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# Clinical Predictors of Bacterial Involvement in Exacerbations of Chronic Obstructive Pulmonary Disease

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(See the editorial commentary by Niederman on pages 987–9)

**Background.** The wide use of antibiotics for treatment of exacerbations of chronic obstructive pulmonary disease (COPD) lacks evidence. The efficacy is debatable, and bacterial involvement in exacerbation is difficult to verify. The aim of this prospective study was to identify factors that can help to estimate the probability that a microorganism is involved in exacerbation of COPD and, therefore, predict the success of antibiotic treatment.

**Methods.** Clinical data and sputum samples were obtained from 116 patients during exacerbation of COPD. Bacterial infection was defined by the abundant presence of  $\geq 1$  potential pathological microorganism in relation to the normal flora in sputum.

**Results.** Of 116 exacerbations, 22 (19%) had bacterial involvement. The combination of a negative result of a sputum Gram stain, a relevant nonclinical decrease in lung function (compared with baseline measurements), and occurrence of  $< 2$  exacerbations in the previous year were 100% predictive of a nonbacterial origin of the exacerbation. The presence of all 3 of these clinical characteristics yielded a positive predictive value of 67% for a bacterial exacerbation.

**Conclusions.** Patients presenting with an exacerbation who have a negative result of a sputum Gram stain, do not have a clinically relevant decrease in lung function, and who have not experienced  $< 2$  exacerbations of COPD in the previous year do not require antibiotic treatment. A treatment protocol taking into account these variables might lead to a 5%–24% reduction in unnecessary treatment with antibiotics, depending on actual prescription rates.

The clinical course of chronic obstructive pulmonary disease (COPD) is, despite optimal pharmacological treatment, one of gradual progressive impairment, which may lead to substantial functional limitations and, eventually, to respiratory failure [1, 2]. Morbidity and mortality among patients with COPD are, for the most part, related to acute exacerbations of COPD [3], which occur an average of 1–3 times per year [4]. The definition of an acute exacerbation of COPD is a major point of criticism in many of the studies dealing with that issue [5,

6]. Recently, an acute exacerbation of COPD was redefined as a sustained worsening of a patient's condition from a stable state (beyond normal day-to-day variations) that is acute in onset and that may warrant additional treatment in a patient with underlying COPD [6, 7].

The etiology of exacerbations is heterogeneous and still under discussion. Recent studies have stated that at least one-third of COPD exacerbations may be triggered by viral infections [8, 9]. Undoubtedly, bacteria also play a role in exacerbations of COPD [10]. It is estimated that up to 50% of sputum samples obtained during exacerbation of COPD yield relevant bacteria [11–14].

The management of exacerbations is usually empirical and includes therapy with corticosteroids and often antibiotics. Recent studies have shown that a course of oral corticosteroids is superior to placebo for the treatment of exacerbations in hospitalized patients and out-

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patients [15, 16]. However, there is a lack of evidence favoring the wide use of antibiotics for treatment of COPD exacerbations, and the efficacy of this treatment is debatable. It is difficult to predict a bacterial cause of an exacerbation of COPD [17, 18].

For a physician, it is hard to decide, on clinical grounds, whether to prescribe antibiotics to a patient with an exacerbation of COPD at the time of presentation. Recently Ewig et al. [18] proposed that antibiotic treatment of acute exacerbations of COPD should only regularly be administered to patients who meet  $\geq 2$  of the Winnipeg criteria for increased dyspnea, sputum volume, and purulence [19, 20], patients with  $\geq 4$  exacerbations during the past year and/or significant cardiopulmonary comorbidity [21], and patients presenting with severe airway obstruction or severe respiratory failure requiring ventilatory support [18]. Evidence for these criteria and the diagnostic value of many diagnostic tools (e.g., sputum purulence, Gram stain, radiography, determination of C-reactive protein levels, and determination of lung function parameters) for predicting a bacteriological origin of exacerbations are still under debate [13, 17, 20, 22–27]. Furthermore, microbiological analyses of sputum samples are often not performed, and microbiological criteria for the interpretation of the results are often poorly defined and are reported to have had little impact on treatment, because the test results are not available at presentation of the exacerbation [28].

The aim of this prospective study was to identify predictive factors for exacerbations of COPD caused by bacteria for which treatment with antibiotics is indicated by correlating clinical signs, symptoms, and rapidly available laboratory data on presentation of an acute exacerbation of COPD and by using clear-cut definitions for interpretation of bacterial culture results.

