Treatment of COPD exacerbations in primary and secondary care

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General Introduction and Outline of this Thesis
Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and irreversible disease typified by a gradual worsening of pulmonary function, with tobacco smoke being the most important risk factor. COPD develops over time and usually becomes manifest in people over 45 years of age. COPD is clinically characterized by symptoms like cough, sputum production and/or dyspnoea. The diagnosis is confirmed by spirometric testing and accordingly has four stages, from mild (GOLD stage 1) to very severe (GOLD stage 4).

COPD poses a major health problem and has large consequences for patients and the community. According to World Health Organization (WHO) estimates, 210 million people have COPD, and globally more than 3 million people died of COPD in 2005, corresponding to 5% of all deaths. In European countries COPD frequencies vary from 4–10% of the adult population; and approximately 200,000–300,000 people die each year because of COPD (based on estimates of the WHO in 42 European countries; 1990). In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56%: 38.6 billion Euros (2001, ERS European Lung White Book). COPD is among the top ten causes of death and is continuing to increase in both prevalence and mortality. By 2020, it is expected that COPD will be the third-leading cause of death worldwide. The impact of disease can be reduced through policies aimed at better diagnosis, evaluation, and management, and improved prevention. Optimal treatment of acute exacerbation of symptoms is a major objective in this chain of measures.

An exacerbation of COPD is generally defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication. The most common causes of exacerbation are lower airway infection and air pollution, but the cause of about one-third of severe exacerbations is still unknown.

Adequate treatment and reduction of the frequency of exacerbations are extremely important. Each exacerbation may have a large and sustained effect on health status. Although the initial recovery can be relatively short, the period to full recovery may be long (weeks). However, a number of patients does not fully recover to baseline symptoms, and a decline in FEV1 as a result of exacerbations might contribute to the process of deterioration of lung function. Patients with frequent exacerbations have a lower quality of life, an increased risk of hospital admission and greater mortality, and generate more costs than patients with less frequent exacerbations.

In the Netherlands, the majority of patients with an exacerbation of COPD is treated by their general practitioner. Treatment usually includes adaptation of daily-used respiratory drugs and/or addition of antibiotics and systemic corticosteroids. The scope of this thesis
is the treatment with antibiotics and/or corticosteroids in patients with an exacerbation of COPD.

**Role of antibiotics in the treatment of exacerbations**

Bacteria are since long considered to play a role in exacerbation of COPD. The most prevalent respiratory pathogens are *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Especially nontypeable *H. influenzae* is known for contributing to the process of colonisation and infection. The presence of new bacterial strains increases the risk of an exacerbation. Inflammation is increased at the time of an exacerbation, is also related to recurrent exacerbations, and contributes substantially to the overall mortality in COPD patients. During exacerbations, at least 50% of patients are found to have bacteria in high concentrations in their lower airways. Bacterial colonisation was related to a higher frequency of exacerbations in patients with moderate to severe COPD, suggesting the clinical relevance of the presence of bacteria in the lower airways. Development of specific immune responses to the causative bacteria, and neutrophilic inflammation during exacerbations support the bacterial cause of a part of all exacerbations. New insights show that underlying mechanisms of exacerbations are more complicated than simple changes in concentrations of bacteria, and emphasize the importance of the host–pathogen interaction in bacterial infection in COPD.

Both bacteria and viruses may interact in a complex inflammatory process and besides bacteria, viruses are studied for their role in inducing exacerbations. Respiratory viruses, most commonly the human rhinovirus, respiratory syncytial virus, influenza virus-A, or parainfluenza virus, infect and replicate in airway epithelial cells, causing epithelial damage and inducing production of proinflammatory mediators, such as IL-8 and IL-6, thus contributing to enhanced airway inflammation. This makes patients with a respiratory virus infection susceptible to a secondary bacterial infection, which may lead to an exacerbation in COPD patients.

Antibiotic treatment in exacerbation of COPD is beneficial especially in patients with severe symptoms, and patients with a low baseline expiratory flow rate. A recent Cochrane review showed that in COPD exacerbations with increased cough and sputum purulence antibiotics, compared with placebo, reduced the risk of short-term mortality (RR 0.23; 95% CI 0.10 to 0.52), and decreased the risk of treatment failure (RR 0.47; 95% CI 0.36 to 0.62) and the risk of sputum purulence at the end of treatment (RR 0.56; 95% CI 0.41 to 0.77). However, analysis restricted to community-based studies did not show these differences. The review supports the use of antibiotics for patients with COPD exacerbations with increased cough and coloured sputum who are moderately or severely ill. In addition, a later systematic review showed that antibiotics did not reduce treatment failures in outpatients with mild to moderate exacerbations. In a primary healthcare setting, antibiotic treatment was shown to neither accelerate recovery nor reduce the number of relapses in COPD patients with exacerbations.
Most studies on antibiotic therapy in exacerbations of COPD evaluated short term recovery from exacerbation with a follow-up period of only a few weeks. The long-term effects of antibiotic treatment have not been studied extensively.

**Emerging resistance of respiratory pathogens**
Whereas specific groups of patients with exacerbation of COPD may profit from antibiotic treatment, the widespread use of antibiotics goes together with increasing resistance rates among most respiratory pathogens. Total consumption of antibiotics is the main driving force of this development. This forces physicians to careful consideration in prescribing antibiotics; over-prescription should be avoided. The Netherlands are known for having the lowest total antibiotic use and accordingly the lowest resistance rates of pathogens in Europe. Nevertheless, about half of the antibiotic prescriptions for respiratory tract infections in Dutch general practice were still criticized as being unnecessary. Resistance develops during treatment in the infecting pathogen as well as in the commensal bacteria, due to selective pressure of antibiotic treatment. Resistance mutations, already present, may become dominant and new resistant strains may emerge. Dose and duration of therapy are both of influence on the development of resistance. The antibiotic concentration should be high enough to prevent the growth of first-step mutants (the mutant prevention concentration, MPC). Suboptimal, prolonged or repeated antibiotic treatment facilitates the emergence of resistance strains of pathogens. Antibiotic courses in COPD exacerbation are usually prescribed for ten days, more based on tradition than on evidence-based guidelines. Studies performed in outpatient children and hospitalized adults with community-acquired pneumonia demonstrated that a 3-day course of amoxicillin was equally effective compared to a conventional long treatment. Provided that this is equally efficacious, a shorter duration of antibiotic courses could contribute to contain growing resistance rates of respiratory pathogens.

