A Prediction Model for Bacterial Etiology in Acute Exacerbations of COPD

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Abstract

Objectives: Bacteria play a leading role in acute exacerbations of chronic obstructive pulmonary disease (COPD), but we lack predictors of bacterial etiology. We developed a prediction model for infection with gram-negative enteric bacteria (GNEB) and *Pseudomonas aeruginosa*.

Methods: Clinical presentation, sputum characteristics, microbial sputum patterns, lung function and previous and concomitant medication were prospectively recorded in patients with moderate to severe exacerbation of COPD. Risk factors for a specific bacterial etiology were c alculated and a prediction model developed.

Results: A total of 193 patients with acute exacerbation were included. In 121 (62.6%) of them a microbial etiology could be identified, most frequently *Haemophilus influenzae* (32 strains), *Streptococcus pneumoniae* (22 strains) and *P. aeruginosa* (12 strains). Multivariate analysis identified severe airflow obstruction and use of systemic steroids as predictors for exacerbation due to gram-negative enteric bacilli and *P. aeruginosa*. A prediction model including FEV1 < 35% of predicted value, systemic steroid use and prior antibiotic therapy within preceeding 3 months had a negative predictive of 89%, being a helpful tool in excluding patients at risk of exacerbation due to gram-negative enteric bacilli and *P. aeruginosa* when all criteria are absent.

Conclusion: A simple prediction model based on three factors may identify COPD patients at low risk for exacerbations with gram-negative enteric bacilli and *P. aeruginosa*. Bacterial Etiology in COPD Exacerbations.

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Introduction

Chronic obstructive pulmonary disease (COPD) represents a substantial and increasing health burden worldwide [1]. Acute exacerbation represents the most important single factor for deterioration in quality of life and increase in symptoms [2]. Infection is considered the leading cause of exacerbation, with a bacterial etiology in approximately 50% of cases [3, 4]. Meta-analyses of 11 randomized, placebo-controlled studies found antibiotic therapy beneficial in specific settings of acute exacerbations [5, 6]. A general trend indicated that patients with a more severe illness were most likely to benefit from antibiotic therapy. In a subset of patients, whose exacerbations were characterized by a combination of increased dyspnoea, increase in sputum volume and purulence in sputum quality, antibiotic therapy was found to be most beneficial. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most prevalent bacteria in acute exacerbation. These findings have guided recommendations for empiric antibiotic therapy in COPD [5, 7, 8]. On the other hand, several reports have suggested that in patients with advanced stages of COPD and with severe exacerbation, gram-negative enteric bacilli and other gram-negative rods, including *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* gain relevance [9–11]. In times of increasing bacterial resistance and limited economic resources comprehensive criteria are needed to direct empiric antibacterial therapy.

We studied prospectively impact of severity of disease, smoking habits, concomitant disease, concomitant medication and other possible modifying factors on microbial patterns in acute exacerbation of COPD. Further, we developed a prediction model with easily accessible criteria to identify patients at risk for infection with gram-negative microorganisms including *P. aeruginosa*.

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Table 1
Characteristics of patients presenting with acute exacerbation of COPD.

Characteristics	Positive bacteriology	Negative bacteriology	p-value
N	121	72	
Female sex, n (%)	49 (40.5)	33 (45.8)	NS
Age, years (range)	60.6 (42–81)	61.8 (43–85)	NS
Smoking history			
Current smoker, n (%)	60 (49.6)	32 (44.4)	NS
Former smoker, n (%)	34 (28.8)	23 (31.9)	NS
Non-smoker, n (%)	19 (15.2)	12 (16.7)	NS
No data	8 (6.4)	5 (6.9)	
Cumulative dose, PY (range)	47.4 (4–180)	47.1 (5–130)	NS
Exacerbation type (Winnipeg)			
Type 1, n (%)	87 (70.4)	29 (40.3)	< 0.001
Type 2, n (%)	33 (28.8)	31 (43.1)	
No data, n (%)	1 (0.8)	12 (16.7)	
Antibiotics prior to inclusion, n (%)	21 (17.4)	25 (34.7)	0.02
FEV1 absolute [in l], mean ± SD	1.33 ± 0.54	1.30 ± 0.64	NS
FEV1 % predicted, mean ± SD	48.6 ± 20.2	48.9 ± 21.7	NS
PEF [in l/s], mean ± SD	3.58 ± 1.49	3.47 ± 1.67	NS
RV%TLC, mean ± SD	58.1 ± 10.7	58.5 ± 15.3	NS

Material and Methods

Study Population and Study Design

From January 1997 to April 2001 patients admitted to our 250-bed chest-hospital and patients presenting to their lung specialist as outpatients with moderate to severe acute exacerbation of COPD were prospectively included into the study. The study was approved by the local ethics committee and written informed consent was obtained from each patient prior to inclusion according to the Declaration of Helsinki.

