Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease (COPD)

Néstor Soler¹ MD, Carlos Agustí¹ MD, Joaquim Angrill¹ MD, Jorge Puig De la Bellacasa² MD, Antoni Torres¹ MD

Servei de Pneumologia¹, Institut Clínic del Tòrax; Servei de Microbiologia² Hospital Clínic. IDIBAPS Facultat de Medicina. Universitat de Barcelona. Barcelona. SPAIN

Corresponding author:

Antoni Torres

Servei de Pneumologia. Institut Clínic del Tòrax. Hospital Clínic.

IDIBAPS. Universitat de Barcelona.

Villarroel 170

08036 Barcelona

Tel.+34932275549

Fax.+34932279813

e-mail: atorres@ub.edu

Abstract

Background: Antibiotics are commonly prescribed in the COPD exacerbations. However, the role of bacteria in these exacerbations is controversial. An observational study was undertaken to identify clinical predictors of bacterial infection as a cause of exacerbation considering the protected specimen brush (PSB) as the gold standard.

Methods: Clinical data, sputum and PSB samples were collected from 40 COPD patients requiring hospitalisation due to severe exacerbations who had not received previous antibiotic treatment.

Results: Quantitative cultures of PSB samples (n=40) yielded 23 potential pathogenic microorganisms (PPMs) at concentrations $\geq 10^2$ colony-forming units (CFU/mL) in 18 patients (45%). Sputum samples were obtained from all patients (n=40). Culture of good quality sputum samples (n=18) yielded 16 PPMs corresponding to 14 patients (35%). The concordance PSB-sputum rate was high (K=0.85, $p < 0.002$). The self-reporting patient observation of sputum purulence (odds ratio 27.20 [95% CI, 4.60-60.69], $p=0.001$), the FEV₁% predicted < 50 (odds ratio 2.27 [95% CI, 1.55-3.21], $p=0.014$), more than 4 exacerbations in the past year (odds ratio 6.9 [95% CI, 0.08-1.08], $p = 0.028$), and previous COPD-hospitalisations (odds ratio 4.13 [95% CI, 1.02-16.07], $p=0.041$) were associated with the presence of PPMs in the distal airways. The operative characteristics for predicting distal airways infection when patients presented purulent exacerbation were: sensitivity [SE] 89.5%, specificity [SP] 76.2%, positive predicted value [PPV] 77.3% and negative predicted value [NPV] 88.9%.

Conclusions: The self-reporting presence of purulence in the sputum, as well as common previous exacerbations and COPD-hospitalisations in patients with severe airflow obstruction (FEV₁% < 50) predict the presence of bacterial infection in the distal airways. The use of these clinical variables may help in selecting candidates to receive antibiotic treatment.

Keywords: sputum purulence, COPD exacerbation, protected specimen brush (PSB), potential pathogenic microorganisms (PPMs)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with intermittent exacerbations that present with worsening symptoms and lung function impairment. These exacerbations contribute to the morbidity and mortality of this disease and considerably affect the quality of life experienced by patients.[1] [2]

The majority of exacerbations are associated with the presence of bacterial pathogens in the lower respiratory tract, although the real cause-effect of bacteria on exacerbations is unclear. Viruses, and to a lesser extent, exposure to allergens or pollutants may also precipitate a sudden deterioration.[3] [4] Although antibiotics are commonly prescribed in COPD exacerbations, evidence of efficacy is debatable, with some controlled studies showing a benefit, whereas others do not.[5] The uncontrolled use of antibiotics in COPD exacerbations is enormously expensive and may contribute to the serious problem of emerging resistance to valuable antibiotics.[6]

Anthonisen and colleagues, in a landmark study [7] demonstrated that patients exhibiting at least two of the three cardinal symptoms of exacerbation: increased dyspnoea, increased sputum volume, and sputum purulence experienced a clear benefit from antibiotic therapy. However, this study was based on an outpatient population, microbiologic samples of respiratory secretions were not taken and the bacterial aetiology of the exacerbations was never confirmed. Bacterial pathogens can be isolated from sputum during exacerbations. Although this technique is simple and cost-effective, very often it is omitted in the clinical management of COPD exacerbations. Sample contamination by oropharyngeal flora and the difficulties in obtaining a good sputum sample are the main shortcomings that justify this omission.[8]

Quantitative culture of protected specimen brush (PSB) is considered the gold standard for the diagnosis of distal airway infections due to its potential for obtaining sterile microbial samples.[9] [10] However, the invasiveness inherent to the bronchoscopic evaluation precludes its use in clinical practice. In this sense, the identification of reliable clinical predictors of bacterial infection as a cause of severe exacerbations based on PSB findings might be of critical importance since it would help to promote a more judicious use of antibiotics in this clinical setting.