## PATIENTS AND METHODS

**Patients.** From May 1999 through March 2000, patients were recruited from the outpatient pulmonary clinic of the Medisch Spectrum Twente, a 1150-bed teaching hospital in Enschede, The Netherlands. To be eligible for the study, the patients had to have met the following criteria: (1) a clinical diagnosis of stable COPD, as defined by American Thoracic Society criteria [29]; (2) no history of asthma; (3) no exacerbation or antecedent use of an antibiotic in the month prior to enrollment; (4) status as a current or former smoker; (5) age of 40–75 years; (6) baseline prebronchodilator forced expiratory volume in 1 s ( $FEV_1$ ) of 25%–80% of predicted value; (7) prebronchodilator ratio of  $FEV_1$  to inspiratory vital capacity (IVC) of  $\leq 60\%$ ; (8) reversibility of  $FEV_1$  after inhalation of 80  $\mu\text{g}$  of ipratropium bromide (via a metered-dose inhalator), with an aerochamber of  $\leq 12\%$  of the predicted value [30]; (9) total lung capacity (TLC) greater than the predicted TLC  $- (1.64 \times \text{SD})$ ; (10) no maintenance treatment with oral steroids or antibiotics; (11)

no medical condition associated with a low survival rate or serious psychiatric morbidities (e.g., cardiac insufficiency and alcoholism); (12) and absence of any other active lung disease (e.g., sarcoidosis). Use of such medications as nasal corticosteroids and theophyllines, chronic use of acetylcysteine, and all other use of bronchodilators was allowed.

The hospital's medical ethics committee approved this study. All patients provided written informed consent.

**Study design.** This study was part of a randomized, double-blind, single center study that investigated the role of inhaled corticosteroids in COPD [31]. From this study, patients were recruited at presentation of the first exacerbation of COPD. Any time that patients experienced worsening of their respiratory symptoms, they were instructed to contact the study personnel by telephone. They were subsequently invited to visit the outpatient department within 12 h for spirometry measurements, sputum sample collection, and consultation with one of the study physicians. Lung function data and sputum samples were collected. On a standardized exacerbation report, staff doctors registered the presence of "major" symptoms (i.e., increase in dyspnea, cough, increase in sputum volume, and sputum purulence) and "minor" symptoms (i.e., nasal discharge/congestion, wheeze, sore throat, cough, fever, and need of extra bronchodilator) [19] and the treatment prescribed. Furthermore, the study physician reported his/her clinical judgment about the severity of the exacerbation (judged as no exacerbation or mild, moderate, or severe exacerbation) before being informed of the results of the lung function tests and Gram stains.

Clinically, an exacerbation was defined as a worsening of respiratory symptoms that led the patient to contact the study office. Classification of the type of an exacerbation was expressed using the Anthonisen score [19]. Lung function was measured by spirometry. Well-trained lung function technicians performed spirometry on water-sealed spirometers, in accordance with standardized guidelines.  $FEV_1$  and IVC were measured until 3 reproducible recordings ( $< 5\%$  difference) were obtained. The highest values were used for analyses. A clinically relevant decrease in  $FEV_1$  was defined as a decrease of  $> 12\%$  and 200 mL from the baseline level [32]. The most recent result of the lung function test in stable state was used as a baseline value to calculate the decrease in  $FEV_1$  at exacerbation. Body mass index (BMI) was computed as  $\text{kg}/\text{m}^2$ . In patients with COPD, a poor nutritional status is indicated by a BMI of  $< 22 \text{ kg}/\text{m}^2$ .

**Sputum samples.** The laboratory technicians processing the sputum samples were unaware of the clinical condition of the patients. Spontaneously expectorated sputum was collected in sterile vials and processed in the laboratory within 4 h after collection. Total sputum samples were homogenized by incubation at  $37^\circ\text{C}$  for 15 min with an equal volume of 0.1% di-

**Table 1. Baseline characteristics of patients, stratified by bacterial exacerbation status, according to the primary criteria for bacterial origin of an exacerbation of chronic obstructive pulmonary disease (COPD).**

