Treatment of COPD exacerbations in primary and secondary care
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Citation for published version (APA):

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Three vs. 10 days of Amoxicillin-clavulanic acid for Type 1 Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Randomised, Double-blind Study

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Clin Microbiol Infect 2007; 13(3): 284-290
Abstract

The optimal duration of antibiotic treatment for acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is unknown. This study compared the outcome of treatment for 3 vs. 10 days with amoxicillin–clavulanic acid of hospitalised patients with AECOPD who had improved substantially after initial therapy for 3 days. Between November 2000 and December 2003, 56 patients with AECOPD were enrolled in the study. Unfortunately, because of the low inclusion rate, the trial was discontinued prematurely. Patients were treated with oral or intravenous amoxicillin–clavulanic acid. Patients who showed improvement after 72 h were randomised to receive oral amoxicillin–clavulanic acid 625 mg or placebo, four times daily for 7 days. The primary outcome measure of the study was clinical cure after 3 weeks and 3 months. Of 46 patients included in the final analysis, 21 were in the 3-day treatment group and 25 were in the 10-day treatment group. After 3 weeks, 16 (76%) of 21 patients in the 3-day treatment group were cured, compared with 20 (80%) of 25 in the 10-day treatment group (difference 3.8%; 95% CI -2 to 20). After 3 months, 13 (62%) of 21 patients were cured, compared with 14 (56%) of 25 (difference 5.9%; 95% CI -3 to 34). Microbiological success, symptom recovery, the use of corticosteroids, the duration of oxygen therapy and the length of hospital stay were comparable for both treatment groups. It was concluded that 3-day treatment with amoxicillin–clavulanic acid can be a safe and effective alternative to the standard 10-day treatment for hospitalised patients with AECOPD who have improved after initial therapy for 3 days.
Introduction

Chronic obstructive pulmonary disease (COPD) affects 3–17% of the adult population in developed countries,\(^1\) with rising morbidity and mortality rates.\(^2,3\) Antibiotic therapy is indicated for cases with severe acute exacerbations of COPD (AECOPD), characterised by an increase in dyspnoea and the volume and purulence of sputum.\(^4,6\) The optimal duration of antibiotic therapy in such cases is unknown. Most recent guidelines do not mention the duration of therapy.\(^7\) The Dutch guidelines\(^8\) recommend treatment for 7 days, and treatment for 7–10 days is probably common practice.

Recent studies concerning community-acquired pneumonia have demonstrated that the clinical effectiveness of treatment with amoxicillin for 3 days is not inferior to that of treatment for 8 days\(^9\) or 5 days.\(^10\) As in the treatment of AECOPD, eradication of the causative microorganism is not usually achieved;\(^11\) a shorter duration of treatment could therefore also be an option for AECOPD. A standard 10-day course of amoxicillin–clavulanic acid (co-amoxiclav) for AECOPD has been compared with treatment for 5 days with gatifloxacin,\(^12\) telithromycin\(^13\) or cefitbuten,\(^14\) but because both the drug and the duration of treatment varied, comparison of these studies is difficult.

If a shorter duration of therapy was also effective and safe for the treatment of AECOPD, this could contribute significantly to an overall decrease in the consumption of antibiotics. The present study describes a randomised, doubleblind multicentre trial designed to compare the efficacy and safety of a short (3-day) treatment period with amoxicillin–clavulanic acid with that of the standard 10-day treatment of hospitalised patients with AECOPD.

Materials and methods

The study was conducted at six hospitals in The Netherlands. The institutional review boards at each study centre approved the study.

Patient selection

Eligible patients were those aged ≥ 18 years who fulfilled the clinical criteria for COPD, and who presented with purulent sputum and a type 1 exacerbation, increased dyspnoea, increased volume and purulence of sputum, or two of these criteria in a patient with chronic heart failure,\(^5\) and a chest radiograph that showed no evidence of pneumonia. COPD was defined as a disorder characterised by abnormal tests of expiratory flow that did not change markedly during an observation period of several months.\(^15\)

Excluded patients were those with a history of allergy to amoxicillin–clavulanic acid, neutropenia (<1.0×10\(^9\) /L), agammaglobulinaemia, cystic fibrosis or bronchiectasis, a life-
expectancy of <1 month, previous treatment with an effective antimicrobial agent for >24 hours before admission, or any other infection necessitating the administration of systemic antibiotics. Patients admitted to an intensive care unit and patients who required ventilation were also excluded.

