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Clinical and Bacteriological Efficacy in Treatment of Acute Exacerbations of Chronic Bronchitis with Cefditoren-Pivoxil versus Cefuroxime-Axetil

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A randomized, double-blind, double-dummy trial was performed comparing 200 mg of cefditoren-pivoxil twice daily for 5 days versus standard cefuroxime-axetil treatment (250 mg twice daily for 10 days) of Anthonisen type I or II acute exacerbations of chronic bronchitis. The modified intention-to-treat population included 541 patients. Patients were assessed during therapy, at the end of therapy (visit 3; primary evaluation time point), and at follow-up. Clinical success was obtained in 79.9% of the 264 patients included in the cefditoren-pivoxil group and in 82.7% of the 277 patients in the cefuroxime-axetil group (treatment difference, 95% confidence interval [CI]: −2.8, −9.7 to 3.6%). Treatment clinical effects were more clearly seen in sputum signs (decreasing volume and purulence from approximately 80% to approximately 10% of the patients). At the end of treatment, exploratory analysis of the per-pathogen bacteriological response showed 72.8% (of 103 isolates) in the cefditoren-pivoxil arm versus 67.0% (of 94 isolates) in the cefuroxime-axetil group (treatment difference; 95% CI: 5.8, −7.0 to 18.6%). Globally, the per-pathogen bacteriological response correlated well with clinical success: 83.5% of 164 baseline isolates from patients with a clinical success were eradicated or presumably eradicated, in contrast to only 3% of 33 isolates from patients with a clinical failure. Clinical success in patients infected with *Haemophilus influenzae*, the most frequent isolate, was 84% (of 50) and 82.5% (of 40) (treatment difference; 95% CI: 1.5, −14 to 17%) in the cefditoren-pivoxil versus the cefuroxime-axetil group. Although this study does not prove that either drug is better than a placebo, cefditoren-pivoxil and the standard 10-day cefuroxime-axetil course had similar point estimates of success in acute exacerbations of chronic bronchitis.

Feelings related to acute exacerbations of chronic bronchitis (AECB), such as embarrassment about symptoms, are identified factors reducing patients' perceived quality of life (17). Although there is not a uniform definition of AECB episodes (15), they are characterized by the following main symptoms: increase in baseline dyspnea, increase in sputum volume, and/or appearance of purulent expectoration (28). According to the presence of these symptoms, exacerbations are classified by Anthonisen as types I (three symptoms), II (two symptoms), and III (one symptom) (1). At least half of AECB cases are presumably caused by bacterial infection (4, 13), which may respond primarily to antibiotics. Despite the fact that many of these patients are treated with antibiotics, the efficacy of this approach has been questioned (11) because previous trials have not shown a benefit over placebo administration (14). Nevertheless, other studies (1, 22) have described small but statistically significant improvements of clinical outcomes in ambulatory patients with type I and type II exacerbations treated with broad-spectrum antibiotics.

Sputum purulence is strongly associated with the presence of bacterial isolates in sputum culture (28). *Haemophilus influenzae* is the most common isolate in patients with AECB, followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis*. Geographical spread of resistance among the three main bacterial isolates in AECB makes the choice of an adequate antibiotic, if needed, difficult. For example, erythromycin resistance of *S. pneumoniae* is geographically associated with penicillin resistance (coresistance) and with ampicillin resistance of *H. influenzae* (coupled resistance) in Spain (20). This is probably due to different antibiotic pressure in each geographical region (8, 20) over time (10), since antibiotic consumption in the community is the main factor that has been clearly related to resistance (9). These facts, together with the current nonsusceptibility prevalence (around 25% for amoxicillin and clarithromycin in *H. influenzae* and 44% and 35% for penicillin and macrolides in *S. pneumoniae*, respectively) in some areas, such as Spain (20), may influence the empirical antibiotic treatment, when used, of AECB episodes.

Cefditoren-pivoxil (CDN) is an oral, β-lactamase-stable, expanded-spectrum cephalosporin with MICs for 90% of AECB isolates (MIC_{90}s) that are lower than those of other oral cephalosporins. For β-lactam antibiotics, the time that drug con-

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centrations in serum exceed the MIC for the pathogen is the key indicator of bacteriological efficacy, 35 to 40% of the time between two doses being the predictive value for maximal bacteriological efficacy (6, 25). When plotting mean concentrations of CDN in serum (29) against the MICs for the main AECB isolates, CDN covers all *H. influenzae* Spanish isolates (MIC range, ≤0.03 to 0.12 μg/ml; MIC_{90}, <0.03 μg/ml) (26) for ≥63% of the dosing interval and 94.1% of the *S. pneumoniae* isolates in Spain (MIC range, <0.03 to 4 μg/ml; MIC_{90}, 0.5 μg/ml) (27) for at least ≅40% of the dosing interval.

