Effect of procalcitonin-guided therapy on antibiotic usage in the management of patients with chronic obstructive pulmonary disease with acute exacerbation

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Background Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. In patients with COPD, the clinical manifestations of acute exacerbations due to infectious and noninfectious causes are similar. The differential diagnosis of these two conditions is very important for administering the correct treatment regimen and for avoiding unnecessary antibiotic use, thus reducing the morbidity, mortality, and care-related costs. The aim of this study was to evaluate the diagnostic role of procalcitonin (PCT) and its sensitivity as a marker of bacterial infection in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients.

Patients and methods A total of 53 patients with AECOPD and 30 apparently healthy individuals (control group) were studied. Serum PCT concentrations were measured, and Gram staining of the sputum and sputum culture were performed for the patients with AECOPD. The patients were classified into two subgroups: the bacterial group and the nonbacterial group. The bacterial group included patients with bacterial COPDAE (n=32) and the nonbacterial group included patients with nonbacterial AECOPD (n=21).

Results The mean level of PCT in patients of the bacterial group (151.65±38.13) was significantly higher than that of the nonbacterial group (60.16±23.98) and control group (36.03 ±16.52) ($P<0.01$). Other parameters such as inflammatory markers were also measured in the studied groups (total leukocyte count, erythrocyte sedimentation rate in the first and second hours, and C-reactive protein). There was no significant correlation between serum PCT level and the studied parameters in the bacterial group ($P>0.05$), and there was no significant correlation between serum PCT level and the studied parameters in the nonbacterial group ($P>0.05$). Pulmonary function testing was done for the studied groups and included forced expiratory volume in 1 s (FEV_1)/forced vital capacity (%) and FEV_1. The association between serum PCT and FEV_1% in the two studied group was not significant ($P>0.05$).

Conclusion PCT can be used as a marker for differentiation between bacterial and nonbacterial COPDAE and could be used to guide antibiotic therapy and reduce antibiotic abuse in hospitalized patients with AECOPD.

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Introduction

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. Inhaled cigarette smoke and other noxious particles such as smoke from biomass fuels cause lung inflammation, a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema) and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation, and in turn to breathlessness and other characteristic symptoms of COPD [1].

Exacerbations of respiratory symptoms often occur in patients with COPD, triggered by infection with bacteria or viruses (which may coexist), environmental pollutants, or unknown factors. Patients with bacterial and viral episodes have a characteristic response with increased inflammation. During respiratory exacerbations there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for increased dyspnea [2]. There is also worsening of V_A/Q abnormalities, which can result in hypoxemia [3]. Other conditions (pneumonia, thromboembolism, and

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acute cardiac failure) may mimic or aggravate an exacerbation of COPD.

Overuse of antimicrobial agents has been described worldwide in both community [4,5] and hospital [6,7] settings. In addition to the effect on patients [8,9], antibiotic misuse can provoke the emergence of bacterial resistance [6,10] and increase healthcare costs [11]. It is evident that optimizing antibiotic use is a challenge that deserves to be undertaken.

In recent times, serum procalcitonin (PCT) has been used as an infection marker [12–15]. As the extent and severity of infection gradually increase in bacterial infections, serum PCT levels have also been shown to increase. There is even a specific cut-off value for PCT for the establishment of a bacterial infection [16,17].

The aim of this study was to investigate whether the measurement of PCT can be used in the differentiation of bacterial and nonbacterial infection as a cause of acute exacerbation of chronic obstructive pulmonary disease (AECOPD), thus helping in planning the treatment.

Patients and methods

The study protocol was approved by local ethical committee and informed consent was taken. This work comprises 83 participants, 53 patients suffering from AECOPD and 30 normal individuals. It was conducted from the first of April 2013 until the end of August 2014 at the National Institute of Chest Diseases and Allergy (Embaba, Egypt).

Patients with AECOPD were contacted from among inpatients. All patients meeting the criteria of selection listed below were included in the study.

Inclusion criteria

Presence of COPD with acute exacerbation according to GOLD [18].

Exclusion criteria

(1) Immunosuppression.
(2) Bronchial asthma.
(3) Presence of infiltration on chest radiography.
(4) Chronic renal failure.
(5) Diabetes mellitus and congestive heart failure.