Definition of severity of airflow limitation was according to the American Thoracic Society [12]. Severity of exacerbation was rated according to Anthonisen's criteria (Winnipeg criteria) [13] that include worsening of dyspnoea, increase of sputum purulence and increase of sputum volume. Type 1 exacerbations (severe) included all three clinical findings, type 2 exacerbations (moderate) exhibited two clinical findings. Patients with type 3 exacerbations (mild) were not included. Each patient was only included once. Asthma, inappropriate lung function testing, radiographic infiltrates, CT-evidence of bronchiectasis, bronchial carcinoma, and cystic fibrosis were exclusion criteria.

Documentation of Data

Demographic data, history of COPD (age above 40 years, smoking history, at least 3 years of continuous cough and sputum production), current clinical and laboratory findings, any antibiotic treatment within the last 3 months, inhaled and/or systemic steroid use (systemic use was defined as > 10 mg prednisolone daily in the last 2 weeks), smoking habits, prior hospitalization within the last 3 months and underlying diseases were recorded. Lung function testing for inpatients was performed close to discharge, outpatients were tested after improvement, using standard pulmonary function equipment. Alternatively, lung function data from a stable phase of COPD within 6 month prior to hospitalization were required.

Bacteriological Analysis

Bacteriologic samples were processed in a single microbiologic institution. Sputum was macroscopically rated as purulent or mucoid. Microscopic evaluation was done according to the criteria of the American Society for Microbiology [14]. At least 25 granulocytes and less than 25 squamous epithelial cells in at least 5 low power fields (× 100) were considered of acceptable quality and further processed.

Standard quantitative bacterial cultures and identification procedures were performed. At least 10^6 cfu/ml indicated significant growth. When more than one organism was recovered from a single specimen or in sequential specimens before antibacterial therapy, (1) the predominant species was considered the leading pathogen, (2) by identical density, the organism of Group 3 was further considered.

Categorization of potential pathogenic microorganisms (PPMs) followed criteria suggested by *Eller* et al. [9]:

Table 2
Microorganisms isolated in patients with acute exacerbation of COPD.

Group 1, n (%)	31 (25.6%)
Streptococcus pneumoniae	22
Staphylococcus aureus	9
Group 2, n (%)	53 (43.8%)
Haemophilus influenzae	32
Haemophilus parainfluenzae	2
Moraxella catarrhalis	19
Group 3, n (%)	37 (30.6 %)
Pseudomonas aeruginosa	12
Klebsiella pneumoniae	4
E. coli	4
Serratia marcescens	4
Neisseria meningitidis	6
Stenotrophomonas maltophilia	1
Hafnia alvei	1
Klebsiella oxytoca	1
Proteus mirabilis	1
Enterobacter spp.	3

Group 1: gram-positive pathogens (pneumococci, *Staphylococcus aureus*); Group 2: *H. influenzae*, *Haemophilus parainfluenzae*, and *M. catarrhalis*; Group 3: gram-negative enteric bacilli, *Neisseria meningitidis*, *P. aeruginosa*, and *S. maltophilia*. Other pathogens were considered non-PPMs.

Statistical Analysis

Results are expressed as means ± SD. Categorical variables were compared using the Chi-square test or Fisher's exact test, when appropriate. Continuous variables were compared using the unpaired Student's t-test or the Mann–Whitney non-parametric test, when appropriate. Multiple comparisons were done by ANOVA with Bonferroni post hoc correction. Absolute and relative FEV1 for the group 3 of pathogens were further dichotomized by means of ROC curve analysis. Multivariate analysis was performed using logistic regression models. Bacteria of Group 3 were used as the dependent variable. Variables with a p-value < 0.1 in univariate analysis were entered in the multivariate analysis. The level of significance was set at < 0.05. Operative indices for variables independently associated with bacteria of Group 3 were calculated.

Results

Patients

A total of 291 patients were screened for this study, 225 subjects as inpatients and 66 individuals as outpatients. Upon further evaluation, 98 patients were excluded for violation of inclusion criteria or meeting of exclusion criteria. 29 (10.0%) individuals did not meet the required criteria for moderate to severe exacerbation as defined above, 26 subjects (8.9%) had pulmonary infiltrates, 16 patients (5.5%) had a history of or newly detected bronchiectasis and 22 (7.6%) did not provide sufficient lung function data. Three patients (1.0%) suffered from bronchial carcinoma and 2 (0.7%) subjects had mycobacterial disease.