In patients with several exacerbations per year with moderate impairment of lung function and comorbidity, a broad- or expanded-spectrum cephalosporin has been recommended (11), such as cefuroxime-axetil (CXM) with 100% of *H. influenzae* isolates, the main isolate in AECB (5), showing susceptibility (20). The pharmacodynamic coverage (pharmacodynamic breakpoints based on the time that drug concentrations in serum exceed the MIC) of *H. influenzae* by CXM ranges from 73 to 83% (20, 25). The present study was carried out to determine whether the clinical efficacy of CDN for 5 days was noninferior to that of the standard CXM treatment for 10 days of AECB in adults by an arbitrarily chosen margin of 10%.

MATERIALS AND METHODS

Study design. This randomized, double-blind, double-dummy, parallel multicenter phase III study consisting of a double-blind treatment period of 10 days, followed by a 20-day follow-up period without treatment, was carried out at a total of 64 centers in Germany, Spain, Austria, Switzerland, and Italy (36, 22, 2, 2, and 2 centers, respectively). The protocol was approved by the ethics committees of the 64 participating centers. All patients gave written informed consent prior to study entry.

Patient selection. Adult patients aged at least 18 years with a diagnosis (based on anamnesis and previous clinical history) of chronic bronchitis (defined as coughing and production of sputum on most days for at least 3 months per year for 2 consecutive years) and with a clinical diagnosis of type I or II AECB, as defined by Anthonisen (1), characterized by intensification of preexisting dyspnea, an increase in sputum volume, and sputum purulence (type I), or the presence of two out of these three symptoms (type II) were eligible for the study. Patients with known hypersensitivity to beta-lactam compounds; female patients who were pregnant, lactating, or using inadequate contraception; and patients with known significant liver impairment or renal insufficiency were excluded. Other exclusion criteria were evidence of congestive heart failure, cystic fibrosis, pneumonia, active tuberculosis, human immunodeficiency virus infection, cancer, antimicrobial therapy in the previous 2 days, concomitant infection requiring antibiotic therapy, and a leukocyte count of less than 4,000/mm^3. Previous inclusion in the present study was also an exclusion criterion.

Treatment. Patients who fulfilled the inclusion and exclusion criteria were randomized (1:1) to receive 200 mg of CDN twice a day for 5 days or 250 mg of CXM twice a day for 10 days. Concomitant medication was prescribed at investigator discretion.

Clinical assessment. Patients were examined at the time of entry into the study (baseline, visit 1), and evaluations were performed during treatment (visit 2; day 3 ± 1), at the end of treatment (visit 3; day 11 ± 1), and at the end of the study (visit 4; day 30 ± 5). At all visits, the following variables were assessed by the investigator on the scales indicated: cough (0 = none, 1 = night or morning only, 2 = episodes during the day, and 3 = nearly continuous [day and night]), dyspnea (0 = none, 1 = only on unusual exertion, 2 = present during normal activity, and 3 = present at rest), wheezing and sputum quantity (0 = none, 1 = ≤30 ml, and 2 = >30 ml), sputum quality (0 = none, 1 = mucoid, 2 = mucopurulent up to 50% pus, and 3 = purulent), rales and rhonchi at auscultation, and forced expiry volume over 1 s (FEV_1)/forced vital capacity (FVC). These data were compared at visits 2, 3, and 4 with those present at baseline to evaluate clinical responses. Resolution was considered complete when all acute clinical signs and symptoms of AECB returned to the baseline level (the patient's normal, nonexacerbated state). Improvement was considered to have occurred when at least 50% of all signs and symptoms of AECB returned to the baseline level (the patient's normal, nonexacerbated state). At visit 3, the clinical response was defined as success (resolution or improvement [resolution of at least 50% of symptoms]) or failure (persistence or progression of symptoms or indeterminate). At visit 4, the clinical response was also defined as success (continued resolution or improvement) or failure (nonresponse or reappearance of signs and symptoms and need for antibacterial therapy).

