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Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD

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ABSTRACT: In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) needing hospitalisation, sputum purulence is associated with bacteria in the lower respiratory tract. We performed a prospective non-randomised interventional pilot study applying a sputum purulence-guided strategy of antibiotic treatment and investigating the relationship between sputum purulence and biomarkers.

In hospitalised patients with acute exacerbation of COPD antibiotics were restricted to those with purulent sputum. The primary end-point was rate of therapeutic failure during hospitalisation. Secondary end-points were parameters reflecting short- and long-term outcomes.

We included 73 patients, 34 with non-purulent sputum. No differences were observed on therapeutic failure criteria (9% non-purulent *versus* 10% purulent (p=0.51)). Serum C-reactive protein (CRP) was significantly increased in the purulent group at admission (11.6 *versus* 5.3, p=0.006) and at day 3 (2.7 *versus* 1.2, p=0.01). Serum procalcitonin (PCT) was similar between the groups. No differences were found in short-term outcomes. The exacerbation rate at 180 days was higher in the purulent group.

These results support the hypothesis of performing a randomised trial using a sputum purulence-guided antibiotic treatment strategy in patients with acute exacerbations of COPD. CRP, but not PCT, may be a useful parameter to increase confidence of the absence of bacterial bronchial infection.

KEYWORDS: Antibiotic treatment, chronic obstructive pulmonary disease, C-reactive protein, procalcitonin, sputum purulence

The course of chronic obstructive pulmonary disease (COPD) is characterised by recurrent acute exacerbations. These are episodes of worsening respiratory symptoms thought to be commonly caused by infections, including respiratory viruses and bacteria [1]. COPD exacerbations have an important impact on heath status, worsen lung function and increase mortality [2, 3]. Thus, there is considerable interest in the effectiveness of interventions used both to treat exacerbations and to prevent further events.

Antibiotics are frequently prescribed in clinical practice. In one recent survey, 85% of patients admitted for exacerbations of COPD to 360 hospitals throughout the United States received antibiotics [4]. Although the evidence for a causative role of bacteria and bacterial strain changes has increased in recent years [5–8], the indication for antibiotics in the treatment of acute exacerbations remains to be established. Only a few valid placebo-controlled trials of antibiotics are available [9–13], and all hint at an impact of antibiotics in sub-groups of patients such as those with more severe exacerbations [11, 13] and patients with increasing and purulent sputum [11], rather than a benefit for all patients. In a recent placebo-controlled trial, doxycycline showed superiority in terms of clinical success and clinical cure on day 10, microbiological success and symptom relief; however, it was equivalent to placebo in terms of clinical success on day 30 [10]. An alternative approach is based

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on the use of biomarkers such as procalcitonin (PCT), rather than severity of exacerbation and sputum colour, suggesting that antibiotic treatment may be unnecessary in more than half of the cases [14]. However, there was no association of Anthonisen types and PCT values.

The excessive use of antibiotics contributes significantly to increasing bacterial resistance and increased medical costs and the risk of drug-related adverse events [15–17]. Given the prevalence of COPD and the long course of the illness, reduction in antibiotic prescription for exacerbations could have an important impact on the selective pressure for the emergence of bacterial resistance [18]. Thus, discriminate use of antibiotics in exacerbations is necessary to improve outcomes in patients with COPD.

In COPD exacerbations sputum purulence is associated with the presence of bacteria in the lower respiratory tract [19]. We have previously evaluated the relationship between referred sputum purulence and the presence of bacteria in the lower respiratory tract in one study using bronchoscopy [20]. We next sought to provide further evidence in support of the efficacy and safety of sputum purulence to guide antibiotic treatment in a pilot study. We performed a pilot study using patient-reported purulence to determine whether to give or not to give antibiotics in hospitalised acute exacerbations of COPD. Additionally, we evaluated the association of patient-reported sputum purulence and biomarkers.

METHODS

Study population

Consecutive patients admitted for an exacerbation of COPD to the emergency department of the University Hospital Clínic of Barcelona, Spain, from January 2007 to May 2008, were potential subjects to be included in the study.

All patients had had pulmonary function evaluation performed prior (stable phase) to the exacerbation [21]. COPD was defined and categorised according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [22]. Airflow obstruction was defined as a post-bronchodilator ratio of forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) of $\leqslant$0.7% predicted.

An acute exacerbation of COPD was defined as ''a worsening of the patient's condition from the stable state that is acute in onset and requires a change in regular treatment in a patient with underlying COPD'' [22].

Exclusion criteria were as follows: 1) diagnosis of neoplasm or coexisting medical conditions that made survival for at least 1 yr unlikely; 2) immunosuppression due to chemotherapy or steroids, HIV or haematologic malignancies; 3) evidence of congestive heart failure at admission; 4) pulmonary infiltrates suggesting pneumonia; 5) admission criteria to an intensive care unit or requirement of noninvasive mechanical ventilation; 6) previous hospitalisation during the past 30 days; and 7) use of antibiotics or corticosteroids within the 30 days before admission.

Study protocol

Patients were evaluated for inclusion in the study within the first 24 h after admission to the emergency department. The decision to hospitalise was made by the physician in charge.