Characteristic	Patients with bacterial exacerbation of COPD	Patients with nonbacterial exacerbation of COPD
No. of patients	22	94
Age, mean years $\pm$ SD	64 $\pm$ 6	64 $\pm$ 7
Male sex, % of patients	82	78
Mean no. of exacerbations in preceding year $\pm$ SD	2.3 $\pm$ 2.2	1.4 $\pm$ 1.8
Smoking status, % of patients		
Ex-smokers	73	65
Current smokers	27	35
Lung function after bronchodilation, <sup>a</sup> mean $\pm$ SD		
FEV <sub>1</sub> , L	1.6 $\pm$ 0.5	1.6 $\pm$ 0.5
Percentage of predicted FEV <sub>1</sub> value	54 $\pm$ 16	55 $\pm$ 15

**NOTE.** FEV<sub>1</sub>, forced expiratory volume in 1 s.

<sup>a</sup> Compared with baseline values.

thiothreitol. Gram-stained sputum samples were examined microscopically and had to contain  $<10^5$  epithelial cells per mL<sup>-1</sup> (i.e.,  $<1$  epithelial cell per high-power field) to be considered representative bronchial samples. Polymorphonuclear cell count was not one of the criteria. A positive Gram stain result suggested the presence of a single pathogenic organism or demonstrated the abundant presence of a potentially pathogenic microorganism (PPM), compared with the background flora (i.e.,  $>1$ -log difference). Appropriate dilutions of homogenized sputum samples were placed on blood, chocolate, cysteine lactose electrolyte deficient medium, and Sabouraud agar plates. Bacterial and mycological isolation and identification were performed with the use of standard techniques of the American Society for Microbiology [33]. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were considered to be PPM. Other bacterial species were classified as normal flora (non-PPM).

A bacterial exacerbation was defined in 2 ways. First, it was defined in accordance with the primary criteria used for pneumonia [33]: by the abundance of  $\geq 1$  PPM (i.e.,  $>10^7$  colony-forming units [cfu]/mL) in excess ( $\geq 1$  log) of the normal microbiological flora in sputum. Second, because these criteria have been under debate with regard to exacerbations of COPD, a secondary analysis was performed using the following secondary criteria for bacterial exacerbation of COPD: PPMs were regarded as significant if they reached a level of absolute growth of  $>10^6$  cfu/mL, except for *S. pneumoniae*, for which a level of growth of  $>10^5$  cfu/mL was deemed sufficient, irrespective of the presence of non-PPMs [13].

**Statistical analyses.** Baseline characteristics are reported as means  $\pm$  SD for continuous variables or as percentages for categorical or dichotomous variables stratified by presence or absence of bacterial exacerbation. To avoid dependency between exacerbations, we included only the first exacerbation during which a sputum sample was obtained.

First, univariate logistic regression analyses were performed to identify the subset of independent variables that were associated with a bacterial exacerbation. The a priori list of potential predicting variables included Gram stain (positive vs. negative), relevant decrease of FEV<sub>1</sub>, clinical judgment (moderate or severe exacerbation vs. mild or no exacerbation), BMI ( $\leq 22$  vs.  $>22$ ), number of exacerbations in the year preceding the study (0–1 vs.  $\geq 2$ ), sex, smoking status, fever, sore throat, nasal discharge, increase in sputum volume, sputum color, dyspnea, and Anthonisen score (type 1 vs. other) [19]. Only those variables with a significance level of  $P \leq .15$  were considered to be candidate variables for the multivariate logistic regression analysis. For the development of the predictive model, we started with all candidate variables (full model). Subsequently, we eliminated the variables step by step, starting with the highest  $P$  value, until the model fit decreased significantly (based on likelihood-ratio test results).

**Table 2. Clinical characteristics of patients, stratified by bacterial exacerbation status, according to the primary criteria for bacterial origin of an exacerbation of chronic obstructive pulmonary disease (COPD).**

Characteristic	Patients with bacterial exacerbation of COPD	Patients with nonbacterial exacerbation of COPD
No. of patients	22	94
Lung function after bronchodilation		
FEV <sub>1</sub> at exacerbation, mean L $\pm$ SD	1.4 $\pm$ 0.5	1.5 $\pm$ 0.5
Relevant decrease in FEV <sub>1</sub> , %	57 <sup>a</sup>	31 <sup>b</sup>
Anthonisen type 1 exacerbation	46	37
Clinical judgment of moderate/severe exacerbation	36	16
Increased sputum volume	81 <sup>a</sup>	68 <sup>c</sup>
Purulent sputum	41	32 <sup>c</sup>
Fever	18	21 <sup>d</sup>
Nasal discharge	46	46 <sup>c</sup>
Sore throat	41	27 <sup>c</sup>
Positive Gram stain result	59	26
BMI of $<22$ kg/m <sup>2</sup>	5	10
Fluticasone propionate use at exacerbation	68	63

**NOTE.** Data are percentage of patients, unless otherwise indicated. BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s.