All cases were subjected to the following:

(1) Full clinical history with special emphasis on personal history including age, occupation, smoking history, history of illness, frequency of exacerbations, drugs used in the treatment of exacerbations, especially antibiotics, its type, dose, and duration.
(2) Clinical examination including general and chest examination.
(3) Chest radiography.
(4) Lung function test (spirometry) before and after the use of bronchodilators using the Electronic Thermistance-ZAN 500 (Nspire Health Town; Germany).
(5) Sputum analysis (Gram staining, culture, and sensitivity): sputum was either induced by the patient or induced by saline nebulization.
(6) Measurement of serum PCT level.
(7) Laboratory investigations of inflammatory markers [complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)].
(8) Renal function, liver function, glycated hemoglobin.

The patients were classified according to the results of sputum culture and sensitivity into sputum culture positive for bacteria (bacterial group) and sputum culture negative for bacteria (nonbacterial group).

Thus, our cases were classified into three groups.

Group I: this group, the control group, comprised 30 apparently healthy volunteers who had no history of COPD and had a clear chest. All were nonsmokers.

Group II: this group, the bacterial group, comprised 32 patients who fulfilled the criteria for COPDAE, and sputum culture was positive for organisms.

Group III: this group, the nonbacterial group, comprised 21 patients who fulfilled the criteria for AECOPD, and sputum culture was negative for organisms.

Specificity

This assay recognizes recombinant and natural human PCT. No significant cross-reactivity or interference was observed.

Sensitivity

The minimum detectable dose of human PCT is typically less than 3.9 pg/ml. The sensitivity of this assay, or lower limit of detection, was defined as the lowest detectable concentration that could be differentiated from 0.

Detection range

The standard curve concentrations used for the enzyme-linked immunosorbent assays were 1000,

500, 250, 125, 62.5, 31.2, and 15.6 pg/ml (range 15.6–1000 pg/ml).

Calculation of results

Calculate the average of the duplicate readings for each standard, control, and sample and subtract the average zero standard optical density. Create a standard curve by reducing the data using computer software capable of generating a four-parameter logistic curve fit. As an alternative, construct a standard curve by plotting the mean absorbance for each standard on the *x*-axis against the concentration on the *y*-axis and draw a best-fit curve through the points on the graph. The data may be linearized by plotting the log of the PCT concentrations versus the log of the optical density and the best-fit line can be determined by regression analysis. It is recommended to use some related software to perform this calculation, such as curve expert 13.0. This procedure will produce an adequate but less precise fit of the data. If samples have been diluted, the concentration read from the standard curve must be multiplied by the dilution factor.

Results

Results are expressed as mean±SD or number (%). Comparison between mean values of different studied variables in the three studied groups was performed using analysis of variance, followed by least significant difference test if a significant result was recorded.

Comparison between categorical data was performed using the χ^2-test. Correlation between serum PCT and different variables was performed using Pearson's correlation coefficient. SPSS (version 16 Windows; IBM, USA) was used for data analysis. *P* values less than or equal to 0.05 were considered significant and those less than 0.01 were considered highly significant (Table 1).

Demographic data

Table 2 shows that 21 patients in the studied group were negative for Gram stain and 32 patients were positive for Gram stain.

Table 3 shows that 21 patients of the studied group were negative for sputum culture and no organisms were detected and 32 patients were positive for sputum culture.

Table 4 shows that the mean serum PCT level in the bacterial group was greater than that in the nonbacterial group, which was greater than the level in the control group.

Table 5 shows that the *P* value of the serum PCT level in the bacterial group in relation to the control group was highly significant.

Table 6 shows that the *P* value of the serum PCT level in the nonbacterial group in relation to the control group was highly significant.

Table 7 shows that the *P* value of the serum PCT level in the bacterial group in relation to the nonbacterial group was highly significant.

Table 8 shows that the level of total leukocyte count (TLC) in the control group was less than the level in the nonbacterial group, which was less than the level in the bacterial group.

Table 9 shows that the level of TLC in the control group was less than the level in the bacterial group, and the difference was highly significant.

Table 10 shows that there was no statistically significant difference in the level of TLC between the nonbacterial group and the control group.

Table 11 shows that the level of TLC in the bacterial group was greater than that in the nonbacterial group and in comparison it was highly significant.

Table 12 shows that the level of ESR in the first and second hour in the bacterial group was greater than the level in the nonbacterial group, which was greater than the level in the control group.

Table 13 shows that the level of ESR in the first and second hour in the bacterial group was greater than the

Table 1 Mean age in the studied groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)	*P* value
Age				
Mean±SD	39.23±12.35	40.57±11.38	40.66±12.55	0.883 (NS**)

NS=*P*>0.05= nonsignificant.
**P<0.01=highly significant.