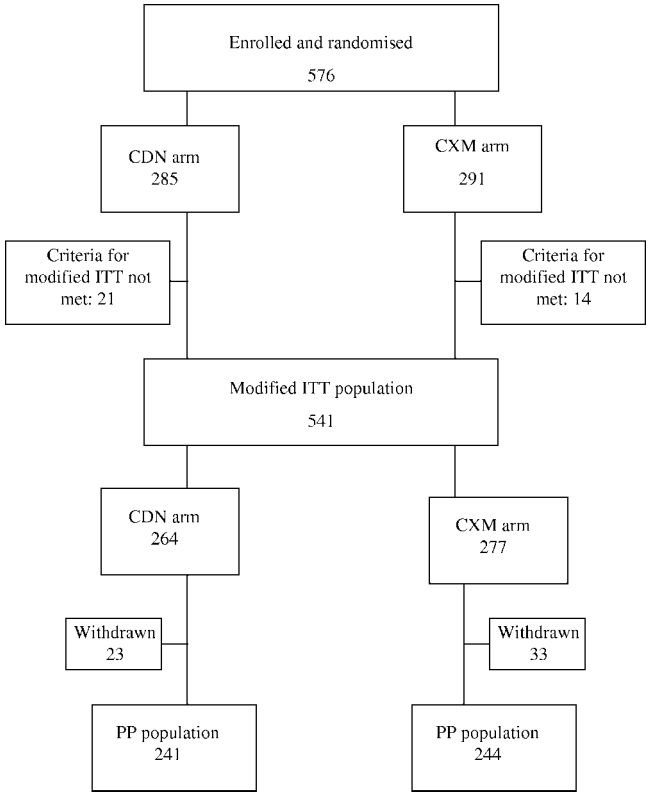

FIG. 1. Disposition of the patients included in this study.

Per-pathogen bacteriological assessment. All sputum samples were sent to the central microbiology laboratory (Microbiology Department, Hospital Ramón y Cajal, Madrid, Spain) for identification of respiratory isolates. Samples were considered suitable for culture only if the number of polymorphonuclear leukocytes was more than 25 per low-magnification field (×100) and if the number of squamous epithelial cells was less than 10 per low-magnification field (×100). The per-pathogen bacteriological response was rated as responder (eradication [number of organisms below the level of detection], presumed eradication [absence of sputum for culture in a patient with clinical improvement]) or nonresponder (persistence, presumed persistence [absence of sputum in a patient with clinical failure], relapse, and reinfection).

Determination of efficacy. The primary efficacy parameter was the clinical response at visit 3. Clinical response at visit 4 and bacteriological response at visit 3 and visit 4 were considered secondary efficacy parameters.

The overall clinical response was evaluated as success if the patient was a responder at both visit 3 and visit 4. If the clinical efficacy evaluation was not possible at visit 4, the overall clinical response was equal to the clinical response at visit 3.

Safety parameters. Laboratory tests were performed at visits 1, 2, and 3. In the case of abnormal values at visit 3, laboratory tests were repeated at visit 4. All adverse events, including abnormalities in laboratory values, were recorded, and severity (mild, moderate, severe) and relationship to the study drug (definitive, probable, possible, improbable) were assessed during the active treatment period and during the follow-up study phase.

Statistical analysis. A total of four patient groups were identified for efficacy analysis. The modified intention-to-treat (ITT) population comprised all randomized patients that met the criteria of AECB and took at least one dose of the study medication. The clinical per-protocol (PP) population was a subset of the ITT population and excluded patients with major protocol violations. The bacteriological ITT population included all patients in the ITT population who had at least one isolate identified at visit 1. The bacteriological PP population in-

TABLE 1. Demographic characteristics of the patients included in this study

Parameter	CDN (n = 285)	CXM (n = 291)
Age (yr, mean ± SD)	61.1 ± 14.9	61.9 ± 14.1
Ht (cm, mean ± SD)	166.5 ± 8.4	166.2 ± 9.6
Wt (kg, mean ± SD)	73.2 ± 14.1	74.6 ± 15.5
Sex (% males)	75.4	75.3
Ethnic group (% white)	98.2	98.3
% Ex-smokers/% smokers/% nonsmokers	47.7/26.3/26	45.7/24.1/30.2
% with hypertension	20.7	24.1
% with obesity	21.8	23.7
% with asthma	6.3	6.2
% with emphysema	4.9	3.4
% with FEV_1/FVC of <70%	90.9	92.8
% with intake of sympathomimetics	62.8	57.7
% with intake of corticosteroids	56.5	52.6
% with intake of antimuscarinic agents	41.4	38.8

cluded all patients in the PP population who had at least one isolate identified at visit 1.

The safety population included all patients with at least one intake of a study medication.

The study was powered as a noninferiority study, and the sample size was calculated in order to demonstrate that CDN was not >10% less effective than the comparator regimen. Sample size was based on a predicted failure rate of 20% in the comparator arm with an arbitrarily chosen 10% equivalence (delta value) between study arms. Thus, with an error probability of 0.025 (alpha error) and of 0.2 for beta, the method of Farrington (7) yielded a sample size of 255 patients per treatment arm. A dropout rate of 10% was assumed, so it was planned to include 284 patients per treatment arm.

The analysis of the primary efficacy criterion (clinical response at visit 3) was performed for the clinical ITT and for the PP population. A two-sided 95% confidence interval (CI) was used to estimate the difference in the proportion of success between the two groups. A conclusion of noninferiority was reached if the lower limit of the CI was not less than −10%.