Sputum was defined as ''purulent'' when patients reported a change in the colour of spontaneously expectorated samples over the past 72 h from uncoloured to yellow-green [19]. Patients who reported sputum purulence were assigned to the purulent group and received standard treatment along with antibiotics. Antibiotic treatment was adjusted according to culture and susceptibility results. Antibiotic treatment duration was 7 days. Patients who did not report changes in sputum colour were assigned to the non-purulent group and received standard treatment without antibiotics. Standard treatment consisted of intravenous prednisolone starting with 40 $mg \cdot day^{-1}$, tapered by 10 mg after 3 days and followed by 30 mg of oral prednisone tapered by 5 mg per 3 days to finish, nebulised short-acting bronchodilators four times daily, oxygen therapy and respiratory physiotherapy. The minimum length of hospitalisation was 3 days, after which the date of discharge was determined by the physician in charge.

Baseline assessment, including demographic and clinical data (age, sex, symptoms and number of prior exacerbations requiring hospitalisation in the previous year, type and number of significant comorbid conditions, body mass index (BMI), smoking status and current treatment for COPD), were collected by means of a standardised questionnaire. Laboratory analyses, chest radiographs and arterial blood gases analyses were obtained in all cases at admission. Patients were classified as type I, II or III according to Anthonisen criteria [11].

On days 1, 3 and 30, patients were assessed clinically: blood samples were drawn for measurement of C-reactive protein (CRP), PCT and systemic cytokines (interleukin (IL)-1β, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α), forced spirometry was performed and sputum samples were collected. Long-term follow-up outpatient visits performed on day 180 after discharge from hospital comprised clinical, laboratory and lung function assessments as well as measurements of serum biomarkers (serum CRP, PCT and cytokines).

Two treating physicians consecutively followed the patients enrolled in the study, carried out the clinical assessment and prescribed antibiotics on the basis of evidence-based guidelines. Investigators did not influence clinical decisions.

End-points

The primary end-point of the study was to evaluate the rate of treatment failure on day 3. After adapting criteria previously described in a randomised trial on COPD exacerbations [23], treatment failure was defined by the occurrence of at least one of the following conditions at 72 h: 1) pulmonary infiltrates suggesting pneumonia during hospitalisation; 2) need for mechanical ventilation after the second day of hospitalisation; 3) in-hospital worsening of dyspnoea plus increase of respiratory or heart rate; 4) need for a new antibiotic treatment; and 5) death by any cause during hospitalisation.

Secondary end-points included treatment length of hospitalisation, in-hospital death, treatment success on day 30 and the following parameters at days 30 and 180: exacerbation number and rate, number and rate of hospitalisations, antibiotic exposure and requirement for corticosteroid treatment.

Short-term treatment success was defined as clinical cure or improvement (a resolution or reduction in the symptoms associated with the exacerbation without new signs or symptoms suggesting respiratory infection) on day 30.

Sputum analysis

Spontaneously expectorated sputum samples were obtained at admission. Gram-staining of sputum in the area of maximal purulence was examined for leukocytes and epithelial cells. Samples of Murray–Washington classification criteria IV (10–25 epithelial cells and >25 leukocytes per field) or V (⩽10 epithelial cells and >25 leukocytes per field) were considered as representative of distal airways and were processed for culture [24]. Microorganisms identified according to standard methods were classified as potential pathogenic microorganisms (PPMs) (including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catharralis*, Gram-negative bacilli, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Aspergillus* spp.) and non-PPMs (including *Haemophilus parainfluenzae*, *Streptococcus viridans*, *Neisseria* spp., *Candida* spp., *Corynebacterium* spp. and *Staphylococcus epidermidis*).

Biomarkers

Plasma CRP was measured using an immunoturbidimetric method employing a commercially available test (Bayer Diagnostics, Leverkusen, Germany) with an Advia 2400 (Siemens AG, Munich, Germany).

PCT was measured using 30 μL of plasma or serum with a time-resolved amplified cryptate emission technology assay (PCT Kryptor; BRAHMS, Berlin, Germany). The assay has a functional sensitivity of 0.06 $\mu g \cdot L^{-1}$, three- to 10-fold above normal mean values.

Circulating serum cytokines, including IL-1β, IL-6, IL-8, IL-10 and TNF-α, were measured using an enzyme amplified sensitivity immunoassay (EASIA-reader; Medgenix Diagnostics, Fleurus, Belgium). The lower limits of quantification for the different assays are as follows: IL-1β: 2 $pg \cdot mL^{-1}$; IL-6: 2 $pg \cdot mL^{-1}$; IL-8: 0.7 $pg \cdot mL^{-1}$; IL-10: 0.2 $pg \cdot mL^{-1}$; and TNF-α: 0.7 $pg \cdot mL^{-1}$.

All biomarkers were measured in serum at days 1, 3, 30 and 180.

Statistical analysis

We included two winter seasons in this pilot study and the period of the study comprised January 2007 to May 2008.

Discrete variables are expressed as counts (percentages) and continuous variables as mean±SD or median and interquartile range (IQR). Comparability of groups was analysed with the Chi-squared test, Fisher's exact test, paired samples t-test or Wilcoxon–Mann–Whitney test. Correlation analyses were performed using Spearman rank and κ coefficient. Clinical outcomes during hospitalisation, on day 30 and 180 of follow-up, were analysed using logistic regression models. Lung function variables were analysed by means of analysis of variance models. All statistical tests were two tailed and the significance level was set at 0.05; $p<0.05$ was defined as significant. All data management and analysis were performed using statistical software SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Ethics

The study protocol was approved by the Ethics Committee of the hospital clinic (Barcelona, Spain). All patients gave written informed consent.

