Efficacy of Antibiotic Therapy for Acute Exacerbations of Mild to Moderate Chronic Obstructive Pulmonary Disease

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***Rationale*: Antimicrobial therapy remains a controversial issue in nonsevere exacerbations of chronic obstructive pulmonary disease (COPD).**

***Objectives*: To evaluate the efficacy of antibiotic therapy in moderate exacerbations of mild-to-moderate COPD.**

***Methods*: This study involved a multicenter, parallel, double-blind, placebo-controlled, randomized clinical trial. Patients aged 40 years or older, smokers, or ex-smokers of 10 pack-years or more with spirometrically confirmed mild-to-moderate COPD ($FEV_1 > 50\%$ predicted and FEV_1/FVC ratio < 0.7) and diagnosed with an exacerbation were enrolled in the study. The patients were randomized to receive amoxicillin/clavulanate 500/125 mg three times a day or placebo three times a day for 8 days.**

***Measurements and Main Results*: The primary outcome measure was clinical cure at end of therapy visit (EOT) at Days 9 to 11. A total of 310 subjects fulfilled all the criteria for efficacy analysis. A total of 117 patients with amoxicillin/clavulanate (74.1%) and 91 with placebo (59.9%) were considered cured at EOT (difference, 14.2%; 95% confidence interval, 3.7–24.3). The median time to the next exacerbation was significantly longer in patients receiving antibiotic compared with placebo (233 d [interquartile range, 110–365] compared with 160 d [interquartile range, 66–365]; $P < 0.05$). The best C-reactive protein serum cut-off for predicting clinical failure with placebo was 40 mg/L, with an area under the curve of 0.732 (95% confidence interval, 0.614–0.851).**

***Conclusions*: Treatment of ambulatory exacerbations of mild-to-moderate COPD with amoxicillin/clavulanate is more effective and significantly prolongs the time to the next exacerbation compared with placebo.**

Clinical trial registered with www.clinical.gov (NCT00495586).

Keywords: chronic obstructive pulmonary disease; antibacterial agents; placebos; randomized controlled clinical trials; disease exacerbation

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is an unresolved debate about adequate prescription of antibiotics for patients suffering from exacerbations of chronic obstructive pulmonary disease. Antibiotic therapy effectively reduces treatment failure and mortality rates in patients diagnosed with chronic obstructive pulmonary disease with severe exacerbations. However, antimicrobial therapy remains a controversial issue in nonsevere exacerbations of chronic obstructive pulmonary disease.

What This Study Adds to the Field

Treatment of moderate exacerbations of mild-to-moderate chronic obstructive pulmonary disease with the first-choice antibiotic (amoxicillin/clavulanate) was more effective than placebo. Among patients with clinical success at the end of therapy visit, those treated with an antibiotic had a significantly prolonged time to the next exacerbation. The capillary C-reactive protein determination was useful as a marker of the response to therapy.

Chronic obstructive pulmonary disease (COPD) affects a large number of individuals worldwide and is characterized by a progressively rising epidemiological, clinical, and socio-economic impact (1). In Spain, the prevalence of COPD is 10.2% in adults older than 40 years, and mild and moderate cases account for 56 and 38%, respectively, of all COPD cases (2). Exacerbations represent a considerable economic burden, but, more importantly, they can lead to accelerated lung function decline (3), more rapid impairment of health-related quality of life (4), and increased mortality (5).

Between 50 to 70% of COPD exacerbations have an infectious etiology (6), and current guidelines base their recommendations about antibiotic prescription mainly on the study by Anthonisen and colleagues (7), which was performed in patients with moderate to very severe COPD. In the 25 years since the Anthonisen study was published, there has been accumulating evidence about the risk factors for treatment failure of exacerbations (8), with severity of airflow impairment being one of the most relevant (9).