The aims of the present study performed in patients with severe COPD exacerbations requiring hospitalisation were: 1) to identify potential - easy to obtain- clinical predictors of bacterial infection as a cause of exacerbation, taking PSB samples as the gold standard, and; (2) to assess the role of sputum culture as an alternative diagnostic technique in this clinical setting.

METHODS

Study population

The study was conducted from October 2002 to April 2004 in a respiratory care unit at the Hospital Clínic in Barcelona. During this period of time, selected patients with COPD exacerbation requiring hospitalisation were screened for participation. Patients were evaluated within the first 24 hours after admission to the emergency department. The Ethical Committee of the Hospital approved the study protocol and written informed consent was obtained in each case.

Definitions

COPD was defined and categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[11] Airflow obstruction was defined as the presence of a post-bronchodilator FEV_1/FVC ratio ≤ 0.7 . The degree of obstruction was considered mild when FEV_1 % predicted $\geq 80\%$, moderate when FEV_1 % predicted was 50-80%, severe when FEV_1 % predicted was 30-50%, and very severe when FEV_1 % predicted was $< 30\%$. Patients with a bronchodilator reversibility test > 200 ml or $> 12\%$ predicted were not included.

Sputum purulence was considered when patients referred to a change in the colour of sputum over the last 72 hours from uncoloured to yellow-green coloration.

Admission criteria for COPD exacerbation

Although guidelines for diagnosis and care of patients with COPD were considered [2] [11], the ultimate decision as to whether patients required admission from the emergency department to the respiratory ward was taken by the pneumologist in charge after careful evaluation of their particular clinical characteristics and of the results of the biochemistry and arterial blood gases.

All patients were reassessed clinically 4 weeks after hospital discharge. Treatment outcome was judged successful when the patient did not have impairment in respiratory symptoms requiring additional outpatient visits, any increase in the baseline treatment, or hospital re-admission.

Exclusion criteria

Common exclusion criteria were: (1) previous diagnosis of bronchiectasis; (2) clinical and radiological evidence of pneumonia or congestive heart failure; (3) necessity of mechanical ventilation on admission; (4) diagnosis of neoplasm or any type of immunosuppression; (5) previous hospitalisation during the last four weeks and; (6) any type of antibiotic treatment received over the 4 weeks prior to admission.

Study protocol

Demographic data, evaluation of current symptoms, number of prior exacerbations requiring hospitalisation, significant comorbid conditions, current treatment, and hospitalisation stay were retrieved by means of a standardized questionnaire. Biochemical, chest-x-ray films and arterial blood gases analysis were obtained in all patients at admission from the emergency department.

Most of the patients included in the investigation (n=36) had a pulmonary function evaluation performed over the last 4-6 months prior to the exacerbation. If these data were not available, forced spirometry test (Collins Survey III Plus, USA) was conducted at least 2 months after the exacerbation when patients remained in a clinical stable condition. [12]

A sample of spontaneous sputum for microbiological evaluation was obtained in all cases. After that, patients received nebulised bronchodilators (albuterol sulfate 5 mg and ipratropium bromide 250 μ g) and intravenous prednisolone.

Bronchoscopy was performed within the first 24 hours after admission. Upper airway anaesthesia was achieved by nebulisation of 8 ml lidocaine 5% through a buccal clip for 15 minutes. The flexible bronchoscope (Olympus BF 30; Olympus, New Hyde Park, NY, USA) was performed trans-nasally avoiding any suction through the inner channel. Using the technique described by Wimberley and colleagues [13], a PSB sample (Microbiology Brush; Mill-Rose Laboratory Inc, Mentor, Ohio, USA) was obtained from a segmental orifice of the

middle lobe or the right lower lobe. Oxygen supplementation was given to all patients by nasal catheter. The following criteria were considered as formal contraindications to perform the bronchoscopy: (1) changes in mental status, (2) dyspnea at rest and, (3) severe or worsening hypoxaemia and hypercapnia with respiratory acidosis.

