Respiratory Medicine (2003) **97**, 770–777

ELSEVIER

respiratoryMEDICINE

Bacterial infections in patients requiring admission for an acute exacerbation of COPD; a 1-year prospective study

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KEYWORDS
Chronic obstructive pulmonary disease;
Acute exacerbations;
Bacterial infections

Summary *Study objective*: To investigate the frequency of respiratory bacterial infections in hospitalized patients, admitted with an acute exacerbation of chronic obstructive pulmonary disease (COPD), to identify the responsible pathogens by sputum culture and to assess patient characteristics in relation to sputum culture results. *Methods:* We prospectively evaluated clinical data and sputum culture results of 171 patients, admitted to the pulmonology department of the University Hospital Maastricht with an acute exacerbation of COPD from 1st January 1999 until 31st December 1999. *Results:* Eighty-five patients (50%) had positive sputum cultures, indicating the presence of bacterial infection. Pathogens most frequently isolated were: *Haemophilus influenzae* (45%), *Streptococcus pneumoniae* (27%), and *Pseudomonas aeruginosa* (15%). Patients with more severely compromised lung function had a higher incidence of bacterial infections ($P = 0.026$). There were no significant differences in age, lung function parameters, blood gas results and length of hospital stay between patients with and without bacterial infection. There were no correlations between the type of bacteria isolated and clinical characteristics. *Conclusion:* Incidence of bacterial infection during acute exacerbations of COPD is about 50%. Patients with and without bacterial infection are not different in clinical characteristics or in outcome parameters. Patients with lower FEV_1 have a higher incidence of bacterial infections, but there is no difference in the type of bacterial infection. In the future, the pathogenic role of bacterial infection in exacerbations of COPD should be further investigated, especially the role of bacterial infection in relation to local and systemic inflammation.

Introduction

Chronic obstructive pulmonary disease (COPD) comprises a heterogeneous group of conditions, characterized by varying degrees of expiratory flow limitation. Exacerbations punctuate the clinical course of COPD in many patients. These episodes of acute exacerbation can vary considerably in severity: part of the exacerbations will remain unreported while some episodes require hospital admission. Hospital admission for acute exacerbations forms the major component of the economical burden of COPD in western countries.[1] These exacerbations are characterized by varying combinations of symptoms as increase in cough, sputum production, worsening of dyspnea or changes in sputum purulence.

Recent studies have indicated that health status of patients with COPD has been influenced by the presence and frequency of these acute

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0954-6111/03/$ - see front matter
doi:10.1016/S0954-6111(03)00026-X

exacerbations.[2,3] The exact role of periods of acute exacerbations in the pathogenesis of COPD remains unclear, especially the relationship between bronchial inflammation and lung defense during these possible noxious events.[4] Some studies have indicated that recurrent exacerbations may be associated with increased airway inflammation, although many factors may influence the state of inflammation in the airways.[5] Recent data also suggest the presence of decreased antiproteinase activity in sputum of patients with recurrent exacerbations.[4]

Exacerbations are not only heterogeneous in severity and symptom characteristics but are also in nature. Although several events may lead to acute exacerbations, respiratory tract infections are often considered as the initiating event contributing to the deterioration in the clinical condition. Especially, the role of bacterial infections and the value of antibiotic therapy have been a matter of debate for many decades.[6–8]

An important problem in defining the role of bacteria in these episodes of acute exacerbation is the bacterial colonization of the lower airways even in the absence of symptoms of an exacerbation.[7] Careful investigations have reported the presence of bacterial pathogens in only about 50% of exacerbations.[9–15] However, these studies have been performed in different populations of COPD patients, and most frequently in outpatients.

Recently, two studies have investigated the type of bacterial pathogens isolated in sputum of COPD patients, hospitalized for an acute exacerbation.[12,13] In these studies a correlation was found between lung function and the type of bacteria isolated: patients with more compromised lung function had a higher incidence of infections with *Pseudomonas aeruginosa* and other Gram-negative bacteria isolated from their sputum. These findings suggested that patients with more advanced lung disease may need a different pharmacological therapy than patients with milder disease.

The generalization of these findings as well as the interpretation of them as disease-specific findings are hampered by limited availability of data on distribution of bacterial flora in COPD patients from different geographical areas as qualitative differences in bacterial flora can be related to many other factors. Therefore, it seems interesting to investigate prospectively the prevalence of acute bacterial infections during these episodes of hospital admission as well as if specific patient profiles are related to a different pattern of microorganisms in patients admitted for an acute exacerbation of the disease.