There is no doubt that antibiotics are not required for the treatment of acute cough (10) or for episodes of acute bronchitis (11). In contrast, there is evidence about the efficacy of antibiotic treatment at the very severe end of the spectrum of COPD, including patients admitted to hospital for an exacerbation (12) or with respiratory failure and mechanical ventilation (13). However, a large number of patients with chronic airflow obstruction and exacerbations are attended in primary care, and definitive evidence to support the use of antibiotics in patients with mild to moderate airflow obstruction is lacking. In a systematic review of antibiotic trials in mild to moderate exacerbations of COPD, Puhan and colleagues (14) were only able to

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identify seven trials up to 2005 (the most recent performed in 1995), which included a total of 990 patients; among these studies, only five reported treatment failure rates. The results of this metaanalysis were not conclusive in favor of antibiotics, which is not surprising because mild to moderate severity was defined in terms of requiring ambulatory management. Using this definition of severity, they pooled together the results of the Anthonisen study in which patients had a mean FEV_1 of 33% predicted (7) and the results of Sachs and colleagues (15) in which patients had a mean age of 51 years, 31% were never smokers, and 10% had a diagnosis of asthma. From the results of their metaanalysis, it was clear that more well designed studies are needed to establish the role of antibiotics in this population.

The four systematic reviews published over the last years reached the same conclusion that the evidence for antibiotic prescription for exacerbations of nonsevere COPD is weak and new and that well designed studies are urgently needed (14, 16–18). We have therefore performed a randomized, double-blind, placebo-controlled trial of amoxicillin/clavulanate for outpatients with a moderate exacerbation of mild-to-moderate COPD.

METHODS

Further details are provided in the online supplement. The protocol was approved by the Research and Ethics Committee of Primary Care Fundació Jordi Gol i Gurina (Barcelona, Spain; project number P6/031).

Randomization

Participants were randomly allocated to receive amoxicillin/clavulanate 500/125 mg (AMX) or placebo (PBO) three times daily for 8 days in blocks of 10 according to a random-number table. Randomization was based on a one-to-one allocation of prenumbered boxes containing 24 capsules. Participants were recruited from 13 primary care centers in Catalonia from October 2007 to July 2010.

Participant Selection and Procedures

Eligible participants were at least 40 years of age, had a diagnosis of mild-to-moderate COPD (defined as having a smoking history of at least 10 pack-years, a ratio of postbronchodilator FEV_1 to FVC of $< 70\%$, and a postbronchodilator $FEV_1 > 50\%$ of the predicted value), and the presence of an exacerbation defined as the occurrence of at least one of the following criteria: increase of dyspnea, increase in sputum volume, or sputum purulence (7).

Exclusion criteria were antibiotic use in the previous 2 weeks, bronchial asthma, cystic fibrosis, bronchiectasis of origin other than COPD, active neoplasm, tracheotomy, need for hospital admission, immunosuppression, hypersensitivity to β-lactams, clavulanate or lactose, institutionalization, and inability to provide informed consent.

On the inclusion visit, a peak expiratory flow measurement was undertaken, and a C-reactive protein (CRP) rapid test was performed. Physicians were instructed to request a chest X-ray in case of suspected pneumonia. The use of a short course of oral corticosteroids at maximum doses of 1 mg/kg/d (but no more than 60 mg/d) during 10 days or less was allowed.

Outcome Measures

The primary endpoint was clinical cure at the end of therapy visit (EOT) at Days 9 to 11 in the intention-to-treat (ITT) population. Clinical response was classified as cure, improvement, or failure. Clinical success was considered when cure or improvement was observed. Secondary outcomes included clinical success at follow-up visit at Day 20, change in peak expiratory flow, time until the next exacerbation, and the association of CRP concentrations with clinical outcome in the placebo arm. Patients were monitored every 3 months over a period of 365 days. All clinical failures occurring during therapy were counted as zero exacerbation-free interval days in agreement with the studies of Chodosh and colleagues (19) and Lode and colleagues (20).

Statistical Analyses

We accepted a null hypothesis if the cure rate in the intervention group was the same as or ±7% of that observed in the placebo arm. The expected rate of cure among patients assigned to antibiotic therapy was 90%. For an α of 0.05 and a β of 0.2 and accepting possible losses of 15%, we calculated a sample size of 677 patients. The best cut-off for CRP serum concentrations to predict clinical success in the placebo group was obtained by means of a receiver operating characteristic (ROC) curve. The time until the next exacerbation was analyzed by a survival analysis using the Kaplan-Meier method. A Gehan-Breslow-Wilcoxon test was applied to compare the survival curves for each treatment group. Finally, a logistic regression model was constructed to identify the variables independently associated with failure.