Study design
Between November 2000 and December 2003, eligible patients were invited to participate in the study and were asked to provide written informed consent. Consenting patients were treated with amoxicillin–clavulanic acid, either orally or intravenously. Other treatment decisions, e.g., the criteria for hospitalisation, treatment with steroids, and oral vs. intravenous antibiotic treatment, were at the discretion of the treating physician. After treatment for 72 h, four respiratory symptoms (dyspnoea, cough, production of sputum and colour of sputum) and general improvement were each rated on a five-point symptom scale. The scales extended from -2 (worsening / not recovered) to 3 (completely recovered). Patients who had improved by two or more points on this scale, who had a temperature <38°C, and who were able to take oral medication, were randomised to receive either oral amoxicillin–clavulanic acid 625 mg or placebo, four times daily for 7 days. If a causative pathogen was isolated, it was a requirement that the pathogen was susceptible to amoxicillin–clavulanic acid.

The randomisation scheme was generated centrally using random tables. Study drugs were distributed to the participating hospitals in blocks of four, containing amoxicillin–clavulanic acid and placebo in a ratio of 1:1. All study drugs were identical in appearance and packaging. Study treatment was not revealed until the analysis was completed, i.e., after each case had been classified as cure, treatment failure / recurrence or indeterminate.

Evaluations
At study entry (day 0), a complete medical history and a sputum culture were obtained, and a chest radiograph was taken. COPD-related symptoms (30 days before admission and at enrolment) were rated using a symptom score. Presence and severity of shortness of breath were rated on a five-point scale, and volume and colour of sputum were rated on a four-point scale. High values indicated more severe symptoms.

Patients were scheduled for follow-up at days 3 (day of randomisation), 7, 10, 14 and 21 after study entry. The following parameters were scored at each follow-up visit: COPD-related symptoms, prescription of antibiotics other than study medication, concomitant medication, and the use of oxygen. A further physical examination, including vital signs, was performed and a sputum culture was obtained. At days 0 and 21, serum was collected to determine antibodies against respiratory viruses. At 3 months, recurrences were determined by asking the patients by telephone about new or worsened signs and symptoms of an AECOPD between day 21 and month 3. Drug-related adverse events were recorded until day 10.
Outcome measures
The primary measures of effectiveness were clinical cure at day 21, indicated as test of cure (TOC), and at 3 months (late follow-up). Secondary outcome measures were: microbiological success at TOC and late follow-up; symptom recovery; the duration and cumulative dose of systemic corticosteroids used (expressed in prednisolone equivalents); the duration of oxygen therapy; the length of hospital stay; and drug-related adverse events. Clinical and microbiological response was classified using existing guidelines (Table 1).

Table 1. Definitions of clinical response according to criteria given by Chow et al.

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Test of Cure (TOC)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure</td>
<td>Recurrence</td>
</tr>
<tr>
<td>Cure</td>
<td>The resolution of acute symptoms and signs to a baseline level of dyspnoea, cough, sputum production and, if elevated at enrolment, resolution of fever.</td>
<td>New or worsened sign and symptoms of an exacerbation of COPD in a patient who was cured at the TOC visit.</td>
</tr>
<tr>
<td>Failure</td>
<td>The lack of any resolution in the magnitude of the dyspnoea, sputum purulence or fever (if present) that prompted enrolment of the patient in the study.</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>If a patient received for reasons other than clinical failure less than 80% of the study drug, or acquired a concomitant infection outside the respiratory tract requiring antibiotic treatment.</td>
<td>A concomitant infection outside the respiratory tract requiring antibiotic treatment, or death unrelated to the primary diagnosis.</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.
Statistical analysis
The study was designed to demonstrate non-inferiority of the short treatment. Based on a level of 5% and a power of 0.80, assuming that 90% of the patients are cured on day 21, and accepting a difference of 10% at the expense of the short treatment, it was calculated that a sample size of 225 was required.

All outcomes were evaluated in an ‘intention-to-treat’ analysis that included all randomised patients who received at least one dose of the study drug. For the clinical and microbiological outcomes, indeterminate cases were classed as failures, and failures and indeterminate cases at TOC were carried forward in the analyses at 3 months.

Microbiological success was defined as demonstrated eradication or presumed eradication (in patients who were cured clinically), while microbiological failure was defined as persistence, presumed persistence (in patients who were classed as clinical failures), relapse, re-infection or superinfection. All other cases were classed as indeterminate for analyses. Microbiological outcome was analysed only for patients who had a pathogen isolated at study entry.