RESULTS

Baseline and clinical characteristics

A total of 184 eligible patients presenting to the emergency department with an acute exacerbation of COPD were evaluated. Of these, 111 patients presented at least one criterion of exclusion (fig. 1). Of the 73 patients included in the study, 39 with purulent sputum were assigned to antibiotic treatment and 34 with non-purulent sputum were assigned to not receive antibiotics.

The baseline characteristics of the two groups are presented in table 1. There was no difference between the groups on demographics, number of comorbidities, BMI, smoking, functional status or exacerbation in the previous year. The predicted FEV_1 and FEV_1/FVC were not different, nor was the severity of COPD according to GOLD grades. In each group 97% of patients were taking inhaled steroids.

The clinical characteristics at admission of both groups are provided in table 2. With regard to the Anthonisen criteria at presentation, in the purulent group, 36 (90%) patients had increased breathlessness over the 48–72 h before admission and 32 (80%) increased sputum volume. By definition all patients had purulent sputum. The rate of type I and II

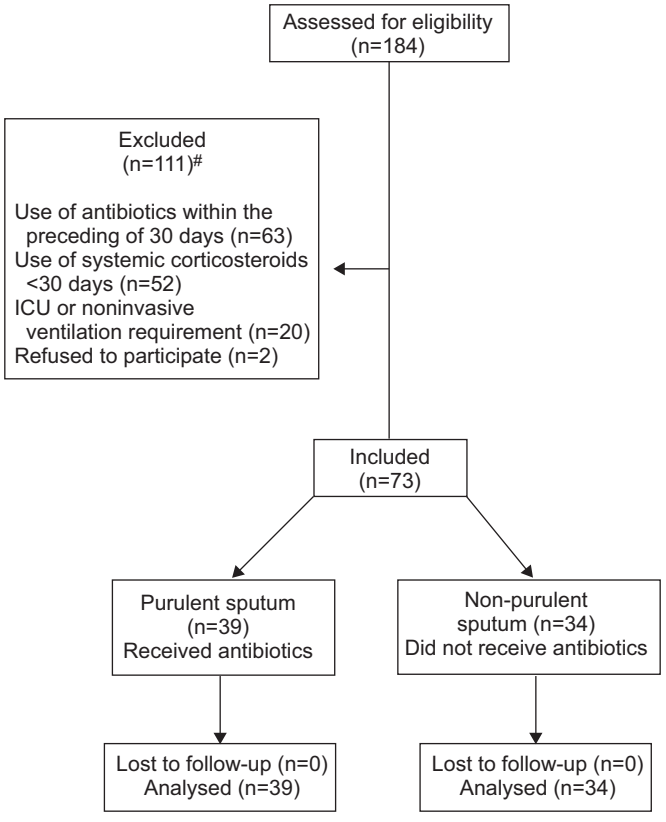

FIGURE 1. Flow diagram of patient inclusion. ICU: intensive care unit. #: patients could have more than one exclusion criterion; excluded: purulent n=60, non-purulent n=51.

TABLE 1 Baseline patient characteristics

	Non-purulent	Purulent	p-value
Subjects n	34	39	
Age yrs	71±9.6	71±9.7	0.87
Male	32 (94)	37 (95)	0.68
Comorbidities	3 (2–4)	3(2–4)	0.97
BMI	0.29 (0.27–0.32)	0.27 (0.24–0.30)	0.63
Smokers	34 (100)	39 (100)	0.98
Current smokers	23 (68)	22 (58)	0.65
Pack-yrs	60 (50–90)	60 (40–80)	0.57
Predicted FEV_1 mL	1216±401	1280±367	0.57
Predicted FEV_1 %	43.7±17.7	44.6±15.04	0.65
Predicted FVC mL	2556±891	2559±557	0.84
FEV_1/FVC %	50.1±15.7	50.0±13.36	0.89
Severity of COPD#			
GOLD stage			
II	5 (16)	9 (24)	0.73
III	9 (29)	10 (26)	0.89
IV	17 (55)	19 (50)	0.80
Domiciliary oxygen	10 (29)	6 (15)	0.15
MRC dyspnoea scale			
0–2	25 (74)	31 (80)	0.54
⩾3	9 (27)	8 (21)	0.74
Acute exacerbations in the previous yr	2.8±1.8	2.4±1.2	0.14
Inhaled corticosteroids	33 (97)	38 (97)	0.46

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise specified. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MRC: Medical Research Council. #: classification of severity of COPD based on lung function tests performed in stable phase.

exacerbations were 82% and 18%, respectively. In the non-purulent group 32 (94%) reported increased breathlessness and 20 (59%) had increased sputum volume. The frequencies for exacerbation type II and III were 18 (53%) and 16 (47%) respectively (table 2).

There were no differences between the groups regarding arterial oxygen tension or arterial carbon dioxide tension values at admission. We found no differences in PCT levels at admission and those obtained on day 3. However, serum CRP values on admission and on day 3 were significantly higher in the purulent group (table 2).

30 (88%) out of 34 patients in the non-purulent group and 38 (97%) out of 39 in the non-purulent group received systemic corticosteroids (p=0.18). One patient in the non-purulent group received antibiotic treatment with amoxicillin-clavulanate. All patients in the purulent group received antibiotics: 11 received amoxicillin-clavulanate, 27 received levofloxacin and one received piperacillin-tazobactam.