**Short course high-dose systemic corticosteroids in exacerbations**
A short course of high-dose systemic corticosteroids is the other main stem of treatment in exacerbation of COPD. Studies conducted in clinical settings showed that a short course of high-dose systemic corticosteroids resulted in a more rapid improvement in expiratory flow rate and dyspnoea score, a shorter hospital stay and a decrease in the rate of treatment failure. A Cochrane review reported significant reduction of treatment failure and need for additional treatment, and an increase in lung function and improvement in shortness of breath over the first 72 hours. It was concluded that there is evidence to support the early use of oral or parenteral corticosteroids for exacerbation of COPD. However, this was associated with an increased likelihood of adverse reactions, especially the risk of hyperglycaemia. One extra adverse effect occurred for every 6 people treated.

Patients in the included studies were predominantly hospitalized or outpatients who had severe exacerbations. In the primary care setting, with the majority of patients classified as
GOLD 1 or 2 (meaning mild to moderate COPD), and probably having less severe exacerbations, the question is whether a short course of oral corticosteroids as therapy of first choice will also lead to a better patient outcome.

Guidelines for the treatment of COPD exacerbation in primary healthcare
In several Western European countries, in the majority of cases, care for COPD patients is delivered by general practitioners. In the Netherlands, 80% of COPD patients monitored by the GP has mild or moderate disease. Also in the care for patients with more severe disease the general practitioner can play a central role, supported by practice assistants and –nurses, e.g. when multi-disciplinary care is requested. Only in a small proportion of patients care is taken over by a pulmonologist.

International evidence-based COPD guidelines for clinical practice are available, for example The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, the combined ATS/ERS guideline, and the NICE guideline. The Dutch College of General Practitioners (NHG) developed a guideline for the diagnosis and treatment of COPD in general practice. This guideline states that in the majority of exacerbations, treatment with bronchodilators is sufficient, but if not, a course of oral corticosteroids (30 mg for 7–14 days) should be prescribed. Antibiotics are advised only in acute severe dyspnoea with symptoms of clinical infection, a low baseline flow rate (forced expiratory volume in 1 second [FEV1] <30%), or insufficient recovery after 4 days.

Despite wide availability of guidelines for COPD, implementing them is a complex process. Many reports have indicated that guidelines in general are underused by physicians and others, and that there are many barriers to an effective translation of recommendations into daily practice. In the Netherlands, an average of 61% of recommendations from primary care guidelines was followed.

Outline of this thesis
This thesis aims to add evidence for antibiotic therapy and treatment with short course oral corticosteroids in exacerbation of COPD in primary and secondary care.

The chapters two and three of this thesis present the results of two studies on the treatment of exacerbations of COPD in the primary care-setting in the Netherlands. Chapter 2 explores how in daily practice exacerbations are treated, using data derived from the electronic medical records from four primary healthcare centres participating in the GP-based continuous morbidity registration network of the Department of General Practice from the Academic Medical Centre - University of Amsterdam. The results were compared with current guidelines for treating exacerbations of COPD, in particular
whether short courses of oral corticosteroids and antibiotics were prescribed in accordance with the Dutch guideline for COPD. Based on the results of this study, a randomized controlled trial was designed to investigate whether patient outcomes in exacerbations of COPD or chronic bronchitis could be improved through optimizing the treatment regimen. A standardized treatment with a high-dose oral corticosteroid course and antibiotic treatment strictly in accordance with the Dutch guideline for COPD was compared with the current usual care. This study is reported in Chapter 3.

As antibiotic use drives the emergence of resistant micro-organisms, the next two chapters discuss the shortening of duration of antibiotic therapy. Chapters 4 presents the results of a systematic review and meta-analysis of randomized controlled trials in acute exacerbations of chronic bronchitis and COPD, mainly in patients with type 1 or 2 exacerbation, i.e. having at least two of the following criteria: increased dyspnoea, increased sputum volume and increased purulence. Antibiotic treatment up to five days was compared with treatment for longer than five days. Chapter 5 reports the results of a randomized clinical trial comparing the efficacy and safety of a short (three-day) treatment period with that of the standard ten-day treatment with amoxicillin–clavulanic acid in hospitalised patients with COPD exacerbation who had improved substantially after initial therapy for three days.

The last two studies originated from large community-based datasets, offering the unique opportunity to evaluate the long-term effects of addition of antibiotics in the treatment of exacerbations. Patients were selected when aged 50 years or older, using maintenance respiratory drugs, and experiencing at least one exacerbation, defined as a prescription of oral corticosteroids without or with antibiotics. Chapter 6 is based on data from the Dutch Pharma database, containing extensive data on pharmacy dispensing records from community pharmacies of more than two million residents of the Netherlands. Both prescriptions from general practitioners and from medical specialists were registered. Patients described in Chapter 7 were known with their general practitioners with a diagnosis of COPD. Data were derived from the Second Dutch National Survey of General Practice (DNSGP-2), carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001, completed with data from the National Information Network of General practice (LINH). The patients in the DNSGP-2 practices are representative for the Dutch general population with respect to age, gender and type of health care insurance. Results shown provide a representative impression of the morbidity and prescribing routine in Dutch general practices. In both datasets we compared, using Kaplan-Meier survival analysis and Cox proportional hazard analysis, the time to a second and third exacerbation for patients treated with or without antibiotics, the risk of a subsequent exacerbation in these treatment groups and we studied the effect of antibiotic use on all-cause mortality.
References


Antibiotics and Steroids for Exacerbations of COPD in Primary Care: Compliance with Dutch Guidelines

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British Journal of General Practice 2006; 56: 662–665
Chapter 2

Abstract

Background
The Dutch College of General Practitioners’ guidelines specify that antibiotics should only be used for severe cases of chronic obstructive pulmonary disease (COPD). However, GPs tend to administer antibiotics rather than a short course of steroid treatment regardless of severity.

Aim
The aim of this study was to determine how GPs use current guidelines in treating exacerbations of COPD, in particular whether short courses of oral steroids and antibiotics are prescribed in accordance with the Dutch guidelines for COPD.

Method
Medical records of patients registered at four primary healthcare centres in the Netherlands were retrospectively analysed for the period March 2001–March 2003.

Results
Of 35 589 patients, 1.3% were registered as having a diagnosis of COPD. In 2 years, 47% of the patients had no exacerbation, 35% had one or two exacerbations, and 18% had three or more exacerbations. Of 536 exacerbations, GPs prescribed a short course of oral steroids in 30% of cases, antibiotics in 29%, steroids combined with an antibiotic in 23%, and no oral steroid course or antibiotic was prescribed in 18%. Prescriptions for patients with three or more exacerbations differed significantly from those for patients with one or two exacerbations.