Demographic Data

Demographic comparison did not reveal significant differences in patients with or without positive bacteriology in respect to age, sex, smoking habits or severity of underlying airflow obstruction or emphysema (Table 1). There was a higher rate of patients without identification of bacteria in sputum, who were treated with at least one antibacterial substance prior to inclusion into this study ($p = 0.02$). Non-smokers were equally frequent in both observation Groups with an average of 16.1% (n = 31) and tended to present with a higher proportion of mild (n = 21, 67.7%) than moderate (n = 6, 19.4%) or severe (n = 4, 9.6%) airflow limitation ($p < 0.001$).

Bacteria Retrieved from Sputum Samples

In 121/193 patients, bacteria were cultured in sputum samples that fulfilled the ASM requirements for suitable quality [14]. The isolated microorganisms are shown in table 2.

In 13 subjects, more than a single PPM was identified. In 11 cases, two pathogens were isolated, in two cases, three bacterial species were present. In three samples with two pathogens, both species were present in a concentration above the threshold of significance of 10^6 cfu/ml, in one case with three bacterial entities, all species, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were quantified with at least 10^7 cfu/ml.

Univariate Analysis of Factors Affecting Bacteriologic Outcome

Patients with bacteria of Groups 1 and 2 were compared to patients with bacteria of Group 3 (Table 3). FEV1 of < 35% of the predicted value as well as low absolute FEV1 and FEV1%VC were strongly associated with presence of bacteria of Group 3 ($p < 0.001$). Subjects presenting with hypercapnia ($PaCO_2 > 45$ mmHg) ($p = 0.02$), as well as subjects with the use of antibiotics prior to inclusion were more likely to have bacteria of Group 3 ($p = 0.035$). The use of systemic steroids was significantly associated with the isolation of microorganisms of Group 3 ($p \leq 0.001$). Prior hospitalization and any number of exacerbations within 12 month prior to inclusion reached borderline significance for the Group 3. Individuals using inhaled steroids alone were more prone to have bacteria of Group 1 or 2 isolated from their sputum than bacteria of Group 3. Active smokers were more likely to have bacteria of Groups 1 and 2, but not Group 3 pathogens ($p = 0.036$). Patients with bacteria of Group 3 had a longer mean lifetime history of cigarette use ($p = 0.031$).

Airflow Obstruction and Bacterial Etiology

ROC curve analysis revealed an FEV1 of less than 1,100 ml as the best predictor for the presence of Group-3 bacteria with a sensitivity of 81% (95% CI 66–94%) and a specificity of 66% (95% CI 55–76%). A FEV1 of < 37.2% of the predicted value achieved a somewhat higher specificity of 82% (95% CI 72–90%) but a lower sensitivity of 74% (95% CI 55–88%) in predicting bacteria of Group 3 in acute exacerbation. Figure 1 shows the distribution of bacteria according to the extent of underlying airflow obstruction.

Multivariate Analysis of Factors Affecting Bacterial Etiology

Multiple logistic regression analysis included an infection of bacteria of Group 3 as the dependent variable and used variables that achieved significance as predictors of a specific eti-

Table 3
Univariate analysis of modifiying factors in cases with bacteria of Group 1/2 and Group 3.