Respiratory samples

A sputum sample was obtained spontaneously from 58 (79%) patients at admission: 24 out of 34 patients in the non-purulent and 34 out of 39 in the purulent group (p=0.091). However, only 41 (56%) fulfilled Murray–Washington criteria grade IV or V and were further processed for bacterial and fungal culture. We obtained 30 (77%) valid samples from the purulent group and 11 (32%) from the non-purulent group (p=0.01).

Culture of good-quality sputum samples yielded 14 PPMs corresponding to 12 (40%) patients in the purulent group and two (18%) patients in the non-purulent group (online supplementary figure E1 and online supplementary table E1).

At presentation, a close correlation was observed between patient self-reported purulent exacerbation criteria and purulence of the sputum sample assessed by Murray–Washington grade (κ=0.91, 95% CI 0.8–1.0).

At admission, the receiver operating characteristics for predicting bacterial isolation of PPMs when patients reported purulent sputum were as follows: sensitivity 76.9%, specificity 67.6%, positive predictive value 73.1% and negative value 71.9%.

Positive sputum cultures by pathogenic bacteria (PPMs) were significantly associated with CRP values on admission (p<0.01). In contrast, positive sputum cultures were not associated with elevated PCT levels (p=0.574). There was no correlation between PCT levels on hospital admission and leukocyte counts (r=0.19, p=0.398) and CRP levels (r=0.052, p=0.917).

Primary end-point

Treatment failure was present in four (10%) patients in the purulent group and three (9%) patients in the non-purulent

TABLE 2 Clinical characteristics at admission

	Non-purulent	Purulent	p-value
Subjects n	34	39	
Temperature ⩾38°C	9 (26)	12 (32)	0.52
Respiratory rate breaths·min^{-1}	25 (23–32)	25 (24–32)	0.93
Heart rate beats·min^{-1}	98 (90–113)	97 (88–110)	0.78
Type of exacerbation (Anthonisen criteria)			
Type I	0	32 (82)	**<0.0001**
Type II	18 (53)	7 (18)	0.076
Type III	16 (47)	0	**0.001**
Leukocyte count ×10^9 cells·L^{-1}	8.82 (7–11)	10.54 (8.4–12.7)	0.19
CRP on admission mg·dL^{-1}	5.3 (0.10–23.0)	11.6 (0.10–33.0)	**0.006**
CRP on day 3 mg·dL^{-1}	1.2 (0.10–15.6)	2.7 (0.10–18.1)	**0.01**
PCT on admission ng·mL^{-1}	0.04 (0.01–0.10)	0.05 (0.02–0.13)	0.89
PCT <0.1 ng·mL^{-1}	24 (46)	28 (54)	
PCT 0.1–0.25 ng·mL^{-1}	4 (36)	7 (63)	
PCT >0.25 ng·mL^{-1}	4 (40)	6 (60)	
PCT on day 3 ng·mL^{-1}	0.03 (0.01–0.05)	0.04 (0.02–0.07)	0.32
CRP on admission mg·dL^{-1}			
Type I		12.4 (0.80–26.2)	
Type II	5.8 (0.10–22.1)	8.7 (1.2–17.3)	0.20
Type III	2.9 (0.20–9.5)		
PCT on admission ng·mL^{-1}			
Type I		0.08 (0.02–0.20)	
Type II	0.03 (0.01–0.10)	0.04 (0.02–0.10)	0.49
Type III	0.02 (0.01–0.10)		
pH	7.39±0.06	7.41±0.05	0.15
P_{a,CO_2} mmHg	45.1±12.3	39.5±6.4	0.14
P_{a,O_2} mmHg	53.3±4.6	57.9±10.1	0.53

Data are presented as n (%), median (interquartile range) or mean±SD, unless otherwise stated. CRP: C-reactive protein; PCT: procalcitonin; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension. p-values in bold are statistically significant.

group (OR 1.18, 95% CI 0.27–5.10; p=0.84). In the purulent group, one patient developed pulmonary infiltrates, one patient presented with clinical deterioration and two patients required mechanical ventilation. All three patients in the non-purulent group developed clinical deterioration. Only one case from the non-purulent group required prescription of antibiotic therapy (table 3).

The results were similar in the sub-group of patients with expectoration in whom a respiratory sample was collected (table 3).

On day 3, clinical success or improvement was observed in 35 (90%) patients from the purulent group and 31 (91%) patients from the non-purulent group (OR 0.98, 95% CI 0.5–1.91; p=0.46).

Secondary end-points

Short-term follow-up

On day 30, treatment success was observed in 37 (95%) patients from the purulent group and 31 (91%) patients from the non-purulent group (OR 1.16, 95% CI 0.35–5.43; p=0.86). 18 (46%) patients in the purulent group and 25 (74%) patients in the non-purulent group showed complete resolution of exacerbation symptoms (p=0.01). The number and rate of exacerbations, hospital admissions, antibiotics or corticosteroids requirement were not different between groups (table 4). At day 30 mortality was 5% (two patients) in the purulent group and 3% (one patient) in the non-purulent group (this patient died at home 7 days after discharge, without previous worsening of respiratory symptoms).

Long-term follow-up

The number of exacerbations (60% *versus* 36%, p=0.04) and the exacerbation rate within 180 days of follow-up (0.6±0.58 *versus* 0.5±0.75, p=0.04) were significantly higher in the purulent group (table 5). The number of hospital admissions for exacerbations (29% *versus* 33%, p=0.69) and the hospitalisation rate (0.29±0.46 *versus* 0.39±0.6, p=0.69) were similar. Antibiotic exposure within 180 days of outpatient follow-up tended to be higher in the purulent group (table 4).