RESULTS

Disposition of patients, demographics, and concomitant medications. Figure 1 shows the disposition of the patients included in this study. A total of 576 patients (278 in Germany, 257 in Spain, and 41 in the remaining countries) signed the informed consent form for participation in this study. Two hundred eighty-five patients were assigned to the CDN arm, and 291 patients were assigned to the CXM arm. Demographic characteristics, concomitant diseases, and the most frequent concomitant medications (sympathomimetics, corticosteroids, and antimuscarinic agents) are shown in Table 1. No differences were found between the two treatment populations. Thirty-five patients (21 patients in the CDN arm and 14 patients in the CXM arm) were excluded from any efficacy analysis for the following reasons: failure to meet the criteria of type I or II AECB (25 patients), previous participation in this study (6 patients), no intake of study medication (2 patients), X-ray diagnosis of pneumonia (1 patient), and tuberculosis diagnosis (1 patient). For efficacy analysis, the ITT population comprised 541 patients, 264 patients in the CDN arm and 277 patients in the CXM arm. Major protocol violations (compliance of <80%, lack of compliance with visit 3 as scheduled, and intake of nonpermitted medications) affected 23 patients in the CDN arm and 33 patients in the CXM arm. Therefore, the PP population consisted of 485 patients, 241 patients in the CDN arm and 244 patients in the CXM arm. Since two patients (both in the CXM arm) out of the 576 randomized patients did not take any dose of the study medication, the safety population comprised 574 patients, 285 patients in the CDN arm and 289 patients in the CXM arm.

Clinical characteristics at baseline and their evolution during the treatment and posttreatment periods. Baseline clinical characteristics and their evolution during the treatment and posttreatment periods are shown in Table 2 for the ITT population and in Table 3 for the PP population. There were no differences in baseline characteristics between the two treatment groups. The effect of both antibiotics is more clearly seen in the characteristics of the sputum; the percentage of patients with >30 ml of sputum decreased from around 75% (visit 1) to 5% (visit 4) for the two populations analyzed (ITT and PP) with both compounds. The same occurred with sputum purulence: an approximately 87% rate of purulent or mucopurulent sputum at baseline and approximately 5% at visit 4. Rales and rhonchi decreased from 77% to approximately 24%, and wheezing decreased from 60% to 15%, with no differences between treatment groups. Much more modest was the effect of both treatments on cough and dyspnea, which decreased from baseline to visit 4 from around 100% to 75 to 80%.

Clinical response. Table 4 shows clinical responses as evaluated at visits 3 and 4, as well as the overall clinical evaluation of both the ITT and PP populations. In the ITT population, at the end of treatment (day 11), the clinical success rate was 79.9% versus 82.7% (treatment difference, −2.8; 95% CI, −9.7 to 3.6%), and at posttreatment (day 30) it was 81.0% versus 85.5% (treatment difference, −4.5; 95% CI, −11.1 to 2.1%) for CDN versus CXM. In the PP population, at the end of treatment (day 11), the clinical success rate was 82.2% versus 83.2% (treatment difference, −1.0; 95% CI, −7.9 to 5.8%), and at posttreatment (day 30) it was 83.0% versus 85.7% (treatment difference, −2.7; 95% CI, −9.4 to 4.1%) for CDN versus

TABLE 2. Signs and symptoms at the four study visits for the modified ITT population (n = 541)

Parameter	CDN (%)				CXM (%)			
	Visit 1 (basal; n = 264)	Visit 2 (n = 264)	Visit 3 (n = 264)	Visit 4 (n = 247)	Visit 1 (basal; n = 277)	Visit 2 (n = 277)	Visit 3 (n = 277)	Visit 4 (n = 262)
Cough	100	97.3	87.5	78.5	100	98.2	93.9	79.8
Dyspnea	98.5	90.2	81.4	78.1	98.6	95.7	83.0	74.4
Wheezing	60.2	42.0	22.7	15.8	59.6	39.7	21.7	14.5
Rales and rhonchi	76.9	56.4	29.5	23.9	77.6	56.0	32.9	22.1
Sputum vol, >30 ml	75.8	28.4	9.1	4.5	75.5	30.7	7.6	5.0
Sputum purulence	87.1	45.1	12.9	4.0	87.7	46.6	9.4	5.7
FEV_1/FVC (mean ± SD)	49.9 ± 11.5	55.4 ± 16.2	56.7 ± 17.4	57.1 ± 18.1	51.0 ± 12.4	57.0 ± 15.8	59.2 ± 17.9	58.9 ± 17.9

TABLE 3. Signs and symptoms at the four study visits for the PP population (n = 485)