RESULTS

Study Recruitment and Follow-up

A total of 353 subjects were screened for inclusion in the study. The recruitment problems were mainly related to the high frequency of previous antibiotic treatment of patients before inclusion and the unusually low prevalence of exacerbations during one winter season. Chest X-ray was performed in 64 cases; among these cases, three were positive for consolidation and were therefore excluded from the study. The flow of patients in the study and causes of exclusion are presented in Figure 1.

Baseline Characteristics

A total of 310 patients (158 patients in the AMX arm and 152 patients in the PBO arm) fulfilled all the criteria for efficacy and safety analysis and constituted the ITT population. Only two patients in the AMX arm failed to comply with medication due to adverse events and were excluded from the per-protocol (PP) population (Figure 1). The mean age was 68.1 (SD, 10.4) years, and 251 were male (81%). Oral corticosteroids were administered to 53 patients (26 [16.5%] in the AMX arm and 27 [17.8%] in the PBO arm). The demographic and clinical characteristics, as well as the characteristics and severity of COPD and the exacerbation, were well matched between the groups (Table 1).

Primary Outcomes

The clinical response at the EOT visit was assessed at 10.2 ± 0.8 days, with no statistical differences being observed at this time point between the two groups (10.2 ± 0.9 d in placebo vs. 10.1 ± 0.8 d in the antibiotic arm). In the ITT population, a total of 117 patients assigned to the AMX group (74.1%) and 91 to PBO group (59.9%) were considered cured at EOT (Days 9–11) ($P = 0.016$), with a difference of 14.2% (95% confidence interval [CI], 3.7–24.3) (Table 2). The results were similar in the PP population (*see* Table E1 in the online supplement). The relative risk of failure among patients treated with placebo was 1.12 (95% CI, 1.02–1.22) compared with an antibiotic. Clinical success was also greater in the AMX group compared with PBO (90.5% vs. 80.9%; $P = 0.022$), with a difference of 9.6% (95% CI, 1.8–17.5) (Table 2). Failure was more frequent with increasing severity of exacerbation according to the Anthonisen criteria (Table E2).