Conclusions
Treatment is often not in accordance with current guidelines; in particular, antibiotics are prescribed more often than recommended.
Introduction

Patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) can be treated with short courses of systemic corticosteroids and/or with antibiotics. Compared with placebo, a short course of systemic steroids results in a more rapid improvement in flow rate\textsuperscript{1–3} and dyspnoea score\textsuperscript{1,2}; shorter hospital stay\textsuperscript{3}; and a decrease in the rate of clinical relapse.\textsuperscript{1–3} Antibiotic treatment appears to be of the greatest benefit to patients with severe symptoms\textsuperscript{4} and/or a low baseline flow rate.\textsuperscript{5–6} For mild episodes, no significant advantage of antibiotic treatment has been demonstrated.\textsuperscript{7–8} In a primary healthcare setting, antibiotic treatment was shown to neither accelerate recovery nor reduce the number of relapses in patients with exacerbations.\textsuperscript{9}

The Dutch College of General Practitioners has developed guidelines for the diagnosis and treatment of COPD in general practice.\textsuperscript{10} These guidelines state that in the majority of exacerbations treatment with bronchodilators is sufficient, but if not, a course of oral steroids (30 mg for 7–10 days) should be prescribed. Antibiotics are advised only in acute severe dyspnoea where there are symptoms of clinical infection, a low baseline flow rate (forced expiratory volume in 1 second [FEV1] <30%), or insufficient recovery after 4 days. Despite wide availability of the guidelines, implementing them is a complex process and it is unclear whether it is viable to apply them in daily practice.

In the Netherlands most patients with exacerbations of COPD are treated by GPs. The aim of this study was to assess whether short courses of steroids and antibiotics are prescribed in accordance with the Dutch guidelines.

Method

Patient population

Four primary healthcare centres took part in the study. These centres participate in the GP-based continuous morbidity registration network of the Department of General Practice, Academic Medical Centre-University of Amsterdam. This network registers chronic diseases among other data in electronic medical records (EMRs). For the period March 2001 until March 2003, we retrospectively analysed EMRs of all registered patients at these four centres.

Data collection

Records of all patients registered with a diagnosis of COPD were retrieved from EMRs with the use of the international classification of primary care code (ICPC) R95.\textsuperscript{11} Consultations for these patients during the 2-year study period were analysed by printing and subsequently reading and coding the EMRs. Two criteria were used to assess an exacerbation of COPD:
• when 'exacerbation' was used by the GP as stated in the EMR; and
• when increased symptoms of COPD (cough, shortness of breath, altered sputum conditions, increased sputum production, wheezing, or illness) were explicitly mentioned in the EMR.

When patients visited their GP for an exacerbation more than once in a period of up to 3 weeks, the whole episode was considered one exacerbation. An exacerbation after full recovery from the previous exacerbation was considered a new episode, according to the GP's description in the EMR, or when the time between two consultations at the GP practice was longer than 3 weeks. Patients who were suspected to have a diagnosis of pneumonia, based on symptoms and physical examination, were excluded.

The number of patients with exacerbations, number of exacerbations per patient, daily medication, and treatment prescribed for the exacerbation were registered. Exacerbations treated by pulmonologists after having been referred by a GP were counted separately.

**Statistical analysis**
SPSS (version) 11.5.1 was used for statistical analysis. Differences between patients groups were analysed using χ² test. Statistical significance was set at p<0.05.

**Results**

**Characteristics of primary healthcare centres and patients**
During the 2-year study period, 35,589 patients were registered at the four primary healthcare centres. Of these patients, 458 were registered with a diagnosis of COPD (1.3%). Median age of patients with COPD was 70 years (interquartile range = 61–77 years). Daily medication for COPD was taken by 380 (84%) patients: 83 (18%) inhaled β2 agonists and/or anticholinergics only and 297 (66%) inhaled corticosteroids, with or without β2 agonists and/or anticholinergics. One hundred patients (22%) used N-acetylcysteine, 22 of them without inhaled corticosteroids.

A total of 572 exacerbations in 2 years were identified in 458 patients (0.62/patient/year). In 215 patients (47%) no exacerbation in 2 years occurred, 162 (35%) had one or two exacerbations, and 81 (18%) exacerbated more often (Table 1). In patients with exacerbations, there was a median of two exacerbations over 2 years (range = 1–13).

**Treatment of exacerbations**
Of the 572 exacerbations, 36 (6%) were treated by pulmonologists. In the remaining 536 exacerbations, GPs prescribed a short course of oral steroids in 161 cases (30%), antibiotics in 157 (29%), and steroids were combined with an antibiotic in 121 (23%). In
97 cases (18%) no steroid course or antibiotic was prescribed, but compliance to daily medication use was checked and/or this medication was adapted (Table 1).

Table 1. Characteristics of patients and treatment of exacerbations

<table>
<thead>
<tr>
<th>Patients</th>
<th>35,589</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence with COPD</td>
<td>458 (1.3)</td>
</tr>
<tr>
<td>Maintenance medication*</td>
<td></td>
</tr>
<tr>
<td>ß2 agonists/ anticholinergics</td>
<td>83 (18)</td>
</tr>
<tr>
<td>Inhaled corticosteroids (+/- ß2/ anticholinergics)</td>
<td>297 (66)</td>
</tr>
<tr>
<td>No daily medication used</td>
<td>71 (16)</td>
</tr>
<tr>
<td>Incidence of exacerbations over 2 years</td>
<td></td>
</tr>
<tr>
<td>Patients with no exacerbations</td>
<td>215 (47)</td>
</tr>
<tr>
<td>Patients with 1 or 2 exacerbations</td>
<td>162 (35)</td>
</tr>
<tr>
<td>Patients with ≥ 3 exacerbations</td>
<td>81 (18)</td>
</tr>
<tr>
<td>Treatment of exacerbations (n=572)</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>157 (29)</td>
</tr>
<tr>
<td>Short course of steroids</td>
<td>161 (30)</td>
</tr>
<tr>
<td>Antibiotics and steroids</td>
<td>121 (23)</td>
</tr>
<tr>
<td>No antibiotics and no steroids</td>
<td>97 (18)</td>
</tr>
<tr>
<td>Treated by pulmonologist</td>
<td>36 (6)</td>
</tr>
</tbody>
</table>

Data are n (%). *Seven patients used medication which fell outside the three medication groups. Three patients used acetylcysteine only, two were on theophylline and maintenance medication was not known for two patients.

Treatment was influenced by patient characteristics. Compared with patients with one or two exacerbations, patients with three or more exacerbations were prescribed significantly more steroid courses and steroids combined with antibiotics, and less antibiotics without steroids or no antibiotics or steroids (p≤0.001 in all cases). In patients younger than 70 years, antibiotics without steroids were prescribed more often than in patients over 70 years of age (p=0.02) (Table 2).

