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SHORT REPORT
Bacterial infection in exacerbated COPD with changes in sputum characteristics

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SUMMARY

We examined the risk factors for bacterial exacerbation, defined as the presence of pathogenic bacteria in sputum, in 90 chronic obstructive pulmonary disease (COPD) patients with an exacerbation and changes in sputum characteristics. Smoking, alcohol, lung function, body mass index, medical visits and treatments were the independent variables assessed using multivariable logistic regression modelling (OR, 95% CI). A bacterial exacerbation was diagnosed in 39 (43·3%) of 90 patients. Bacterial exacerbations were more prevalent among current smokers (OR 3·77, 95% CI 1·17–12·12), in patients with poor compliance with inhalation therapy (OR 3·25, 95% CI 1·18–8·93) and with severe lung function impairment (FEV_1 OR 0·96, 95% CI 0·93-1·00). Prior use of antibiotics was a risk factor for *Pseudomonas aeruginosa* infection (OR 6·06, 95% CI 1·29–28·44) and influenza vaccination appeared to have a protective effect against this infection (OR 0·15, 95% CI 0·03–0·67). We conclude that severe impairment of lung function, smoking and poor compliance with therapy are risk factors for bacterial infection in COPD, and *P. aeruginosa* should be suspected in patients who have been treated with antibiotics and in those not vaccinated against influenza.

Using techniques that avoid contamination of the sample by oropharyngeal secretions, such as the protected specimen brush, bacterial infection has been associated with 45–55% of chronic obstructive pulmonary disease (COPD) exacerbations [1–3]. Sputum culture has the advantage over such invasive procedures of being widely available, and results are considered representative of lower airway secretions when strict cytologic criteria are used for selecting the sample [4, 5]. Up to 80% of COPD patients with changes in their sputum characteristics during an exacerbation, such us increased volume and purulence, can be shown to have a bacterial infection [6]. In these patients, antibiotic therapy improves acute symptoms [7] and decreases the sputum bacterial load [6]. *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella*

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catarrhalis are the most common microorganisms grown in this clinical context, but *Pseudomonas aeruginosa* is also frequently isolated from patients with severe disease [3, 8]. This organism is generally not susceptible to antibiotics commonly used to treat COPD infections, and so identification of risk factors for *P. aeruginosa* infection is therefore important for the optimization of antibiotic therapy for these patients [9].

The interaction between patient characteristics, such us severity of disease and prior treatment, and bronchial infection in COPD requiring hospital admission has only been sporadically investigated, and recent work has only indicated a higher prevalence of infection when COPD is severe [10]. The aim of this study was to assess a wide range of possible risk factors for bacterial infection in a sample of 90 exacerbated COPD patients reporting an increase in sputum production and/or purulence.

A subset of exacerbated COPD patients who participated in a study of risk factors of COPD exacerbation in the Barcelona area, and reported an increase in volume and/or purulence in sputum on admission (Estudi dels Factors de Risc d'Agudització de la Malaltia pulmonar obstructiva crónica, EFRAM) [11, 12], were included in the present study. COPD exacerbation was the initial admission diagnosis for all enrolled cases in the EFRAM study, defined as an increase in dyspnoea, sputum production or purulence [7]. The diagnosis of COPD was based on medical history, current symptoms, chest X-rays and pulmonary function tests, following the guidelines of the European Respiratory Society [13]. Patients whose chest X-ray suggested bronchiectasis or who had a first diagnosis of pneumonia were not enrolled. A sputum sample was obtained within 48 h of admission to hospital and prior to antibiotic treatment. Patients who had received any type of antibiotic treatment in the week before admission were not included. For patients who had more than one episode of exacerbation in the EFRAM study, only the first episode with a sputum sample available was considered.

All enrolled patients were asked to complete a questionnaire upon admission that included questions on sociodemographic variables, smoking, alcohol consumption, comorbidity, COPD-related medical visits within the last year, current treatments and characteristics of the exacerbation [11, 12]. Outpatient and emergency room visits were not considered as admission to hospital. Rehabilitation was defined as self-reporting respiratory or other prescribed exercises. Compliance with inhalation therapy was assessed using specific checklists as described elsewhere [11, 14]. At least 3 months after hospitalization and during a stable period, forced spirometry and reversibility testing were performed according to standard techniques [15], using reference values obtained from selected volunteers from the Barcelona area [16].