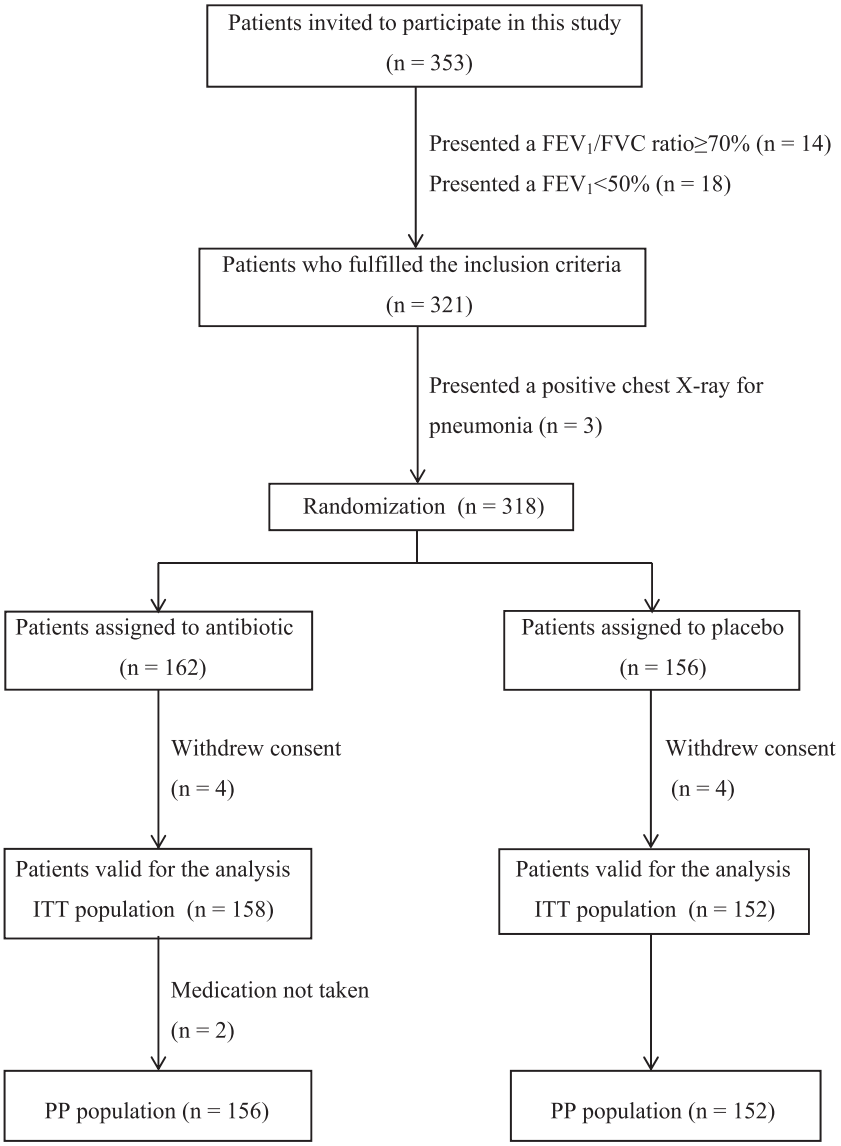

Figure 1. Flow of patients throughout the study. ITT = intention-to-treat; PP = per-protocol.

Secondary Outcomes

Cure at Day 20 was significantly greater among patients assigned to AMX (129 cases, 81.6% vs. 103 in PBO [67.8%]; $P = 0.006$) (Table 2). The best CRP serum cut-off for predicting clinical success with PBO obtained by the ROC curve was 40 mg/L (Figure 2). At this concentration, the sensitivity and specificity were 0.655 and 0.876, respectively, and the area under the curve was 0.732 (95% CI, 0.614–0.851). A total of 77.3% of CRP determinations presented concentrations lower than 40 mg/L. In these cases, clinical success with PBO was observed in 106 cases (87.6%), being significantly higher than the 34.5% of success rate observed among the 34 patients with CRP $\geq$ 40 mg/L ($P < 0.001$).

A total of 173 exacerbations were reported during the year of follow-up among patients who had clinical success at EOT (83/143 in the AMX group [58.0%] and 90/123 in the PBO group [73.2%]). Figure 3 shows the Kaplan-Meier survival analysis revealing the time in days until the next exacerbation for both treatment groups. The median time to the next exacerbation was significantly longer in patients receiving AMX compared with PBO (233 d; interquartile range [IQR], 110–365 d compared with 160 d [IQR, 66–365 d]; $P = 0.015$). The time to the next exacerbation was statistically shorter among patients with CRP levels above 40 mg/L for both groups but was still significantly longer in the AMX group (Table E3).

Candidate variables included in the multivariate regression analysis were: treatment group, age ($\geq$ 65 yr), sex, pack-years, high blood pressure, heart failure, coronary heart disease, diabetes mellitus, FEV_1 ($\geq$ 65%), increase of dyspnea, increase of sputum volume, sputum purulence, CRP ($\geq$ 40 mg/l), fever ($>$ 38°C), and basal peak-flow. Failure at Days 9 to 11 was significantly associated with CRP $\geq$ 40 mg/L (OR, 7.9; 95% CI, 3.9–16.3), PBO treatment (OR, 2.9; 95% CI, 1.4–6.0), and the presence of coronary heart disease (OR, 2.6; 95% CI, 1.0–6.7) (Table 3).

Adverse Events

A total of 35 adverse events were reported to be at least possibly drug related, of which 32 corresponded to gastrointestinal