Characteristic or parameter	Group-1/2 bacteria (n = 84)	Group-3 bacteria (n = 37)	p-value
Sex female, n (%)	36 (42.9)	13 (35.1)	NS
Age >65 years, n (%)	35 (41.7)	13 (35.1)	NS
Any smoking history	60 (78.9)	34 (91.9)	0.084
Active smoker, n (%)	44 (73.3)	16 (47.1)	0.036
Ex-smoker, n (%)	16 (26.7)	18 (32.9)	NS
Cumulative dose (PY), mean ± SD	31.8 ± 31.6	47.1 ± 35.1	0.038
Body mass index			
BMI, mean ± SD	25.5 ± 5.1	24.8 ± 6.2	NS
BMI < 19, n (%)	9 (10.8)	7 (20.0)	NS
BMI > 25, n (%)	44 (53.0)	15 (42.9)	NS
Co-morbidities			
Hypertension, n (%)	17 (20.2)	11 (29.7)	NS
Diabetes mellitus, n (%)	14 (16.7)	9 (24.3)	NS
Renal disease, n (%)	2 (2.4)	3 (8.1)	NS
Concomitant medication			
Systemic steroids, n (%)	32 (40.0)	29 (78.4)	< 0.001
Any steroid use, n (%)	52 (65.0%)	33 (89.2%)	0.006
Antibiotics prior to inclusion, n (%)	11 (13.9)	10 (31.3)	0.035
Prior hospitalization, n (%)	34 (81.0)	28 (96.6)	0.052
Exacerbation (last 12 months), n (%)	22 (68.8)	20 (90.9)	0.054
Lung function parameter			
FEV1 absolute (l), mean ± SD	1.44 ± 0.53	1.08 ± 0.47	< 0.001
FEV1 % predicted, mean ± SD	53.2 ± 20.4	37.0 ± 15.4	< 0.001
FEV1 (< 35% of predicted), n (%)	13 (15.5)	21 (56.8)	< 0.001
RV % TLC, mean ± SD	56.0 ± 10.3	63.7 ± 9.7	0.02
Blood gas analysis			
Hypoxia ($PaCO_2$ < 60 Torr), n (%)	15 (33.3)	11 (37.9)	NS
Hypercapnia ($PaCO_2$ > 45 Torr), n (%)	9 (20.0)	13 (44.8)	0.02
Laboratory testing			
Leucocyte count, mean ± SD	10.7 ± 3.7	12.1 ± 4.8	NS
Non-segmented granulocytes, mean ± SD	0.4 ± 1.4	1.1 ± 1.8	NS
C-reactive protein, mean ± SD	48.7 ± 126	75.4 ± 174	NS
Hemoglobin (g/dl), mean ± SD	14.4 ± 1.6	14.5 ± 1.8	NS

Group 1/2: *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis;* Group 3: gram-negative enteric bacilli, *P. aeruginosa, Stenotrophomonas maltophilia*

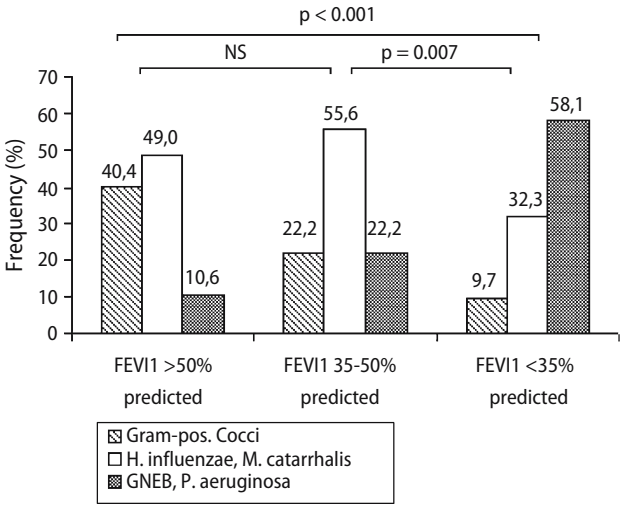

Figure 1. Potential pathogenic microbes isolated from sputum in acute exacerbation of COPD according to severity of airflow limitation.

ology in the univariate analysis. Only an impairment of FEV1 to less than 35% of the predicted value and use of systemic steroids was independently associated with isolation of Group 3 including *P. aeruginosa* in sputum of patients with acute exacerbation. Results are presented in table 4.

Prediction Model for Bacterial Etiology in Acute Exacerbation

A simple prediction model for bacterial etiologies in infection used three equal criteria. Severe airflow obstruction (FEV1 less than 35% predicted) and the use of systemic steroids were identified as independent determinants in the multivariate analysis and "antibacterial therapy prior to inclusion" served as an additional variable. Operative indices are given in table 5. The overall sensitivity and positive predictive value of the prediction model remained relatively low with the use of either two or all three criteria. Nevertheless, the model exhibited a specificity of 96% to predict the presence of Group 3 of bacteria, including *P. aeruginosa* when all three criteria were present. A negative predictive value of 89–95% indicated that more complicated pathogens were unlikely to be a cause of infection when only one or none of the three criteria were present.

Discussion

Based on data of a prospective study we developed a prediction model that includes three parameters (FEV1 < 35% of predicted value, systemic steroid use and prior antibiotic therapy in the preceeding 3 months). This model has a negative predictive of 89–95%, being a helpful tool in excluding patients at risk of exacerbation due to gram-negative enteric bacilli and *P. aeruginosa* when all criteria are absent.

Bacterial infection as a frequent cause of acute exacerbation is now well established in the general understanding of COPD [4, 15]. However, determining the precise role of bacterial infection in COPD is made difficult by two facts: (1) bacterial colonization of the lower airways is frequent in patients with stable COPD, and (2) the difficulty to obtain valid respiratory samples from patients with an acute deterioration of respiratory performance. Using protected specimen brushing, colonization rates are 25–40% in subjects with stable mild to moderate COPD [16, 17], but also in asymptomatic smokers [18]. Pathogens in these studies comprised organisms that are commonly also found in acute exacerbations.

