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SHORT COMMUNICATION

Bacterial infection and risk factors in outpatients with acute exacerbation of chronic obstructive pulmonary disease: A 2-year prospective study

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Bacterial infection and risk factors in outpatients with acute exacerbation of chronic obstructive pulmonary disease: A 2-year prospective study
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Background and objectives: Acute exacerbations of COPD (AECOPD) are commonly observed in community-based patients worldwide. The factors causing exacerbation are largely unknown. This study was undertaken to determine the predominant bacterial pathogens cultured from sputum in community-based patients with AECOPD, to assess the risk factors associated with exacerbations and to compare these findings with published studies.
Methods: Forty-five patients with stable COPD were prospectively followed in the outpatients' clinic of King Abdulaziz University Hospital. At the first visit, personal data, CXR and measurement of baseline PEF were obtained from each patient. In the subsequent visits, sputum culture and CXR were carried out during exacerbations.
Results: Over a period of 24 months, patients made a total of 139 visits for exacerbations, and 69.8% had a positive sputum culture for a single pathogen. *Moraxella catarrhalis* (25.2%), *Pseudomonas aeruginosa* (12.2%) and *Haemophilus influenzae* (11.5%) were the most common isolated organisms. Patients with a lower level of baseline PEF had a significantly increased frequency of exacerbations ($r = 0.337$, $P = 0.024$). However, there was a weak correlation between exacerbation frequency and duration of COPD and exposure to cigarette smoking.
Conclusion There was a higher incidence of *Moraxella catarrhalis* and *Pseudomonas aeruginosa* than reported in previous studies. These findings should influence antibiotic selection for exacerbations. COPD patients with a low baseline PEF are at a higher risk of having repeated exacerbations and gram-negative pathogens.

Key words: acute exacerbation, AECOPD, bacterial culture, COPD, risk factor, Saudi Arabia.

INTRODUCTION

Acute exacerbation of COPD (AECOPD) is associated with increased morbidity, mortality, hospital admission and impairment of health-related quality of life.[1–5] AECOPD is characterized by an increased dyspnoea, sputum volume, sputum purulence and worsening of lung function.[6,7] Most AECOPD are triggered by respiratory infection.[8–10] Approximately 50% of these are caused by bacterial pathogens, 30% by viral infection and less than 10% by atypical bacteria.[10–12] In several studies, *Haemophilus influenzae*, *Streptococcus pneumoniae* and, to lesser extent, *Moraxella catarrhalis* have been reported to be the more common bacterial pathogens isolated during exacerbations.[10–15] *Pseudomonas aeruginosa* was less common and found in patients with severe airflow limitation, especially those who have been treated with antibiotics, and not vaccinated against influenza.[9,15,16] *Mycoplasma pneumonia* and *Chlamydophila pneumonia* may be responsible for less than 10% of exacerbations.[15,17–19] The average COPD patient experiences two to four exacerbations per year.[7] The more severe the COPD, the more frequent the exacerbations, hospitalizations and bacterial infections. The objectives of this study were to determine the predominant bacterial pathogens isolated from sputum from outpatients with AECOPD, to assess the risk factors that may be associated with exacerbations and to compare these findings with those reported in the literature.

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PATIENTS AND METHODS

A total of 45 stable COPD patients were recruited. All patients had regular follow up in the outpatients' clinic of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. The 30-month long study involved 6 months for patient recruitment. Each patient was followed for 24 months from the time of enrolment into the study. At the first visit, while stable, personal data including, age, gender, nationality, history of smoking (smoker, ex-smoker and non-smoker), duration of smoking, pack/years, duration of COPD, duration of follow up, measurement of baseline level of PEF and CXR were obtained and/or carried out for each patient. In subsequent visits, sputum culture and CXR were carried out for each patient during exacerbations. Diagnoses of COPD and that of AECOPD were made according to the American Thoracic Society guidelines.[7] An exacerbation was suspected as occurring whenever a patient experienced an increased dyspnoea, sputum production and sputum purulence (major symptoms), as well as cough, wheeze, sore throat and cold with nasal discharge or nasal congestion (minor symptoms). A patient was diagnosed as having an exacerbation in the presence of (i) two major symptoms or one major and two minors features; and (ii) clinical judgement of exacerbation by the patient's own chest physician. All patients who participated in the study gave consent. Patients were excluded from the study if they had bronchiectasis, asthma, pneumonia, interstitial lung disease, cancer, severe immunosuppression, or if they were on chemotherapy. All patients were monitored by the same physician in the course of the study. Each patient had been instructed to report to outpatient during exacerbation. PEF was measured using a Mini-Wright Peak Flow Meter (Clement Clarke International Ltd, Edinburgh Way Harlow, Essex, England, UK). Predicted values of PEF were obtained from the standard flow charts.[20] Patients with baseline PEF <250 L/min were considered to have severe COPD while those with a PEF >250 L/min had mild to moderate disease. Sputum during exacerbations was collected in sterile vials and sent to the microbiology laboratory within 10 min. Gram stain was carried out. Samples had to contain >25 leucocytes and <10 epithelial cells to be accepted for culture. The identification of bacterial growth was carried out by standard means.[21] Growth of a single bacterial pathogen was defined as monoculture whereas the presence of multiple organisms was considered a mixed culture. The organism with the most colonies was considered the predominant bacterium.