TABLE 1. BASELINE CHARACTERISTICS OF THE INTENTION-TO-TREAT POPULATION

Patient Characteristics	AMX (*n* = *158*)	PBO (*n* = *152*)
Age, yr, mean (SD)	68.4 (9.9)	67.8 (11.0)
Male sex, n (%)	132 (83.5)	119 (78.3)
Smoking status, n (%)		
Current	86 (54.4)	89 (58.6)
Former	72 (45.6)	63 (41.4)
Pack-years, mean (SD)	38.3 (16.9)	37.9 (19.1)
Previous medication, n (%)		
Short-acting β-agonists	35 (22.2)	36 (23.7)
Long-acting β-agonists	6 (3.8)	13 (8.6)
Anticholinergics	55 (34.8)	52 (34.2)
Theophyllines	2 (1.3)	2 (1.3)
Oral corticosteroids	1 (0.6)	2 (1.3)
Inhaled corticosteroids	15 (9.5)	23 (15.1)
Long-acting β-agonists + inhaled corticosteroids	31 (19.6)	19 (12.5)
High blood pressure, n (%)	64 (40.5)	73 (48.0)
Diabetes mellitus, n (%)	29 (18.4)	28 (18.4)
Heart failure, n (%)	2 (1.3)	3 (2.0)
Coronary heart disease, n (%)	15 (9.5)	19 (12.5)
FVC, ml, mean (SD)	2,753.4 (851.5)	2,763.4 (955.5)
FVC, %, mean (SD)	70.2 (15.8)	71.5 (18.3)
FEV_1, ml, mean (SD)	1,709.6 (548.6)	1,722.3 (641.5)
FEV_1, %, mean (SD)	64.2 (11.8)	65.9 (12.1)
FEV_1/FVC ratio, mean (SD)	62.3 (6.0)	62.2 (5.8)
Basal peak-flow, L/min, mean (SD)	225.3 (83.6)	227.6 (81.9)
COPD classification, n (%)		
Mild	15 (9.5)	20 (13.2)
Moderate	143 (90.5)	132 (86.8)
Drugs administered for the exacerbation, n (%)		
Short-acting β-agonists, n (%)	54 (34.2)	53 (34.9)
Oral corticosteroids, n (%)	26 (16.5)	27 (17.8)
Increase of the sputum volume, n (%)	125 (79.1)	117 (77.0)
Increase of dyspnea, n (%)	109 (69.0)	98 (64.5)
Sputum color, n (%)		
Uncolored	73 (46.2)	53 (34.9)
Yellowish	36 (22.8)	46 (30.3)
Yellow-greenish	49 (31.0)	53 (34.9)
Sputum purulence, n (%)*	85 (53.8)	99 (65.1)
Fever, n (%)	12 (7.6)	14 (9.2)
Type of exacerbation,† n (%)		
Type I	40 (25.3)	45 (29.6)
Type II	81 (51.3)	72 (47.4)
Type III	37 (23.4)	35 (23.0)
CRP, median (IQR)	18 (35.0)	17 (23.0)

Definition of abbreviations: AMX = amoxicillin/clavulanate; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; IQR = interquartile range; PBO = placebo.

* $P < 0.05$.

† Type I: all the Anthonisen criteria present (increased dyspnea, increased sputum volume and purulent sputum). Type II: only two criteria present; type III: only one criterion present.

adverse events, two were suspected allergic reactions, and one did not provide sufficient information. Among patients assigned to AMX, 23 presented an adverse event (14.5%), which was higher than the PBO group (12 cases [7.9%]; $P = 0.048$). Most of the adverse reactions observed were mild. Study drug treatment was prematurely discontinued because of gastrointestinal adverse events in two patients assigned to AMX.

TABLE 2. SUMMARY OF CLINICAL EFFICACY RESULTS AT END-OF-TREATMENT VISIT IN THE INTENTION-TO-TREAT POPULATION

	AMX n/Total (%)	PBO n/Total (%)	*P* Value
Primary outcomes			
Clinical cure at Days 9–11	117/158 (74.1)	91/152 (59.9)	0.016
Clinical success at Days 9–11	143/158 (90.5)	123/152 (80.9)	0.022
Secondary outcomes			
Clinical cure at Day 20	129/158 (81.6)	103/152 (67.8)	0.006
Clinical success at Day 20	143/158 (90.5)	122/152 (80.3)	0.015
Days until next exacerbation, median (IQR)	233 (110–365)	160 (66–365)	0.015
Change of peak expiratory flow from basal and EOT visits, L/min, mean (SD)	52.8 (61.8)	38.5 (56.0)	0.039

Definition of abbreviations: AMX = amoxicillin/clavulanate; EOT = end of treatment; IQR = interquartile range; PBO = placebo.