Once bronchoscopy was performed, empirical antibiotic treatment (oral amoxicillin-clavulanate, oral levofloxacin, oral clarithromycin or intravenous ceftriaxone) was initiated and the regimen was later adjusted according to microbiological results obtained by PSB specimens. Antimicrobial treatment was not stopped in case of negative microbiological findings.

Microbiological evaluation

Sputum samples were collected in sterile vials and processed in the laboratory within 2 hours after collection. A Gram's stain of sputum in the area of maximal purulence was examined for leukocytes and epithelial cells. Only sputum samples of Murray-Washington classification degrees IV or V were processed for culture (degree IV =10-25 epithelial cells and >25 leukocytes per field; degree V =<10 epithelial cells and >25 leukocytes per field using a low magnification lens [x100]).[14] Sputum specimens not fulfilling these criteria were not considered as representative of distal airways and were not processed for culture. PSB samples were serially diluted (dilutions of 1:10, 1:100, and 1:1000). All microbiological specimens were plated on blood, chocolate, Wilkins-Chalgren, and Sabouraud agar and Ziehl-Neelsen staining and Lowenstein culture were performed on all samples. The cultures were evaluated for growth after 48 hours, negative bacterial cultures for fungi after 4 weeks, and Lowenstein cultures after 6 weeks. Susceptibility testing was performed using the broth micro-dilution or β -lactamase test and classified as sensitive, intermediate or resistant according to the criteria published by the National Committee for Clinical Laboratory Standards. [15] The results of the PSB were expressed quantitatively as *colony-forming units* (CFU/mL). Bacterial load was considered significant when reaching $\geq 10^2$ CFU/mL in PSB specimens, as described by Cabello and colleagues. [16]

Microorganisms identified according standard methods [17] were classified as potential pathogenic microorganisms (PPMs): *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, Gram Negative Bacilli, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and non-potential pathogenic microorganisms (non-PPMs): *Streptococcus viridans*, *Neisseria* spp, *Candida* spp, *Corynebacterium* spp, *Haemophilus parainfluenzae* and *Staphylococcus epidermidis*.

Paired serum samples for serology were collected (at hospital admission and within the third and sixth weeks thereafter) for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Coxiella burnetii* and respiratory viruses (influenza virus A, influenza virus B, parainfluenza virus 1, 2 and 3, respiratory syncytial virus (RSV) and adenovirus). The presence of an infection by atypical bacteria or respiratory viruses was established according to the criteria described previously. [18]

Statistical analysis

Continuous variables were reported as medians and range values. Continuous variables were compared using the nonparametric Mann-Whitney U test and categorical variables by the chi-square test or Fisher exact test when appropriate. All reported *p* values were two-tailed and the level of significance was 5%. Kappa coefficient was used to measure the agreement between sputum and PSB samples. Only valuable sputum samples were considered for correlations with PSB.

The potential influence of different variables on the presence of PPMs in the distal airway was evaluated by univariate analysis. The assessed variables were: smoking habit (0=current smoker; 1=past smoker), pulmonary function (0=FEV₁ $\geq$ 50%; 1=FEV₁ <50%), presence of comorbidities (0=no; 1=yes), previous oral corticosteroid treatment (daily oral prednisone >10 mg) (0=no; 1=yes), number of exacerbations last year (0=<4; 1= $\geq$ 4), number of hospitalisations during the past 3 years (0=0; 1= $\geq$ 1); sputum characteristics

(0=mucous; 1=purulent), fever at admission (0=no; 1=yes), PaO₂ at admission (0=PaO₂ ≥ 60 mmHg; 1=PaO₂ < 60 mmHg), PaCO₂ at admission (0=PaCO₂ < 45 mmHg; 1=PaCO₂ ≥ 45 mmHg) and white blood cell count (BCC) at admission (0=BCC < 12 x 10⁹/L; 1=BCC ≥ 12 x 10⁹/L). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were computed for variables associated with the presence of PPMs in the airways. All data were analyzed using the statistical package SPSS for Windows version 10.0 (SPSS, Chicago, IL, USA).

