# Original Article

## Comparison between azithromycin and amoxicillin in the treatment of infectious exacerbation of chronic obstructive pulmonary disease*

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## Abstract

**Objective:** To compare the efficacy, safety, and tolerability of azithromycin and amoxicillin in the treatment of patients with infectious exacerbation of chronic obstructive pulmonary disease. **Methods:** This study was conducted at six medical centers across Brazil and included 109 patients from 33 to 82 years of age. Of those, 102 were randomized to receive either azithromycin (500 mg/day for three days, n = 49) or amoxicillin (500 mg every eight hours for ten days, n = 53). The patients were evaluated at the study outset, on day ten, and at one month. Based on the clinical evaluation of the signs and symptoms present on day ten and at one month, the outcomes were classified as cure, improvement, or treatment failure. The microbiological evaluation was made through the culture of sputum samples that were considered appropriate samples only after leukocyte counts and Gram staining. Secondary efficacy evaluations were made in order to analyze symptoms (cough, dyspnea, and expectoration) and pulmonary function. **Results:** There were no differences between the groups treated with azithromycin or amoxicillin in terms of the percentages of cases in which the outcomes were classified as cure or improvement: 85% *vs.* 78% (p = 0.368) on day ten; and 83% *vs.* 78% (p = 0.571) at one month. Similarly, there were no significant differences between the two groups in the secondary efficacy variables or the incidence of adverse effects. **Conclusion:** Azithromycin and amoxicillin present similar efficacy and tolerability in the treatment of acute exacerbation of chronic obstructive pulmonary disease.

**Keywords:** Amoxicillin/therapeutic use; Azithromycin/therapeutic use; Bronchitis, chronic/drug therapy;Pulmonary disease, chronic obstructive/drug therapy; Comparative study.

* Multicenter study

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Submitted: 28 June 2005. Accepted, after review: 12 April 2006.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by progressive airflow limitation that is not fully reversible.[1] Most of the cases occur in patients who are smokers or former smokers, and COPD is characterized by an accelerated decrease in the forced expiratory volume in one second.[2] In addition, COPD presents a spectrum of pathological alterations and clinical manifestations.[3] Within this spectrum, chronic bronchitis is defined as chronic productive cough for at least three months during two consecutive years.[4] Chronic bronchitis is characterized by the obstruction of small-diameter airways and increased mucous production. In addition, many patients with chronic bronchitis present varying degrees of emphysema, characterized by the destruction of air spaces and loss of lung elasticity.[3] Therefore, it is sometimes difficult to discern the individual contribution of these two pathological processes, chronic bronchitis and emphysema, to the clinical manifestations in a patient. Although the epidemiology of COPD is not well known in Brazil yet, an epidemiological population-based study, conducted in the metropolitan area of the city of São Paulo, demonstrated that 15.8% of individuals above 40 years of age meet the criteria for COPD.[5] In addition, COPD was the fourth leading cause of hospitalizations in Brazil in adults in 2002.[6]

Patients with COPD present frequent episodes of infectious exacerbation. These episodes are characterized by rapid worsening of pulmonary function, worsening of airway obstruction, and increased mucus production. It is estimated that patients with COPD have, on average, up to three annual episodes of infectious exacerbation.[4] Despite the multifactorial origin of the exacerbation, infection is its principal cause, being responsible for 50 to 80% of the cases.[4,6,7] Among these, the most frequent are the bacterial infections, and the most commonly found pathogens are *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*.[6] Compared to a placebo, antibiotics are considered efficacious, shortening the duration of the infectious exacerbation.[8,9] Therefore, patients with infectious exacerbation of COPD frequently require treatment with oral broad-spectrum antibiotics, which can be administered in a reasonable manner, with safety and expected efficacy in most cases. Various classes of antibiotics are currently available for this purpose. The objective of the present study was to compare the efficacy, safety and tolerability of two oral antibiotics, azithromycin and amoxicillin, in the outpatient treatment of individuals with infectious exacerbation of COPD.