Sputum samples were considered suitable for culture when <10 epithelial cells and >25 leukocytes per low power magnification field were visualized [5]. In two patients who did not produce sputum and for whom fiberoptic bronchoscopy was indicated (pulmonary nodule, haemoptysis) the sputum sample was obtained using a protected specimen brush (Mill-Rose Laboratories Inc., Mentor, OH, USA) as previously described [2]. Sputum samples were processed by standard microbiological methods [17] and bacteria were considered clinically significant according to the criteria of Cabello et al. [18]. A diagnosis of bacterial related exacerbation was established for all samples growing one or more pathogenic bacteria. For samples obtained using a protected specimen brush, isolates were considered significant when they gave counts of $\geqslant 1000$ c.f.u./ml of one or more pathogenic bacteria.

Data were analysed using the SPSS software package (Chicago, IL, USA). Results were expressed as means with standard deviations and absolute and relative frequencies. To check for possible selection bias, exacerbated COPD patients included in the present study were compared with exacerbated patients in the EFRAM study who reported sputum changes but did not fulfill the inclusion criteria (Student's t test or χ^2 test). Bacterial related and non-related COPD exacerbations, defined according to the result of the sputum culture (either spontaneous sputum or brush specimen), were analysed for associations with individual characteristics. Univariate and multivariate analyses were performed using logistic regression modelling, for the following potential risk factors: age, gender, smoking (current or passive), alcohol consumption, comorbidity (expressed as dichotomized variables), FEV_1%, body mass index (expressed as continuous variables), COPD-related admissions (dichotomized as $\leqslant 2$ or >2) and non-admission visits (dichotomized as $\leqslant 4$ or >4) within the last year, treatments (influenza vaccination, domiciliary oxygen, rehabilitation, inhaled or oral corticosteroids, antibiotics within the previous 3 months), and compliance with prescribed inhalation therapy. Finally,

Table 1. *Descriptive statitistics of COPD patients*

	Sputum sample		
	Available	Not-available	*P*
N	90	175	
Sputum sample			
Upon admission, *n* (%)	68 (77·3)	—	—
The second day after admission, *n* (%)	20 (22·7)	—	—
Upon admission with PSB*, *n* (%)	2 (2·2)	—	—
Sociodemographic and clinical characteristics			
Age, *m* (S.D.)	67·5 (9·9)	69·4 (7·8)	0·12
Gender (male), *n* (%)	86 (95·6)	164 (93·7)	⩾0·20
Current smoking, *n* (%)	21 (23·3)	47 (26·9)	⩾0·20
FEV1 %, *m* (S.D.)†	31·3 (15·9)	33·3 (14·6)	⩾0·20
>2 hospital admissions in last year, *n* (%)	44 (48·9)	71 (40·6)	⩾0·20
>4 non-admission visits in last year‡, *n* (%)	37 (41·1)	77 (44·0)	⩾0·20
Therapy			
Influenza vaccination	63 (70·0)	127 (72·6)	⩾0·20
Domiciliary oxygen	33 (36·7)	55 (31·4)	⩾0·20
Inhaled corticosteroids	46 (51·1)	115 (65·7)	0·06
Oral corticosteroids§	23 (25·6)	51 (29·1)	⩾0·20
Rehabilitation	17 (18·9)	27 (15·4)	⩾0·20
Antibiotics in prior 3 months	17 (18·9)	37 (21·1)	⩾0·20

* PSB; protected specimen brush.
† Available from 222 subjects.
‡ At emergency room or outpatient clinic.
§ More than 2 weeks last year. Comparison of the two groups using a Student's *t* test or χ^2 test.

the same approach was used to determine specific risk factors for *P. aeruginosa* infection. Results were given as crude and adjusted odds ratios (OR), with 95% confidence intervals (CI). All variables showing an association with the outcome variables ($P<0·25$) in the univariable analysis were included in the multivariable model, and the most parsimonious model that still explained the data was accepted as final [19]. All statistical tests were two-sided, and a *P*-value $\leqslant 0·05$ was considered as statistically significant.

Ninety of the 265 (34·0%) COPD exacerbation episodes included in the EFRAM study and reporting changes in their sputum characteristics in addition to dyspnoea impairment fulfilled the enrollment criteria for the present study. Patients were mostly men with a high prevalence of current smoking and severe lung function impairment (mean FEV1 31·3%). An increase in sputum production was more often reported (88·9%) than sputum purulence (75·6%). When COPD patients in the present study were compared with non-included patients with the same characteristics in the EFRAM study, no significant differences were found, suggesting that the selected sample was representative of exacerbated COPD patients requiring admission and reporting sputum changes (Table 1).