The overall mortality rate at 180 days was 9.6% (seven patients): four (10%) in the purulent group and three (9%) in the non-purulent group (OR 1.18, 95% CI 0.27–5.10; p=0.84). In the purulent group, two patients died from respiratory failure associated with hospital-acquired pneumonia, and three patients died from medical conditions other than COPD. In two cases, the cause of death remained unknown.

TABLE 3 Clinical outcomes during hospitalisation and on day 30 of follow-up

	Non-purulent	Purulent	p-value
Subjects	34	39	
Primary end-point			
All patients			
Treatment failure on day 3	3 (9)	4 (10)	0.84
Requirement for MV		2	
Pulmonary infiltrates		1	
Clinical deterioration	3	1	
Death from any cause			
Patients with expectoration#			
Treatment failure on day 3	2 (8)	3 (9)	>0.99
Requirement for MV		1	
Pulmonary infiltrates		1	
Clinical deterioration	2	2	
Death from any cause			
Secondary end-points			
In-hospital outcome			
Length of hospital stay days	6.1±4.0	5.9±2.3	0.50
In-hospital death			
Day 30 of follow-up			
All patients			
Treatment success on day 30	31 (92)	37 (94)	0.86
Complete clinical resolution			
Clinical improvement	25 (74)	18 (46)	0.01
Absence of clinical resolution	6 (18)	19 (49)	0.053
Patients with expectoration#	2 (6)	0 (0)	0.12
Treatment success on day 30	22 (91)	32 (95)	>0.99
Complete clinical resolution	18 (75)	16 (47)	0.033
Clinical improvement	4 (17)	16 (47)	0.016
Absence of clinical resolution	2 (8)	2 (6)	>0.99
New exacerbations	7 (21)	8 (20)	0.99
Exacerbation rate	0.2±0.52	0.2±0.49	0.99
Hospital re-admissions	5 (14)	4 (10)	0.72
Hospital re-admissions rate	0.2±0.41	0.2±0.40	0.10
Patients with antibiotic requirement	4 (11)	7 (17)	0.59
Patients with corticosteroids requirement	7 (20)	7 (17)	0.47
CRP	0.96 (0.38–2.70)	0.63 (0.38–2.70)	0.91
PTC	0.03 (0.01–0.12)	0.05 (0.01–0.19)	0.31
Death by any cause	1 (3)	2 (5)	

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. MV: mechanical ventilation; CRP: C-reactive protein; PTC: procalcitonin.
#: 24 out of 34 patients in the non-purulent group and 34 out of 39 patients in the purulent group had expectoration and respiratory sample.

Lung function

Paired lung function data were available for all patients at admission, at 30 days after admission and long-term follow-up at 180 days (excluding deaths). Lung function variables were analysed by means of analysis of variance models. No statistically significant difference was observed between the non-purulent and purulent group in the change from baseline in FEV_1 on day 30 (least square mean (LSM) -0.11±0.09, 95% CI -0.31–0.09; p=0.27). Likewise there was no statistically significant difference between the non-purulent and purulent groups in the change from baseline in FVC on day 30 (LSM -0.10±0.09, 95% CI -0.51–0.03; p=0.60). Complete data related to lung function are detailed in table 5.

Biomarkers

Serum CRP

The median (IQR) CRP at admission was 11.6 (0.10–33.0) in the purulent group and 5.3 (0.10–23.0) in the non-purulent group (p=0.006). At day 3 the values were 2.7 (0.10–18.1) and 1.2 (0.10–15.6), respectively (p=0.01) (table 2). The mean change in serum CRP on day 3 was -8.13±8.31 $mg \cdot dL^{-1}$ in the purulent and -4.24±5.93 $mg \cdot dL^{-1}$ in the non-purulent group (p=0.07) (fig. 2a). At 30 and 180 days the CRP levels were similar between the groups (tables 3 and 4 and fig. 3a).

CRP levels at admission were not affected by COPD severity stages, presence of cardiovascular disease, previous inhaled

TABLE 4 Clinical outcomes on day 180 of follow-up

	Non-purulent	Purulent	p-value
Subjects	34	39	
New exacerbations	12 (36)	23 (60)	**0.04**
Exacerbation rate	0.5±0.75	0.6±0.58	**0.04**
Hospital admissions	11 (33)	11 (29)	0.69
Hospitalisation rate	0.39±0.6	0.29±0.46	0.69
Patients requiring treatment with antibiotics	11 (32)	8 (46)	0.09
Overall antibiotic therapy courses	13	23	0.72
Overall antibiotic therapy days	77	126	0.06
Patients requiring treatment with corticosteroids	11 (32)	21 (54)	0.47
CRP	0.60 (0.20–0.90)	0.60 (0.40–1.60)	1.0
PTC	0.06 (0.02–0.17)	0.05 (0.03–0.14)	0.27
Death by any cause	3 (9)	4 (10)	0.84

Data are presented as n, n (%), mean±SD, or median (interquartile range), unless otherwise stated. CRP: C-reactive protein; PTC: procalcitonin. p-values in bold are statistically significant.

corticosteroid use and the number of hospitalisations in the last year (p=0.19, p=0.26 and p=0.57, respectively). Positive sputum bacteriology findings were significantly associated with CRP levels $\geqslant 5$ mg·dL^{-1} (p<0.001). In patients with CRP levels $\geqslant 5$ mg·dL^{-1}, the length of hospital stay tended to be higher (p=0.064). CRP levels in non-survivors within 180 days of follow-up tended to be higher (p=0.072).