## Methods

The patients who were considered for inclusion in the study were between 30 and 70 years of age and had been diagnosed with infectious exacerbation of COPD. The diagnosis was confirmed based on the presence of at least two of the following criteria: increased cough, increased expectoration or worsening of dyspnea. Subjects were required to have been under outpatient treatment and to have had a simple chest X-ray that showed no evidence of pneumonia performed within the 48 hours preceding their inclusion in the study. Female patients who were breastfeeding, pregnant or planning to become pregnant (during the study or up to one month after the end of the study) were excluded, as were women of childbearing age who were not using some efficacious method of contraception. Additional exclusion criteria were as follows: having a history of hypersensitivity to azithromycin or amoxicillin; undergoing treatment with systemic antibiotics within the two weeks preceding the study outset; use of antibiotics foreseen for other clinical condition, as well as the use of allopurinol, probenecid, digoxin, warfarin or ergotamine during the study; having a history of human immunodeficiency virus infection, acute bronchitis or bronchiectasis; having been suspected of having lung abscess or empyema; having a history of or having been suspected of having active tuberculosis, cystic fibrosis or lung cancer (primary or metastatic); having any clinical or psychological condition deemed by the examiner to potentially impair participation in the study; having a history of alcohol or substance abuse; undergoing treatment with immunosuppressive drugs, including doses of corticosteroids higher than the equivalent to 10 mg/day of prednisone; presenting any of the following laboratory test results: leukocyte count lower than 2500/mm$^3$ – neutrophil count lower than 1000/mm$^3$ – elevated transaminase levels of over twice the upper limit of normality – alkaline phosphatase or bilirubin levels greater than 1.5 times the upper

limit of normality; donating blood during the study or within one month after the conclusion of the study; participating in clinical studies, including this one, within one month prior to the inclusion in the present study.

All of the patients included in the study gave written informed consent. The protocol was approved by the ethics in research committee of each of the six centers participating in the study, which was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Guidelines for Good Clinical Practice in Clinical Trials and the federal resolutions that regulate clinical research in Brazil.

The patients considered for inclusion in the study were evaluated in the initial medical visit, during which clinical histories were taken, complete physical examinations were performed, laboratory tests were conducted, simple chest X rays were taken, spirometry was performed, and purulent sputum (recently expectorated) was submitted to microbiological analysis. Evaluation of sputum was performed after Gram staining and culture of samples considered appropriate, defined as those containing more than 25 leukocytes and less than 10 squamous epithelial cells per low-power microscopic field (×100).[10] The patients were then randomly allocated to receive azithromycin (500 mg/day, p.o., for three consecutive days) or amoxicillin (500 mg/8 h, p.o., for ten consecutive days). After ten days, the patients were again examined: histories were re-taken; vital signs were checked; spirometry was performed; and another sputum sample was submitted to microbiological evaluation. The third and final examination was performed at approximately one month after the initiation of treatment and included the same procedures conducted in the second examination. Patients were required to report all medications taken during the study. The quantities of azithromycin and amoxicillin used by the patients were calculated in order to evaluate adherence to the treatment.

In order to evaluate efficacy and safety, two patient samples were analyzed. The evaluation of safety was performed with an intention-to-treat patient sample, comprising all of the patients who took at least one dose of one of the drugs used in the study. Another patient sample was evaluated per protocol (PP sample) and was composed of the patients who took the appropriate drug dosage (defined as between 80 and 100% of the pills prescribed) and had not violated the protocol in any way.

In the second and third examinations, the clinical response of the patients was classified as cure, improvement or treatment failure. Cure was defined as the resolution of the signs and symptoms of acute exacerbation, which reverted to the usual pattern for each patient. Improvement was defined as the disappearance of fever, with incomplete resolution of the other signs and symptoms, without the need for additional antibiotics. Treatment failure was defined as the lack of resolution of signs and symptoms or the need for further use of antibiotics. The primary evaluation of treatment efficacy was based on the percentage of patients who presented cure or improvement. The secondary parameters of efficacy were the evaluations of signs and symptoms and the results of microbiological evaluations.

All adverse events reported by the patients, or observed by the examiners, over the course of the study, were recorded. The incidence of serious adverse events, defined as any events that resulted in death, hospitalization, prolongation of hospitalization, persistent/significant incapacitation, or risk to the life of the patient, was also analyzed. Cases in which the treatment was discontinued, whether due to its inefficacy or to related adverse events, were evaluated.

The demographic variables and baseline patient characteristics were compared through the calculation of descriptive measurements and analysis of variance (ANOVA) for quantitative variables, and using the chi-square test or Fisher's exact test, as needed, for qualitative variables. The differences between the percentages of patients presenting cure or improvement in each group were compared using tests of proportions and their respective 95% confidence intervals. The same statistical technique was applied in the microbiological evaluation. The results of the pulmonary function tests were analyzed using ANOVA for repeated measurements. The statistical analyses were performed using the SAS program (Statistical Analysis System, Cary, NC, USA). All of the hypothesis tests were two-tailed, and the level of significance was set at 5%.

