibiotics when PCT <0.5 ng/mL or PCT <80% of its peak levels. Between the control group (n = 314) and PCT guided antibiotic therapy group (n = 307), the duration of antibiotic treatment was significantly shorter in the PCT guided antibiotic therapy group than in the control group (10.3 days *vs.* 13.3 days, P <0.001) without a difference in 28-day mortality (21.2% *vs.* 20.4%, absolute difference 0.8% [95% confidence interval: -4.6 - 6.2]). The authors concluded that PCT guided antibiotic therapy could reduce the exposure of antibiotics without excessive adverse outcomes for critically ill patients with suspected sepsis. Another large multicenter randomized controlled trial (Safety and Efficacy of Procalcitonin Guided Antibiotic Therapy in Adult Intensive Care Units [SAPS] trial) conducted in fifteen ICUs in the Netherlands among critically ill patients receiving antibiotic treatment with suspected or proven sepsis [49] used the similar cut-offs of PCT guidance from the previous PRORATA trial [48] to discontinue antibiotics when PCT ≤0.5 ng/mL or PCT levels were decreased ≥80% of its peak levels.

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Critically ill patients requiring prolonged antibiotic therapy, severe immunosuppression, low chance of survival, or severe infections due to viruses were excluded from the study. Between the control group (n = 785) and PCT guided antibiotic therapy group (n = 761), the duration of antibiotic treatment was significantly shorter in the PCT guided antibiotic therapy group than in the control group (5.0 days *vs.* 7.0 days, P <0.001). Furthermore, 28-day mortality was significantly lower in the PCT guided antibiotic therapy group than in the control group (19.6% *vs.* 25.0%, P = 0.0122). Of note, there was no difference in terms of duration of ICU stay or in-hospital stay between the groups. The authors concluded that PCT guided antibiotic therapy in critically ill patients with suspected or proven sepsis may lead to a reduction of antibiotic treatment duration with a decrease in mortality. The results of other randomized controlled trials that evaluated the use of PCT in critically ill patients were analyzed in meta-analyses. A meta-analysis published in 2018 included patient-level data from 11 randomized trials with 4,482 patients [50]. Compared with the control group (n = 2,230), the PCT guided antibiotic therapy group (n = 2,250) had the shorter duration of antibiotic therapy (9.3 days *vs.* 10.4 days, P <0.001) with a decreased 28-day mortality (21.1% *vs.* 23.7%, P = 0.03). However, the length of hospital stay and ICU stay was similar between the groups. Thus, the authors concluded that PCT guided antibiotic therapy in ICU patients with sepsis may result in a reduction of antibiotic exposure with improved survival.

The use of PCT for guidance of antibiotic treatment and its monitoring in the management of sepsis in Korea was approved by the Ministry of Health and Welfare in 2015 based on the potential clinical benefits found in the clinical trials [51]. In the USA, the use of PCT for guidance of antibiotic discontinuation in sepsis management was approved by the FDA in 2017 based on the data from clinical trials [40]. Moreover, the Surviving Sepsis Campaign Guidelines 2021 from the Society of Critical Care Medicine (SCCM) recommends PCT as one of the tools that can be utilized for assessing the feasibility of discontinuation of antibiotic therapy along with clinical evaluation [52].

IMPACT OF PROCALCITONIN GUIDANCE

Following the publication of clinical trials, guidelines, and approval of PCT usage by government agencies, real-world experiences of PCT guided antibiotic therapy in the clinical settings have been reported. A single-center study evaluated the impact of PCT guided antibiotic stewardship in a community hospital [53]. The mean duration of antibiotic therapy was significantly shorter in the group compliant with PCT guided antibiotic stewardship than in the group without compliance (5.1 days *vs.* 6.6 days, P <0.001). Another study conducted in a community hospital ICU investigated the difference between pre- and post-implementation of PCT combined antibiotic stewardship program [54]. Despite of low adherence rate of 34%, the implementation of PCT combined antibiotic stewardship program resulted in a decrease of 27% in antibiotic use without an increase in adverse outcomes. Furthermore, a similar single-center, cross-sectional study showed that the use of PCT guided antibiotic therapy in ICU patients led to a decrease in hospital costs in addition to the reduction of antibiotic therapy duration when compared to pre-intervention (4.9 days *vs.* 6.2 days, P = 0.04) [55].

