

The Use of Serum Procalcitonin as a Diagnostic and Prognostic Biomarker in Chronic Obstructive Pulmonary Disease Exacerbations: A Literature Review Update

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a major complication in COPD patients which can be triggered by bacterial or viral infections, environmental pollutants and other causes. Procalcitonin (PCT), a peptide that markedly increases in cases of bacterial infection, has been extensively investigated as a biomarker in the diagnosis, prognosis and treatment in patients with AECOPD. A number of studies published in the last decade, tried to investigate whether PCT levels can differentiate between bacterial and other causes of exacerbations, if they can be used as a guide for optimal antibiotic therapy and if they can be a tool in the assessment of the severity and the need for further interventions in the management of those patients. This review aims to gather, summarize and critically present all the available data to date.

Keywords: Procalcitonin; PCT; COPD; Chronic obstructive pulmonary disease; AECOPD; COPD exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) remains a common health and social problem with high morbidity and mortality rates [1]. Exacerbations of the disease pose a critical threat to public health and are related to a variable underlying pathophysiology. The identification of biological markers able to assess this clinical entity, is an area of ongoing interest. Serum procalcitonin (PCT) measurement has been used as a tool for the evaluation and treatment of patients with acute exacerbation of COPD (AECOPD) yielding various results, probably due to the heterogeneity of the

affected population, as well as its complicated pathogenicity.

The aim of this review is to summarize the current bibliography regarding the potential uses of PCT as a diagnostic and prognostic biomarker in patients suffering from AECOPD. A PubMed/Medline search was conducted from inception to March 2018, applying no language restrictions. The search terms used were: (“calcitonin” [MeSH Terms] OR “calcitonin” [All Fields] OR “procalcitonin” [All Fields]) AND (“pulmonary disease, chronic obstructive” [MeSH Terms] OR (“pulmonary” [All Fields] AND “disease” [All Fields] AND “chronic” [All Fields] AND “obstructive” [All Fields])). A total of 142 articles were originally retrieved. All original studies examining PCT serum levels in adult patients with AECOPD were included. Bibliographies from the extracted articles were also reviewed to identify any additional relevant publications. This resulted in a total of 31 original clinical studies and three systematic meta-analyses.

Acute Exacerbations of COPD

AECOPD is a sudden worsening of COPD symptoms (shortness of breath, changes in the quantity and color of expectorated sputum) and may be triggered by a bacterial or viral infection, environmental pollutants, cold weather or interruption of regular treatment. The underlying pathophysiology consists of an increased airway inflammation which results in hyperinflation, and reduction in expiratory air flow and gas exchange [2, 3].

AECOPD is the leading cause of hospital admissions and death in patients suffering from this clinical entity. Each exacerbation worsens the patient’s respiratory function, performance status, coexisting conditions and increases the risk of subsequent exacerbations [4]. A novel approach to estimate the severity of AECOPD and predict its outcome is the use of serum biomarkers. Exacerbations of the disease are characterized by the presence of elevated inflammatory biomarkers, such as total white blood cell count (WBC), C-reactive protein (CRP), plasma fibrinogen, IL-6 and PCT, which increase acutely during the course of the deterioration of the disease [5, 6].

PCT as a Serum Biomarker

PCT, a precursor of calcitonin, is a 116-amino acid peptide

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member of the calcitonin superfamily. PCT is released from the thyroidal C cells and is the precursor of calcitonin. Its normal serum concentrations are less than 0.05 ng/mL. PCT is an acute-phase protein with faster kinetics than CRP and erythrocyte sedimentation rate (ESR) [7]. The biological activity of procalcitonin is considered to be part of the complex inflammatory cascade of the immune system.

PCT has been shown to be elevated in bacterial infections, but remains low in viral infections and other inflammatory conditions [8, 9]. Based on that, it has been proposed that PCT could be useful in the evaluation of patients with COPD during the phase of acute exacerbation of bacterial origin. However, the chronically elevated inflammatory status of the underlying disease and the commonly developed colonization of the airways in these patients pose some limitations in the interpretation of PCT levels during the acute exacerbation.