Data management and statistical analysis

Data management was carried out using SPSS 10 (Chicago, IL, USA). Descriptive statistics (mean, SD and frequencies) were carried out to describe the studied variables. χ^2-test was used from cross tabulation. The level of significance was set at $P < 0.05$ throughout the analysis. *T*-test and ANOVA were used to compare means. Correlations were carried out between quantitative variables.

RESULTS

A total of 45 patients with 139 acute exacerbations were evaluated prospectively. The mean age (mean ± SD) was 66.9 ± 11.4 years, 78% were Saudis and 71% were male. The mean duration of COPD was 13.3 ± 8.0 years, while the mean duration of follow up was 4.2 ± 1.98 years. The mean number of exacerbations per patient over the study period was 2.18 ± 2.3. Three-quarters of the patients were either current smokers (33.3%) or ex-smokers (40%), while the remaining (26.6%) were non-smokers. The mean duration of smoking was 28.7 ± 16.8 years and the mean pack-years of smoking was 73 ± 39.8. Of the 45 patients, 64.4% had severe disease (PFE < 250 L/min) (Table 1). Pathogens were isolated in 69.8% of the 139 AECOPD episodes. The most common pathogens were *Moraxella catarrhalis* (25.2%), *Pseudomonas aeruginosa* (12.2%) and *Haemophilus influenzae* (11.5%) (Table 2). There was a statistically significant correlation between baseline PEF and frequency of AECOPD. The correlation coefficient was $r = 0.337$ ($P = 0.024$) (Fig. 1). There was a weak but not statistically significant correlation between frequency of AECOPD and duration of COPD, duration of smoking and pack-years of smoking ($r = 0.153$, 0.221 and 0.200; $P = 0.316$, 0.145 and 0.266, respectively). (Table 3). The overall incidence of the most isolated organisms, in particular gram-negative, was higher among COPD patients with severe disease (Table 4).

Table 1 Baseline characteristics of patients ($n = 45$) with acute exacerbation of COPD

Characteristics	Findings *n*	%
Nationality		
Saudis	35	77.8
Non-Saudis	10	22.2
Age (mean ± SD), years	67 ± 11.4	
Gender		
Male	32	71.1
Female	13	28.9
History of smoking		
Smokers	15	33.3
Ex-smokers	18	40.0
Non-smokers	12	26.6
Severe COPD (PEF < 250 L/min)	29	64.4
Duration of COPD (mean ± SD) years	13.3 ± 8.0	
Duration of follow up (mean ± SD) years	4.2 ± 1.98	
Frequency of exacerbation (mean ± SD)	2.2 ± 2.33	
Duration of smoking (mean ± SD) years	28.7 ± 16.8	
Pack-year smoking (mean ± SD)	72.7 ± 39.8	
Baseline PEF L/min (mean ± SD)	230.7 ± 51.6	
Predicted PEF L/min (mean ± SD)	467.2 ± 15.9	

Table 2 Frequency of bacterial pathogens cultured from sputum during exacerbations ($n = 139$)

Bacterial pathogens isolated	*n*	%
Moraxella catarrhalis	35	25.2
Pseudomonas aeruginosa	17	12.2
Haemophilus influenzae	16	11.5
Alpha hemolytic streptococcus	10	7.2
Klebsiella pneumonia	6	4.3
Streptococcus pneumoniae	5	3.6
Acinetobacter	3	2.2
Pasteurella	3	2.2
Streptococcus group B	2	1.4
Escherichia coli	1	0.7
Normal flora	41	29.5
Total	139	100

Table 3 Correlation between frequencies of exacerbations, and PEF and other risk factors

Variables	*r*	*P*-value
Frequency of exacerbation with		
Age	–0.030	0.846
Baseline PEF	–0.337	0.024*
Duration of COPD	0.153	0.316
Duration of smoking	0.221	0.145
Pack-year smoking	0.200	0.266

*P-value is significant at <0.05.