Table 2 Gram stain results in the studied group

Characteristics	*n* (%)
Negative (no organism)	21 (39.6)
Positive (organism)	32 (60.4)

Table 3 Sputum culture results in the studied groups

Characteristics	*n* (%)
Negative (no growth)	21 (39.6)
Positive (growth)	32 (60.4)

Table 4 Comparison between mean values of serum procalcitonin in the studied groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)
Mean±SD	36.03±16.52	60.16±23.98	151.65±38.13

Table 5 Comparison between mean values of serum procalcitonin in the bacterial and control groups

	Control group (*N*=30)	Bacterial group (*N*=32)	*P* value
Mean±SD	36.03±16.52	151.65±38.13	0.001**

***P*<0.01=highly significant.

Table 6 Comparison between mean values of serum procalcitonin in the nonbacterial and control groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	*P* value
Mean±SD	36.03±16.52	60.16±23.98	0.004**

***P*<0.01=highly significant.

Table 7 Comparison between mean values of serum procalcitonin in the bacterial and nonbacterial groups

	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)	*P* value
Mean±SD	60.16±23.98	151.65±38.13	0.001**

***P*<0.01=highly significant.

Table 8 Comparison between mean values of TLC in the studied groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)
TLC	4716.67±827.16	4761.90±624.88	13 900.0±2031.0

TLC, total leukocyte count.

Table 9 Comparison between mean values of TLC in the control and bacterial groups

	Control group (*N*=30)	Bacterial group (*N*=32)	*P* value
TLC	4716.67±827.16	13 900.0±2031.0	0.001**

TLC, total leukocyte count.
***P*<0.01 relative to the control group.

Table 10 Comparison between mean values of TLC in the control and nonbacterial groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	*P* value
TLC	4716.67±827.16	4761.90±624.88	NS

NS, nonsignificant; TLC, total leukocyte count.

Table 11 Comparison between mean values of TLC in the two studied groups

	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)	*P* value
TLC	4761.90±624.88	13 900.00±2031.00	0.001**

TLC, total leukocyte count.
**$P<0.01$=highly significant.

Table 12 Comparison between mean values of ESR (first and second hour) in the studied groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)
First hour	4.40±2.18	7.19±2.87	30.47±7.54
Second hour	11.13±3.57	10.90±2.97	65.84±19.64

ESR, erythrocyte sedimentation rate.

Table 13 Comparison between mean values of ESR (first and second hour) in the bacterial group relative to the control group

	Control group (*N*=30)	Bacterial group (*N*=32)	*P* value
First hour	4.40±2.18	30.47±7.54	0.001**
Second hour	11.13±3.57	65.84±19.64	0.001**

ESR, erythrocyte sedimentation rate.
**$P<0.01$ relative to control group.

Table 14 Comparison between mean values of ESR (first and second hour) in the nonbacterial group relative to the control group

	Control group (*N*=30)	Nonbacterial group (*N*=21)	*P* value
First hour	4.40±2.18	7.19±2.87	0.001**
Second hour	11.13±3.57	10.90±2.97	0.001**

ESR, erythrocyte sedimentation rate.
**$P<0.01$ relative to control group.

Table 15 Comparison between mean values of ESR (first and second hour) in the bacterial and nonbacterial groups

	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)	*P* value
First hour	7.19±2.87	30.47±7.54	0.001**
Second hour	10.90±2.97	65.84±19.64	0.001**

ESR, erythrocyte sedimentation rate.
**$P<0.01$=highly significant.

Table 16 Comparison between mean values of CRP in the studied groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)
CRP	5.87±2.78	2.33±1.02	12.09±3.42

CRP, C-reactive protein.

Table 17 Comparison between mean values of CRP in the control and bacterial groups

	Control group (*N*=30)	Bacterial group (*N*=32)	*P* value
CRP	5.87±2.78	12.09±3.42	0.001**

CRP, C-reactive protein.
**$P<0.01$ relative to the control group.

level in the control group and the difference was highly significant.

Table 14 shows that the level of ESR in the first and second hour in the nonbacterial group was greater than the level in the control group and the difference was highly significant.

Table 15 shows that the difference in the level of ESR in the first and second hour between the bacterial and nonbacterial group was highly significant.