PCT in the Diagnosis of the AECOPD Etiology

A summary of the original studies reviewed, including their relevant findings regarding PCT in the diagnosis and treatment of AECOPD, is presented in Table 1.

One of the main questions asked in the majority of the studies is whether PCT levels can be used to distinguish AECOPD of bacterial origin from that of other causes. This distinction would prove very useful in everyday clinical practice, as it would reveal the patients that will require and benefit from antibiotic use during the AECOPD. Several studies found that PCT levels can be used in the differential diagnosis of bacterial AECOPD from non-bacterial causes proposing some possible cut-off values [10, 13, 24, 29].

In a small case-control study in 2009 by using a cut-off point of 0.155 µg/L for PCT, the sensitivity and specificity for the diagnosis of bacterial infection in patients with an AECOPD were 93.3% and 60% respectively [41]. In ICU patients with AECOPD, Nseir et al concluded to a cut-off value of 0.5 µg/L suggesting bacterial isolation [13] and Ergan et al found that the optimal admission PCT threshold was 0.25 µg/L in order to identify patients with a bacterial exacerbation [29]. Daubin et al concluded to the stricter cut-off value of 0.1 µg/L by founding a positive bacterial culture in a significant number of patients with PCT_{max} values > 0.1 and < 0.25 µg/L [42].

Nevertheless, there are also a number of studies concluding that PCT values do not significantly differ between bacterial and non-bacterial AECOPD. Two case-control studies comparing PCT levels between AECOPD patients with purulent and non-purulent sputum by Soler et al and Gao et al found that the differences were statistically insignificant [21, 37]. Chang et al in 2015 also found that they were no significant differences in PCT levels between bacterial positive and bacterial negative AECOPD patients, neither between virus-positive and virus-negative AECOPD patients [28].

In a large prospective cohort study enrolling 224 patients in 2012, Falsey et al found that high PCT levels were correlated with more severe illness and point to the possibility of pneumonia in hospitalized individuals with AECOPD, but low values do not rule out bacterial infection [20]. Two fur-

ther studies by Lacoma et al and Çolak et al concluded that AECOPD patients with pneumonia have significant higher PCT values than those without pneumonic involvement [19, 38]. Higher PCT levels have also been linked to exacerbation severity and the need for non-invasive positive pressure ventilation (NPPV) [15, 22, 33] as well as to an increased length of hospitalization [36].

Flattet et al in a large recent retrospective cohort study enrolling 359 patients found that although higher PCT levels were significantly associated with a worse prognosis (hazard ratio (HR): 1.009 (1.001 - 1.017)), respiratory rate at admission seems to be the most prognostic clinical parameter and baseline pulmonary function of the patient remains the strongest predictor of mortality and readmission [35].

PCT-Guided Antibiotic Therapy in AECOPD

Although the role of PCT in the distinction between bacterial, viral and other causes of AECOPD is still a subject of debate, with conflicting results and relatively small studies conducted so far, data regarding its role in the guidance of antibiotic therapy in those patients are more conclusive. In one of the earlier studies in 2007, Stolz et al in a randomized control trial with 208 AECOPD inpatients showed that PCT guidance reduced antibiotic prescription (40% versus 72%, respectively; $P < 0.0001$) and antibiotic exposure (relative risk (RR): 0.56; 95% confidence interval (CI): 0.43 - 0.73; $P < 0.0001$) compared to standard therapy. Both groups had a similar rehospitalization rate, and mean time to the next exacerbation in the preceding 6 months [12].

Two more randomized controlled trials published in 2016 also concluded that PCT-guided protocols have similar overall treatment success rates compared to standard treatment [30] and they reduce the duration of antibiotic exposure without showing significant difference in rehospitalization, death or ICU admission, all within 28 days [31]. Although in 2010, Daniels et al, in a retrospective cohort study including 243 AECOPD of 205 patients, concluded that doxycycline had a significant effect in patients with a PCT level < 0.1 µg/L, suggesting that patients with low PCT values do benefit from antibiotics [16], Wang et al, in his randomized control trial, showed that antibiotic treatment is no better than placebo in AECOPD with a PCT level < 0.1 µg/L [30].