Sethi et al. [19] have demonstrated that repetitive identification of bacteria of identical species in COPD patients does not argue against their causative role in acute exacerbation, since acquisition of a genotypically new strain within an identical species was significantly associated with an acute exacerbation. The same group argued for bacteria's role in exacerbations by demonstrating that a specific immune response to *H. influenzae* is statistically more frequent in cases with an exacerbation than in cases with bacteria present but no exacerbation [20].

Severity of airflow obstruction as a predictor for microbial patterns in exacerbations has been assessed by several investigators [9–11, 21, 22]. Despite differences in study design, study populations, and sampling techniques, the microbial patterns in mild to severe obstruction were comparable between the studies. The reason why severe airflow limitation is correlated with bacteria different from pathogens in mild to moderate obstruction is unresolved. Several factors have been implicated. Repetitive use of antibiotics in patients with frequent exacerbations might drive colonizing pathogens towards more resistant gram-negative species, including organisms with complicated resistance patterns, e.g., *P. aeruginosa* or

Table 4
Factors independently associated with identification of gram-negative enteric bacteria or *P. aeruginosa* (multiple logistic regression analysis; independent variable of this analysis is bacteria of Group 3).

Dependent variable	Significance	OR	95% CI of OR	
			Upper value	Lower value
FEV1 < 35% predicted	0.017	5.9	1.4	25.4
Systemic steroids on admission	0.017	8.4	1.5	48.6

OR: odds ratio; CI: confidence interval

Table 5
Predictive model of infection with GNEB and *P. aeruginosa* based on three variables.

Number of variables[a] present	Sensitivity % (n/total)	Specificity % (n/total)	Positive predictive value % (n/total)	Negative predictive value % (n/total)
1	89 (23/26)	40 (59/147)	21 (23/111)	95 (59/62)
2	62 (16/26)	75 (110/147)	30 (16/53)	92 (110/120)
3	31 (8/26)	96 (142/147)	61 (8/13)	89 (142/160)

[a] Variables consist of FEV1 < 35% predicted, use of systemic steroids at presentation and use of antibacterial substances prior to presentation

S. maltophilia [4]. Our data support this view in part. While prior use of antibiotics was correlated with the isolation of gram-negative enteric bacteria (GNEB) and *P. aeruginosa* ($p = 0.035$), previous hospitalization and exacerbation within 12 month prior to inclusion only achieved borderline significance. Furthermore, in the group of the gram-negative microorganisms were also included a number of patients with exacerbation due to *N. meningitidis*, which is usually a non-problematic pathogen.

Deterioration of lung function is accompanied by chronic inflammation, impaired local immune responses and damage to bronchial and parenchymal structures. These alterations might provide a microenvironment particularly suitable for adherence and survival of more complicated pathogens [23]. Although this view is intriguing, it requires investigative effort to provide more insight into mode of action. The connection between impairment of lung function and bronchiectasis is well documented [24]. Furthermore, in some cases unsuspected bronchiectasis has been identified in patients with recurrent exacerbations caused by *P. aeruginosa* [25]. However, we carefully excluded patients with documented bronchiectasis in order to avoid this overlap.

Despite convincing evidence to restrict inhaled glucocorticoids to defined subsets of patients [26–29] and reports that support a restricted use of systemic steroids [30], the majority of our patients (72%) had received either inhaled or systemic glucocorticoids or a combination of these. The use of systemic steroids was independently associated with the presence of Group 3 bacteria. This is in accordance with the findings of *Eller* et al. [9], who suggested a higher chance for isolation of gram-negative enteric bacilli or *Pseudomonas* spp. in COPD patients receiving systemic glucocorticoids.

We developed a simple model to predict the likelihood of an exacerbation with GNEB and *P. aeruginosa*. It includes parameters that can be easily assessed upon first patient-physician contact. Apart from the two identified independent risk factors we included the parameter "prior use of antibiotics" on the grounds of its proven relevance as a predictor of etiology in community acquired pneumonia [31]. The strength of our model was to predict absence of GNEB and *P. aeruginosa* as bacterial entities in acute exacerbation when either two or three of the criteria were absent. The positive predictive value and the model's sensitivity for a more complicated bacterial etiology were weak, probably owing to the limited number of patients that we investigated. Although this model appears as a potentially helpful tool to assess an individual's risk for a more severe bacterial etiology in acute exacerbation, it requires confirmation in a substantially larger population of COPD patients.

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