Steroid courses were usually prescribed in a dose of 30 mg per os daily for 7 or 10 days. The most frequently prescribed antibiotics were amoxicillin/ clavulanate (co-amoxiclav) for 7 or 10 days (34%), doxycycline for 8 days (28%), amoxicillin for 7 days (18%), and azithromycin for 3 days (12%).
Table 2. Treatment of exacerbations: influence of patient characteristics

<table>
<thead>
<tr>
<th>Exacerbations</th>
<th>Age in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 or 2 (n=205)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>76 (37)</td>
</tr>
<tr>
<td>Short Course of Steroids</td>
<td>42 (20)</td>
</tr>
<tr>
<td>Antibiotics and Steroids</td>
<td>27 (13)</td>
</tr>
<tr>
<td>No antibiotics/no steroids</td>
<td>60 (29)</td>
</tr>
</tbody>
</table>

* Numbers are n (%). ‡ X² test.

Discussion

Summary of main findings
In this retrospective analysis of the medical records of patients with COPD in general practice, almost half of the patients had no acute exacerbation in the 2-year study period, one-third had one or two exacerbations, and one in five patients with COPD exacerbated more often. In instances where patients had an exacerbation of COPD, GPs often did not prescribe treatment in accordance with the Dutch College of General Practitioners guidelines for COPD. Antibiotics were often prescribed (52% of the exacerbations), and in almost 30% an antibiotic was the only medication prescribed.

GPs in the four primary healthcare centres treated half of the exacerbations with steroid courses. Evidence from the literature indicates that short courses of steroids are beneficial in exacerbations of COPD, and most international guidelines advise short courses of oral steroids for patients at home. However, only the GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease) include FEV1 below 50%. The Dutch College of General Practitioners guidelines for COPD are even more restrictive by advising short courses of oral steroids only in more severe exacerbations. In this sense, GPs appear to follow the Dutch guidelines.

GPs in this study prescribed antibiotics in 23% of cases combined with steroids and in 29% of the cases without steroids. The Dutch guidelines for COPD are restrictive
regarding when to prescribe antibiotics for exacerbations of COPD. They are more restrictive than the international standards, which mention altered sputum characteristics as an indication for antibiotics. It is unlikely that slightly more than half of all exacerbations in the current study fulfil the criteria of the Dutch guidelines for prescribing antibiotics. The prescription of antibiotics for exacerbations of COPD in daily practice will be even higher, as exacerbations with signs of pneumonia were excluded from the study. The possibility that GPs may sometimes label an exacerbation as pneumonia to justify prescribing antibiotics cannot be excluded.

Guidelines are there to assist GPs to treat patients using an evidence-based approach and are not a protocol that always has to be followed in a strict way. As in general practice assessing the severity of an exacerbation may be difficult in some cases, GPs may prescribe antibiotics to be on the safe side. It is unclear why antibiotics were prescribed much more frequently than indicated in the Dutch guidelines. The Dutch guidelines may be too stringent to be followed in daily practice; for example, GPs may suspect that withholding antibiotics may lead to hospitalisation. Alternatively, deviation from the guidelines may not be clinically justified in many cases. It is unclear whether guidelines or prescribing patterns should be changed, and further study is required.

Prescriptions in patients with one or two exacerbations differed significantly from prescriptions for patients with three or more exacerbations. Short courses of oral steroids were prescribed more frequently in patients with three or more exacerbations, and antibiotics only were prescribed less frequently. Treatment in patients with three or more exacerbations was more in accordance with the Dutch guidelines than treatment in patients having one or two exacerbations.

**Limitations of the study**

Analysing medical records has its limitations. Because this evaluation was conducted retrospectively, information about specific symptoms during exacerbations of COPD could not be obtained. Although all patients were registered using the ICPC code for COPD, and the diagnoses of COPD made by GPs were confirmed by spirometric testing for almost all patients, it cannot be ruled out that the study might have included some patients with asthma.

**Comparison with existing literature**

Research published in 1998 showed that GPs prescribe antibiotics more frequently and steroid courses less frequently than indicated by the Dutch guidelines. Although the Dutch guidelines have been revised several times since then, little has changed in the treatment of exacerbations of COPD in primary health care. An evaluation of the most important barriers to change is indicated.
Implications for clinical practice
In the general population there is an association between antibiotic consumption and resistance to pathogens.\textsuperscript{15–18} Unnecessary use of antibiotics should be avoided to prevent antimicrobial resistance of pathogens. Therefore, the current authors suggest that concerted efforts should be made to fully implement the Dutch guidelines for COPD.

Funding body
The study received an unrestricted grant from ‘PICASSO for COPD’, an initiative of Pfizer, Boehringer Ingelheim and the research institute Caphri (Care and Public Health Research Institute) from the University of Maastricht, the Netherlands (Project 004).

Ethics committee
As the medical records of patients were retrospectively analysed, ethical approval was not applicable to the current research.

References
Does Standard Treatment with an Oral Corticosteroid Course Improve Patients’ Recovery from Exacerbation of COPD or Chronic Bronchitis in Primary Care?
A Randomised Study

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Submitted for publication
Abstract

Background
Treatment of exacerbations of COPD in primary care in the Netherlands is often not in accordance with the Dutch guidelines. In clinical settings, a short course of high-dose systemic corticosteroids results in a more rapid improvement in patient outcome, and a decrease in the rate of clinical relapse.

Objectives
To investigate whether, also in general practice, a standardized treatment with oral corticosteroids improved patient outcome in exacerbations of COPD and chronic bronchitis.

Methods
General practices were randomised to treatment with a high-dose oral corticosteroid course and antibiotics in accordance with the national guideline; or treatment ‘as usual’. Primary endpoints were time to recovery, clinical results at three weeks, and recurrences after three months.

Results
Of 100 patients enrolled, 89 were included in the final study analysis, 53 in the intervention and 36 in the control group. Oral corticosteroid courses were prescribed in 90% (48/53) in the intervention and 75% (27/36) in the control group, and antibiotics in 19% (10/53) and 44% (16/36) respectively. At three weeks, the mean CCQ scores did not return to baseline level in both study arms; rates of cure, improvement and failure were comparable for both groups. At three months, 23% of patients in the intervention group and 25% of the control group had a recurrence.