Parameter	CDN (%)				CXM (%)			
	Visit 1 (basal; n = 241)	Visit 2 (n = 241)	Visit 3 (n = 241)	Visit 4 (n = 229)	Visit 1 (basal; n = 244)	Visit 2 (n = 244)	Visit 3 (n = 244)	Visit 4 (n = 237)
Cough	100	97.9	88.0	79.0	100	98.0	93.4	81.0
Dyspnea	98.3	90.9	80.9	76.9	98.4	95.5	82.4	75.1
Wheezing	60.6	42.7	23.7	16.2	57.4	38.9	22.1	14.3
Rales and rhonchi	77.2	56.8	31.1	24.5	77.0	56.1	32.4	22.8
Sputum vol, >30 ml	75.9	29.0	10.0	4.8	76.2	31.6	7.8	4.2
Sputum purulence	87.1	46.1	13.7	3.9	87.7	47.5	9.4	5.5
FEV_1/FVC (mean ± SD)	49.9 ± 11.6	55.7 ± 16.1	57.0 ± 17.3	57.6 ± 18.3	50.9 ± 12.6	56.9 ± 15.7	59.2 ± 18.0	58.5 ± 17.7

CXM. The results fail to exclude the noninferiority margin of −10% in the ITT population at visit 4 and overall and in the PP population in the overall analysis (Table 4).

Per-pathogen bacteriological response. At baseline (visit 1) in the ITT population, 103 isolates were found in 85 patients in the CDN group and 94 isolates were found in 84 patients in the CXM group; in the PP population, 97 isolates were found in 80 patients in the CDN group and 90 isolates were found in 80 patients in the CXM group, which were the basis for the exploratory bacteriological evaluation (Table 5). No differences in the per-pathogen bacteriological response were found between treatment arms at visit 3 or visit 4 in both the ITT and PP population exploratory analyses.

Of the 103 isolates found at baseline in 85 CDN-treated patients, 85 isolates were from patients who afterwards showed clinical success at visit 3 (all but 11 were eradicated or presumably eradicated) and 18 isolates were from patients who afterwards showed clinical failure at visit 3 (of these, only 1 isolate was eradicated or presumably eradicated). Of the 94 isolates found at baseline in 84 CXM-treated patients, 79 isolates were from patients who afterwards showed clinical success at visit 3 (all but 16 were eradicated or presumably eradicated) and 15 isolates were from patients who afterwards showed clinical failure at visit 3 (of these, none was eradicated or presumably eradicated; all 15 were nonresponders in the per-pathogen bacteriological exploratory evaluation).

Clinical versus bacteriological response. Of the 197 isolates found at baseline (ITT population, 169 patients evaluable for bacteriological efficacy), 90 (45.7%) were *H. influenzae*, 29 (14.7%) were *S. pneumoniae*, 16 (8.1%) corresponded to *M. catarrhalis*, and 10 (5.1%) were *H. parainfluenzae*. The remaining 26.4% of the isolates were members of the family *Enterobacteriaceae*, nonfermentative gram-negative bacilli, and *Staphylococcus aureus*.

No differences were found in the exploratory per-patient analysis of clinical responses of patients infected by key pathogens (Table 6).

Safety evaluation. All patients who received at least one dose of the study drug (574 patients) were included in the safety analysis. During the entire study, including the follow-up period, adverse events were reported for a total of 127 patients (22.1%), 66 patients (23.2%) in the CDN arm and 61 patients (21.1%) in the CXM arm. During the active treatment period, 25 (8.8%) and 38 (13.1%) patients treated with CDN and CXM, respectively, experienced adverse events. The overall incidences of adverse events that were considered related to the study medication were 7.7% and 11.4% in the CDN and CXM groups, respectively. The most common adverse events are shown in Table 7. A total of 43 patients experienced serious adverse events during the entire study period, 24 patients (8.4%) in the CDN arm and 19 patients (6.6%) in the CXM group. Four patients in each treatment group experienced the following serious adverse events within the active treatment period: acidosis, depression, bronchospasm, and respiratory failure in the CDN group and dyspnea, ileus, respiratory failure, and persistent fever in the CXM group.

Nine deaths occurred during the study, six patients in the CDN group and three patients in the CXM group. In the CDN group, one hospitalized patient (72 years old) with cor pulmonale died during the active treatment period due to cardiac failure. The remaining five patients (≥70 years old) died during the follow-up study period due to pneumonia (two cases), respiratory failure (two cases), or cardiac failure (one case). All deaths occurring in this group were evaluated as clinical failures. The three deaths in the CXM group occurred in the follow-up study period in patients aged >69 years because of cardiac failure associated with pulmonary damage and chronic cor pulmonale (evaluated as clinical failure), cardiorespiratory insufficiency post total gastrectomy due to gastric adenocarcinoma diagnosed at day 25 of the follow-up (evaluated as clinical success), and a traffic accident on day 15 of the follow-up (evaluated as clinical success). In both groups, all deaths occurred in patients with severe comorbidity, and a relationship with the study drugs was assessed as improbable.