Furthermore, we questioned if the presence of bacterial infection influences the clinical outcome of hospital admissions for acute exacerbations.

Material and methods

Study population and study design

All patients, admitted with an acute exacerbation of COPD to the pulmonology ward of the University Hospital Maastricht, between 1st January 1999 and 31st December 1999, were prospectively evaluated. All patients were diagnosed as having COPD, according to the criteria of the American Thoracic Society.[16] Acute exacerbation was defined by the presence of an increase in at least two of the three following symptoms: dyspnea, cough and sputum purulence.

Admission to the hospital was deemed necessary based on the clinical situation of the patient or the presence of complicating factors as respiratory failure. In all cases, the need for admission was decided by a senior chest physician, experienced in the management of COPD patients. Chest X-rays were performed in each patient on admission and patients with lobar infiltrates or radiologic signs of pneumonia on chest X-ray were excluded from the study.

Patients were included only once in the study even if hospitalized more frequently. For all included patients the following data were assessed: medical history, lung function measurements, blood gases, duration of hospital stay, previous treatment, chronic corticosteroid use and results of sputum cultures. Medical history, previous treatment and use of corticosteroids were recorded from the patients charts on standardized forms. Chronic use of oral corticosteroids was defined as the use of daily oral corticosteroids for at least 1 year in a dosage of at least 5 mg Prednisolone or equivalent. On admission, arterial blood gases at rest were assessed by puncture of the radial artery during room air breathing. Patients were discharged from the pulmonary ward by decision of a senior chest physician, unaware of the goals of the present study. Total duration of hospital stay was recorded, counting from the first day of admission before 0.00 h until the day of discharge.

Patients were treated with a standard protocol consisting of intravenous administration of corticosteroids and theophylline and nebulization of salbutamol and ipratropiumbromide as bronchodilating agents. O_2 was titrated by follow-up of blood gas values as well as continuous monitoring of

oxygen saturation. Antibiotics were not prescribed until the results of the sputum cultures were available, unless the clinical condition of the patient necessitated early intervention based on documented resistance pattern of isolated microorganisms.

Lung function data

Spirometries were performed daily during admission for the exacerbation. Spirometries were performed using the portable pneumotachograph from Jaeger pulmonary function equipment (Würzburg, Germany). The value after recovery, prior to discharge from the hospital was used in the analyses. Based on the ATS criteria,[16] lung function was rated in three stages of severity: stage I: FEV_1 of $\geqslant 50\%$ predicted, stage II: FEV_1 between 35% and 50% predicted, stage III: FEV_1 $\leqslant 35\%$ predicted.

Sputum cultures

At least one sample of spontaneously expectorated sputum for microbiologic evaluation was obtained in all patients during admission. This is part of a common medical practice in our hospital for patients admitted for an acute exacerbation, and also it is recommend in the recently published GOLD guidelines for the management of COPD.[17] Samples were collected in sterile sputum cups and sent to the laboratory within 1 h after expectoration.

A Gram stain of the sputum in the area of maximal purulence was examined for polymorphonuclear leukocytes and epithelial cells. The number of leukocytes was semiquantitatively described as: none, sporadic, few, moderate or many. A sputum sample was considered representative if many leukocytes were present in the absence of epithelial cells. Another portion of a documented purulent material was used for microbiological analysis. Sputa were processed according to standard microbiological methods.[18] A sputum culture was considered as positive (proving bacterial infection) if significant bacterial growth was present as defined by the number of bacteria (higher than 10^5 colony forming units = cfu) in a representative sample. Identified bacteria were classified into three groups: group 1 included *Haemophilus influenzae* and *Moraxella catarrhalis*, group 2 included *Streptococcus pneumoniae* and other Gram-positive cocci and group 3 included Pseudomonas and other Gram-negative microorganisms. Other identified bacteria are considered non-pathogenic microorganisms (NPMs), belonging to the oropharyngeal or gastrointestinal flora.

A microbial resistance pattern was available for all pathogens. For all pathogens resistance patterns were determined for Amoxicillin, Amoxicillin/Clavulanic acid, Doxycyclin and Co-trimoxazole. In case of isolation of Pseudomonas and other Gram-negative species resistance patterns to Gentamycin, Piperacillin, Ciprofloxacine, Ofloxacine and Cefuroxim were determined additionally.