Conclusion
The study protocol was effectively implemented, but standard treatment with a high-dose oral corticosteroid course did not improve patient outcomes of exacerbations in general practice. Antibiotic prescription was reduced with 25% without a loss in patient outcome.
Introduction

In patients with an exacerbation of COPD in clinical settings, hospitalized and outpatients, a short course of high-dose systemic corticosteroids results in a more rapid improvement in expiratory flow rate\textsuperscript{1-3} and dyspnoea score\textsuperscript{1,2}, a shorter hospital stay\textsuperscript{3} and a decrease in the rate of clinical relapse.\textsuperscript{1,3} Antibiotic treatment is found to be of greatest benefit to patients with severe symptoms\textsuperscript{4} and/or severe airway obstruction before treatment.\textsuperscript{5,6}

However, the majority of patients presenting with an exacerbation of COPD is treated by their general practitioner (GP). In the primary care setting, with the majority of patients classified GOLD class 2\textsuperscript{7} it has not been studied whether a short course of oral corticosteroids as therapy of first choice will lead to a better patient outcome. In a recent pilot study performed in four primary health care centres in the Netherlands, we found that in case of exacerbations, fewer steroid courses and more antibiotics were prescribed than could be expected according to the Dutch College of General Practitioners’ guidelines for diagnosis and treatment of COPD.\textsuperscript{8,9} Antibiotics are advised only in case of symptoms of clinical infection, a low baseline expiratory flow rate, or insufficient clinical recovery four days after initial treatment. Sub-optimal treatment may prolong the duration of exacerbations and may increase the number of hospital referrals. Moreover, unnecessary use of antibiotics can contribute to the growing resistance rates among respiratory pathogens.\textsuperscript{10-12}

Departing from accepted practice, we investigated, in a randomized trial carried out in a primary care setting, whether patient outcomes in exacerbations of COPD or chronic bronchitis could be improved through optimizing the treatment regimen. A standardized treatment with a high-dose oral corticosteroid course was compared with the current usual care.

Methods

This randomised, open label study was conducted in eight primary health care centres and 18 general practices in the referral area of the two participating hospitals in Amsterdam, the Netherlands: the Academic Medical Centre – University of Amsterdam and the Onze Lieve Vrouwe Hospital, a large inner-city community-based hospital. Eligible patients were invited to participate between November 2004 and July 2006.

Patients

Patients were eligible for inclusion if the diagnosis of COPD according to the international classification of primary care code (ICPC) R95,\textsuperscript{13} or chronic bronchitis, was registered in the electronic medical record of the participating general practitioner, in order to depart from accepted practice. COPD was defined according to the ATS (American Thoracic
Society) guidelines as a disorder characterized by abnormal tests of expiratory flow (FEV1) that did not change markedly over periods of several months observation. Chronic bronchitis was defined as the production of sputum on most days for at least three months of the year during the previous two years. An exacerbation was defined as increased dyspnoea within the last four weeks, with or without increased volume of sputum and/or increased purulence of sputum and/or cough for which an adaptation of medication was considered indicated by the GP.

Inclusion criteria for the current study were age above 40 years and seeking medical attention of the GP because of increased pulmonary symptoms. Excluded from the study were patients with poor cognitive functioning, poor mastering of the Dutch language, a life expectancy less than one month, any other infection necessitating the administration of systemic antibiotics, severe underlying disease (AIDS, neutropenia < 1.0 x 10^9/l) and age above 80 years.

**Study design**

Primary health care centres and general practices were assigned to either the control or the intervention study arm, based on a computer generated randomisation code and with weighing for number of patients per practice or health care centre. To prevent contamination, randomisation per health care centre or general practice was performed to secure that all the patients in one health care centre or family doctors’ practice would be assigned to the same study arm. We checked if clustering within health care centres and general practices was related to the initial treatment of the exacerbation.

In the intervention study arm, before the study started, a protocol was implemented in which initial treatment of exacerbations was standardized. This protocol was based on the Dutch College of General Practitioners’ guideline for COPD and the LTA-COPD (National Agreement between GPs and medical specialists) and the recent Cochrane review on the use of systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. In addition, the possibility of a special once-only standardized consultation of a pulmonologist was included in the intervention arm protocol. Before the start of the study a meeting was organised between the study team, the GPs in the intervention arm, and the pulmonologists of the referral hospitals involved in order to discuss and refine this protocol. According to this protocol, in case of our predefined definition of exacerbation in COPD, all patients were treated with a course of oral corticosteroids, 30 mg daily for 7-10 days. Antibiotics were prescribed in accordance with the Dutch guideline for COPD only in case of clinical infection (temperature above 38.5°C, severe illness), a low baseline expiratory flow rate (FEV1 < 30% of the predicted value), or insufficient clinical recovery after four days of corticosteroids. Antibiotics of choice were amoxicillin, co-amoxiclav, doxycyclin or another broad-spectrum antibiotic for 7 days. The possible indications for the once-only consultation of the pulmonologist were a possible alternative diagnosis, doubt about the safety of treatment at home (in particular imminent respiratory insufficiency), and lack of improvement after four days of corticosteroid therapy. During this consultation at the emergency or outpatients’
department, a chest radiograph and an arterial blood gas analysis were performed, the use of daily medication was checked, and the effect of nebulized bronchodilator therapy was observed. If no alternative diagnosis could be made, a sputum culture was obtained. If an alternative diagnosis was found, treatment was instituted accordingly. In other cases the treatment started by the GP was continued or started according to the study protocol and in case of insufficient response on oral corticosteroids, a course of antibiotics was prescribed. GPs in the control study arm (usual care) received only global information about the study.

Evaluations
At study entry, when the patient presented at the GP (day 0), the investigator contacted the patients by telephone, and a short medical history was obtained, including maintenance medication and the medication prescribed for the current exacerbation. With inclusion we assessed the health status of the patients (retrospectively, i.e. 30 days before admission, and at time of enrolment) using the Clinical COPD Questionnaire (CCQ)\(^\text{17}\) (see appendix A). This validated 10-item questionnaire is divided into three domains: symptoms, functional state and mental state. It utilises a seven-point Likert scale where 0 = asymptomatic/no limitations and 6 = extremely symptomatic/total limitation. The final score is the mean of all ten items (range 0 to 6), and scores for the three domains can be calculated separately. The effect size of the CCQ score has been examined by Kocks et al.,\(^\text{18}\) suggesting that a change in the final score of 0.4 or more from baseline represents the smallest change in health status that can be considered to be clinically significant.

After enrolment, patients were asked prospectively to record the CCQ in a diary (24-hour version of the CCQ) for ten consecutive days. Patients were scheduled for follow-up by telephone at two weeks, three weeks and three months after study entry. At these evaluation moments, the CCQ score was assessed, and the patients were asked for use of antibiotics, oral steroids and daily medication and any visit to the GP or a hospital for COPD related complaints. To stage the patient’s disease severity, recently performed (within the last two years) pulmonary function tests, conducted in stable disease were looked up or newly carried out after the exacerbation when not available.