RESULTS

Patients

During the study period, 112 COPD exacerbated patients admitted to the emergency room and requiring hospitalisation were screened (figure 1). Fifty-four patients were excluded because they had received antibiotics in the previous month. Four additional patients refused the bronchoscopic procedure and in 14 this technique was considered too risky due to clinical and/or arterial blood gases deterioration. Median predicted FEV₁% was 37 (19-72), median predicted FVC% was 75 (64-89), and median FEV₁/FVC% was 42 (34-67). Twenty-one patients (53%) were on inhaled steroids (maximum, 1600 µg/day) and 9 (23%) were on daily oral steroid treatment (maximum, 10 mg/day). All patients complained of increased breathlessness at presentation, 20 (50%) had increased sputum volume, and 22 (55%) referred purulent sputum over the last 48-72h previous to admission (table 1).

Table 1. Characteristics of patients with COPD and severe exacerbation requiring hospitalisation (n=40)

Characteristic	Values	Range
Age, years (median)	69	43-83
Male, n (%)	40 (100)	
Current smoker, n (%)	6 (15)	
Past-smoker, n (%)	34 (85)	
Co morbid conditions, n (%)	26 (65)	
Cardiovascular disease	21 (52)	
Diabetes mellitus	6 (15)	
Renal failure	2 (5)	
Exacerbations last year, n (%)		
< 4 episodes	19 (48)	
> 4 episodes	21 (52)	
Exacerbation criteria, n (%)		
Increased dyspnea	40 (100)	
Increased sputum volume	10 (25)	
Purulent sputum	22 (55)	
Fever at admission, n (%)	12 (30)	
Domiciliary oxygen, n (%)	10 (25)	
Oral steroid therapy ⁺ , n (%)	9 (22)	
FEV ₁ % predicted (median)	37	19-72
FVC% predicted (median)	69	64-89
FEV ₁ /FVC% (median)	42	34-67
White blood cell count x 10 ⁹ /L (median)	11590	5100-22700
PaO ₂ mmHg (median)	62	40-75
PaCO ₂ mmHg (median)	44	23-62

Abbreviations: FEV₁, forced expiratory volume in one second as a percentage of predicted; FVC, forced vital capacity as a percentage of predicted.

⁺More than 10 mg. of prednisolone daily

There were no differences between patients with purulent exacerbations (n=22) and those with mucoid exacerbations (n=18) with regard to age, smoking habit, forced spirometry data, use of domiciliary oxygen, presence of co-morbidities, current inhaled therapy (β -agonists, ipratropium bromide or corticosteroids), PaO₂ or PaCO₂ values at admission and days of hospitalisation.

Respiratory samples

Bronchoscopic-guided PSB samples were obtained in the 40 patients included. No serious complications during the bronchoscopic procedure were evidenced.

Cultures of PSB at $\geq 10^2$ CFU/mL yielded 23 PPMs in 18 of 40 (45%) patients. The concentration reached a cut-off $\geq 10^3$ in 13 of the 18 patients with PPM's in the PSB. Also, PSB cultures evidenced the growth of 21 non-PPMs in 10 patients (25%). The most frequent PPMs isolated were *Streptococcus pneumoniae* (7 patients, 17.5%), *Haemophilus influenzae* (7, 17.5%), *Pseudomonas aeruginosa* (4, 10%) and *Moraxella catarrhalis* (2, 5%). A sputum sample was obtained spontaneously in all patients (n=40) but only 18 (45%) fulfilled the Murray-Washington criteria (grade IV or V) and were further processed for culture. [13] Culture of good quality sputum samples yielded 16 PPMs corresponding to 14 patients (35%) and 4 non-PPMs reported as *mixed community flora* corresponding to 4 patients (10%) (table 2).

Table 2. Bacterial microorganisms isolated in sputum and PSB samples

	Sputum samples (n=40)	PSB samples (n=40)		
Bacterial load, CFU/mL		$\geq 10^2$	$\geq 10^3$	$\geq 10^4$
Positive bacterial culture, n (%)	18 (45)	27 (68)	24 (60)	9 (23)
PPMs, n (%) ⁺	14 (35)	18 (45)	13 (33)	4 (10)
<i>Haemophilus influenzae</i>	5	7	7	4
<i>Streptococcus pneumoniae</i>	6	7	3	1
<i>Moraxella catarrhalis</i>	2	2	2	-
<i>Escherichia coli</i>	1	1	-	-
<i>Enterobacter</i> spp.	-	1	1	-
<i>Pseudomonas aeruginosa</i>	2	4	3	-
Total	16	22	16	5
Non-PPMs	4 (10)	10 (25)	8 (20)	5 (13)
<i>Streptococcus viridans</i>	-	10	9	4
<i>Staphylococcus epidermidis</i>	-	6	5	4
<i>Candida albicans</i>	-	2	1	-
<i>Nesiseria</i> spp.	-	3	1	-
Mixed community flora	4	-	-	-
Total	4	21	16	8

Abbreviations: CFU/mL, colony-forming units; PPMs, potentially pathogenic microorganisms.