Table 16 shows that the level of CRP in the nonbacterial group was less than the level in the control group, which was less than the level in the bacterial group.

Table 17 shows that the level of CRP in the bacterial group was higher than the level in the control group and the difference was highly significant.

Table 18 shows that the level of CRP in the nonbacterial group was higher than the level in the control group and the difference was highly significant.

Table 19 shows that the level of CRP in the bacterial group was greater than that in the nonbacterial group and in comparison it was highly significant.

Table 20 shows that the mean forced expiratory volume in 1 s (FEV_1)/forced vital capacity (%)in the bacterial group and nonbacterial group was less than that in the control group. FEV_1 in the control group was greater than that in the bacterial group and the nonbacterial group.

Table 21 shows that the association between serum PCT and FEV_1% in the two studied groups was not significant.

Table 22 shows that there was no significant correlation between serum PCT level and different studied parameters in the bacterial group.

Table 23 shows that there was no significant correlation between serum PCT level and different studied parameters in the nonbacterial group.

Discussion

Appropriate antibiotic use is one of the main goals of the medical community [19]. Overuse of antimicrobial agents has been reported worldwide in both community [4,5] and hospital [6,7] settings. In addition to the effect on patients [8,9], antibiotic misuse can provoke the emergence of bacterial resistance [6,10] and increase healthcare costs [11]. It is evident that optimizing antibiotic use is a challenge that deserves to be undertaken.

In recent times, serum PCT has been used as an infection marker. As the extent and severity of infection gradually increase in bacterial infections, serum PCT levels have also been shown to increase [12].

Table 18 Comparison between mean values of CRP in the control and nonbacterial groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	*P* value
CRP	5.87±2.78	2.33±1.02	0.001**

CRP, C-reactive protein.
**$P<0.01$ relative to control group.

Table 19 Comparison between mean values of CRP in the bacterial and nonbacterial groups

	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)	*P* value
CRP	2.33±1.02	12.09±3.42	0.001**

CRP, C-reactive protein.
**$P<0.01$=highly significant.

Table 20 Comparison between mean values of FEV_1/FVC (%) and FEV_1 in the studied groups

	Control group (*N*=30)	Nonbacterial group (*N*=21)	Bacterial group (*N*=32)
FEV_1/FVC (%)	84.40±3.56	58.14±6.19	58.50±5.98
FEV_1 (%)	88.60±4.70	52.24±10.01	53.59±11.33

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 21 Association between serum procalcitonin and FEV_1 (%) in the two studied groups (*N*=53)

	Serum procalcitonin Nonbacterial (<100 pg/l) (*N*=21)	Bacterial (≥100 pg/l) (*N*=32)	*P* value
FEV_1 (%)			
Moderate (*N*=36)	14 (66.7)	22 (68.8)	0.874 (NS)
Severe (*N*=17)	7 (33.3)	10 (31.2)	

FEV_1, forced expiratory volume in 1 s; NS, nonsignificant.
Results are expressed as *n* (%).
NS=*P*>0.05=nonsignificant.

Table 22 Correlation between serum procalcitonin and different studied parameters in the bacterial group (*N*=32)

	Mean±SD	Serum procalcitonin Pearson's correlation	*P* value
ESR first hour	30.47±7.54	–0.156	0.394 (NS)
ESR second hour	65.84±19.64	–0.239	0.188 (NS)
FEV_1 (%)	53.59±11.33	0.337	0.059 (NS)
TLC	13 900.0±2031.0	–0.100	0.585 (NS)
CRP	12.09±3.42	0.073	0.691 (NS)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in 1 s; TLC, total leukocyte count.
NS=*P*>0.05=nonsignificant.

Table 23 Correlation between serum procalcitonin and different studied parameters in the nonbacterial group (*N*=21)

	Mean±SD	Serum procalcitonin Pearson correlation	*P* value
ESR first hour	7.19±2.87	0.325	0.150 (NS)
ESR second hour	10.90±2.97	0.242	0.290 (NS)
FEV_1 (%)	52.24±10.01	–0.040	0.862 (NS)
TLC	4761.90±624.88	0.085	0.713 (NS)
CRP	2.33±1.02	0.075	0.747 (NS)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in 1 s; TLC, total leukocyte count.
NS=*P*>0.05=nonsignificant.