Outcome measures
The primary endpoint of the study was the improvement in health status within three months of follow-up. The secondary endpoint was the improvement in the health care process. The improvement in the patient’s state of health was assessed by: the time to recovery; the clinical result at three weeks, indicated as Test of Cure (TOC); and the occurrence of and time to a new exacerbation between three weeks and three months after the initial exacerbation. The duration of the exacerbation was assessed by the course of the final CCQ-scores. The clinical results at TOC were classified as cure, improvement, or failure, based on the final CCQ-scores, using existing definitions.\(^\text{19}\) We considered the patient cured if the CCQ score at three weeks was back to baseline level, and improved if the CCQ score at three weeks was lower than the score at enrolment (day 0), but not back to baseline-level. Patients who were neither cured nor improved were classified as failures.
Improvement in the health care process was determined by total use of oral corticosteroids, use of antibiotics, and the use of health care services in primary and secondary care, i.e. visits to the GP and the hospital within the study and follow-up period.

**Statistical analysis**

All randomized patients with COPD classified GOLD 1-4 or at risk for COPD who completed follow-up were included in the analysis. The study was designed to demonstrate that a shorter duration of the exacerbation could be obtained if the initial treatment of the exacerbation is optimal. Based on an $\alpha$ level of 5% and a power of 0.80, assuming a mean duration of nine days of an exacerbation (SD 4), 64 patients in each study arm were needed to demonstrate a reduction of two days in the duration of the exacerbation. Clustering within health care centres and general practices with respect to the initial treatment of the exacerbation were assessed for both treatment groups by calculating Pearson’s correlation coefficient. The mean total CCQ scores (range 0-6) and domain-scores (range 0-6) (and 95% CI) at each time point were calculated. Both study groups were compared using the t-test, Mann-Whitney test, and $\chi^2$ test, where applicable. P-values < 0.05 were considered statistically significant. Statistical analyses were performed with SPSS v. 14.0.2 (SPSS Inc., Chicago, IL, USA).

**Results**

**Patients**

In 21 months, 100 patients were enrolled in the study, 61 patients in the intervention and 39 in the control group. Three patients withdrew their consent for participation and did not take part in the follow-up. Eight patients could not be classified according to GOLD, because either spirometric values could not be obtained (n=3) or spirometry was normal in never-smoking patients (n=5). These patients were excluded from the analysis, leaving 89 patients, 53 in the intervention study arm and 36 in the control arm (Figure 1). These patients were included in 16 centres. The median number of patients per GP was 2.0 (Interquartile Range (IQR) 1.0-3.0).

**Baseline characteristics**

All patients were registered by the GP with ICPC code (R95) for COPD. Sixty patients (67%) had COPD classified GOLD 1-4. Twenty-nine smoking patients (32%) with spirometric values within normal range were classed ‘at risk for COPD’. The two treatment groups had similar baseline characteristics, except for age. Patients in the intervention group were younger, median age 65 years (IQR 58-73) compared to 72 years (IQR 62-80) in the control group (p=0.02). Table 1 shows the baseline characteristics of the randomized patients.
CCQ scores and treatment at enrolment

At enrolment, the mean total CCQ score in the intervention arm was 3.4 (95% CI 3.1 to 3.6) and in the control arm 3.6 (95% CI 3.3 to 4.0) (p=0.22); a clinically significant deterioration of 1.5 and 1.7 points respectively. Table 2 shows the total CCQ scores and domain scores at baseline, at enrolment and at three weeks.

In both study groups, the initial treatment showed a high number of prescriptions of oral corticosteroid courses: 90% (48/53) in the intervention group compared with 75% (27/36) in the control group (p<0.05). In contrast, antibiotics were prescribed less often in the intervention group, in 19% (10/53), as compared to 44% (16/36) in the control group (p<0.01). Table 3 shows initial treatment in both study arms. Clustering within health care centres and general practices did not play a role in the initial treatment of the exacerbation (Pearson’s correlation coefficient -0.23 for the intervention group and 0.19 for the control group).
Table 1. Baseline characteristics of the randomised patients

<table>
<thead>
<tr>
<th></th>
<th>Intervention n=53</th>
<th>Control n=36</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (45)</td>
<td>20 (56)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>29 (55)</td>
<td>16 (44)</td>
<td></td>
</tr>
<tr>
<td>Age, years (median; interquartile range)</td>
<td>65 (58-73)</td>
<td>72 (62-80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Daily used medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ß2 agonists/ anticholinergics</td>
<td>12 (23)</td>
<td>4 (11)</td>
<td>ns</td>
</tr>
<tr>
<td>Ics* (+/- ß2 agonists/anticholinergics)</td>
<td>37 (70)</td>
<td>28 (78)</td>
<td></td>
</tr>
<tr>
<td>No daily used medication</td>
<td>4 (8)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Classification of COPD by severity†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At risk</td>
<td>17 (32)</td>
<td>12 (33)</td>
<td>ns</td>
</tr>
<tr>
<td>GOLD I (mild COPD)</td>
<td>3 (6)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>GOLD II (moderate COPD)</td>
<td>20 (38)</td>
<td>13 (36)</td>
<td></td>
</tr>
<tr>
<td>GOLD III (severe COPD)</td>
<td>10 (19)</td>
<td>7 (19)</td>
<td></td>
</tr>
<tr>
<td>GOLD IV (very severe COPD)</td>
<td>3 (6)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Number of exacerbations in previous year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (37)</td>
<td>17 (47)</td>
<td>ns</td>
</tr>
<tr>
<td>1-4</td>
<td>28 (55)</td>
<td>18 (50)</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>4 (8)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Underlying disease#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>30 (57)</td>
<td>20 (56)</td>
<td>ns</td>
</tr>
<tr>
<td>Other pulmonary</td>
<td>16 (30)</td>
<td>9 (25)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6 (11)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (8)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (6)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Smoker (current or ex-smoker)</td>
<td>52 (98)</td>
<td>34 (94)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data are n (%), unless stated otherwise. *Ics: inhaled corticosteroids. †GOLD: Global Initiative for Chronic Obstructive Lung Disease. #Some patients had more than one.

Results at three weeks
The course of the total CCQ score and the three domain-scores were similar for both study arms (Table 2). In both study arms the mean CCQ scores at three weeks did not return to the baseline level. Therefore, the mean time to recovery could not be assessed.
In both study arms, the lowest mean CCQ score was reached at day ten, and was 2.2 points (95% CI 1.9 to 2.6 and 1.8 to 2.6 respectively).