A comparison of clinical outcomes in patient CRP levels <5 mg·dL^{-1} and $\geqslant 5$ mg·dL^{-1} on admission is shown in online supplementary table E2.

Serum PCT

PCT levels were low in both groups and not significantly different either at admission or after 72 h (table 2 and fig. 2b). Similarly, PCT levels at day 30 and at day 180 of follow-up did not differ between the groups (tables 3 and 4 and fig. 3b). Data of clinical outcomes in patients with PCT levels on admission <0.25 ng·mL^{-1} and $\geqslant 0.25$ ng·mL^{-1} were analysed separately by groups (online supplementary table E2). The length of hospital stay did not differ (p=0.09). However, there was a trend for PCT levels $\geqslant 0.25$ ng·mL^{-1} to be associated with increased number of deaths after 180 days of follow-up (p=0.06).

Systemic cytokines

Cytokine measurements are presented in online supplementary table E3. IL-1β, IL-6, IL-10 and TNF-α did not differ significantly at admission, after 72 h and on day 30 after hospital discharge. In contrast, serum IL-8 levels were significantly elevated in the purulent group (343.77±136.98 *versus* 82.32±222.68 pg·mL^{-1}, respectively; p=0.024). After 72 h of hospitalisation and 30–40 days of follow-up, serum IL-8 levels were no longer significantly different (513.60±210.31 *versus* 163.61±99.61 pg·mL^{-1}, respectively; p=0.061, and 571.74±164.01 *versus* 328.30±59.97 pg·mL^{-1}, respectively; p=0.279). The levels of IL-1β remained constant during the first 72 h, thereafter decreasing at 30 days. Systemic cytokine levels in the purulent group did not correlate either the serum CRP levels (IL-8, r=0.24, p=0.260; IL-1β, r=0.042, p=0.840; IL-6, r=0.056, p=0.780; IL-10, r=0.33, p=0.110) or serum PCT values (IL-8, r=0.34, p=0.102; IL-1β, r=0.19, p=0.340; IL-6, r=0.33, p=0.090; IL-10, r=0.04, p=0.826).

TABLE 5 Evaluation of lung function during follow-up: ANOVA

Parameter	Non-purulent	Purulent	Difference	95% CI for LSM difference	p-value
FEV_1 L					
30 days-baseline	1. 17	1.28	-0.11±0.09	-0.31–0.09	0.27
180 days- baseline	1.18	1.27	-0.09±0.08	-0.25–0.08	0.30
180 days-30 days	1.33	1.39	-0.06±0.08	-0.25–0.01	0.47
FVC L					
30 days-baseline	2.57	2.67	-0.10±0.09	-0.51–0.03	0.60
180 days- baseline	2.45	2.69	-0.24±0.16	-0.58–0.09	0.14
180 days-30 days	2.66	2.87	-0.21±0.14	-0.49–0.06	0.12

Data are presented as least square mean (LSM) or LSM±SE, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

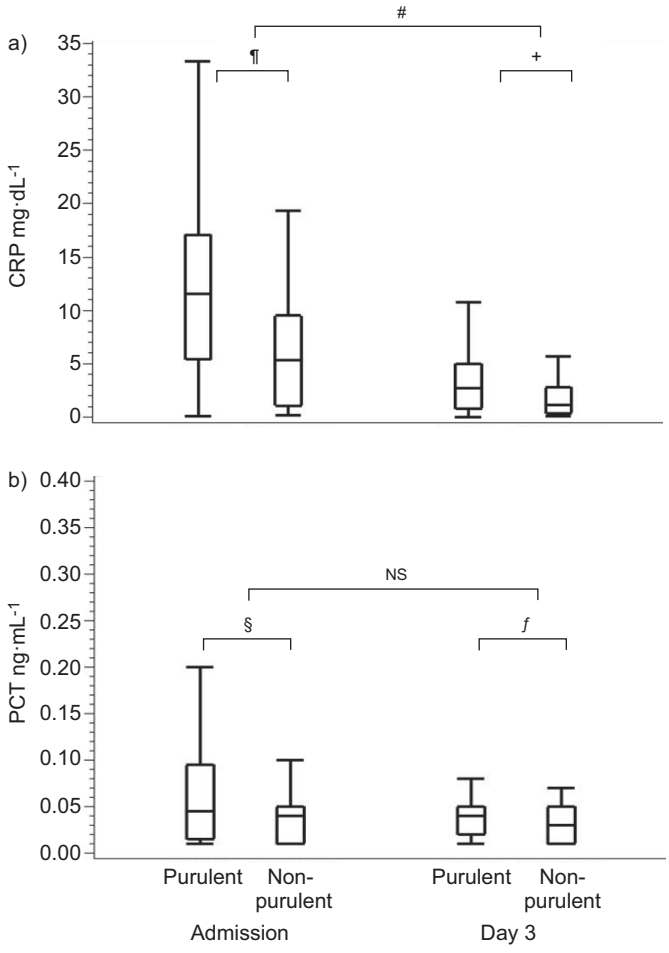

FIGURE 2. Serum a) C-reactive protein (CRP) and b) procalcitonin (PCT) values at admission and day 3 of hospitalisation. #: p=0.07; ¶: p=0.006; +: p=0.01; §: p=0.88; ƒ: p=0.32. Two-tailed p-values shown for comparison of CRP levels between the purulent and non-purulent group, and between admission and day 3.