PCT is induced during systemic inflammations of bacterial origin, defined as sepsis, and hence it can be used to discriminate between bacterial and nonbacterial inflammations [20]. In delayed bacterial infections (3–30 days), the sensitivity and specificity reached 100%. Serum PCT level above 0.5 ng/ml indicates bacterial infections, whereas levels above 2 ng/ml indicate sepsis [21].

Our study includes 30 individuals as a control group and 53 patients with AECOPD, of whom 21 patients were negative in Gram staining and 32 patients were positive. It also shows that 21 patients were negative in sputum culture (no organisms were detected in the sputum) and 32 patients were positive (organisms were detected in the sputum).

The mean level of PCT in the bacterial group (bacterial growth) was 151.65±38.13, which was greater than the level in the control group (36.03±16.52) and greater than the level in the nonbacterial group (60.16±23.98). The level of PCT in the nonbacterial group (no bacterial growth) was greater than the level in the control group.

The *P* value of the serum PCT level in the bacterial group in relation to the control group was highly significant. The *P* value of the serum PCT level in the nonbacterial group in relation to the control group was also highly significant.

The mean value of PCT in the bacterial group (151.65 ±38.13) was greater than the mean value in the nonbacterial group (60.16±23.98), and the difference was statistically significant.

The mean value of PCT in the bacterial group was always equal to or more than 1.00 pg/ml, whereas it was less than this level in the nonbacterial group, indicating that this level of PCT (1.00 pg/ml) is the cutoff limit of PCT to differentiate between cases of AECOPD due to bacterial causes and those not due to bacterial causes.

Organisms were detected in the sputum culture of the bacterial group, whereas no organisms were detected in the nonbacterial group, and thus PCT has a specificity of 100% in our results, confirming the very high sensitivity of PCT.

Mohamed Hoesein *et al.* [22] had concluded that PCT is a good marker for differentiation between bacterial and nonbacterial COPDAE and could be used to guide initiation and assessment of response to antibiotic therapy in patients with COPD exacerbations, suggesting that the use of PCT-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. In their results, the cut-off point of PCT to differentiate between bacterial and nonbacterial causes of AECOPD was the same as our results.

In another study it was concluded that therapy with antibiotics influences recovery only in selected cases of COPD exacerbations. They evaluated the efficacy and safety of PCT in guidance compared with standard therapy with antibiotic prescriptions in patients experiencing exacerbations of COPD, and concluded that PCT guidance for exacerbation of COPD offers a sustained advantage over standard therapy in reducing antibiotic use for up to 6 months with a fewer number needed to treat as serum levels of PCT increase rapidly. The ubiquitous release of PCT during infections is induced either directly by microbial toxins (e.g. endotoxin) and/or indirectly by humoral factors or by cell-mediated host response [23].

In other studies, PCT guidance markedly and safely reduced antibiotic prescriptions and the duration of antibiotic therapy in patients with lower respiratory tract infections. Therefore, these studies hypothesized that PCT concentrations can serve as a marker for different antibiotic prescriptions in patients who are experiencing exacerbations of COPD. To test this hypothesis, these researchers conducted a study in which they prospectively randomized patients presenting with an exacerbation of COPD to be treated according to internationally accepted guidelines (i.e. the standard therapy group) or on the basis of PCT levels (i.e. the PCT group) on hospital admission.

CRP levels, ESR, and white blood cell values are also available parameters for the diagnosis of inflammation, but their sensitivity and specificity are lower than those of PCT in differentiating acute bacterial infection from other types of nonbacterial inflammation [24]. High concentrations of PCT have been reported in patients with bacterial infections and septic inflammation [25]. The results showed that PCT values in suspected sepsis groups were significantly higher than those in nonsuspected sepsis groups ($P<0.001$). It is well known that CRP is a very sensitive marker and may be increased with minor or viral infections and other insults such as trauma. The cellular origin of PCT is not known exactly but possibly it originated from leukocytes and neuroendocrine cells of the lung or intestine [26]. Their results show an excellent sensitivity and specificity of PCT. They conclude that PCT serum levels might be a useful diagnostic tool in emergency department management of sepsis before documentation of bacteria, and early empiric antibiotic therapy might be started before documentation of bacteria in the emergency department. The use of PCT measurement to guide antibiotic therapy should be a practical approach in critically ill patients with suspected sepsis.

Conclusion

(1) PCT guidance can markedly and safely reduce antibiotic prescriptions in patients with AECOPD.
(2) PCT could be a suitable biomarker of exacerbations of COPD, and can be used to target management and allows a reduction in antibiotic use for the treatment of AECOPD patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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