A meta-analysis conducted in early 2018 by Lin et al with data from 4 randomized control trials involving 679 patients with AECOPD found that PCT-guided treatment significantly reduced antibiotic use (OR: 0.26, 95% CI: 0.14 - 0.50, $P < 0.0001$) when compared to standard treatment, without increasing clinical failure (OR: 1.10, 95% CI: 0.70 - 1.74, $P = 0.68$; $I_2 = 0\%$) or mortality (OR: 0.86, 95% CI: 0.44 - 1.68, $P = 0.66$). The rates of exacerbation at the follow-up period and readmission were similar in both groups [43]. Mathioudakis et al in a meta-analysis of eight clinical trials evaluating 1,062 patients with AECOPD, published in early 2017, concluded that PCT-guidance decreased antibiotic prescription (RR: 0.56, 95% CI: 0.43 - 0.73) and total antibiotic exposure (mean difference: -3.83, 95% CI: -4.32 - -3.35), with no impact on clini-

Table 1. Summary of Studies

First author	Publication year/country Design	Participants/arms	Relative findings	Association between PCT and bacterial AECOPD
Chang C[10]	2006/China Case-control	45 AECOPD 15 bacterial 30 non-bacterial	PCT levels in the bacterial group were significantly higher than in the non-bacterial (P = 0.00). PCT levels did not significantly differ in the stable state.	YES
Stolz D[11]	2007/Switzerland Prospective cohort	167 AECOPD	PCT levels were significantly elevated (P < 0.001) during the exacerbation, but they were not associated with a longer hospital stay or long-term clinical failure.	
Stolz D[12]	2007/Switzerland Randomized control trial	208 hospitalized for AECOPD 102 procalcitonin-guided treatment 106 standard treatment	PCT guidance reduced antibiotic prescription (40% versus 72%, respectively; P < 0.0001) and antibiotic exposure (relative risk (RR): 0.56; 95% confidence interval (CI): 0.43 - 0.73; P < 0.0001) compared to standard therapy. Within 6 months the rehospitalization rate and the mean time to the next exacerbation were similar in both groups.	
Nseir S[13]	2008/France Prospective cohort	98 AECOPD requiring intubation and mechanical ventilation	PCT levels > 0.5 ng/mL and positive Gram stain of endotracheal aspirate, were independently associated with bacterial isolation in severe AECOPD.	YES
Daubin C[14]	2008/France Prospective cohort	39 hospitalized for AECOPD	There was no association between the PCT _{max} levels and the severity of COPD (P = 0.07). Patients with PCT _{max} > 0.25 µg/L were more critically ill. A low likelihood of bacterial infection correlated with a PCT less than 0.1 µg/L.	
Rammaert B[15]	2009/France Prospective cohort	116 AECOPD requiring intubation and mechanical ventilation	PCT level was independently associated with increased risk for ICU mortality (P = 0.018).	
Daniels JMA[16]	2010/Netherlands Retrospective cohort	243 AECOPD of 205 patients	Most patients (75%) had low PCT levels, with mostly elevated CRP levels. CRP levels were higher in the presence of bacteria. Doxycycline had a significant effect in patients with a PCT level < 0.1 µg/L.	NO
Hu XJ[17]	2010/China Case-control	114 56 AECOPD 58 healthy controls	The sensitivity, specificity, PPV, NPV and diagnostic accuracy rate of PCT were higher than those of CRP.	
Kherad O[18]	2010/Switzerland Prospective cohort	86 AECOPD	PCT levels did not significantly differ between virus-associated exacerbations and others.	
Lacoma A[19]	2011/Spain Case-control	318 COPD 46 stable 217 AECOPD 55 pneumonia 224 AECOPD	PCT and CRP levels showed significant differences among the three groups, being higher in the pneumonia group, followed by the AECOPD group (P < 0.0001).	
Falsey AR[20]	2012/USA Prospective cohort		Mean PCT levels were significantly higher in patients with pneumonia but they were not useful in the distinction between bacterial and viral or noninfectious causes of AECOPD.	NO
Soler N[21]	2012/Spain Case-control	73 hospitalized AECOPD 39 with purulent sputum 34 with non-purulent sputum	Serum PCT was similar in both groups on admission and after 72 h.	NO
Pazarli AC[22]	2012/Turkey Case-control	118 COPD 68 AECOPD 50 stable	PCT levels were higher in AECOPD patients than in stable COPD patients and were especially increased in cases of severe AECOPD and in those receiving NPPV among them.	
Huerta A[23]	2013/Spain Prospective cohort	249 hospitalized COPD 133 AECOPD 116 CAP + COPD 369 AECOPD	PCT levels were significantly higher at day 1 and day 3 in patients with CAP + COPD than in those hospitalized for AECOPD.	
Zhang Y[24]	2014/China Case-control		Before treatment, PCT levels in the infective group were significantly higher than those in the non-infective group.	YES
Verduri A[25]	2015/Italy Randomized control trial	184 AECOPD	The AECOPD rate at 6 months between standard and PCT-guided antibiotic treatment was not significant. The results regarding the non-inferiority of the PCT-guided plan were inconclusive.	
Grollmund E[26]	2015/Switzerland Prospective cohort	469 hospitalized AECOPD 252 pneumonic 217 non-pneumonic	Weak statistical significant correlations were found between discharge PCT levels and 5 - 7 year non-survival.	