TABLE 4. Visit 3, visit 4, and overall clinical success, treatment differences, and CIs for the modified ITT and PP populations

Period	ITT population[a]		Treatment difference (95% CI)	PP population[a]		Treatment difference (95% CI)
	CDN	CXM		CDN	CXM	
Visit 3	264 (79.9)	277 (82.7)	−2.8 (−9.7 to 3.6)	241 (82.2)	244 (83.2)	−1.0 (−7.9 to 5.8)
Visit 4	247 (81.0)	262 (85.5)	−4.5 (−11.1 to 2.1)	229 (83.0)	237 (85.7)	−2.7 (−9.4 to 4.1)
Overall	264 (71.6)	277 (76.2)	−4.6 (−12.3 to 2.5)	241 (73.4)	244 (75.8)	−2.4 (−10.1 to 5.4)

[a] The number of patients (percent clinical success) is shown.

TABLE 5. Exploratory analysis of posttreatment per-pathogen bacteriological response (eradication plus presumed eradication), treatment differences, and CIs for the modified ITT and PP populations

Parameter	ITT population				PP population			
	Visit 3		Visit 4		Visit 3		Visit 4	
	CDN	CXM	CDN	CXM	CDN	CXM	CDN	CXM
No. of baseline pathogens	103	94	100	86	97	90	95	84
Eradication, *n* (%)	15 (14.6)	8 (8.5)	6 (6.0)	6 (7.0)	14 (14.4)	8 (8.9)	6 (6.3)	6 (7.1)
Presumed eradication, *n* (%)	60 (58.3)	55 (58.5)	59 (59.0)	53 (61.6)	58 (59.8)	51 (56.7)	58 (61.1)	53 (63.1)
Bacteriological response, *n* (%)	75 (72.8)	63 (67.0)	65 (65.0)	59 (68.6)	72 (74.2)	59 (65.6)	64 (67.4)	59 (70.2)
Treatment difference (95% CI)	5.8 (−7.0 to 18.6)		−3.6 (−17.3 to 9.8)		8.6 (−4.4 to 21.8)		−2.8 (−16.5 to 10.5)	

DISCUSSION

Although a number of AECB episodes are self-limiting (24), it has been suggested that antibiotic treatment resulted in fewer failures with deterioration versus placebo (1), but other authors question the antimicrobial treatment approach to this disease (11). If a decision to prescribe antibiotics is made, the choice of the antimicrobial to be used is important (2) because of different susceptibility and resistance patterns of target bacteria in different areas. Furthermore, an important area of uncertainty is the optimal length of antibiotic therapy, ranging from 5 to 14 days, 7 to 10 days being the most frequently prescribed course of therapy (12). The adequacy of antibiotic treatment (adequate antibiotic dosage and adequate length of treatment) is important on the basis of the compelling evidence that the most costly aspect of AECB is treatment failure (16). Recent guidelines recommended adequate antimicrobial therapy for patients showing signs and symptoms of bacterial infection, acknowledging the uncertainty in the data on the use of antibiotics against this disease (18).

In this study, the baseline characteristics of the patients (age, 61.5 ± 14.5 years; prestudy smoking history) and the required symptoms of exacerbation (Anthonisen types I and II) ensured the inclusion of patients with underlying chronic bronchitis and may have increased the chance of infection of bacterial origin. Approximately 31% (169 out of 541) of the patients had one or more isolates isolated at visit 1, a result similar to those of other studies (21, 23). *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* are isolated in 70% of infectious AECB cases (4). In our study, 45.7% (90 out of 197) of the isolates were *H. influenzae*, 14.7% were *S. pneumoniae*, and 7.1% were *M. catarrhalis*. Despite the fact that antibiotic treatment, if prescribed, should be directed at all of these pathogens (19), *H. influenzae* remains the main target of antibiotic treatment.

Although increases in the antimicrobial resistance of prevalent isolates of community-acquired respiratory tract infections are of global concern (20), this may not be reflected in clinical trial populations. Moreover, previous reports have shown that patients with resistant pathogens may have success rates similar to those of patients with susceptible pathogens (30). In these situation, physicians should consider, in addition to the patient's condition, local epidemiology of AECB-related pathogens and their in vitro susceptibility to interpret the results of a study (30). Both of the oral cephalosporins used in this study exhibited very good activity against *H. influenzae* (20, 26), the main AECB isolate, against which a clinical response (84% versus 82.5% for CDN versus CXM, respectively) was obtained as shown in Table 6. The lower rate of *S. pneumoniae* susceptibility to CXM (20) than to CDN (27) is not reflected in this clinical trial since only 5.4% (29 out of 541) of the patients presented an *S. pneumoniae* isolate. In any case, and as specified in Results, the exploratory analysis of per-pathogen bacteriological responses correlated well in this study with clinical responses; of the 164 isolates obtained at baseline from patients with clinical success, 137 (83.5%) were eradicated or presumably eradicated, while of the 33 isolates obtained at baseline from patients with clinical failure, this bacteriological outcome only occurred in one case (3%).