<sup>a</sup> Based on information from 21 patients.

<sup>b</sup> Based on information from 91 patients.

<sup>c</sup> Based on information from 93 patients.

<sup>d</sup> Based on information from 92 patients.

**Table 3. Positive and negative predictive values for the 3 variables (and combinations of the 3 variables), according to the primary criteria for bacterial origin of an exacerbation of chronic obstructive pulmonary disease, in the final multivariate logistic regression model.**

Variable	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)
Positive Gram stain result	35 (20–50)	89 (82–96)
Relevant decrease in FEV <sub>1</sub> <sup>a</sup>	30 (16–44)	88 (80–96)
No. of exacerbations in the year preceding the study	32 (19–45)	90 (83–97)
Positive Gram stain result, relevant decrease in FEV <sub>1</sub> , and no. of exacerbations in the year preceding the study	67 (36–97)	100
Positive Gram stain result and relevant decrease in FEV <sub>1</sub>	50 (26–75)	92 (69–115)
Positive Gram stain result and no. of exacerbations in the year preceding the study	63 (49–78)	97 (93–101)
Relevant decrease in FEV <sub>1</sub> and no. of exacerbations in the year preceding the study	43 (27–59)	89 (81–97)

**NOTE.** FEV<sub>1</sub>, forced expiratory volume in 1 s.

<sup>a</sup> A clinical relevant decrease in FEV<sub>1</sub> was defined as a decrease of >12% and of 200 mL, compared with the baseline value.

Finally, we calculated positive and negative predictive values for the variables in the final multivariate regression model (separately and combined). We plotted receiver operating characteristic (ROC) curves and estimated the area under the curve (AUC) and 95% CIs. The AUC was used to provide an overall estimate of the diagnostic performance of the prediction rule to differentiate bacterial exacerbations from nonbacterial exacerbations.

For the secondary analysis, the same statistical procedure was applied. In this analysis, only the microbiological criterion for a bacterial exacerbation was changed, as described above.

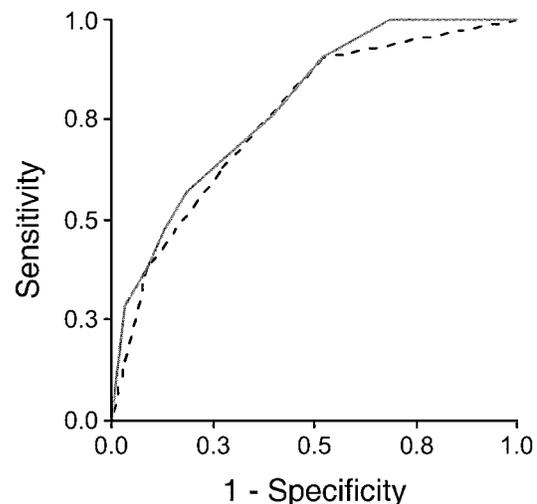
## RESULTS

In total, 123 sputum samples were obtained at the time of presentation with the first acute exacerbation of COPD. For 116 of these 123 exacerbations, the presence of a bacterial infection could be analyzed. According to the primary criteria used for pneumonia [33], 22 patients (19%) had a bacterial exacerbation, and 94 patients (81%) did not. Table 1 shows the baseline characteristics of the patients stratified by presence or absence of bacterial exacerbation.

The following variables were associated with a bacterial exacerbation according to the primary criteria in univariate analysis: Gram stain result, relevant decrease in the FEV<sub>1</sub>, clinical judgment, BMI, and number of exacerbations in preceding year. These were included in a multivariate logistic regression model (table 2). This analysis revealed that Gram stain result, decrease in the FEV<sub>1</sub>, and number of exacerbations in preceding year together best predict the existence of a bacterial exacerbation (final model). Table 3 shows the positive and negative predictive values of all combinations of these variables, together and separately. The positive predictive value for these variables together is 67% (95% CI, 36%–97%), and the negative predictive value

if all 3 are absent is 100%. The second best combination (Gram stain result and number of exacerbations in the year preceding the study) reduced the positive predictive value to 63% and the negative predictive value to 97%. The ROC curves for all 3 variables and the second best combination (Gram stain and number of exacerbations in the year preceding the study) yielded AUCs of 0.78 (95% CI, 0.68–0.88) and 0.76 (95% CI, 0.64–0.87), respectively (figure 1).