Table 2. *Bacterial species recovered from COPD sputum samples* (*N=90*)

Haemophilus influenzae, *n* (%)	12 (13·3)
Streptococcus pneumoniae, *n* (%)	11 (14·4)
Moraxella catarrhalis, *n* (%)	3 (3·3)
Pseudomonas aeruginosa, *n* (%)	12 (13·3)
Enteric Gram negative bacilli, *n* (%)	1 (1·1)
Any potentially pathogenic bacteria, *n* (%)	39 (43·3)

Thirty-seven patients produced sputum samples with >25 leukocytes and <10 epithelial cells that grew potentially harmful bacteria. Additionally, protected specimen brush samples of two patients grew >1000 c.f.u./ml of these bacteria. In total, 39 of the 90 (43·3%) patients grew clinically significant bacteria (Table 2).

Positive sputum cultures emerged as significantly associated with current smoking (OR 3·77, 95% CI 1·17–12·12), poor compliance with inhalation therapy (OR 3·25, 95% CI 1·18–8·93) and severe functional impairment (FEV1: OR 0·96, 95% CI 0·93–1·00) (Table 3). Additionally, when *P. aeruginosa* infection

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Table 3. *Risk factors for bacterial infection in COPD patients requiring admission for exacerbations*

	Sputum culture				
	Positive	Negative	Crude OR (95% CI)	Adjust. OR (95% CI)	*P*
Total	39	51	—	—	—
Age	67·6 (9·8)	67·4 (10·0)	1·00 (0·96–1·04)	—	—
Male	37 (94·9)	49 (96·1)	0·75 (0·10–5·61)	—	—
Current smoking	13 (33·3)	8 (15·7)	2·69 (0·98–7·35)	3·77 (1·17–12·12)	0·03
Passive smoking*	9 (23·1)	12 (23·5)	0·97 (0·36–2·61)	—	—
Alcohol, previous 2 weeks	10 (25·6)	16 (31·4)	0·75 (0·30–1·91)	—	—
Comorbidity	34 (87·2)	46 (90·2)	0·74 (0·20–2·76)	—	—
FEV1 %†	27·6 (11·2)	34·1 (18·3)	0·97 (0·94–1·00)	0·96 (0·93–1·00)	0·05
Body mass index	24·5 (5·3)	24·5 (5·2)	1·00 (0·92–1·08)	—	—
COPD-related visits last year					
>2 hospital admissions	13 (33·3)	22 (43·1)	0·66 (0·28–1·57)	—	—
>4 non-admission visits‡	11 (28·2)	26 (51·0)	0·38 (0·15–0·92)	—	—
Therapy					
Influenza vaccination	24 (61·5)	39 (75·5)	0·49 (0·20–1·23)	—	—
Domiciliary oxygen	17 (43·6)	16 (31·4)	1·69 (0·71–4·02)	—	—
Inhaled corticosteroids	19 (48·7)	27 (52·9)	0·84 (0·37–1·94)	—	—
Oral corticosteroids§	10 (25·6)	13 (25·5)	1·01 (0·39–2·62)	—	—
Rehabilitation	6 (15·4)	11 (21·6)	0·66 (0·22–1·98)	—	—
Antibiotics previous 3 months	10 (25·6)	7 (13·7)	2·17 (0·74–6·34)	—	—
Poor compliance with inhalation	19 (48·7)	16 (31·4)	2·08 (0·88–4·92)	3·25 (1·18–8·93)	0·02

Multivariable logistic regression modelling adjusting for FEV1 % and all covariates showing association ($P \leqslant 0{\cdot}25$).
* In current non-smokers.
† Available from 81 subjects.
‡ At emergency room or outpatient clinic.
§ More than 2 weeks last year.

was specifically assessed in the multivariable analysis, positive cultures were significantly linked to lack of influenza vaccination (OR 0·15, 95% CI 0·03–0·67) and antibiotic use within the past 3 months (OR 6·06, 95% CI 1·29–28·44) (Table 4).

In our study sputum cultures demonstrated bacterial infection in more than 40% of the COPD exacerbations with changes in sputum characteristics and infection severe enough to require hospital admission. Increased dyspnoea, sputum production and/or purulence are the criteria currently used to identify COPD exacerbations. Wilson et al. [20] found that 45% of the exacerbated patients reported increased dyspnoea, 77% increased sputum production and 66% purulence. The prevalence of these criteria differs in exacerbated COPD patients requiring admission, most of whom report dyspnoea impairment [8]. Stockley et al. [6] found a higher prevalence of bronchial infection when sputum purulence is reported at the beginning of an episode of exacerbation. This is in agreement with the hypothesis that COPD patients with changes in sputum represent a specific subpopulation for whom the pathogenesis of the exacerbation is closely related to infection.

