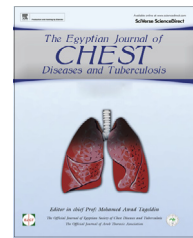




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ORIGINAL ARTICLE

Procalcitonin as a diagnostic marker in acute exacerbation of COPD

K.H. Mohamed ^{a,*}, M.M. Abderabo ^a, E.S. Ramadan ^a, M.M. Hashim ^b,
 S.M. Sharaf ^c

^a Department of Chest Diseases, Faculty of Medicine, Zagazig University, Egypt

^b Department of Internal Medicine, Faculty of Medicine, Zagazig University, Egypt

^c Department of Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt

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KEYWORDS

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Abstract *Background:* Rational prescription of antibiotics in acute exacerbations of COPD (AECOPD) requires predictive markers. Acute phase reactants are capable of demonstrating the inflammation; however, they cannot be employed to make a difference between bacterial and non-bacterial causes of the inflammation. Recently, measurement of procalcitonin (PCT) levels appears to be useful in order to minimize this problem. We aimed to evaluate the diagnostic and prognostic role of procalcitonin in (AECOPD).

Patients and methods: A total of 50 patients with AECOPD and 10 of apparently healthy individuals (control group) were studied. On presentation, serum PCT concentrations were measured, and quantitative sputum culture was performed for AECOPD. The patients were reevaluated when they had returned to their stable clinical state. Pathogenic bacterial microorganism (PBM) was only regarded as significant if they reached a growth 10^5 CFU/ml, indicating the presence of bacterial exacerbation of COPD. The patients were classified into two subgroups: group A included patients with bacterial AECOPD ($n = 20$), group B included patients with nonbacterial AECOPD ($n = 30$).

Results: On presentation, the levels of PCT for patients of group A (2.69 ± 0.62 ng/mL) were significantly higher than group B (0.07 ± 0.02 ng/mL) and control group (0.05 ± 0.02 ng/mL) ($p < 0.001$). When they had returned to their stable state, the levels of PCT for patients of group A decreased to (0.06 ± 0.03 ng/mL), which was significantly lower than that in exacerbation (2.69 ± 0.62 ng/mL) ($p < 0.001$); But in patients of group B compared with exacerbation the levels

* Corresponding author.

E-mail address: khaledmohamed@hotmail.com (K.H. Mohamed).

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of PCT did not change (0.068 ± 0.02 ng/mL) ($p > 0.05$). In the stable state, there were no differences in the PCT measurement between the two subgroups as well as between patients and control. Furthermore, a significant correlation was recorded between PCT levels in group A at time of presentation and temperature ($r = 0.898$, $p < 0.05$), leucocytic count ($r = 0.889$, $p < 0.05$), FEV1% of predicted ($r = 0.898$, $p < 0.05$), ESR ($r = 0.899$, $p < 0.05$), CRP ($r = 0.895$, $p < 0.05$) and duration of hospital stay ($r = 0.897$, $p < 0.05$).

Conclusions: Procalcitonin is a good marker for differentiation between bacterial and nonbacterial AECOPD and could be used to guide antibiotic therapy and reduce antibiotic overuse in hospitalized patients with AECOPD.