Table 1. Summary of Studies - (continued)

First author	Publication year/country Design	Participants/arms	Relative findings	Association between PCT and bacterial AECOPD
Tamriverdi H[27]	2015/Turkey Prospective cohort	77 hospitalized AECOPD	Mean PCT levels were significantly higher in patients with positive sputum cultures than in those with negative sputum cultures. The AUC value of PCT was significantly better for predicting bacterial infection as compared to the CRP level or the neutrophil to lymphocyte ratio (P = 0.042) but the specificity, sensitivity (< 80%) and the AUC value were low.	YES
Chang CH[28]	2015/Taiwan Prospective cohort	72 AECOPD in the Emergency Department	PCT levels (as well as WBC and CRP) of the bacteria-positive and bacteria-negative groups were not statistically different. PCT, WBC and CRP levels also did not significantly differ between the virus-positive and virus-negative group.	NO
Ergan B[29]	2016/Turkey Retrospective cohort	63 AECOPD admitted in the ICU	Admission PCT levels were significantly higher in patients who died during hospitalization (0.66 versus 0.17 ng/mL; P = 0.014). The optimal admission PCT threshold was 0.25 ng/mL in order to identify patients who had a bacterial exacerbation.	YES
Wang JX[30]	2016/China Randomized control trial	191 hospitalized for AECOPD with PCT < 0.1 ng/mL 95 antibiotic 96 control	There was no significant difference (P = 0.732) in the overall treatment success rate between the control group (95.8%) and the antibiotic group (93.7%).	
Corti C[31]	2016/Denmark Randomized control trial	120 hospitalized for AECOPD 62 PCT guided therapy 58 control	The median duration of antibiotic exposure was 3.5 in the PCT-arm versus 8.5 days in the control arm (P = 0.0169). A composite harm end-point consisting of rehospitalization, death or ICU admission, all within 28 days, showed no significant difference.	
Picart J[32]	2016/Reunion Retrospective cohort	245 hospitalized AECOPD 124 patients before PCT-guided protocol 121 after PCT-guided protocol	Prescription of antibiotics decreased by 41% after protocol introduction (59% versus 35%, P < 0.001), without any increase in morbidity and mortality at day 30. Antibiotic duration and length of hospital stay did not change.	
Zhu JJ[33]	2016/China Case-control	153 AECOPD admitted in the ICU	PCT and blood lactic acid levels reflect the infection severity and are influenced by the effectiveness of NIV in the treatment of AECOPD during ICU stay.	
Pizzini A[34]	2017/Austria Case-control	102 48 CAP 20 CAP + COPD 34 AECOPD	PCT levels were significantly higher in patients with CAP compared to those with AECOPD upon hospital admission.	
Flattet Y[35]	2017/Switzerland Retrospective cohort 2017/Thailand Prospective cohort	359 AECOPD 68 AECOPD in the Emergency Department	Higher PCT levels were significantly associated with a worse prognosis (HR: 1.009 (1.001 - 1.017)). Higher PCT levels were observed in patients with longer hospitalization (\geq 7 days) when compared to those shorter stay (< 7 days) (0.38 ng/mL versus 0.1 ng/mL; P = 0.035). PCT levels did not show any statistical significant difference among bacterial exacerbations.	NO
Gao D[37]	2017/China Case-control	35 AECOPD & healthy 8 purulent sputum 12 non-purulent sputum 15 healthy controls	PCT levels in the AECOPD patients were significantly higher compared to the control group. The differences between the purulent and the non-purulent group were statistically insignificant.	NO
Çolak A[38]	2017/Turkey Case-control	116 76 AECOPD 40 pneumonia	Serum PCT levels were significantly higher in the pneumonia group compared to the AECOPD group (P < 0.001).	
Li Y[39]	2017/China Case-control	214 AECOPD & healthy 98 infection 66 non-infection 50 healthy controls	PCT levels of the infection group were significantly higher than those of the non-infection and the normal control group before treatment (P < 0.05).	YES
Bremmer DN[40]	2018/USA Retrospective cohort	305 AECOPD 166 before PCT guidance 139 after PCT guidance	PCT-guided treatment was associated with a reduced number of antibiotic days (5.3 versus 3.0; P = 0.01) and inpatient length of stay (4.1 days versus 2.9 days; P = 0.01). 30-day readmission rates due to respiratory causes were unaffected.	