Statistical analysis

The statistical analyses were performed using the Statistical Products and Service Solutions (SPSS; Chicago, IL, USA) for Windows Package. Groups were compared by analysis of variance (ANOVA). The χ^2 test was used to compare categorical variables. Results are presented as mean $\pm$ SD unless stated otherwise.

Results

Patient characteristics

Between 1st January 1999 and 31st December 1999 171 patients were included with acute exacerbation of COPD. Characteristics of the study population are summarized in Table 1. Most patients were elderly with severely impaired lung function (mean FEV_1 was 0.84 l or 34.6% predicted).

Hypoxia as well as hypercapnia were very common findings on admission; 141 (= 85%) of the patients had arterial oxygen tension <8.7 kPa, arterial carbon dioxide tension higher than 5.9 kPa was measured in 93 patients (= 55%).

Sixty-three patients (= 37%) had been treated with antibiotics prior to admission to the hospital. Prescribed antibiotics by general practitioners were: Doxycycline (37%), Amoxicillin (21%), Amoxicillin/Clavulanic acid (29%) and Azithromycine (10%). Information concerning the remaining 3% could not be retrieved. Forty-three percent of the patients had also received a boost of oral corticosteroids prior to admission.

Mean hospital stay was 11.7 days and median hospital stay was 10 days. Thirteen patients died during their hospital stay, resulting in an in-hospital mortality of 8%.

Seventeen patients were admitted to ICU because of progressive respiratory failure: In 15 patients failure of conservative treatment in the first 48 h necessitated referral to the ICU; in two patients clinical condition deteriorated after initial

Table 1 Clinical characteristics of the COPD population and the patients with and without bacterial infection

	Whole group ($n = 171$)	Negative sputum culture ($n = 86$)	Positive sputum culture ($n = 85$)	*P*-value
Age (years)	70.6±8.6	71.7±7.8	69.5±8.9	0.023
FEV_1 (l, % pred)	34.6±12.6	34.1±13.3	35.2±1.9	NS
PaO_2 (kPa)	7.49±2.2	7.16±2.0	7.82±2.5	NS
$PaCO_2$ (kPa)	6.74±2.1	6.12±2.1	6.66±2.2	NS
Hospital stay (days)	11.7±8.8	10.5±5.6	12.9±10.8	NS
Sex (M/F)	104/67	50/36	54/31	NS
Pretreatment with antibiotics (y/n)	63/108	30/56	33/52	NS
Pretreatment with corticosteroids (y/n)	73/98	29/57	31/54	NS
Chronic corticosteroids (y/n)	17/154	8/78	9/76	NS
ICU admission (y/n)	17/154	10/76	7/78	NS
Died during admission (y/n)	13/158	6/80	7/77	NS

improvement. Intubation and mechanical ventilation was necessary in 10 patients, four patients received non-invasive ventilation (BiPAP) and in three patients conservative treatment could be continued under close supervision. Patients transferred to ICU had a longer duration of hospital stay ($P = 0.005$; mean 17.3 days, median 15 days). One patient died during ICU admission (6%).

Microbiological analysis

Sputum cultures could be obtained in 142 patients (=83%). Other patients were unable to expectorate sputum spontaneously during hospitalization. Samples were considered not representative based on microbiological criteria in 54 cases.

In 85 of the 88 representative samples (97%) a significant bacterial growth was reported; in 61 samples (72%) there was growth of one single species in significant concentrations, in 22 samples (26%) there was growth of two different species in significant concentrations and in four samples (5%) growth of three different species in significant concentrations was present.

The most frequently isolated species were *H influenzae* (23 cases as single pathogen, 15 cases in combination with other pathogens, overall 38/85 cases or 45%) and *S. pneumoniae* (nine cases as single pathogen, 15 cases in combination with other pathogens, overall 24/85 cases or 28%).

P. aeruginosa was isolated in 13/85 cases (15%). Other bacteria isolated were: *M. catarrhalis* (three cases as single pathogen, two cases in combination, overall 5/85 cases or 6%), and *Klebsiella pneumoniae* (one case as single pathogen, three cases in combination, overall 4/85 cases or 5%). In 14/85 cases (16%) NPMs were found. These data are schematically presented in Fig. 1.