Differences in success rates were calculated, together with their 95% CIs. The median symptom scores at each time-point, the duration and cumulative dose of systemic corticosteroids used, the duration of oxygen therapy and the length of hospital stay were calculated. The treatment groups were compared using the t-test, Mann–Whitney test, or chi-square test, as appropriate. The safety of each treatment was described by frequency statistics. Statistical analyses were performed with SPSS v.11.5.2 software (SPSS Inc., Chicago, IL, USA).

Results
Patients
The required sample size of 225 patients could not be achieved. The main reason for the recruitment problems was that many patients received antibiotic treatment from their general practitioner before being admitted, which was an exclusion criterion. Some patients did not fulfil the criteria for a type 1 exacerbation, most frequently because they did not produce sputum. Other patients were admitted to an intensive care unit, and therefore could not be included in the study. As no improvement in the inclusion rate was expected, recruitment was stopped.

During the course of 3 years, 56 patients were enrolled in the study (Figure 1). After treatment for 3 days, six patients did not meet the pre-specified randomisation criteria, and two patients withdrew from the study at their own request. The remaining 48 patients were randomised; 23 were assigned to the 3-day regimen, and 25 were assigned to the 10-day regimen. In the 3-day group, two patients were removed from the analysis because of
Three vs 10 Days of Amoxicillin-clavulanic acid for Type 1 Acute Exacerbations of COPD

Figure 1. Trial profile.
COPD, chronic obstructive pulmonary disease; co-amoxiclav, amoxicillin-clavulanic acid.
a protocol violation; one patient had a causative pathogen that was not susceptible to the study drug, and one patient had an infiltrate on the chest radiograph at day 0. The two excluded patients did not receive any study medication and were not included in the intention-to-treat analysis. Thus, in total, 46 patients were included in the final analysis.

The baseline characteristics were comparable for both treatment groups (Table 2; Figure 2). A pathogen was detected in the sputum of 19 patients, with more than one pathogen found for four patients. The pathogens detected most frequently were *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. A recent infection with influenza virus A or B was detected in four patients. None of the patients had bacteraemia.

**Primary outcomes**

In the intention-to-treat analysis, 16 (76%) of 21 patients in the 3-day treatment group were cured at TOC, compared with 20 (80%) of 25 patients in the 10-day treatment group (difference -3.8%; 95% CI -28 to 20). At late follow-up, 13 (62%) of 21 patients in the 3-day treatment group were cured, compared with 14 (56%) of 25 patients in the 10-day treatment group (difference 5.9%; 95% CI -23 to 34) (Figure 3).

**Secondary outcomes**

Of the patients with a positive sputum culture at study entry, nine (82%) of 11 patients were microbiologically cured at TOC in the 3-day treatment group, compared with six (75%) of eight patients in the 10-day treatment group. Four patients were classified as microbiological failures: two patients in the 3-day treatment group had a relapse without clinical symptoms; one patient in the 10-day treatment group had a superinfection with clinical symptoms; and one patient in the 10-day treatment group was classed as indeterminate, because of antibiotic treatment received for prostatitis. At 3 months, the microbiological cure rates were eight (73%) of 11 patients in the 3-day treatment group, compared with five (62%) of eight patients in the 10-day treatment group. Two patients, one in each treatment group, had a recurrence; antibiotic therapy was started in the absence of microbiological data, and these cases were classed as microbiological failures.

At each time-point during follow-up, the scores of the COPD-related symptoms in both treatment groups were similar (Figure 2). Upon admission, scores for shortness of breath, and volume and colour of sputum, were higher than the pre-exacerbation scores at 30 days before enrolment. The scores for shortness of breath and sputum volume returned to the pre-exacerbation scores at day 3; the score for sputum colour returned to the pre-exacerbation score at day 7.

In total, 42 (91%) patients were prescribed systemic steroids, as can be expected for hospitalised patients. Systemic corticosteroids were used for a median of 12 days (interquartile range (IQR) 7–18 days) in the 3-day treatment group, compared with 14 days (IQR 8–21 days) in the 10-day treatment group (p=0.31). The cumulative dose of prednisolone equivalents was 333 mg in the 3-day treatment group (IQR 185–443 mg), compared with 415 mg (IQR 343–593 mg) in the 10-day treatment group (p=0.05).
### Table 2. Baseline characteristics of the randomised patients (intention-to-treat population)