cal outcomes such as rate of treatment failure (RR: 0.81, 95% CI: 0.62 - 1.06), length of hospitalization (MD: -0.76, 95% CI: -1.95 - 0.43), exacerbation recurrence rate (RR: 0.96, 95% CI: 0.69 - 1.35) or mortality (RR: 0.99, 95% CI: 0.58 - 1.69). Nonetheless, due to the methodological limitations and the small overall study population, the quality of the available evidence was considered low to moderate, and the authors highlighted the need for further, well-designed randomized control trials [44].

A theoretical model comparing the health and economic consequences of a PCT-guided prescription practice and clinical decision-making strategy compared to current practice in hospitalized patients with AECOPD in three countries, showed that a PCT-guided strategy is also likely to be more cost-effective compared to current practice. The percentages of patients who start with antibiotic treatment, as well as the duration of antibiotic therapy, are reduced with the PCT algorithm, and this leads to a decrease in total costs per patient [45].

Although the body of evidence suggesting the use of PCT in the decision process when treating patients with AECOPD is growing, with several randomized control trials and meta-analyses supporting its use, the implementation of the guidance in everyday clinical practice has been poor. In a series of cross-sectional and longitudinal multivariable analyses with data from 2009 - 2011 and 2013 - 2014 from a sample of 505 hospitals in the USA, no significant difference was found in antibiotic treatment rates or duration of therapy between hospitals that had adopted PCT guidance compared with those that had not [46]. This could be attributed to a reluctance of clinicians to change their practice, but it could also be quite more complicated. The prevalence of COPD is very high and the variability of patients and their comorbidities are very extensive. Further research to strengthen current evidence is warranted.

Conclusions

In the last decade, several studies have tried to establish the potential roles PCT could play in the diagnosis and management of patients with AECOPD. Most of the currently available studies are relatively small and have several limitations and weaknesses. Nevertheless, its use towards the rationalization of antibiotic prescription in those patients seems very promising. An optimized antibiotic treatment will benefit both the COPD patient and the healthcare system. Studies determining prognosis stratification and planned interventions in specific patient groups will be very useful. Further investigation of PCT levels and the optimal cut-off values in order to differentiate between the underlying causes of the acute exacerbations is also warranted.

Conflict of Interest

This work was supported solely by Department funds. All authors state that they do not have any conflicts of interest to report.

Author Contributions

NP did literature search and wrote the paper. DS wrote and edited the paper. AP did literature search. IK did literature search. DV wrote and supervised the paper.

Disclosure

All authors have read, approved the manuscript and meet the ICMJE authorship criteria.

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