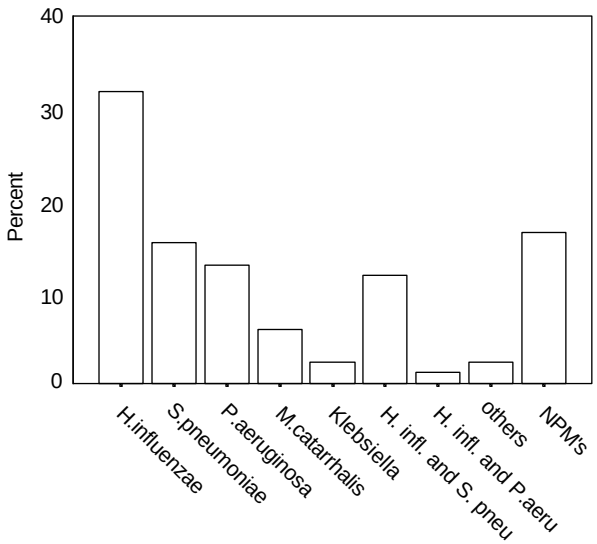

Fig. 1 Types of isolated microorganisms found during acute exacerbations of COPD.

No resistant strains of *S. pneumoniae* to Amoxicillin were isolated. For *H. influenzae* as well as for *M. catarrhalis* two β-lactamase producing strains were identified. No resistant Pseudomonas strains were isolated in the studied population. No significant differences were found in mean FEV_1, PaO_2 and $PaCO_2$ between the patients with and without positive sputum culture (Table 1).

A course of antibiotics or a boost of corticosteroids, prescribed prior to admission, did not influence the outcome of sputum cultures. 52.4% who had received antibiotics and 51.7% of patients who had received a boost of corticosteroids prior to admission had bacterial infection.

No difference in duration of hospitalization could be demonstrated between patients with and without bacterial infection on admission.

In the group of patients with positive sputum culture ($n = 85$), 10 patients were transferred to ICU of whom five patients were intubated for mechanical ventilation, while in the negative sputum culture group ($n = 86$) seven patients were transferred to ICU of whom four required mechanical ventilation.

Admission to ICU was not related to the presence and type of bacterial infection during exacerbation.

In comparison of patients with Pseudomonas infection to those with *H. influenzae* or *S. pneumoniae* infections, it was demonstrated that the former group was significantly older; other parameters were not different between these groups.

Lung function parameters

Based on lung function data obtained prior to discharge from the hospital, marked airflow obstruction was present in the majority of the patients: 81 patients (47%) had severe COPD 55 patients (32%) had moderate COPD and 22 patients (13%) had mild COPD, according to ATS staging. In 12 patients, no spirometric data could be obtained during hospital stay. Ten patients had an established diagnosis of severe COPD based on clinical records. In two patients, the diagnosis of COPD was established on clinical grounds and the information regarding medical history as obtained by their general practitioner (Fig. 2).

The incidence of bacterial infection was significantly related to the degree of airflow limitation

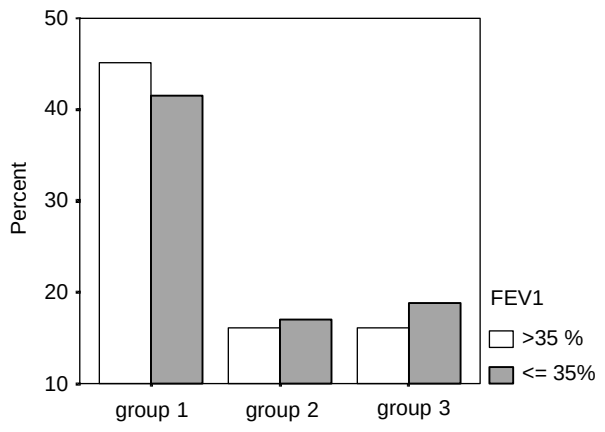

Fig. 2 Positive sputum cultures after stratification.

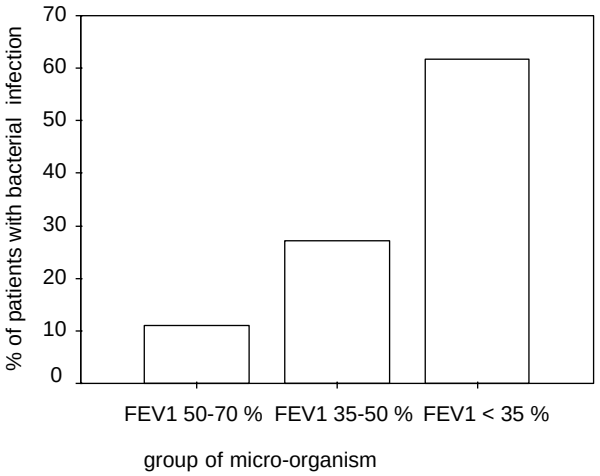

Fig. 3 Distribution of groups of bacteria isolated according to FEV_1 impairment.