**Table 2.** Total CCQ- and domain scores* at baseline, first visit to GP, and at 3 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention n=53</th>
<th>Control n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>1.9 (1.6-2.2)</td>
<td>1.9 (1.6-2.1)</td>
</tr>
<tr>
<td>Functional</td>
<td>2.1 (1.8-2.5)</td>
<td>2.1 (1.7-2.5)</td>
</tr>
<tr>
<td>Mental</td>
<td>2.2 (1.8-2.6)</td>
<td>2.2 (1.8-2.6)</td>
</tr>
<tr>
<td></td>
<td>0.7 (0.4-1.1)</td>
<td>0.6 (0.3-1.0)</td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>3.4 (3.1-3.6)</td>
<td>3.6 (3.3-4.0)</td>
</tr>
<tr>
<td>Functional</td>
<td>4.1 (3.8-4.4)</td>
<td>4.5 (4.1-4.8)</td>
</tr>
<tr>
<td>Mental</td>
<td>3.6 (3.2-4.0)</td>
<td>3.7 (3.2-4.2)</td>
</tr>
<tr>
<td></td>
<td>1.5 (1.0-1.9)</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td><strong>3 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>2.3 (2.0-2.6)</td>
<td>2.1 (1.8-2.4)</td>
</tr>
<tr>
<td>Functional</td>
<td>2.6 (2.2-3.0)</td>
<td>2.5 (2.1-2.9)</td>
</tr>
<tr>
<td>Mental</td>
<td>2.6 (2.2-3.0)</td>
<td>2.4 (1.9-2.9)</td>
</tr>
<tr>
<td></td>
<td>0.9 (0.6-1.3)</td>
<td>0.6 (0.3-0.9)</td>
</tr>
</tbody>
</table>

Data are mean scores (95% CI). *7-point scale: 0=asymptomatic/no limitations; 6=extremely symptomatic/totally limited.

At three weeks, indicated as test of cure, the CCQ score was available for 100% of the analyzed patients (n=89). The CCQ-scores returned to baseline level in 22/53 (41%) patients in the intervention arm compared to 15/36 (42%) patients in the control arm. Also in 22/53 (41%) patients in the intervention arm the CCQ-scores improved compared to the score at enrolment, but did not reach baseline level, compared to 16/36 (44%) in the control arm. In 7/53 (13%) and in 4/36 (11%) patients respectively the total CCQ score did not improve (p=0.94). Of three patients no baseline score was obtained, thus the distinction between cure and improvement could not be made.

After initial treatment, additional therapy was prescribed in 23% (12/53) of patients in the intervention arm compared to 28% (10/36 patients) in the control arm (p=0.09). The results at three weeks are displayed in Figure 1 and Table 3. In patients with GOLD1-4 failure occurred in the intervention arm in 2/36 (6%) and in the control arm in 2/24 (8%), compared to 5/17 (29%) and 2/12 (17%) in patients at risk for COPD respectively.
Results at three months

Between three weeks and three months, recurrences were reported in 12/53 patients (23%) in the intervention arm compared with 9/36 (25%) in the control arm (p=0.80). One patient, in the control arm, died as a result of a new exacerbation, 55 days after enrolment in the study. The median time to recurrence was 62 days (IQR 39 to 72 days) in the intervention group and 71 days (IQR 65 to 85 days) in the control group (p=0.80). During follow-up, in the intervention group 28/53 patients (53%) visited their GP compared to 20/36 (56%) in the control group (p=0.80). The hospital was visited by 7/53 (13%) and 6/36 (17%) patients respectively (p=0.65) (Table 3). Of these patients, three in each study arm (6% and 8% respectively) were admitted. GPs in the intervention group referred three patients for the once-only consultation.

Table 3. Results at inclusion, three weeks and three months

<table>
<thead>
<tr>
<th></th>
<th>Intervention n=53</th>
<th>Control n=36</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial treatment of exacerbation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short course of oral steroids</td>
<td>40 (75)</td>
<td>18 (50)</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>2 (4)</td>
<td>7 (19)</td>
</tr>
<tr>
<td></td>
<td>Antibiotics and steroids</td>
<td>8 (15)</td>
<td>9 (25)</td>
</tr>
<tr>
<td></td>
<td>Adaptation in daily used medication</td>
<td>3 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cure*</td>
<td>22 (41)</td>
<td>15 (42)</td>
</tr>
<tr>
<td></td>
<td>Improvement*</td>
<td>22 (41)</td>
<td>16 (44)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>7 (13)</td>
<td>4 (11)</td>
</tr>
<tr>
<td></td>
<td>Additional therapy</td>
<td>12 (23)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>3 months#</td>
<td>Recurrence</td>
<td>12 (23)</td>
<td>9 (25)</td>
</tr>
<tr>
<td></td>
<td>Visit GP</td>
<td>28 (53)</td>
<td>20 (56)</td>
</tr>
<tr>
<td></td>
<td>Visit hospital</td>
<td>7 (13)</td>
<td>6 (17)</td>
</tr>
</tbody>
</table>

*Three patients (two in the intervention and one in the control group) were cured or improved. #Between 3 weeks and 3 months.
Discussion

Summary of main findings
In this randomised open-label study conducted in a primary care setting, treatment according to the study protocol could be effectively implemented in the intervention group. The prescription rate of corticosteroid courses increased in this group whereas antibiotics were prescribed significantly less often. So prescription behaviour of GPs is amenable to guided change.

However, we could not demonstrate that standardized treatment of exacerbations with a course of oral corticosteroids in a population predominantly at risk, or with mild to moderate COPD improved patient outcomes compared to ‘usual care’. On the other hand, the reduction with 25% of antibiotic prescriptions in the intervention group compared to the control group did not result in a less favourable patient outcome.
Strengths and limitations of the study

The strength of this study was the randomised, comprehensive approach. The majority of patients with COPD exacerbations is treated in primary care. Most research on this topic is conducted in clinical settings, so available literature cannot automatically be applied to the primary care setting.

Unfortunately, the target inclusion was not achieved within the study period, especially in the control arm. This could have caused selection bias. However, intense screening of the electronic medical records for three months at the end of the study period in control practices did not reveal any patient who was unjustly not included in the study. Moreover, baseline characteristics of both study groups did not demonstrate relevant differences in patient characteristics. Therefore, we think GPs in the control arm did not include patients in the study selectively.

The prescription rate of oral steroids in the control group was surprisingly high with 75%. This is 22% higher than found in our pilot study, based on electronical medical records, conducted previously in four of the participating primary health care centres. In the present study, two of these centres were randomized to the 'usual care' group. Previous participation in the pilot study may have influenced prescription behaviour. In addition, there could be a trial participation effect. The high prescription rate of oral steroids resulted in an unexpected but diminished contrast between the two study groups and might at least in part explain the fact that no significant differences were found between the groups.

Comparison with existing literature

A recent Cochrane review supports the use of systemic corticosteroids, reporting significant reduction of treatment failure and need for additional treatment, and an increase in lung function and dyspnoea over the first 72 hours. The patients in the studies involved were predominantly inpatients who had more severe COPD compared to the patients investigated in the present study. Whether the conclusions of the Cochrane review are valid in a general practice based group of patients with less severe disease remains a question. Oral corticosteroid course may not be as beneficial in mild COPD as in severe COPD.