In addition, several studies supported the use of PCT in the global pandemic caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19). Treatment with an antiviral agent against COVID-19 infection is recommended based on the severity of COVID-19 infection and host factors

[56]. Routine use of empiric antibiotic therapy is not recommended unless there is evidence or suspicion of having bacterial co-infections. However, it is often difficult to distinguish between COVID-19 infection and COVID-19 infection complicated with bacterial co-infections, particularly in severe COVID-19 infection cases. Therefore, this difficulty in discerning may lead to risks of having an increased consumption of unnecessary antibiotics, as evidenced in a recent study [57]. However, the use of PCT may aid in clinical management. COVID-19 infection itself has not been associated with significant elevation of PCT [58], and elevation of PCT in patients with COVID-19 infection has been reported to occur in secondary bacterial infections, suggesting the potential role of PCT in the antibiotic stewardship in the COVID-19 era [59]. For example, the implementation of a guideline to withhold antibiotic treatment in COVID-19 patients with PCT levels ≤0.25 ng/mL resulted in a reduction in antibiotic consumption without an increase in mortality [60].

Besides the possible short-term effects of reduction of antibiotic consumption without increased adverse outcomes, the long-term effects impacted by the PCT guided antibiotic stewardship were analyzed in a recent multicenter trial (Procalcitonin-guided Antimicrobial Therapy to Reduce Long-Term Sequelae of Infections [PROGRESS]) [61]. In this trial, sepsis patients were randomized to receive PCT guided antibiotic therapy or standard of care. The primary outcome of the long-term infection-associated adverse events at day 180 was defined as the incidence of new infection by multi-drug resistant organisms (MDROs) or *Clostridioides difficile*, or any mortality associated with baseline infection by MDROs or *C. difficile*. Compared with the control group, the PCT guided antibiotic therapy group had a significantly lower rate of long-term infection-associated adverse events (7.2% *vs.* 15.3%, $P = 0.045$). Also, the short-term effects were demonstrated as the duration of antibiotic treatment was shorter (5 days *vs.* 10 days, $P < 0.001$) with lower 28-day mortality (15.2% *vs.* 28.2%, $P = 0.02$) in the PCT guided antibiotic therapy group than in the control group. Despite the similar fecal colonization rate with *C. difficile* and MDROs by day 180 between the two groups, the risk of development of long-term infection-associated adverse events was different. In the control group, the risk was significantly higher in the colonized patients than in the non-colonized patients. However, in the PCT-guided antibiotic therapy group, the risk of development of long-term infection-associated adverse events was not different by the presence or absence of colonization, suggesting the protective effects on the integrity of the mucosal barrier by the reduction of antibiotic consumption. The authors concluded that PCT-guided antibiotic therapy in sepsis patients may reduce antibiotic exposure and 28-day mortality with an additional reduction of long-term infection-associated adverse events.

CONCLUSION

PCT is a biomarker with favorable sensitivity and specificity for acute bacterial infections. Its excellent correlation with the severity of acute bacterial infections and the characteristic kinetics in response to antimicrobial treatment makes PCT as one of the valuable tools in clinical management. The growing body of evidence has demonstrated that PCT-guided antibiotic therapy in patients with sepsis or LRTIs may reduce the duration of antibiotic treatment without an increase in adverse outcomes, even in the current COVID-19 pandemic era. Additional effects following the reduction of antibiotic treatment by PCT-guided antibiotic therapy may include possible prevention of long-term infection-associated adverse events such as new infection or mortality by MDROs or *C. difficile*. However, judicious use of PCT-guided antibiotic therapy in conjunction with clinical assessment is required, as

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suggested in the guidelines. Also, further interventional or observational studies are needed to best determine the role of PCT-guided antibiotic therapy in various clinical settings.

SUPPLEMENTARY MATERIAL

Review article Korean version

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