⁺Data referred to total number of the cases.

Four patients with significant concentrations of PPMs in the PSB samples had a negative sputum culture. In contrast, only one patient with a positive sputum culture had a negative PSB specimen (figure 2). Accordingly, for the PPMs recovered above the predefined cut-off $\geq 10^2$ CFU/mL, the results of PSB and sputum cultures agreed in 85% of the patients ($K=0.85$, $p<0.002$).

Serology

Serological samples were positive according to the established criteria in 7 of 39 cases (18%), with 2 cases of *Chlamydia pneumoniae*, 2 cases of Influenza A virus, and one case each of *Mycoplasma pneumoniae*, parainfluenza virus and respiratory syncytial virus. Two patients with serological evidence of *Chlamydia pneumoniae* infection had a concomitant *Haemophilus influenzae* isolated in the PSB samples.

Susceptibility tests of antibiotics for the PPMs isolated by PSB were performed. Of 7 *Haemophilus influenzae* strains isolated, three (43%) were β -lactamase positive and, of the four strains of *Moraxella catarrhalis* isolated, three (75%) were β -lactamase positive. Two strains of *Streptococcus pneumoniae* showed high resistance to penicillin ($MIC \geq 2$ $\mu\text{g/ml}$), two strains had intermediate resistance ($MIC 0.1\text{-}1.0$ $\mu\text{g/ml}$) and only three strains were susceptible to penicillin ($MIC \leq 0.06$ $\mu\text{g/ml}$).

Predictive factors associated with distal airway infection by PPMs

The results of the univariate analysis showed that factors associated with the presence of PPMs in the distal respiratory tract were the self-reporting patient observation of sputum purulence ($p < 0.0001$), a severe airflow obstruction defined by a $FEV_1\% < 50\%$ ($p = 0.014$), more than 4 exacerbations in the past year ($p = 0.028$), and having required at least one hospitalisation for COPD exacerbation over the last 3 years ($p = 0.041$) (table 3). Factors not related with the presence of PPMs in the lower airways were smoking habit, PaO_2 and $PaCO_2$ values at admission, previous domiciliary oxygen therapy and inhaled or oral steroid treatment. The results of the univariate analysis did not change when a cut-off $\geq 10^3$ CFU/mL. was considered.

Clinical significance of the sputum analysis

Seventeen of the 22 patients (77%) that referred a purulent appearance of the sputum had PPMs above the pre-defined cut-off point in the PSB sample, but only 5 (23%) of them had negative cultures. By contrast, only 1 patient that referred mucoid sputum had significant PPMs in the PSB sample (figure 3). This patient was the only with a good quality sputum sample that was further processed for culture. Using 10^2 CFU/mL. in the PSB, the operative characteristics for predicting lower airway infection when patients referred the presence of purulent sputum were as follows: sensitivity (SE) 89.5%, specificity (SP) 76.2%, positive predictive value (PPV) 77.3% and negative predictive value (NPV) 88.9%. Likewise, the operative characteristics for the valid sputum cultures at admission were: SE =72.2%, SP =89.4, PPV = 92.9%, and NPV =95.5%.

When Anthonisen criteria were analyzed, 20 patients presented three cardinal symptoms at admission (type 1-exacerbations), 12 patients presented two criteria with sputum purulence in only 2 cases (type 2-exacerbations) and 8 patients presented one criteria - exclusively for increased dyspnoea - (type 3-exacerbations). We found that the airway infection rate by PPMs in patients with exacerbation type 1, 2 and 3 was 80%, 35% and 6% respectively. The impact of increased dyspnoea and increased sputum volume was inappreciable when analyzing these two major criteria independently.