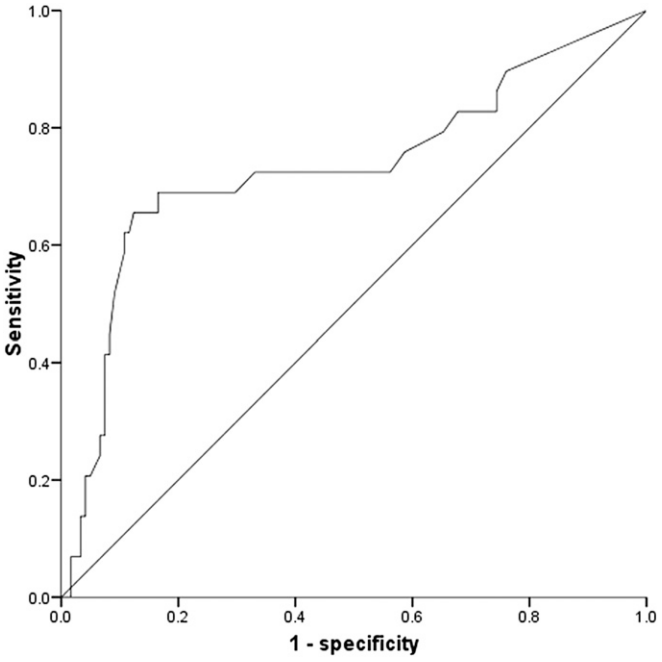

Figure 2. Receiver operating characteristic curve of C-reactive protein for predicting clinical success among patients not treated with antibiotics.

DISCUSSION

It is widely recognized that there is a lack of placebo-controlled trials with antibiotics in mild-to-moderate COPD (14); therefore, the indication for antibiotic therapy in these patients is based on the scarce evidence derived from clinical trials in severe, mostly hospital-based patients with COPD. Our results showed that treatment of moderate exacerbations of mild-to-moderate COPD with amoxicillin/clavulanate was more effective than placebo, with an absolute difference of cure rates of 14.2% and a number needed to treat of seven. In addition, those treated with an antibiotic had a significantly prolonged time to the next exacerbation. The results reported also demonstrate the usefulness of capillary CRP used as a point-of-care test as an excellent predictor of clinical outcome in exacerbations of mild-to-moderate COPD.

Our study has several limitations. The required sample size could not be achieved for a variety of reasons: a large number of screened patients had received antibiotic treatment before, and others did not fulfill spirometric criteria of mild-to-moderate COPD. In addition, this trial was only partially funded by two independent academic institutions without any other source of funding, which resulted in insufficient economic incentive to the investigators for such a demanding trial. Because this study was scheduled to be terminated in 3 years and no improvement in the inclusion rate was expected, recruitment was discontinued. However, the expected sample size was calculated with the conservative assumption of a bilateral contrast of hypothesis and possible 15% losses, and only 2.5% of the patients were lost for the primary outcome. Despite this weakness, a significant difference was found between antibiotic and placebo.

Another limitation is that an objective assessment of symptom resolution at EOT (further than the evolution of peak flow measurements) was not considered in this trial. We considered clinical response as cure, improvement, or failure on the basis of the assessment performed by the physician after obtaining the clinical history and performing the physical examination.

The use of oral corticosteroids for exacerbations was not regulated by the study protocol. However, they only were prescribed in 17% of the cases, without differences between groups, and therefore are not expected to have significantly influenced the results.

Another limitation of this study is the definition of exacerbation used. It is recognized that diagnosis of exacerbation is clinical because there are no reliable complementary tests or biomarkers for its diagnosis (21). We defined exacerbation based on the presence of at least one of the Anthonisen criteria (7) despite the fact that antibiotic therapy is only recommended in patients with two or three of these criteria. However, we wanted to replicate the real experience in primary care where guidelines are not always followed and antibiotic treatment is prescribed even in patients with just one criterion (22). In fact, more restrictive inclusion criteria limited to types I and II exacerbations (i.e., those more likely to be bacterial) should have resulted in even more favorable results for antibiotic therapy. In