Antimicrobial prescribing should aim to eradicate or maximally reduce the pathogen bacterial load (3). The exploratory analysis of the relationship of the bacteriological response and the clinical response suggests that the response may be more rapidly seen in signs that depend on bacterial location (a more rapid and greater decrease over time in sputum volume and purulence and rales and rhonchi) than in those depending in part on previous structural damage (dyspnea).

Both compounds also exhibited a profile of adverse events

TABLE 6. Exploratory per-patient analysis of clinical success by key baseline pathogens

Pathogen	*n* (%)		Treatment difference (95% CI)
	CDN	CXM	
Haemophilus influenzae	50 (84.0)	40 (82.5)	1.5 (−14.0 to 17.1)
Streptococcus pneumoniae	13 (92.3)	16 (81.3)	11 (−13.0 to 35.0)
Moraxella catarrhalis	10 (90.0)	6 (100)	−10 (−29.2 to 11.2)
Haemophilus parainfluenzae	6 (83.3)	4 (100)	−16.7 (−47.1 to 15.7)

TABLE 7. Frequencies of the most common adverse events reported during the active treatment period

Adverse event[a]	% of patients	
	CDN (*n* = 285)	CXM (*n* = 289)
Diarrhea	1.8	2.1
Abdominal pain	1.4	1.4
Headache	0.7	1
Constipation	0.7	0.3
Nausea	0.4	1
Vomiting	0.4	1
Diaphoresis	0.4	0.7
SGOT/SGPT increase	0	2.4
Blood urea increase	0	0.7
Heartburn	0	0.7

[a] SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

compatible with that of cephalosporins (gastrointestinal system disorders being the most frequently reported adverse events) and with that expected in patients with AECB.

Although a delta value of 10% is larger than the margin of benefit of the control over a placebo (based on a previous study showing that the control drug is only 3% better than a placebo (1), a 5-day course of CDN and the standard 10-day CXM course had similar point estimates of success in the treatment of AECB.