Table 3. Predictive factors for bacterial infection in severe COPD exacerbated patients (n = 40)

	Positive PSB culture n / total / (%) [*]	Odds ratio (95% CI)	p value
Comorbid conditions			
Yes	14/26 (54)	3.41 (0.84-6.08)	0.08
No	4/14 (29)		
Domiciliary oxygen			
Yes	5/10 (50)	3.50 (0.75-16.28)	0.15
No	13/30 (43)		
FEV ₁ % predicted < 50			
Yes	17/34 (50)	2.27 (1.55-3.21)	0.01
No	1/6 (16)		
Oral steroids therapy			
Yes	4/9 (44)	0.85 (0.19-3.79)	0.83
No	14/31 (45)		
Current smoking habit			
Yes	3/6 (50)	0.89 (0.16-2.88)	0.89
No	15/34 (44)		
Fever at admission			
Yes	5/12 (42)	3.39 (0.57-10.10)	0.16
No	13/28 (46)		
PaO ₂ at admission < 60 mmHg			
Yes	11/20 (55)	2.78 (0.77-10.04)	0.11
No	7/20 (55)		
PaCO ₂ at admission > 45 mmHg			
Yes	7/19 (37)	0.29 (0.08-1.08)	0.15
No	11/21 (52)		
White blood cell count > 12 x 10 ⁹ /L			
Yes	13/25 (52)	1.62 (0.44-5.94)	0.46
No	5/15 (33)		
≥ 4 exacerbations last year			
Yes	13/21 (62)	6.91 (1.24-38.52)	0.03
No	5/19 (26)		
Hospitalisation last 3 years			
Yes	14/25 (56)	4.13 (1.02-16.67)	0.04
No	4/15 (27)		
Purulent sputum			
Yes	17/22 (78)	27.20 (4.60-60.69)	0.001
No	1/18 (5)		

Abbreviations: FEV₁, forced expiratory volume in one second as a percentage of predicted; PSB, protected specimen brush; ^{*}Bacterial load > 10² CFU/mL.

DISCUSSION

The present study shows that purulence in the sputum is the hallmark of bacterial airway infection in patients with COPD on exacerbation. Contrary to patients with mucoid sputum, most of those who referred purulence had positive PSB cultures with high PPMs counts in distal airways. This finding emphasizes the usefulness of simple cardinal symptoms in selecting candidates to receive antibiotic treatment, even in the context of severe exacerbations requiring hospitalisation.

Although culture of good quality sputum samples reliably reproduces distal airways infection by PPMs, the high number of technical unsatisfactory samples limits its clinical use.[19]

Different studies using sputum cultures have evidenced good correlations between purulence and bacterial exacerbations [20] [21] [22], but our study is the first using the uncontaminated PSB specimens as a gold standard to define the presence or absence of distal airways infection. Interestingly, our results demonstrate that a self-reporting presence of purulence in the sputum predicts the presence of bacteria at high concentrations in the airways with a positive predictive value (PPV) of 77% and negative predictive value (NPV) of 89%. Also, suffering previous hospitalisations, more than 4 COPD exacerbations per year and a severe airway obstruction ($FEV_1 < 50\%$) reinforce the probability of having high bacterial counts in the distal airways. Although these data seem reliable for deciding which patients should and should not be treated with antibiotics, several precautions must be taken into account for the proper evaluation of the results of the present study. First, we have not performed a multivariate analysis to better identify variables independently associated with the presence of high bacterial counts in the distal airways because this methodology might be influenced by the small sample size of the population evaluated and the results obtained might be difficult to interpret. Second, the population evaluated is constituted by selected patients with severe COPD on exacerbation that had not received antibiotics and that were fit enough to undergo a bronchoscopic exploration. Furthermore, although PSB is considered a gold standard for defining infection in pneumonia, there is a lack of technical standardization for performing this technique in COPD exacerbations. Finally, after bronchoscopy, all the patients included were treated with antibiotics precluding any conclusion with regard to the outcome of the exacerbation. In this sense, it is clear that our results must be confirmed in properly designed clinical studies evaluating the response to antibiotics in unselected patients with and without purulence criteria. Also, and as pointed out by Niederman, it is necessary to use end points other than bacteriologic eradication, such as time to resolution of symptoms or disease free intervals. [23] [24]. The pathogenic role of bacteria in exacerbations is controversial. It is well known that bacteria chronically colonize some patients with COPD, but the mere presence of bacteria in airway secretions does not necessarily establish an aetiological role in exacerbation. [25] The present study uses quantitative cultures of PSB samples as a gold standard to define the presence or absence of bacterial infection.[10] Recently, Rosell and colleagues performed a pooled analysis of different studies that used the PSB in COPD patients. [26] Based on the results obtained in 337 individuals (70 healthy subjects, 181 stable COPD patients and 36 exacerbated patients) these authors established a threshold of 10^2 CFU/mL as abnormal. The prevalence of positive cultures $\geq 10^2$ CFU/mL was much higher in exacerbated COPD patients than in stable COPD patients. Colonisation by PPMs was observed in almost 30% of the stable COPD patients, but a minimal proportion of cases had bacteria in high concentrations. In our study, 13 out of the 18 patients (72%) with PPMs above the predetermined threshold had counts of $\geq 10^3$ CFU/mL, a threshold that is normally used to define pneumonia. Besides, our study is unique because the patients included had not received antibiotics over the last four weeks further supporting the etiologic role of the bacteria isolated in the exacerbation. Likewise, knowing that a particular patient has had previous hospitalisations for COPD exacerbation, has suffered more than 4 exacerbations