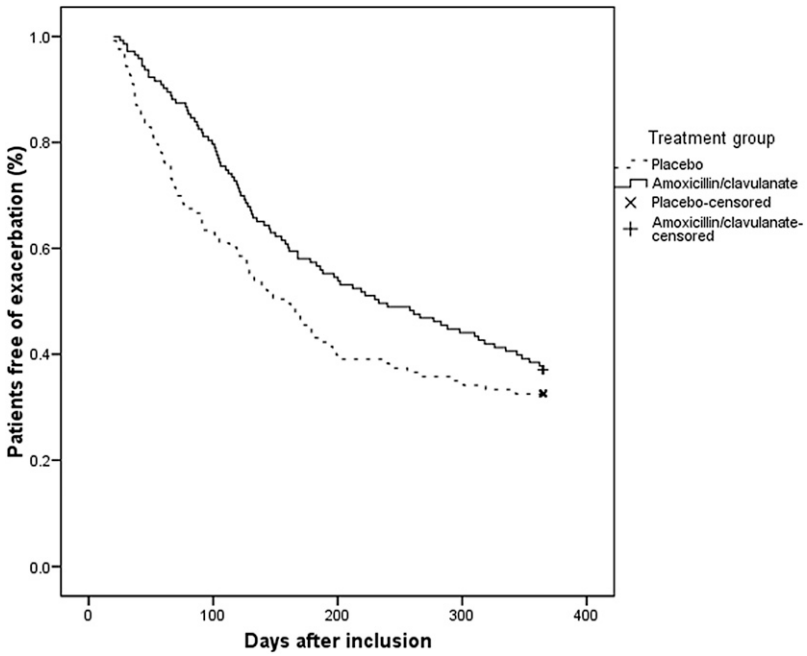

Figure 3. Kaplan-Meier survival analysis of exacerbation-free interval in patients with clinical success at Days 9 to 11.

TABLE 3. BIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION ANALYSIS FOR PREDICTING CLINICAL FAILURE AT DAYS 9 TO 11

	Bivariate analysis			Multivariate analysis		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Treatment with placebo	2.2	1.2–4.4	0.018	2.9	1.4–6.0	0.005
High blood pressure	1.8	0.9–3.5	0.071			
Coronary heart disease	2.5	1.1–5.7	0.034	2.6	1.0–6.7	0.047
Increase of dyspnea	2.1	1.0–4.6	0.056			
Increase of sputum purulence	2.3	1.1–4.7	0.025			
CRP ⩾ 40 mg/L	6.6	3.3–13.0	<0.001	7.9	3.9–163	<0.001

Definition of abbreviations: CI = confidence interval; CRP = C-reactive protein; OR = odds ratio.

any case, it is important to highlight that up to 60% of patients were cured and 81% improved without antibiotics, although the long-term outcomes were poorer. It is relevant to investigate the characteristics of patients that can be safely managed in primary care without antibiotics to prevent the overuse of these drugs and the increasing problem of bacterial resistance (23).

All the patients participating in this study were instructed to contact their physician immediately if there was any change in their health status. We were not able to count the unreported exacerbations in this study because patients were not given a symptom diary. However, there is no reason to suspect that underreporting of exacerbations may have been different in any of the treatment arms.

The design of this trial has incorporated several features that were not considered in the previous placebo-controlled trials: *1*) the accurate diagnosis of mild-to-moderate COPD based on spirometry and smoking habits; *2*) great emphasis was put on excluding possible cases of pneumonia, which was suspected in up to 18% of cases in which a chest X-ray was performed and confirmed in only three patients, who were excluded from the study; and *3*) the use of peak flow assessment as a secondary outcome measure. An increase of peak expiratory flow was observed in both groups, but the change was significantly greater among patients receiving antibiotic therapy. In one metaanalysis including three trials that provided data on peak flow measurements in a total of 285 patients, no differences were observed in the improvement of the peak expiratory flow between antibiotic therapy and placebo (16).

Amoxicillin/clavulanate was chosen because it is recommended by most of the current clinical guidelines because it covers pneumococci and *Haemophilus* well (9, 24, 25). Amoxicillin, trimethoprim/sulfamethoxazole, tetracycline, and erythromycin were not chosen because failure rates with their use may almost double in outpatients with COPD exacerbations compared with amoxicillin/clavulanate, azithromycin, or ciprofloxacin (26). One metaanalysis of antibiotic comparison trials demonstrated that amoxicillin results in suboptimal outcomes with increased risk of clinical failures in COPD exacerbations (27). New macrolides were not used because they are not considered as first-line treatment for exacerbations of COPD, and, because we had no microbiological assessment, we wanted to exclude the possibility of clinical improvement due to an antiinflammatory effect (28). Fluoroquinolones were not chosen because, even if they proved to be superior to amoxicillin/clavulanate in severe COPD, with the associated risk factors and bacterial exacerbations (29) it is not demonstrated that fluoroquinolones provide better clinical outcomes in these patients with mild-to-moderate COPD without risk factors (30). Additionally, the prevalence of *Pseudomonas* in exacerbations of COPD with $FEV_1 > 50\%$ is negligible (31). Because some studies have shown that amoxicillin/clavulanate may be more effective than narrow-spectrum antibiotic, the extrapolation of our results to other antibiotics could be misleading.