## Results

Of the 109 patients included in the study, 102 took at least one dose of the prescribed antibiotic

and constituted the intention-to-treat sample. Of those 102 patients, 19 discontinued the treatment for one of the following reasons: adverse events (n = 11); lack of treatment efficacy (n = 4); withdrawal of informed consent (n = 2); and protocol violation (n = 2). Therefore, 83 intention-to-treat sample patients completed the study: 41 treated with azithromycin; and 42 treated with amoxicillin. The mean age of the 102 participants in the study was 60 years (range, 33-82 years), and 59 patients were male (58%). These and other demographic and clinical characteristics are shown in Table 1. There were no significant differences between the two groups in terms of any of these characteristics.

On day ten of the treatment, 97 patients were appraisable for clinical response. Of the 5 patients in the intention-to-treat sample who were not appraisable, 2 had been treated with azithromycin and 3 with amoxicillin. There were no statistically significant differences between the two groups when we compared the percentages of patients presenting cure or improvement. Table 2 shows that these percentages were as follows: 85% in the group treated com azithromycin, and 78% in the group treated with amoxicillin (p = 0.368). One month after the end of the treatment, it was possible to evaluate the clinical response in 96 cases. Of the 6 patients who were not appraisable, 3 had received azithromycin, and 3 had received amoxicillin. Once again, there were no statistically significant differences between the two groups when we compared the percentages of patients presenting cure or improvement: 83% and 78% in the groups treated with azithromycin and amoxicillin, respectively (p = 0.571). Similar results were found when the analysis of efficacy was performed in the PP sample (data not shown).

The microbiological response was evaluated on day ten in 97 patients and after one month in 86 patients. The pathogens most frequently isolated in culture, regardless of the phase of the treatment, were the bacteria of the following types: *Moraxella catarrhalis*, *Streptococcus alpha hemolyticus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Table 3). There were no differences between the two groups when we

**Table 1** – Demographic characteristics of the patients studied.

| Variable | Azithromycin (n = 49) | Amoxicillin (n = 53) | p |
|---|---|---|---|
| Age, years | | | |
| Range | 41 to 77 | 33 to 82 | |
| Mean | 60.4 | 59.8 | 0.740 |
| Gender | | | |
| Males | 32 | 27 | 0.142 |
| Females | 17 | 26 | 0.142 |
| Current or former smoking | 47 | 51 | 0.927 |
| Symptom intensity at the study outset | | | |
| Cough | | | |
| Absent | 0 | 0 | 0.414 |
| Mild | 2 | 5 | 0.414 |
| Moderate | 33 | 37 | 0.414 |
| Severe | 14 | 11 | 0.414 |
| Expectoration | | | |
| Absent | 0 | 0 | 0.326 |
| Mild | 4 | 9 | 0.326 |
| Moderate | 31 | 33 | 0.326 |
| Severe | 14 | 11 | 0.326 |
| Dyspnea | | | |
| Absent | 10 | 7 | 0.810 |
| Mild | 7 | 8 | 0.810 |
| Moderate | 28 | 33 | 0.810 |
| Severe | 4 | 5 | 0.810 |

Intention-to-treat sample, n = 102.

**Table 2 -** Comparative efficacy between azithromycin and amoxicillin, on day 10 and on day 30 after the initiation of treatment.

| | On day 10 | | p |
|---|---|---|---|
| Clinical response | Azithromycin (n = 47) | Amoxicillin (n = 50) | |
| Cure or improvement | 85% | 78% | 0.368 |
| Treatment failure | 15% | 22% | |
| | On day 30 | | |
| Clinical response | Azithromycin (n = 46) | Amoxicillin (n = 50) | |
| Cure or improvement | 83% | 78% | 0.571 |
| Treatment failure | 17% | 22% | |

compared the various categories of microbiological responses (data not shown). Similarly, there were no differences when we evaluated cough, expectoration and dyspnea (Table 4). Nor were there any differences in pulmonary function on day 10 or at one month after treatment outset (Table 5).