per year and has a severe airway obstruction ($FEV_1 < 50\%$) may reinforce the decision to prescribe antibiotic therapy.

Contrary to Stockley and colleagues [21], we did not perform an analysis of the colour of the sputum. Although, we acknowledge the subjectivity inherent to the self-reporting aspect of the sputum, it proved to be very valuable. The sensitivity and specificity of the self-reporting presence of purulence in the sputum was 90% and 76% respectively. Apart from its simplicity, the self-reporting criteria of the sputum characteristics have the adding advantage that they can be evaluated in every patient. By contrast, in the series by Stockley and colleagues [21] and in our own series, 25% and 35% of the patients included respectively had sputum samples that were not processed for culture because their quality was considered unsatisfactory. On the other hand, Murphy and colleagues [27], using molecular typing showed that sputum cultures could underestimate the frequency of bacterial colonization of the respiratory tract. This observation confirms the limitation of sputum culture as a valid technique to evaluate the role of bacteria in exacerbations.

Purulence should be expected when bacteria are causing infection since the activation of host defences includes neutrophil recruitment to the airways. On the contrary, our results confirm that mucoid sputum very rarely reflects bacterial airway infection. This finding is remarkable since in our series most of the non-valuable sputum samples for culture came from patients who referred mucous sputum, and clinicians may be afraid of not giving antibiotics to a patient with an unsatisfactory sputum sample even though they report that it was mucoid. In this sense, our results support the findings by Stockley and colleagues, showing that patients with mucoid sputum during the acute exacerbation improved without antibiotic therapy. In the present study, we could only incriminate bacteria as a cause of the exacerbation in 45% of the episodes evaluated (patients with PPMs in high concentrations in the distal airways). Our results are in accordance with others investigations showing that only half of the episodes of exacerbation are bacterial in origin, whereas the remainder should be attributed mainly to virus, and to a lesser extent to toxics and other environmental causes. [28] The fact that in our series, 18% of the patients evaluated had positive serology in front of different respiratory viruses or had atypical bacteria further emphasizes the role of these microorganisms in exacerbations, as Blasi and colleagues have recently shown using molecular typing. [29] The myriad of microorganisms that potentially cause an exacerbation in COPD patients underlines the importance of properly selecting patients that are expected to benefit from antibiotic treatment.

In summary, our results show that 45% of the patients with a COPD exacerbation requiring hospitalisation have high concentrations of PPMs in PSB samples, suggesting a bacterial aetiology. We found that the self-reporting observation of purulence in the sputum is strongly associated with the presence of bacterial COPD exacerbations. In addition, previous hospitalisations, more than 4 exacerbations per year and having severe airflow obstruction can predict the presence of high bacterial counts in the distal airways. The use of these simple parameters may help in selecting candidates to receive antibiotic treatment, however properly outcome based studies are needed to confirm our results.

GRANTS

Supported by: *Marató TV3* (04050530 and 04040210), grant FISS (PI041136 and PI030113), *Red Gira* (V-2003-REDG063-0) and *Red Respira* (V-2003-REDC11B-0).

COMPETING INTERESTS

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article to be published in THORAX editions and any other BMJPG Ltd products to exploit all subsidiary rights, as set out in our licence.