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REFERENCES

1. **Anthonisen, N. R., J. Manfreda, C. P. Warren, E. S. Hershfield, G. K. Harding, and N. A. Nelson.** 1987. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann. Intern. Med. **106:**196–204.
2. **Appelbaum, P. C., S. H. Gillespie, C. J. Burley, and G. S. Tillotson.** 2004. Antimicrobial selection for community-acquired lower respiratory tract infections in the 21st century: a review of gemifloxacin. Int. J. Antimicrob. Agents. **23:**533–546.
3. **Ball, P., F. Baquero, O. Cars, T. File, J. Garau, K. Klugman, D. E. Low, E. Rubinstein, R. Wise, and the Consensus Group on Resistance and Prescribing in Respiratory Tract Infection.** 2002. Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimized resistance emergence. J. Antimicrob. Chemother. **49:**31–40.
4. **Ball, P., and B. Make.** 1998. Acute exacerbations of chronic bronchitis: an international comparison. Chest **113**(3 Suppl.)**:**199S–204S.
5. **Barberán, J., M. J. Giménez, L. Aguilar, and J. Prieto.** 2004. Evidencia científica y concepción global del tratamiento empírico de la infección de vías respiratorias bajas en la comunidad. Rev. Esp. Quimioter. **17:**317–324.
6. **Craig, W. A.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. **26:**1–12.
7. **Farrington, C. F., and G. Manning.** 1990. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat. Med. **9:**1447–1454.
8. **Garcia-Rey, C., L. Aguilar, F. Baquero, J. Casal, and R. Dal-Re.** 2002. Importance of local variations in antibiotic consumption and geographical differences of erythromycin and penicillin resistance in *Streptococcus pneumoniae*. J. Clin. Microbiol. **40:**159–164.
9. **Garcia-Rey, C., A. Fenoll, L. Aguilar, and J. Casal.** 2004. Effect of social and climatological factors on antimicrobial use and *Streptococcus pneumoniae* resistance in different provinces in Spain. J. Antimicrob. Chemother. **54:**465–471.
10. **Granizo, J. J., L. Aguilar, J. Casal, C. Garcia-Rey, R. Dal-Re, and F. Baquero.** 2000. *Streptococcus pneumoniae* resistance to erythromycin and penicillin in relation to macrolide and beta-lactam consumption in Spain (1979–1997). J. Antimicrob. Chemother. **46:**767–773.
11. **Grossman, R. F.** 1997. Guidelines for the treatment of acute exacerbations of chronic bronchitis. Chest **112**(6 Suppl.)**:**310S–313S.
12. **Guest, N., and C. E. Langan.** 1998. Comparison of the efficacy and safety of a short course of ceftibuten with that of amoxycillin/clavulanate in the treatment of acute exacerbations of chronic bronchitis. Int. J. Antimicrob. Agents. **10:**49–54.
13. **Gump, D. W., C. A. Phillips, B. R. Forsyth, K. McIntosh, K. R. Lamborn, and W. H. Stouch.** 1976. Role of infection in chronic bronchitis. Am. Rev. Respir. Dis. **113:**465–474.
14. **Jorgensen, A. F., J. Coolidge, P. A. Pedersen, K. P. Petersen, S. Waldorff, and E. Widding.** 1992. Amoxicillin in treatment of acute uncomplicated exacerbations of chronic bronchitis. A double-blind, placebo-controlled multicentre study in general practice. Scand. J. Prim. Health Care **10:**7–11.
15. **Madison, J. M., and R. S. Irwin.** 1998. Chronic obstructive pulmonary disease. Lancet **352:**467–473.
16. **Miravitlles, M., C. Murio, T. Guerrero, R. Gisbert, and the DAFNE Study Group.** 2002. Decisiones sobre Antibioticoterapia y Farmacoeconomia en la EPOC. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. Chest **121:**1449–1455.
17. **Nicolson, P., and P. Anderson.** 2000. The patient's burden: physical and psychological effects of acute exacerbations of chronic bronchitis. J. Antimicrob. Chemother. **45:**25–32.
18. **Pauwels, R. A., A. S. Buist, P. M. Calverley, C. R. Jenkins, S. S. Hurd, and the GOLD Scientific Committee.** 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am. J. Respir. Crit. Care Med. **163:**1256–1276.
19. **Pechere, J. C., and L. Lacey.** 2000. Optimizing economic outcomes in antibiotic therapy of patients with acute bacterial exacerbations of chronic bronchitis. J. Antimicrob. Chemother. **45:**19–24.
20. **Perez-Trallero, E., C. Garcia-de-la-Fuente, C. Garcia-Rey, F. Baquero, L. Aguilar, R. Dal-Re, J. Garcia-de-Lomas, and the Spanish Surveillance Group for Respiratory Pathogens.** 2005. Geographical and ecological analysis of resistance, coresistance and coupled-resistance to antimicrobials in and between respiratory pathogenic bacteria in Spain. Antimicrob. Agents Chemother. **49:**1965–1972.
21. **Pfaller, M. A., A. F. Ehrhardt, and R. N. Jones.** 2001. Frequency of pathogen occurrence and antimicrobial susceptibility among community-acquired respiratory tract infections in the respiratory surveillance program study: microbiology from the medical office practice environment. Am. J. Med. **111**(Suppl. 9A)**:**4S–12S
22. **Saint, S., S. Bent, E. Vittinghoff, and D. Grady.** 1995. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA **273:** 957–960.
23. **Sethi, S., J. Breton, and B. Wynne.** 2005. Efficacy and safety of pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 milligrams twice daily for 5 days versus amoxicillin-clavulanate at 875/125 milligrams twice daily for 7 days in the treatment of acute exacerbations of chronic bronchitis. Antimicrob. Agents Chemother. **49:**153–160.
24. **Sethi, S., N. Evans, B. J. Grant, and T. F. Murphy.** 2002. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. N. Engl. J. Med. **347:**465–471.
25. **Soriano, F.** 2004. Importancia de los parámetros farmacocinéticos y farmacodinámicos en la elección del tratamiento antimicrobiano de la infección respiratoria. Med. Clin. Monogr. (Barcelona) **5:**6–11.
26. **Soriano, F., J. J. Granizo, P. Coronel, M. Gimeno, E. Rodenas, M. Gracia, C. Garcia, R. Fernandez-Roblas, J. Esteban, and I. Gadea.** 2004. Antimicrobial susceptibility of *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Moraxella catarrhalis* isolated from adult patients with respiratory tract infections in four southern European countries. The ARISE project. Int. J. Antimicrob. Agents **23:**296–299.
27. **Soriano, F., J. J. Granizo, A. Fenoll, M. Gracia, R. Fernandez-Roblas, J. Esteban, I. Gadea, P. Coronel, M. Gimeno, E. Rodenas, and F. Santos.** 2003. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* isolated in four southern European countries (ARISE project) from adult patients: results from the cefditoren surveillance program. J. Chemother. **15:**107–112.
28. **Torres, A.** 2004. Tratamiento antibiótico de las agudizaciones de la enfermedad pulmonar obstructiva crónica. Papel de la nueva formulación de liberación prolongada de amoxicilina-ácido clavulánico 2.000/125 mg. Med. Clin. Monogr. (Barcelona) **5:**37–41.
29. **Wellington, K., and M. P. Curran.** 2004. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. Drugs **64:**2597–2618.
30. **Wilson, R., L. Allegra, G. Huchon, J. L. Izquierdo, P. Jones, T. Schaberg, P. P. Sagnier, and the MOSAIC Study Group.** 2004. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. Chest **125:**953–964.