Table 4 Distribution of the 139 isolated pathogens among cases of COPD patients by level of PEF

	COPD patients			
	PEF <250 L/min		≥250 L/min PEF	
Organism	*n*	%	*n*	(%)
Moraxella catarrhalis	28	80.0	7	20.0
Pseudomonas aeruginosa	14	82.4	3	17.6
Haemophilus influenzae	13	81.3	3	18.3
Haemolytic streptococcus	7	70.0	3	30.0
Klebsiella	5	83.3	1	16.7
Streptococcus pneumoniae	3	60.0	2	40.0
Acinetobacter	2	66.7	1	33.3
Pasteurella	2	66.7	1	33.3
Streptococcus group B	1	50.0	1	50.0
Escherichia coli	1	100.0	0	0.0
Normal flora	28	68.2	13	31.7

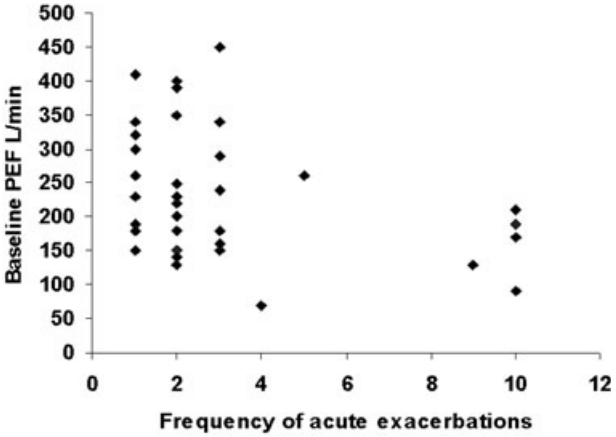

Figure 1 Correlation between baseline PEF and frequency of acute exacerbations. Correlation coefficient = 0.337, $P = 0.024$.

DISCUSSION

The main findings of the study were that (i) almost three-quarters of patients with exacerbation had a positive sputum culture for a single pathogen; (ii) *Moraxella catarrhalis, Pseudomonas aeruginosa* and *Haemophilus influenzae* were the most commonly isolated organisms; and (iii) patients with low baseline PEF had a significantly higher incidence of exacerbations. In practice, bacterial culture of expectorated sputum is valuable, easily carried out and a non-invasive way of obtaining information about infection of the airways in ambulatory care, and represents lower airway secretion flora.[22] Eighty per cent of the patients with a COPD exacerbation had bacterial infection with changes in their baseline sputum characteristics.[22] However, contamination with oropharyngeal secretions can occur. Therefore, bronchoscopy has been used in previous studies to obtain sterile sampling, particularly for those requiring hospitalization or mechanical ventilation.[22–24] The use of bronchoscopy was not feasible in an ambulatory care setting. In this study, 69.5% of exacerbations had bacterial pathogens cultured from sputum. This finding was comparable to that of previous studies where bacterial pathogens have been isolated in 50% to 80% of exacerbations.[13–16,24,25] In previous studies, isolation of *Pseudomonas aeruginosa* was less common and mainly cultured in patients having severe airflow limitation or those requiring mechanical ventilation.[15,16] In contrast, the current findings show a higher prevalence of *Pseudomonas aeruginosa*. Many of the patients had severe disease and/or were heavy smokers, while some used self-medicated antibiotics for exacerbations, which may explain the high prevalence of *Pseudomonas aeruginosa*. In previous studies, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* have been reported as the most common isolated pathogens during exacerbations.[13–16] However, in the current study, *Streptococcus pneumoniae* was rarely isolated, while *Moraxella catarrhalis* was cultured more frequently during exacerbations, findings comparable with some previous studies.[26–28] The higher prevalence of *Moraxella catarrhalis* may be related to several factors, including increased awareness of the organism, increased virulence caused by production of beta-lactamase and increased use of steroids.[10,27–29] These

findings are clinically important as they may influence the selection of antibiotics during management of exacerbations. Antibiotics covering gram-negative organisms, as well as *Pseudomonas aeruginosa*, might need to be selected empirically as the antibiotic of choice for treating outpatients with exacerbations. The role of viruses in COPD exacerbations is well established and accounts for almost 30% of exacerbations. Diagnosis can be obtained by detecting a fourfold rise in specific antibody titres and occasionally by culture and PCR assessment.[11,12,17] Influenza had the highest incidence among the isolated viruses, while parainfluenza, rhinovirus and corona virus were less common.[12] The significant incidence of influenza virus as a cause of AECOPD stresses the importance of yearly influenza immunization in these patients. Atypical bacteria are implicated in 5% to 10% of COPD exacerbations of which *Chlamydophila pneumoniae* has the highest incidence of isolated pathogens while *Mycoplasma pneumoniae* is more rarely observed.[17–19] However, in the current study, the role of bacteria has merely been evaluated. These results show, for the first time, a negative correlation between low baseline PEF and the frequency of exacerbation, emphasizing the importance of using simple pulmonary function testing in an outpatient setting to help predict which patients may be at high risk of exacerbation. In addition, the study revealed that less than 80% of the gram-negative pathogens were isolated in COPD patients with severe disease (PEF < 250 L/min), findings which have not been previously reported. As such, further studies are needed to confirm these results and to define their clinical significance. In common with other studies, age, duration of smoking and pack-year of smoking were not found to be risk factors for exacerbations.[1,4,30,31] Although not significant, current smokers and ex-smokers had a higher frequency of exacerbations than non-smokers. A high prevalence of *Pseudomonas aeruginosa* was observed and this information may result in changes to antibiotics selection for AECOPD. However, significant limitations, including a low number of patients as well as the risk of sputum contamination with oropharyngeal secretions, must be considered.

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