<http://thorax.bmjournals.com/ifora/licence.pdf>

LEGENDS OF THE FIGURES

Figure 1: Study profile

Figure 2: Microbiological profile

Figure 3: Flow diagram showing relationships between sputum characteristics and PSB results

References

- 1 Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349**: 1269-1276.
- 2 Celli BR, MacNee W, and committee members. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23**: 932-946.
- 3 Sehti S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; **117**: 380S-385S.
- 4 Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbation. *Thorax* 2002; **57**: 759-76.
- 5 Saint S, Bent S, Vittinghoff E, *et al.* Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-analysis. *JAMA* 1995; **273**: 957-960.
- 6 Kim S, Emerman Ch, Cydulka RK, *et al.* Prospective multicenter study of relapse following emergency department treatment of COPD exacerbation. *Chest* 2004; **125**: 473-481.
- 7 Anthonisen NR, Manfreda J, Warren CPW, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; **106**: 196-204.
- 8 Lentino J-R, Lucks D-A. Non-value of sputum culture in the management of lower respiratory tract infections. *J Clin Microbiol* 1987; **25**: 693-697.
- 9 Monsó E, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. *Am Respir Crit Care Med* 1995; **152**: 1316-1320.
- 10 Soler N, Torres A, Ewig S, *et al.* Bronchial microbial patterns in severe exacerbations of chronic pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; **157**: 1498-1505.
- 11 Pouwels R, Buist S, Calverley P, Jenkins Ch, Hurd S, on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *Am J Respir Crit Care Med* 2001; **163**: 1256-1576.
- 12 Miravittles M, Espinosa C, Fernández-Laso E, *et al.* Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999; **116**: 40-46.
- 13 Wimberley N, Faling L-J, Bartlett J-G. A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. *Am Rev Respir Dis* 1979; **119**: 339-339.
- 14 Murray P-R, Washington J-A. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; **50**: 339-344.
- 15 National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing (Vol. 17). Philadelphia, PA: NCCLS, 1997: **M57-M100**; Vol. 1.
- 16 Cabello H, Torres A, Celis R, *et al.* Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997; **10**: 1137-1144.

- 17 Ballows A, Hauser WJ, Herrmann KL, *et al.* Manual of Clinical Microbiology, 5th Ed. Washington DC. American Society of Microbiology 1991.
- 18 De Roux A, Marcos MA, Garcia E, *et al.* Viral community-acquired pneumonia in immunocompromised adults. *Chest* 2004; **125**: 1343-1351.
- 19 Monsó E, Rosell A, Bonet G, *et al.* Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 1999; **13**: 338-342.
- 20 Monsó E, Garcia-Aymerich, Soler N, *et al.* Bacterial infection in exacerbated COPD with changes in sputum characteristics. *Epidemiol Infect* 2003; **131**: 799-804.
- 21 Stockley RA, O'Brien Ch, Pye A, *et al.* Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; **117**: 1638-1645.
- 22 Eller J, Ede A, Schaberg T, *et al.* Relation between bacteriologic etiology and lung function. *Chest* 1998; **113**: 1542-1548.
- 23 Niederman MS. Who should receive antibiotics for exacerbations of chronic bronchitis? A plea for more outcome-based studies. *Clin Infect Dis* 2004; **39**: 987-988.
- 24 Van der Valk P, Monninkhof E, Van der Palen J, *et al.* Clinical predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease. *Clin Infect Dis* 2004; **39**: 980-986.
- 25 Sethi S, Evans N, Grant B, *et al.* New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; **347**: 465-471.
- 26 Rosell A, Monsó E, Soler N, *et al.* Microbiological determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med* 2005; **165**: 891-897.
- 27 Murphy TF, Brauer AL, Schiffmacher AT, *et al.* Persistent colonization by *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **170**: 266-272.
- 28 Rohde G, Wiethage A, Borg I, *et al.* Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; **58**: 37-42.
- 29 Blasi F, Damato S, Consentini R, *et al.* *Chlamydia pneumoniae* and chronic bronchitis: association with severity and bacterial clearance following treatment. *Thorax* 2002; **57**: 672-676.

Figure 1.

Figure 2.

Abbreviations: PSB, protected specimen brush; PPMs, potentially pathogenic microorganisms.

*All samples contained <25 neutrophils/low-power field.

Figure 3.