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Introduction

COPD constitutes a major health problem [1]. Acute exacerbations of COPD (AECOPD) have considerable impact on morbidity, mortality and quality of life [2]. Common triggers for AECOPD include viral and/or bacterial infection of the tracheobronchial tree and air pollution, but the cause of approximately one-third of severe exacerbations cannot be identified [3]. Whereas patients with signs of bacterial infection and more severe exacerbations seem to benefit from antibiotics, prescribing antibiotics for viral infections or noninfectious causes of AECOPD is ineffective and increases the risk of toxicity and the development of bacterial resistance [4,5]. In patients with COPD, the clinical manifestations of systemic inflammation due to infectious and non-infectious causes are similar. The differential diagnosis of these two conditions is very important in order to administer the correct treatment regimen and avoid unnecessary antibiotic use, thus reducing the morbidity, mortality and care-related costs. The decision to use antibiotics and selection of the type of antibiotic may be difficult in a significant number of cases, primarily due to the challenges encountered in confirming the diagnosis of bacterial infections. Classical diagnostic parameters including CRP and leukocyte count do not have sufficient specificity in differentiating between bacterial infections, non-infectious systemic inflammations or viral infections. Therefore, more specific and reliable markers that might be helpful in deciding the treatment are needed in these patients [6]. Nevertheless, antibiotic use in AECOPD is undoubtedly still excessive, exposing patients to considerable cost and potential adverse effects, and driving antibiotic resistance. In this context, a rapid, specific test to identify lower respiratory bacterial infections would be a major advancement, limiting the inappropriate use of antibiotics which is considered to be a main cause of the spread of antibiotic-resistant bacteria [7]. Serum procalcitonin levels are suggested to be one of the biomarkers for predicting a bacterial infection [8]. Procalcitonin (PCT) is a protein having a molecular weight of 13 kDa and it consists of 116 amino acid residues. The exact regions of its secretion are not yet clear [9]. Some literature suggests that PCT is secreted from neuroendocrine cells of the liver, small intestine and thyroid cells. In healthy humans, its normal serum level is 0.1 ng/mL. In a previous study, administration of bacterial endotoxin to healthy individuals resulted in an increase in PCT levels starting two hours after administration, with a peak value reached in 12 h [10]. Consequently, the serum level remains constant for another 12 h and decreases back to normal level in 20–24 h.

PCT gives rapid response to bacterial infections [11]. Studies performed in patients with pneumonia revealed that serum PCT levels have high sensitivity and specificity in showing the inflammatory response caused by pneumonia [12]. It has also been suggested in some studies that serum PCT levels might have a relatively higher sensitivity and specificity in differentiating pneumonias of bacterial origin from those of viral origin [13]. The aim of this study was to investigate whether the measurement of PCT can be used in the differentiation of bacterial and non-bacterial infection causes of COPD exacerbation, thus helping in planning the treatment.

Patients and methods

Patients

Fifty COPD patients (37 males and 13 females) admitted to the medical ward due to exacerbation between April 2010 and June 2011 were included in this prospective study after giving written informed consent. Exclusion criteria included presence of infiltrates on chest radiographs taken at admission and suspected of pneumonia, receiving antibiotics before admission or presence of other chronic pulmonary diseases.

Definition

The diagnosis of COPD was based on clinical history, physical examination findings, and spirometric criteria according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [14]. An exacerbation of COPD was defined as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD [15].

Methods

- Complete medical history.
- General and local chest examination.
- Chest radiography.
- Spirometry was performed according to American Thoracic society Guidelines.
- Routine blood tests (including CBC, ESR and CRP).
- Blood cultures, sputum culture, and Gram stain (Sputum was induced with hypertonic saline if subjects were unable to expectorate an adequate sputum sample spontaneously).

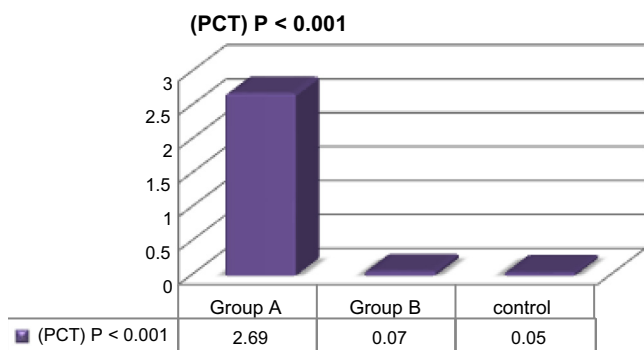


Figure 1 Furthermore; a significant correlation was recorded between PCT levels in group A at time of presentation and FEV1% of predicted ($r = 0.898, p < 0.05$), leucocytic count ($r = 0.889, p < 0.05$), duration of hospital stay ($r = 0.897, p < 0.05$), body temperature ($r = 0.898, p < 0.05$), CRP ($r = 0.895, p < 0.05$) and ESR ($r = 0.899, p < 0.05$) and Table 3.