In the group treated with azithromycin, 96% of the patients took all three doses prescribed. In the group treated with amoxicillin, 92% of the patients took at least 90% of the pills prescribed. A total of 33 patients treated with azithromycin had at least one adverse event, compared with 27 of the patients treated with amoxicillin. The principal adverse events attributed to the treatment were of a gastrointestinal nature (nausea, epigastric pain and diarrhea). Such events occurred in 5 patients treated with azithromycin and in 9 patients treated with amoxicillin. A total of 5 patients treated with azithromycin and 2 treated with amoxicillin presented adverse events considered serious according to the protocol. Such events included worsening of the respiratory condition with bronchoconstriction (in 4 patients), convulsive seizures (in 1) and rib fracture (in 1). None of these events were considered to be secondary to the use of the antibiotics in the study.

## Discussion

The present study demonstrated that azithromycin and amoxicillin present similar efficacy and tolerability in patients with infectious exacerbation of COPD. Clinical response rate, defined as the percentage of patients who achieved cure or improvement of the signs and symptoms of the infectious exacerbation condition, was similar in the two groups and comparable to the results obtained

**Table 3 -** Clinical evolution of patients and bacteria isolated per examination.

| Pathogen | Nº of patients with isolated bacteria (clinical classification of the evolution) | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| | Inclusion | Day10 | Day 30 |
| *Haemophilus influenzae* | 3 | 1<br>(treatment failure) | 1<br>(treatment failure) |
| *Haemophilus parainfluenzae* | | | 1<br>(cured) |
| *Klebsiella pneumoniae* | 1 | 7<br>(2 cured) | |
| *Moraxella catarrhalis* | 10 | 7<br>(1 cured)<br>(4 improvements)<br>(2 treatment failures) | 3<br>(all cured) |
| *Pseudomonas aeruginosa* | 2 | 3<br>(2 cured)<br>(1 improvement) | 1<br>(cured) |
| *Streptococcus pneumoniae* | 5 | 2<br>(1 improvement)<br>(1 treatment failure) | 3<br>(2 cured)<br>(1 treatment failure) |

**Table 4 -** Comparison of symptoms between the two groups, on day 10 and on day 30 after the initiation of treatment.

| | | Day 10 | | | | Day 30 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Azithromycin | | Amoxicillin | | Azithromycin | | Amoxicillin | |
| | | n | % | n | % | n | % | n | % |
| Cough | Severe | 3 | 6.4 | 2 | 4 | 0 | 0.0 | 2 | 4.4 |
| | Moderate | 14 | 29.8 | 14 | 28 | 10 | 24.4 | 8 | 17.8 |
| | Mild | 25 | 53.2 | 32 | 64 | 25 | 61.0 | 27 | 60.0 |
| | Absent | 5 | 10.6 | 2 | 4 | 6 | 14.6 | 8 | 17.8 |
| | Total | 47 | 100.0 | 50 | 100 | 41 | 100.0 | 45 | 100.0 |
| Expectoration | Severe | 1 | 2.1 | 1 | 2 | 1 | 2.4 | 0 | 0.0 |
| | Moderate | 13 | 27.7 | 20 | 40 | 5 | 12.2 | 4 | 8.9 |
| | Mild | 27 | 57.5 | 22 | 44 | 24 | 58.5 | 30 | 66.7 |
| | Absent | 6 | 12.8 | 7 | 14 | 11 | 26.8 | 11 | 24.4 |
| | Total | 47 | 100.0 | 50 | 100 | 41 | 100.0 | 45 | 100.0 |
| Dyspnea | Severe | 4 | 8.5 | 2 | 4 | 0 | 0.0 | 2 | 4.4 |
| | Moderate | 14 | 29.8 | 15 | 30 | 6 | 14.6 | 5 | 11.1 |
| | Mild | 15 | 31.9 | 19 | 38 | 20 | 48.8 | 23 | 51.1 |
| | Absent | 14 | 29.8 | 14 | 28 | 15 | 36.6 | 15 | 33.3 |
| | Total | 47 | 100.0 | 50 | 100 | 41 | 100.0 | 45 | 100.0 |

$p > 0.05$ for the comparisons between the groups.

in other studies with a similar design. Similarly, there were no significant differences in other parameters of efficacy or in the toxicity attributed to the treatment.