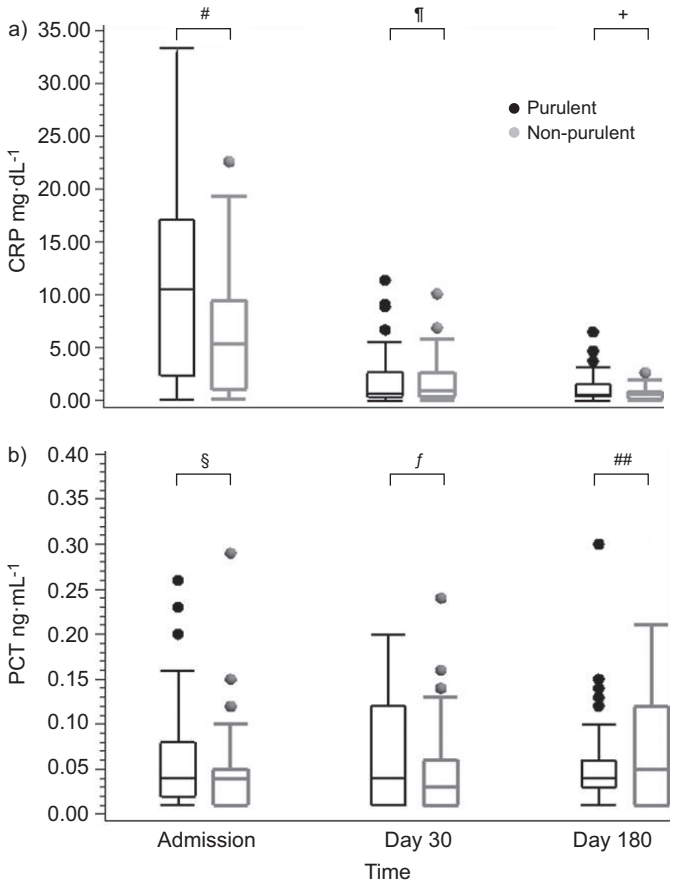

FIGURE 3. Serum a) C-reactive protein (CRP) and b) procalcitonin (PCT) values at admission, day 30 and day 180 of follow-up. #: p=0.006; ¶: p=0.91; +: p=1.0; §: p=0.88; ƒ: p=0.31; ##: p=0.27. Two-tailed p-values shown for comparison of CRP levels at admission and day 30 and day 180.

DISCUSSION

The main findings of this pilot study are the following: 1) in selected patients with acute exacerbations of COPD, patient-reported non-purulent sputum may be a valid criterion to withhold antibiotics; 2) no adverse short- or long-term outcomes were observed following this approach; 3) CRP but not PCT is associated with sputum purulence.

In a classical study published in 1987, ANTHONISEN *et al.* [11] showed that patients with type I exacerbations, *i.e.* increased dyspnoea, sputum volume and purulence, benefit from treatment with antibiotics, whereas this benefit is smaller in type II and is not evident in type III exacerbations. It is important to note that in the original study ambulatory patients were evaluated. To date, the recommendations on antibiotic treatment of most authoritative guidelines are based on this classification [11]. It is generally assumed that purulent sputum reflects the presence of bacterial infection, and that these patients are those who benefit from antibiotics; however it has been well established that in ''real life'' a big majority of hospitalised patients with COPD exacerbation, are, in fact, treated with antibiotics regardless of sputum characteristics or criteria used by ANTHONISEN [11].

STOCKLEY *et al.* [19] were the first to demonstrate the favourable predictive potential of sputum purulence and the presence of bacterial pathogens, and our group confirmed this association using a bronchoscopic approach [20].

To our knowledge, only one small previous study based the decision to treat with antibiotics on sputum colour [19]. This study found that purulent sputum identified a subset of patients likely to benefit most from antibiotic therapy. Conversely, all patients who produced white mucoid sputum during the acute exacerbation improved without antibiotic therapy, and sputum characteristics remained the same even when the patients had returned to their stable clinical state. The current study supports these findings, showing that a sputum purulence-guided antibiotic decision strategy allows antibiotic treatment in patients with non-purulent reported sputum to be withheld. Both short-term and long-term outcomes were not different from the purulent group who received antibiotics.

In contrast to the predictions originally reported by STOCKLEY *et al*. [19], the operative characteristics of non-purulent sputum for the absence of pathogenic bacteria were limited at best (sensitivity of 73.1%, specificity 71.8%, a positive predictive

value of 76.9% and a negative predictive value of 67.6%). These are figures comparable to those recently reported by BURLEY *et al*. [25] (sensitivity 60% and specificity 67%, positive predictive value 73% and negative predictive value 53%). Other authors have also questioned the relationship of sputum colour with bacterial load [26]. In a bronchoscopic validation study published in *Thorax*, however, we found a high concordance between bacterial pathogens in samples retrieved *via* protected specimen brush and sputum ($\kappa=0.85$, $p<0.002$) [20]. Whereas such predictions may be insufficient to support antibiotic treatment by carrying a considerable risk of over-treatment, they may still be useful to guide the withholding of antibiotics.