(Fig. 3): patients with severe COPD had significantly more bacterial infections than patients classified as moderate ($P = 0.015$) or mild COPD ($P = 0.08$).

However, the type of bacteria isolated was not related to the degree of airflow limitation (Fig. 3).

Discussion

The present study confirms previous data reporting a higher incidence of bacterial infections in patients with a severe impairment in lung function during hospital admissions for acute exacerbations. However, no relationship between the type of bacteria isolated and the degree of lung function impairment could be demonstrated. The presence of bacterial pathogens was found in 50% of all admitted patients. No differences in clinical characteristics could be demonstrated between patients with and without isolation of bacterial pathogens neither with the type of bacterial pathogens. Microorganisms most frequently isolated were *H. influenzae* (45%) and *S. pneumoniae* (27%). Other pathogens isolated were *P. aeruginosa* (15%), *M. catarrhalis* (6%) and *K. pneumoniae* (5%). The presence of bacterial pathogens did not influence the clinical outcome defined by the length of hospital stay and the need for ICU admission.

One of the most important findings in the present study is the relation between the occurrence of bacterial infections and the degree of airflow

limitation: patients with a lower FEV_1 had a higher incidence of bacterial infection. This is in line with previous studies on the prevalence of bacteria in stable COPD patients.[8]

However, opposite to previously reported data we found no shift in the type of microorganism isolated in patients with more severely compromised lung function.[12,13] Indeed, both Eller and Miravitlles reported in patients with lower FEV_1 a higher incidence of Pseudomonas and Enterobacteriacae in their sputum. They hypothesized a possible relationship between the decline in lung function and occurrence of Pseudomonas and other Gram-negative species in sputum. Our data were even obtained in patients with more severely compromised lung function.

The incidence of *Pseudomonas* infections in our study was comparable with the data reported by Miravitlles, but markedly lower than in the study of Eller. Further data with more specific characterization of the patients suffering from acute exacerbations will be required in order to relate these findings to the disease condition itself. The presence of bronchiectasis,[19] nutritional status,[20] as well as previous use of antibiotics[21] can influence the type and frequency of colonization of the airways in COPD.

Remarkably, the incidence of positive sputum cultures in half of our patient population was quite similar to previous data.[2,10,14,15] In exacerbated outpatients, prevalence of positive bacterial cultures, obtained by protected specimen brush, was 51.6%.[10] In a bronchoscopic study of 54 mechanically ventilated patients with acute exacerbation of COPD, bacterial infection was found in 50% of patients.[14] In another study among mechanically ventilated patients using protected specimen brush, Fagon et al.[22] reported distal bronchial infection in 50% of patients during acute exacerbation. In a large study of 1016 in-patients with acute exacerbation respiratory infection was found in 47% of sputum cultures.[15] Therefore, it seems a consistent finding that bacterial infection is present in 50% of exacerbations, in hospital as well as in outpatient populations.

However, it remains difficult to distinguish bacterial colonization of the lower airways from an actual bacterial infection. In a bronchoscopic study among 18 stable COPD patients, using protected specimen brush samples, Cabello et al.[11] found that the distal airways were colonized (defined as $\geqslant 10^2$ cfu/ml) in 83% of COPD patients. Quantitative cultures of BAL samples in the same patient group remained negative in 88%, suggesting colonization rather than infection. In another study using protected specimen brush samples, Monso et al.[10] found positive cultures in 25% of stable COPD patients and 52% of exacerbated COPD patients. In the stable COPD patients, concentrations of bacteria were much lower, again indicating colonization instead of bacterial infection.

Besides differences in quantity of isolated microorganisms, recent studies suggest differences in the level of inflammation in stable COPD patients as well as during exacerbations between both conditions of the presence of bacteria in the airways. Bresser et al.[23] demonstrated that persisting strains of *H. influenzae* induce a weaker inflammatory response than non-persisting strains, while the local airway inflammation in COPD patients clinically infected with *H. influenzae* is much more pronounced.[24] Sethi et al.[25] demonstrated that exacerbated chronic bronchitis patients with *H. influenzae* and *M. catharralis* isolated from sputum had increased airway inflammation when compared to pathogen-negative exacerbations.