Analysis of the prescription of antibiotics by chest physicians showed that antibiotic therapy was appropriate for only 14 (28%) of 50 recipients with exacerbations, as determined on



**Figure 1.** Receiver operating characteristic curves for the model with all 3 predictors (Gram stain result, decrease in the forced expiratory volume in 1 s, and number of exacerbations in preceding year; *solid line*) and for the model with Gram stain result and number of exacerbations in the preceding year (*dotted line*).

**Table 4. Prescription of antibiotics, in relation to a bacterial exacerbation of chronic obstructive pulmonary disease (COPD), according to primary criteria.**

Therapy	No. (%) of patients		Total no. of patients ( <i>n</i> = 116)
	Bacterial exacerbation of COPD ( <i>n</i> = 22)	Nonbacterial exacerbation of COPD ( <i>n</i> = 94)	
Antibiotics received	14 (64)	36 (38)	50
No antibiotics received	8 (36)	58 (62)	66

the basis of our microbiological criteria for a bacterial exacerbation. Moreover, 8 (36%) of 22 bacterial exacerbations were not treated with antibiotics (table 4).

If the variables of negative Gram stain result, no reduction in FEV<sub>1</sub>, and 0–1 exacerbations in the preceding year were taken into account, 11 (40%) of 28 exacerbations were found to have been unnecessarily treated with antibiotics. Table 5 shows the implications for the combinations of all 3 of these predictors for antibiotic therapy.

Only 35% of those with positive results of Gram stains of sputum samples obtained at presentation for the exacerbation had a positive culture result. Furthermore, for 59% of those with positive sputum culture results, the results of Gram stains were also positive.

The prevalence of bacterial exacerbation increased from 19% using the primary criteria to 46% (56 of 123 cases) using the secondary criteria. Forty percent of these so-classified bacterial infections occurred in individuals who also had a positive Gram stain result. The variables significantly associated with a bacterial exacerbation in univariate analysis were Gram stain result, clinical judgment, BMI, number of exacerbations in preceding year, sputum color, and increase in sputum volume. These were included in a multivariate logistic regression model. This analysis revealed that Gram stain result and number of exacerbations in preceding year together best predicted the existence of bacterial exacerbation according to the less-strict criteria. The positive predictive value of these variables together is 75% (95% CI, 54%–96%), and the negative predictive value is 62% (95% CI, 55%–69%).

## DISCUSSION

The most common decision a doctor has to make when treating a patient with an acute exacerbation in COPD is whether to prescribe antibiotic therapy. We are not aware of a study combining the aforementioned clinical signs, symptoms, and rapidly available laboratory data at first presentation as predictors of an acute bacterial exacerbation of COPD. This study, which investigated the clinical predictors of bacterial involvement in exacerbations of moderate-to-severe COPD, revealed 4 important new findings. First, we found a 100% negative predictive

value for nonbacterial involvement with a combination of a negative result of a sputum Gram stain, a clinically nonrelevant decrease in lung function (compared with baseline measurements), and <2 exacerbations in the previous year. Second, the best positive predictive value for a bacterial exacerbation of COPD was a combination of a positive result of a sputum Gram stain, a clinically relevant decrease in lung function, and  $\geq 2$  exacerbations of COPD in the previous year. Third, the classic Anthonisen type I criteria (dyspnea, sputum volume, and sputum purulence) were not predictors of bacterial origin of an exacerbation. Finally, using the clear-cut definition of bacterial infection from the American Society for Microbiology criteria for pneumonia in defining bacterial origin of COPD exacerbations [33], this study found that only 19% of the primary exacerbations originated with a bacterial infection.

It takes ~45 min to obtain the results of a Gram stain and basic spirometry. The 100% negative predictive value for a nonbacterial origin of an exacerbation, which occurred in 25% of all exacerbations in this study, might help physicians decide whether to forego what may be unnecessary treatment. Also the combination of the variables negative results of a sputum Gram stain and <2 exacerbations in the previous year results in a high negative predictive value and a comparable diagnostic performance, as estimated by the AUC. This study demonstrated once again that more-objective criteria for use of antibiotic therapy in exacerbations of COPD are needed to prevent overuse of antibiotics [25, 34].