An additional finding increases confidence in such guidance: non-purulent sputum was associated with lower systemic inflammatory response as assessed by serum CRP. This finding is in line with the observation of STOLZ *et al*. [27], who found a close association between Anthonisen type I and higher CRP values. These findings support the usefulness of patient-reported sputum colour to detect patients without bacterial infection.

Systemic IL-8 was higher in the non-purulent patients. In fact, the levels of systemic IL-8 increase during an acute exacerbation and are associated with neutrophil count in sputum [28]. However, when new bacterial strains are explored by molecular tests in the event of an acute exacerbation of COPD, systemic IL-8 does not appear to be related to the aetiology (bacterial *versus* non-bacterial) and is a non-specific biomarker in this context [29].

The assessment of outcomes was extensive, including clinical criteria, exacerbation rates, re-hospitalisation rates, antibiotic treatment exposure, mortality as well as lung function, evaluation of biomarkers and systemic cytokines. It is important to note that the patterns of acute treatment response on day 3 after hospitalisation were similar in the non-purulent group not treated with antibiotics, both in regard to clinical parameters as well as in the reduction in CRP values. Obviously, the reduction in symptoms and systemic inflammation in the non-purulent group was mainly induced by systemic steroid treatment. It is also crucial that the withholding of antibiotic treatment in the non-purulent group was not followed by an excess of acute exacerbations requiring antibiotics or corticosteroids or hospitalisations thereafter. Moreover, improvements in lung function did not differ over time.

This study confirms the finding of STOLZ *et al*. [14] that sputum purulence (and Anthonisen type as well) is only weakly associated with PCT. This is a disturbing finding since PCT is thought to consistently reflect bacterial infection. Strictly speaking, this could mean that either purulent sputum, albeit reflecting the presence of pathogenic bacteria, does not truly reflect bacterial infection or that PCT may be a valid predictor of systemic but not of bronchial bacterial infection. In fact, several studies support the relevance of newly acquired bacterial strains thereby weakening the evidence for the bacterial bronchial colonisation infection pathway [6, 7, 29, 30]. However, studies based on PCT-guided antibiotic treatment of acute exacerbations have so far only demonstrated that subjects with low PCT do not clinically worsen more than those with higher PCT but do not allow inferences about the meaning of increased PCT. Alternatively, and in our view, sputum purulence and PCT most probably reflect different and poorly understood aspects of a highly complex local inflammatory process. There is a clear need for more investigation in this regard.

Interestingly, higher systemic inflammatory response at admission as reflected by CRP and PCT showed a trend to an association with increased mortality at 180 days of follow-up. This is in contrast to findings by STOLZ *et al*. [27] who found copeptin but not CRP and PCT to be predictive of long-term survival. Further data are needed to explore these associations.

The strengths of our study include a careful selection of the study population, extensive characterisation of the patients at baseline and at presentation, a very careful investigation of sputum samples applying strict criteria, selection of sound primary and secondary end-points, and an extensive repeated re-evaluation including clinical and epidemiological data as well as lung function, biomarkers and systemic cytokines resulting in a comprehensive short- and long-term follow-up. However, there are two inherent limitations which should be addressed. First, this was not a randomised study. Studies available so far suggest that such studies may be difficult to conduct. Based on the landmark randomised and placebo-controlled study by ANTHONISEN *et al.* [11], our approach provides additional evidence that antibiotic treatment decision may be guided by patient-reported sputum purulence. If applied in clinical practice a thorough follow up in order to recognise individual patients with treatment failures is mandatory. Secondly, patients pre-treated with antibiotics had to be excluded as did those requiring mechanical ventilation and noninvasive ventilatory support. Thus, the findings of this study are limited to hospitalised patients without antibiotic pre-treatment and acute exacerbations not requiring ventilatory support. However this population is especially important given that exacerbation of COPD is one of the 10 leading causes of hospitalisation [31] and more than 85% of patients with exacerbation of COPD receive antibiotics [4].

We strongly argue that small but detailed studies such as the present one can provide just as important insights as large observational studies. Only recently, ROTHBERG *et al*. [32] carried out a retrospective study including 84,621 patients from 413 acute care facilities throughout the USA and reported an impressive 13% decrease in treatment failure in hospitalised patients with acute exacerbations treated with antibiotics. Mortality was also reduced, and the protective effect was robust across all sub-groups, whereas adverse effects from antibiotics were minimal. However, this result is in contrast to virtually all studies to date, hinting at sub-groups that might benefit from antibiotic treatment [9–12, 14, 19]. In fact, apart from the known risks of retrospective data analyses, the authors cannot be certain that patients with acute pneumonia were not included in the study.

Finally, the utility of this pilot study is to investigate the hypothesis of using patient-reported purulence to give or not to give antibiotics in hospitalised acute exacerbations of COPD. In line with this hypothesis we have started a double-blind randomised study (registered at clinicaltrials.gov with identifier number NCT 01091493).

In conclusion, our data suggest that a patient-reported sputum-colour-guided strategy of antibiotic treatment in hospitalised patients with acute exacerbation of COPD (not requiring ventilator support) could be an alternative approach to initiate antibiotic treatment and support the hypothesis of performing a randomised trial using sputum purulence-guided antibiotic treatment in this population. At least CRP may be a useful additional parameter to increase confidence about the absence of a bacterial pathogen and infection. PCT levels are only weakly associated with bacterial infection, and PCT-guided antibiotic treatment represents an approach different from sputum purulence which is incompletely understood.

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STATEMENT OF INTEREST

Statements of interest for S. Ewig, A. Huerta and A. Torres can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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