Another strength of the study was the evaluation of long-term outcomes of antibiotic treatment, such as time to the next exacerbation. It is well documented that there is a relationship between better bacterial eradication, a higher rate of clinical cure, and prolonged time to the next exacerbation (17, 29, 32). Our results consistently showed a prolonged median time to the next exacerbation with amoxicillin/clavulanate (233 vs. 160 d). We used a conservative approach, evaluating only the time to the next exacerbation in patients with clinical success at the EOT, because those who failed were treated with antibiotics different from the study medication and were more likely to have an early relapse (33), Therefore, their inclusion could have biased our results toward an even larger difference in favor of the antibiotic. The consistency in short- and long-term results with antibiotic strongly suggests that they are produced by the antimicrobial activity of the drug. Bacterial eradication could not be assessed in our study because microbiological analysis of sputum is not readily available in primary care centers. In fact, we did not aim to demonstrate the antibacterial efficacy of amoxicillin/clavulanate in patients with exacerbated COPD, which has been proven in previous studies and ratified by its position in guidelines (9, 24, 25). Positive cultures are only obtained in 20 to 60% of sputum samples of patients included in clinical trials with types I and II exacerbations (29, 32, 34). The GOLD and Spanish guidelines recognize that sputum cultures take too long (at least 2 d) and frequently do not give reliable results for technical reasons (35, 36). Thus, we wished to reflect clinical practice in which microbiological examinations are not routinely requested in ambulatory exacerbations of COPD (i.e., those that did not require hospitalization).

In a previous placebo-controlled study using amoxicillin/clavulanate for 5 days in patients with chronic bronchitis and $FEV_1 < 80\%$ predicted, Allegra and colleagues (37) demonstrated a significantly better success rate with antibiotic (86.4%) compared with placebo (50.3%). They stratified the patients according to FEV_1, and the milder patients (two clusters analyzed together, mean FEV_1 of 54 and 71% for each cluster and with a total of 231 patients) obtained a better success rate with the antibiotic (84.8 vs. 59.4%; $P < 0.001$). No microbiological investigations were performed.

The clinical success rate achieved in our study with an antibiotic (90%) is higher than that observed in previous placebo-controlled trials, particularly 68% in the study by Anthonisen and colleagues (7), 80% in the study by Daniels and colleagues (34), and 86.4% in the study by Allegra and colleagues (37), all of which included patients with severe COPD. In fact, there seems to be a gradient in rate of success with antibiotic and placebo according to the severity of airflow obstruction. In the Anthonisen trial with a mean FEV_1 of 33%, the success with placebo was 55% (7); in the study by Daniels and colleagues (34), with a mean FEV_1 between 44 and 47%, the success with placebo was 69%; and in our study, with a mean FEV_1 of 65%, it was 81%. We cannot compare our results with those of other antibiotic trials in exacerbations, because most of them included patients with chronic bronchitis (i.e., without airflow obstruction or without lung function measurements), never smokers, and patients younger than 40 years or even patients with asthma (11, 15).

In conclusion, this clinical trial demonstrated the superiority of amoxicillin/clavulanate for short- and long-term clinical outcomes in moderate exacerbations of mild-to-moderate COPD compared with placebo. Several metaanalyses on the effectiveness of antibiotic treatment have recently been published with controversial results because most of the clinical trials

considered in these reviews had small sample sizes, unclear definitions of COPD and its severity, heterogeneous inclusion criteria, and the use of antibiotics, which is not recommended as first-choice therapy (16–18). The current study also provides evidence of the usefulness of point of test CRP quantification as an easy-to-perform test that may help in the adequate prescription of antibiotics in these patients.

Author disclosures are available with the text of this article at www.atsjournals.org.

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