Various factors must be considered when choosing antibiotics for the treatment of patients with infectious exacerbation of COPD.[11] Noteworthy among these factors are the spectrum of action, the expected rate of bacterial resistance, convenient dosage schedule and adequate penetration into respiratory secretions. Various antibiotics used in the treatment of infectious exacerbation of COPD have many of these characteristics. Azithromycin is a broad-spectrum macrolide antibiotic, indicated for the pathogens most commonly implicated in community-acquired respiratory infections.[12] In an international study, in which the rates of in vitro resistance to various antibiotics were compared among respiratory pathogens, the results of the samples from Brazil revealed that *S. pneumoniae* and *H. influenzae* presented, respectively, 95% and 100% sensitivity to azithromycin.[13] The administration of azithromycin for three days guarantees adequate antibiotic levels for up to ten days. This pharmacokinetic property makes azithromycin an antibiotic with a quite satisfactory dose schedule. In addition, azithromycin presents excellent penetration into respiratory secretions.[14]

**Table 5 -** Comparison of pulmonary function between the two groups on day 10 and on day 30 after the initiation of treatment.

| | Azithromycin | | | Amoxicillin | | |
|---|---|---|---|---|---|---|
| | Study outset (n = 49) | On day 10 (n = 44) | On day 30 (n = 40) | Study outset (n = 53) | On day 10 (n = 49) | On day 30 (n = 41) |
| FEV1 (L) | 1.6 ± 0.8 | 1.7 ± 0.8 | 1.8 ± 0.8 | 1.6 ± 0.9 | 1.6 ± 0.8 | 1.9 ± 0.9 |
| [% predicted] | 66.1 ± 0.3 | 70.25 ± 0.3 | 74.4 ± 0.3 | 66.9 ± 0.4 | 66.9 ± 0.3 | 79.5 ± 0.4 |
| VC (L) | 2.6 ± 0.9 | 2.7 ± 1.0 | 2.9 ± 0.9 | 2.7 ± 1.1 | 2.7 ± 1.0 | 2.9 ± 1.1 |
| [% predicted] | 84.7 ± 0.3 | 87.9 ± 0.33 | 94.4 ± 0.3 | 89.4 ± 0.36 | 89.4 ± 0.33 | 96.0 ± 0.36 |

Values are shown as mean ± standard deviation. FEV1: forced expiratory volume in the first second; VC: vital capacity. $p > 0.05$ for the comparisons between the groups.

Other randomized studies have compared azithromycin and amoxicillin in the treatment of patients with acute exacerbation of chronic bronchitis. In some studies, amoxicillin was administered in combination with clavulanic acid, an inhibitor of some of the beta-lactamases produced by respiratory pathogens. A meta-analysis comprising fourteen randomized studies in which azithromycin and amoxicillin were compared showed that the two present similar efficacy, and that the incidence of adverse events was lower among individuals receiving amoxicillin, with or without clavulanic acid.[15] The efficacy of azithromycin has been shown to be equivalent to that of other classes of antibiotics, including moxifloxacin,[16] levofloxacin[17] and pivampicillin,[18] as well as to that of other macrolides, including roxithromycin,[19] clarithromycin[20] and dirithromycin.[21, 22]

Due to the similar efficacy of the various antibiotics used in the treatment of acute exacerbation of chronic bronchitis, it is of interest to evaluate which of the drugs employed are associated with a more satisfactory pharmacoeconomic profile. In a Latin-American study, it was estimated that antibiotics account for only 19.7% of the direct cost of treating infectious exacerbations.[23] Although this is a relatively low proportion of the total cost of the treatment, there might be antibiotics with more favorable cost-effectiveness ratios. In other words, it is possible to minimize or even invert the cost difference among different antibiotics when other aspects of the treatment, such as efficacy and toxicity, are taken into account. There have been few studies addressing this issue, the results of which are applicable on a large-scale.[24] In a retrospective study, the use of third-generation antibiotics (azithromycin, ciprofloxacin and amoxicillin/clavulanic acid) in comparison to that of first-generation antibiotics (amoxicillin, sulfamethoxazole/trimethoprim, erythromycin and tetracycline) was found to be associated with lower rates of treatment failure/hospitalization, longer intervals between exacerbation episodes and (a tendency toward) lower overall treatment costs.[25]

The results of the present study confirm the efficacy and tolerability of azithromycin for the outpatient treatment of episodes of infectious exacerbation of COPD. In this context, it can be expected that the treatment with azithromycin will promote cure or clinical improvement in most patients, with acceptable toxicity and costs. Taking these characteristics into consideration, in addition to the convenient dosage schedule offered by azithromycin, the use of this drug can be considered one of the treatments of choice for patients with infectious exacerbation of COPD.

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