In our population, ~40% of the exacerbations of moderate-to-severe COPD were treated with antibiotics, a figure that represents the Dutch practice fairly well. Use of our prediction rule would reduce this percentage to 35%, an absolute reduction of 5%. Because regular prescription rates for these patients in other countries are much higher, the potential savings made by applying this prediction rule might increase to 24% in sit-

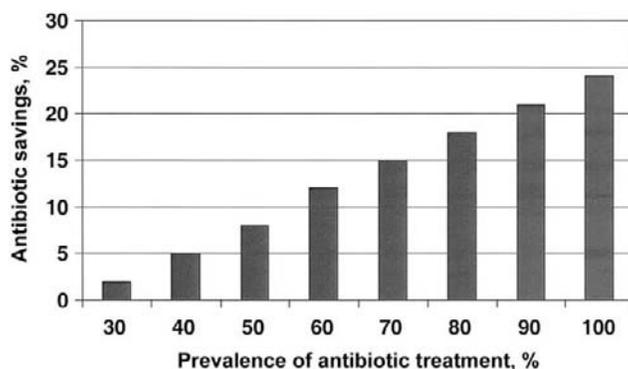
**Table 5. Implications of the combination of all 3 predictors for antibiotic use.**

Variables	No. (%) of patients		Total no. of patients
	Bacterial exacerbation of COPD	Nonbacterial exacerbation of COPD	
Three predictors present	6 (67)	3 (33)	9
Three predictors absent <sup>a</sup>	0 (0)	28 (100)	28
Other <sup>b</sup>	16 (20)	63 (80)	79
All	22 (19)	94 (81)	116

**NOTE.** The 3 predictors were positive Gram stain result, relevant decrease in forced expiratory volume in 1 s, and  $\geq 2$  exacerbations in the year preceding the study.

<sup>a</sup> Negative Gram stain result, no relevant decrease in forced expiratory volume in 1 s, and <2 exacerbations in the year preceding the study

<sup>b</sup> Patients with 1 or 2 positive predictors.



**Figure 2.** Potential savings in the rate of antibiotic treatment for different prescribing prevalences

uations in which every exacerbation of COPD is treated with antibiotics (figure 2).

The positive predictive value for a bacterial exacerbation of these variables (positive result of a sputum Gram stain, a relevant decrease in lung function, and  $\geq 2$  exacerbations in the previous year) was 67%, raising the likelihood of a bacterial exacerbation (19%) by 48%. Unfortunately, this only pertains to 8% of the exacerbations.

The yield of Gram stains has proven to be highly dependent on whether a skilled investigator applies strict criteria [35]. In a study of nosocomial pneumonia, the negative predictive value for Gram stains of endotracheal aspirate specimens was reported to be as high as 94%, which is comparable to the results we obtained using the primary exacerbation criteria [36]. Similar to other studies [23], in our study, the presence of a positive sputum Gram stain result at presentation does not predict a positive culture result very well; on the other hand, a positive culture result was not a strong predictor of a positive sputum Gram stain result. Prior measurements of lung function are reported to be useful for comparison with measurements made during an acute exacerbation [1], but the importance of change from baseline spirometry findings as a tool for predicting a bacterial cause of an exacerbation has not yet been demonstrated.

Historically, on the basis of the results of the Anthonisen study, patients presenting with type I criteria (dyspnea and change in sputum characteristics [increased volume or purulence]) are almost always treated with antibiotics [19]. Although these criteria define a type of exacerbation, they do not define its (bacterial) etiology. We found no association between bacterial exacerbations and Anthonisen type 1 exacerbations.

Because we included patients with less severe COPD, compared with the Anthonisen study, the prevalence of PPMs during the exacerbation is expected to be lower [13] and might explain the lack of the aforementioned association in our study between bacterial exacerbations and Anthonisen type 1 exacerbations [5, 13, 37, 38].

In contrast to the study of Stockley et al. [17], sputum pu-

rulence was not a predictor of bacterial exacerbation. This not only means that patients with mucoid sputum production during the exacerbation are known to improve without antibiotic therapy [17], but also that patients with purulent sputum during the exacerbation might not be candidates for antibiotic treatment.

In conclusion, we believe that patients who present with an exacerbation of COPD and who have a negative sputum Gram stain result, no clinically relevant decrease in lung function (compared with baseline measurements), and a history of  $< 2$  exacerbations of COPD in the previous year do not need additional antibiotic treatment for an exacerbation. However, before it is implemented in clinical practice, this prediction rule should be validated in an external population. Furthermore, future studies are needed to determine whether other subgroups of patients with COPD exist in whom bacteria are likely to play an important role and for whom antibiotic treatment is thus indicated.

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