Sputum specimens were considered adequate by standard criteria of > 25 polymorphonuclear leukocytes and < 10 epithelial cells per high power field [16].

- A serological diagnostic for antibodies to legionella pneumophila was also performed by indirect immunofluorescence, associated with a detection of Legionella pneumophila serogroup 1 antigen in urine samples.
- Chlamydia pneumoniae and Mycoplasma pneumoniae were also detected by PCR assay.

Measurement of serum procalcitonin

All blood samples were centrifuged, decanted, aliquoted, and frozen at -80 °C until analyzed at the end of the study period. PCT was measured using a sensitive immunoassay (Kryptor

PCT, Brahms, Hennigsdorf, Germany) with a functional assay sensitivity of 0.06 ng/mL, about fourfold above the mean normal levels [17].

Statistical analysis

All analyses were performed using computer software (SPSS, version 10.0; SPSS, Inc; Chicago, IL). Data are presented as mean ± SD unless stated otherwise. Correlations between PCT and other values were examined with Spearman rank correlation. Statistical significance was accepted for a *p*-value of < 0.05 (see Fig. 1).

Results

The mean age of the patients with bacterial COPD exacerbation (group A) was 62 ± 4.2 years, and included 5 females and 15 males. The mean age of the patients with non-bacterial COPD exacerbation (group B) was 66.3 ± 10.5 and included 8 females and 22 males and the mean age of the control group was 56.3 ± 11.5 and included 2 females and 8 males. Demographic characteristics of the patient and control groups are shown in Table 1 (See Table 2).

Discussion

Serum procalcitonin levels are suggested to be one of the biomarkers for predicting a bacterial infection [8]. In this study, we have demonstrated that The levels of PCT for patients of group A with bacterial COPD exacerbation were significantly higher than group B with non-bacterial COPD exacerbation and control group ($p < 0.001$). Chang et al. [18] showed that patients admitted with COPD exacerbation and positive sputum cultures for bacterial pathogen had significantly higher PCT

Table 1 Demographic characteristics of the groups.

	(A) Bacterial COPD exacerbation (n = 20)	(B) Non-bacterial COPD exacerbation (n = 30)	Control (n = 10)
Age (year)	62 ± 4.2	66.3 ± 10.5	56.3 ± 11.5
Sex (M/F)	15/5	22/8	8/2
Smoking history (n/ pack-year)	18/38 ± 6	24/42 ± 11	6/28 ± 6
FVC (%)	82 ± 3.7	84 ± 4.7	88 ± 4.7
FEV1 (%)	52 ± 10.4	54 ± 8.4	88 ± 10.4
FEV1/FVC	62 ± 6.3	64 ± 6.1	85 ± 5.1

The levels of PCT for patients of group A (2.69 ± 0.62 ng/mL) were significantly higher than group B (0.07 ± 0.02 ng/mL) and control group (0.05 ± 0.02 ng/mL) ($p < .001$) Table 2 and Fig. 1.

Table 2 Initial infection parameters in the study and control groups.

	(A) Bacterial COPD exacerbation (n = 20)	(B) Non-bacterial COPD exacerbation (n = 30)	Control (n = 10)
PCT (ng/mL)	*2.69 ± 0.62	0.07 ± 0.02	0.05 ± 0.02
White blood cell (mm ³)	*12500 ± 4500	6500 ± 2600	6400 ± 2400
CRP	*71.4	22.7	3.4
ESR (mm/h)	*48 ± 17	16 ± 3.6	8 ± 2.6
Duration of hospital stay (day)	*7 ± 2.3	4 ± 1.3	

* $p < 0.001$ statistically significant.