<table>
<thead>
<tr>
<th></th>
<th>3-day n = 21</th>
<th>10-day n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (48)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (52)</td>
<td>9 (36)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>69 (59–76)</td>
<td>66 (61–71)</td>
</tr>
<tr>
<td><strong>Classification of COPD by severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD 0, I</td>
<td>2 (9)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>GOLD II</td>
<td>10 (48)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>GOLD III, IV</td>
<td>9 (43)</td>
<td>14 (56)</td>
</tr>
<tr>
<td><strong>Daily used medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No daily used medication</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>ß2 agonists/anticholinergics</td>
<td>3 (14)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Ics (+/- ß2 agonists/anticholinergics)</td>
<td>11 (52)</td>
<td>16 (64)</td>
</tr>
<tr>
<td><strong>Underlying disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>12 (57)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>3 (14)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>10 (48)</td>
<td>15 (60)</td>
</tr>
<tr>
<td><strong>Temperature &gt; 37.5 °C</strong></td>
<td>11 (52)</td>
<td>14 (56)</td>
</tr>
<tr>
<td><strong>Symptom scores, median (IQR)+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2 (2-3)</td>
<td>3 (2-3)</td>
</tr>
<tr>
<td>Sputum volume</td>
<td>2 (1-2)</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>Sputum color</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td><strong>Detected pathogen at study entry$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Influenza A/ B</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>RS virus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><em>M. pneumoniae</em></td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*GOLD, Global Initiative for Chronic Obstructive Lung Disease; ‡ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range. #One patient was receiving theophylline. ¶Some patients had more than one underlying disease. +Shortness of breath was rated on a five-point scale; volume and colour of the sputum are both rated on a four-point scale. High values indicate more severe symptoms. $More than one pathogen was isolated from some patients.
Figure 2. Symptom scores for both treatment groups.
The symptom scores of both treatment groups are expressed as medians and interquartile ranges. Day -30 represents the pre-exacerbation level; day 0 is the day of starting antibiotic therapy; day 21 is Test of cure.
Oxygen was used for a median of 3 days (IQR 0–7 days) in the 3-day treatment group, compared with 7 days (IQR 0–7 days) in the 10-day treatment group (p=0.77); the median length of hospital stay was 9 days (IQR 7.5–10 days) in the 3-day treatment group, compared with 9 days (IQR 6.5–12.0 days) in the 10-day treatment group (p=0.86). Adverse events until day 10 of treatment were reported by one patient in the 3-day treatment group, and by five patients in the 10-day treatment group (p=0.11). All the adverse events reported were mild and were related to the gastrointestinal tract.

Figure 3. Clinical success in the ‘intention-to-treat’ population.
Discussion

In this multicentre, placebo-controlled, double-blind trial, the early and late cure rates obtained following treatment with amoxicillin-clavulanic acid for 3 days were comparable to those obtained following treatment with the standard 10-day regimen for hospitalised patients with AECOPD who have improved after initial therapy for 3 days, although a clinically relevant difference could not be excluded. The microbiological results, symptom recovery, the use of systemic corticosteroids and oxygen, length of hospital stay and reported adverse events were also comparable for both groups.

The strengths of this study were the double-blind, randomised design and the fact that only patients who required antibiotic therapy (i.e. those with a type 1 exacerbation) were included in the study. No previous studies comparing short- and long-term treatment durations with amoxicillin-clavulanic acid have been published, but studies in which amoxicillin-clavulanic acid for 10 days was compared with a shorter duration of an alternative antibiotic also showed equal efficacy for the short treatment.

The major limitation of this study was the limited number of patients. Although no differences in clinical cure rates, or in any of the secondary endpoints, were found among patients in the 3-day and 10-day treatment groups, the confidence intervals were wide. Given the extent of antibiotic consumption associated with exacerbations of COPD, which is endorsed by guidelines and a recent Cochrane analysis a larger study is clearly indicated.

At a population level, there is a clear relationship between total antibiotic consumption and resistance rates among pathogens. Respiratory tract infections are the main indications for antibiotic use in the community, and AECOPD contributes to this on a large scale. In recent years, resistance rates among common respiratory pathogens for a number of antimicrobial agents have clearly increased. To address this problem, new antimicrobial agents have been tested and have been found to be clinically and bacteriologically effective. However, restricted use of the antibiotics available currently could be a more efficient alternative. A shorter duration of treatment might diminish overall antibiotic use, and thereby contribute to the containment of the growing resistance rates among respiratory pathogens.

Acknowledgements

We gratefully thank C. Weenink, A. J. M. Wever and J. van ’t Wout for contributing to the enrolment of patients and their follow-up. We also thank the patients who participated in this study, the medical and nursing staff of the participating centres, and GlaxoSmithKline for supplying the study medication and placebo. The study was supported by The Health Care Insurance Board (College voor Zorgverzekeringen), Diemen, The Netherlands (grant OG99-038).
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