Other studies indicate that bacterial infection contributes significantly to the inflammatory process in the airways. In acute exacerbations of COPD associated with *H. influenzae* infection, an increase in sputum IL-8, TNF-α and neutrophil elastase was found in contrast to exacerbations without bacterial infection, indicating increased airway inflammation in the presence of *H. influenzae*.[26] This inflammatory process in the airway continues despite antibiotic and steroid therapy for exacerbations, as was demonstrated by unchanging sputum cell counts during the course of an exacerbation.[27]

However, the possible role of bacterial infections in the pathogenesis of acute exacerbations is still incompletely understood.

In the present study, the outcomes in terms of hospital stay or subsequent need for ICU admission were not related to the presence or the type of bacterial infections. Our findings are in line with the disputed role of antibiotics in the treatment of acute exacerbations. Studies concerning the effect of antibiotic treatment have shown either no benefit or minimal clinical benefit from antibiotic treatment.[7] Meta-analysis of randomized controlled clinical trials demonstrated a clinically unimportant improvement in patients receiving antibiotics.[28] A recently performed meta-analysis on antibiotic treatment in acute exacerbations concluded that patients with more severe exacerbations are more likely to benefit from antibiotic treatment.[29]

A recent study in exacerbated outpatients by Adams et al.[9] demonstrated lower relapse rates in outpatients treated with antibiotics, compared to patients untreated with antibiotics, but even

higher relapse rates in patients treated with Amoxicillin. These results indicate that type of antibiotics used to treat acute exacerbations have an impact on the failure rate.

In this respect, it is interesting to compare exacerbations of COPD to ventilator-associated pneumonia (VAP), a combination of clinical parameters in mechanically ventilated patients, that is presumed to be caused by bacteria and treated with antibiotics. In a recent bronchoscopic study among VAP patients, using protected specimen brush and BAL samples, bacterial infection was not proven in 43% of patients and withholding antibiotics in these patients had no effect on outcomes.[30] In another bronchoscopic study of VAP patients, the bacterial burden was not correlated with inflammatory mediators or with patient outcome.[31]

Some limitations of the present study need further discussion. Spontaneously expectorated sputum was used for microbiological sampling, in contrast to for example induced sputum or bronchoscopic sampling. The suitability of sputum samples to analyze bacterial infection is a matter of debate. Recently, a good concordance between the results of two sampling methods, valid sputum samples and quantitative protected specimen brush, was shown.[32] At present, especially in patients with severe COPD, spontaneously expectorated sputum seems a clinically reliable method to assess the presence and type of bacterial infections when other methods have to be avoided.

The present study has not included data on viral infections or infections with atypical organisms like Chlamydia and Mycoplasma. The presence of viral infection and Mycoplasma and Chlamydia during COPD exacerbations has been evaluated in different studies. In an outpatient population of mild-to-moderate COPD exacerbations, incidence of *Chlamydia pneumoniae* was found to be 4%.[33] In a study of mechanically ventilated patients with acute exacerbations of COPD, an incidence of *C. pneumoniae* of 18% was found.[14] The same study found no evidence for *Mycoplasma pneumoniae* infection and an incidence of 16% for respiratory viruses. In a Turkish study of outpatients with acute exacerbation, incidence of *C. pneumoniae* was 22% and *M. pneumoniae* incidence was 6%.[34]

So far, most studies concerning respiratory pathogens have been performed in either outpatient populations with mild exacerbation, or mechanically ventilated patients with severe exacerbations in an ICU setting. Neither of these populations can be considered representative for the majority of admissions for COPD exacerbations in a clinical setting, as in the present study. Therefore, the role of these non-bacterial pathogens in the pathogenesis of COPD exacerbations needs further exploration.

The present study indicates that the role of bacterial infections in the complex pathogenesis of COPD exacerbations as well as its clinical significance needs further evaluation in the near future and cannot be restricted to the limited discussion of the role of antibiotic treatment in the management of these acute events in the clinical course of patients with acute exacerbations. Especially, the role of bacterial infections in relation to the local and systemic inflammatory response has to be unraveled. The impact of acute exacerbations on the socio-economic burden of this disease as well as on the health status of the individual patient urgently needs to prioritize acute exacerbations in order to better understand the natural course of COPD.

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