Table 3 Correlation between clinical and laboratory findings in group A.

Parameters in group A	Correlation with	<i>r</i>	<i>P</i>
PCT	FEV1	0.898	<i>p</i> < 0.05
PCT	White blood cell	0.889	<i>p</i> < 0.05
PCT	Duration of hospital stay	0.897	<i>p</i> < 0.05
PCT	Body temperature	0.898	<i>p</i> < 0.05
PCT	CRP	0.895	<i>p</i> < 0.05
PCT	ESR	0.899	<i>p</i> < 0.05

When they had returned to their stable state, the levels of PCT for patients of group (A) decreased to (0.06 ± 0.03 ng/mL), which was significantly lower than that in exacerbation (2.69 ± 0.62 ng/mL) ($p < .001$); But in patients of group (B) compared with exacerbation the levels of PCT did not changed (0.068 ± 0.02 ng/mL).

Table 4 Procalcitonine level at exacerbation and stable states in bacterial and non bacterial groups.

Patient group	group A			group B		
	Initial value	Stable state	significance	Initial value	Stable state	significance
Procalcitonine level (ng/mL)	2.69 ± 0.62 ng/mL	0.06 ± 0.03 ng/mL	$p < .001$	0.07 ± 0.02 ng/mL	0.068 ± 0.02 ng/mL	$P > 0.05$

values. A similar result was found in our study. Also other study showed that the level of circulating procalcitonin is increased in severe bacterial infections, but remains fairly low in viral infection and non specific inflammatory diseases [9]. The sensitivity and specificity of PCT in bacterial infections were found to be 92.6% and 97.5%, respectively [19]. Serum PCT level above 0.5 ng/mL indicates bacterial infections, whereas levels above 2 ng/mL show sepsis [10]. When the threshold level of PCT indicative of bacterial infection was accepted as 0.5 ng/mL, the positive and negative predictive values were found to be 100% and 87%, respectively [19]. We found that PCT has a significant correlation with both ESR, CRP, leucocytic count and body temperature, suggesting that when these parameters are used in combination with the PCT increases the predictive value in identifying bacterial infection. A significant correlation was found between the PCT level and the duration of hospital stay and FEV1 in COPD exacerbations of bacterial etiology in our study, indicating that high PCT may point to increasing severity of AECOPD. The level of circulating procalcitonin is increased in severe bacterial infections. Since the extent and severity of infection gradually increase in bacterial infections, serum PCT levels have also been shown to increase [9]. In previous study A significant correlation was established between serum procalcitonin (PCT) levels and duration of hospital stay, ESR and sputum purulence ($P = 0.002$, $P = 0.007$, respectively). But there was no significant correlation between serum PCT levels and white blood cell count and. They concluded that serum PCT measurements would be effective in guiding the treatment in patients with acute exacerbations of COPD [6]. When they had returned to their stable state, the levels of PCT for patients of group A, were significantly lower than that in exacerbation. This agree with a recent study, included nineteen patients with acute exacerbation of COPD and 16 patients with stable COPD as the control group, the investigators found that the mean serum PCT levels in COPD patients with exacerbations was 1.8 ng/mL and in stable COPD patients was 0.2 ng/mL [6] (see Table 3).

Our findings suggest that, serum PCT levels have high sensitivity and specificity in displaying the inflammatory response in patients admitted with COPD exacerbation. In the stable COPD patients, serum PCT levels were found to be within normal limits. These findings agree with previous studies [20,21]. In conclusion: our study demonstrates that procalcitonin is a good marker for differentiation between bacterial and nonbacterial AECOPD and could be used to guide initiation and assessing response to antibiotic therapy in patients with COPD exacerbations suggesting that the use of procalcitonin-guided antibiotic therapy has the potential to decrease unnecessary antibiotic use in nonbacterial COPD exacerbations, thereby decreasing the spread of antibiotic-resistant bacteria and reducing antibiotic-related adverse reactions (see Table 4).

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