We found lung function to be a risk factor for bacterial infection in our patients. Patients with severe COPD had a higher prevalence of positive cultures, mainly growing *H. influenzae*, *S. pneumoniae* and *P. aeruginosa*. This is consistent with the study of Miravitlles et al. [10] who found that the sputum cultures from half of the exacerbated COPD patients grew potentially pathogenic bacteria and that bacterial infection was associated with severity of lung function impairment. A similar study found positive sputum cultures in more than 60% of the cases [8], with a higher prevalence of *P. aeruginosa* in those with severe disease (11·5%) than in those with mild COPD (3·3%). Here we found that current smoking (OR 3·77, 95% CI 1·17–12·12) and poor compliance with inhalation therapy (OR 3·25, 95% CI 1·18–8·93), in addition to lung function impairment, were clearly associated with bacterial infection. Current smoking has been related to bronchial colonization by pathogenic bacteria [21, 22], and a strong association

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Table 4. *Risk factors for* Pseudomonas aeruginosa *in COPD patients requiring admission for exacerbation*

	Sputum culture				
	Positive	Negative	Crude OR (95% CI)	Adjust. OR (95% CI)	*P*
N	12	78			
Age	69·3 (12·4)	67·2 (9·5)	1·02 (0·96–1·09)	—	—
Male	11 (91·7)	75 (96·2)	0·44 (0·04–4·61)	—	—
Current smoking	5 (41·7)	16 (20·5)	2·77 (0·77–9·88)	—	—
Passive smoking*	4 (33·3)	17 (21·8)	1·79 (0·48–6·68)	—	—
Alcohol, previous 2 weeks	5 (41·7)	21 (26·9)	1·94 (0·55–6·78)	—	—
Comorbidity	12 (100·0)	68 (87·2)	—	—	—
FEV1 %†	27·3 (7·4)	32·0 (16·8)	0·98 (0·93–1·02)	0·97 (0·91–1·02)	0·27
Body mass index	24·2 (6·1)	24·6 (5·1)	0·98 (0·87–1·11)	—	—
COPD-related visits last year					
>2 hospital admissions	2 (16·7)	33 (42·3)	0·27 (0·06–1·33)	—	—
>4 non-admiss. visits‡	3 (25·0)	34 (43·6)	0·43 (0·11–1·72)	—	—
Therapy					
Influenza vaccination	5 (41·7)	58 (74·4)	0·25 (0·07–0·86)	0·15 (0·03–0·67)	0·01
Domiciliary oxygen	3 (25·0)	30 (38·5)	0·53 (0·13–2·13)	—	—
Inhaled corticosteroids	5 (41·7)	41 (52·6)	0·64 (0·19–2·21)	—	—
Oral corticosteroids§	5 (41·7)	18 (23·1)	2·38 (0·67–8·42)	2·52 (0·58–10·84)	0·21
Rehabilitation	1 (8·3)	16 (20·5)	0·35 (0·04–2·93)	—	—
Antibiotics pr. 3 months	5 (41·7)	12 (15·4)	3·93 (1·07–14·44)	6·06 (1·29–28·44)	0·02
Poor compliance with inhalation	5 (41·7)	30 (38·5)	1·14 (0·33–3·93)	—	—

Multivariable logistic regression modelling adjusting for FEV1 % and all covariates showing association ($P \leqslant 0{\cdot}25$) in the univariate model.

* In current non-smokers.

† Available from 81 subjects.

‡ At emergency room or outpatient clinic.

§ More than 2 weeks last year.

between active smoking and *H. influenzae* infection in exacerbated COPD has been reported [10]. Additionally, our findings suggest that a subset of COPD patients whose compliance with treatment was poor, and for whom monitoring during stable periods might have been inadequate, may be at increased risk for infection.

We found that antibiotic treatment during the previous 3 months was related to *P. aeruginosa* infection (OR 6·06, 95% CI 1·29–28·44) and that the prevalence of this bacterial infection was lower in patients vaccinated against influenza (OR 0·15, 95% CI 0·03–0·67). These associations confirm an earlier study [8], which suggested that previous antibiotic treatment was related to the isolation of *P. aeruginosa* and other Gram negative bacteria. The apparent protective effect of influenza vaccination on *P. aeruginosa* infection has to our knowledge not been previously reported, and is consistent with influenza being a risk factor for pneumonia [23]. The association of some individual characteristics with the presence of *P. aeruginosa* may be significant in distinguishing patients with this infection and instituting specific anti-pseudomonal treatment.

We conclude that the prevalence of bacterial infection in exacerbated COPD patients requiring admission and reporting changes in their sputum will be higher when current smoking, poor compliance with inhalation therapy and severe lung function impairment are identified. *P. aeruginosa* infection should be suspected in patients who have been treated with antibiotics and in patients who have not been vaccinated against influenza.

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