Another Cochrane review concluded that antibiotic treatment in exacerbations of COPD reduced mortality and treatment failure. Most studies involved in this review were conducted in clinical settings, frequently in hospitalized patients, with merely severe exacerbations. The benefits of antibiotic treatment could not be confirmed by community based studies. For patients treated in general practice, studies showed no advantage of antimicrobial therapy. Also in the primary care population we studied, with most patients classified GOLD 2, a 25% reduction of antibiotic use did not result in poorer outcomes.
We found that the mean CCQ scores at three weeks did not return to baseline level. Although the baseline CCQ score was gained retrospectively and thus might be susceptible of some recall bias, these findings are in line with the results of other prospective studies, in which 14% of patients did not attain symptomatic recovery within a period of 36 days.\textsuperscript{24}

**Conclusion**

We demonstrated that treatment according to the study protocol can be effectively implemented in primary care. An increase in oral corticosteroid course prescriptions for exacerbations and a reduction of antibiotic prescriptions was achieved. However, we could not demonstrate that standardized treatment of exacerbations with a course of oral steroids in a population predominantly at risk for or with mild to moderate COPD improved patient outcomes within three months of follow-up compared to ‘usual care’. Oral corticosteroid course may not be as beneficial in mild COPD as in severe COPD. The disadvantages of oral corticosteroid use should also be taken into account. One extra adverse effect (especially hyperglycaemia) was reported for every six patients treated\textsuperscript{16}.

Other characteristics than GOLD classification might be essential to differentiate between those who will benefit from oral corticosteroids and those who will not. The same consideration holds for the role of antibiotics in the treatment of exacerbations in primary care. Future research therefore, should focus on elucidation of such patient characteristics in those with exacerbations of COPD in primary care.

**Ethical approvals**

The Committees on Medical Ethics of the two participating hospitals in Amsterdam, the Netherlands: the Academic Medical Centre – University of Amsterdam and the Onze Lieve Vrouwe Hospital, both approved the study design. All patients gave their written informed consent before study enrolment. This study is registered with isrctn.org (ISRCTN 43868741).

**Funding**

‘PICASSO for COPD’, an initiative of Pfizer, Boehringer Ingelheim and the research institute Caphri (Care and Public Health Research Institute) from the University of Maastricht, the Netherlands (Project 004).

**Acknowledgements**

We gratefully thank the participating GPs for contributing to patients’ enrolment in the study, and all the patients who participated in the study.
References


## Appendix A. The Clinical COPD Questionnaire

<table>
<thead>
<tr>
<th>CLINICAL COPD QUESTIONNAIRE</th>
<th>Please circle the number of the response that best describes how you have been feeling during the past week. (Only one response for each question)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On average, during the past week, how often did you feel:</strong></td>
<td><strong>never</strong></td>
</tr>
<tr>
<td>1. Short of breath at rest?</td>
<td>0</td>
</tr>
<tr>
<td>2. Short of breath during physical activities?</td>
<td>0</td>
</tr>
<tr>
<td>3. Concerned about getting a cold or your breathing getting worse?</td>
<td>0</td>
</tr>
<tr>
<td>4. Depressed (down) because of your breathing problems?</td>
<td>0</td>
</tr>
</tbody>
</table>

**In general, during the past week, how much of the time:**

| 5. Did you cough? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 6. Did you produce phlegm? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |

**On average, during the past week, how limited were you in these activities because of your breathing problems:**

| 7. Strenuous physical activities (such as climbing stairs, lifting, doing sports)? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. Moderate physical activities (such as walking, homework, carrying things)? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 9. Daily activities at home (such as dressing, washing yourself)? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 10. Social activities (such as talking, being with children, visiting friends/relatives)? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |

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Short-Course Antibiotic Treatment in Acute Exacerbations of Chronic Bronchitis and COPD: A Meta-analysis of Double-blind Studies

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Abstract

Background
A study was undertaken to determine whether a short course of antibiotic treatment (≤5 days) is as effective as the conventional longer treatment in acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (COPD).

Methods
MEDLINE, EMBASE and the Cochrane central register of controlled trials were searched to July 2006. Studies considered eligible were double-blind randomised clinical trials including adult patients >18 years of age with a clinical diagnosis of exacerbation of COPD or chronic bronchitis, no antimicrobial therapy at the time of diagnosis and random assignment to antibiotic treatment for ≤5 days versus >5 days. The primary outcome measure was clinical cure at early follow-up on an intention-to-treat basis.

Results
21 studies with a total of 10 698 patients were included. The average quality of the studies was high: the mean (SD) Jadad score was 3.9 (0.9). At early follow-up (<25 days), the summary odds ratio (OR) for clinical cure with short treatment versus conventional treatment was 0.99 (95% CI 0.90 to 1.08). At late follow-up the summary OR was 1.0 (95% CI 0.91 to 1.10) and the summary OR for bacteriological cure was 1.05 (95% CI 0.87 to 1.26). Similar summary ORs were observed for early cure in trials with the same antibiotic in both arms and in studies grouped by the antibiotic class used in the short-course arm.

Conclusions
A short course of antibiotic treatment is as effective as the traditional longer treatment in patients with mild to moderate exacerbations of chronic bronchitis and COPD.
Introduction

Chronic bronchitis is one of the five leading causes of death worldwide and affects 3–17% of the adult population in developed countries. Acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (COPD) occur frequently. Causes include air pollutants, allergens and viruses, as well as bacterial pathogens. The predominant bacterial pathogen implicated in acute exacerbations of chronic bronchitis and COPD is *Haemophilus influenzae*, which is present in 50% of all bacterial exacerbations, with approximately a further one-third of isolates being either *Streptococcus pneumoniae* or *Moraxella catarrhalis*.

Most patients with acute exacerbations of chronic bronchitis and COPD are treated with antibiotics, but the benefit of antibiotic therapy remains controversial. This controversy is fuelled by data suggesting that at least one-third of exacerbations are non-infectious in origin. In addition, clinical trials of antibiotics have yielded conflicting data, with several large studies failing to demonstrate superiority of antibiotic therapy over placebo. Other trials indicated that antibiotic therapy is effective in patients who have at least two of the following symptoms: increased dyspnoea, increased sputum volume and increased sputum purulence (ie, a type 1 or 2 exacerbation), and in those with more severe airflow obstruction. A meta-analysis recently included in the Cochrane Library confirms these findings by demonstrating that, in acute exacerbations of chronic bronchitis and COPD with increased cough and sputum purulence, the use of antibiotics reduces the risk of short-term mortality by 77% and decreases the risk of treatment failure by 53%.

This raises the question of how long the duration of antibiotic therapy should be. Antibiotic consumption in acute exacerbations of chronic bronchitis and COPD occurs on large scale and this may contribute to increasing resistance rates of the relevant pathogens. Up to 27% of *H. influenzae* and >90% of *M. catarrhalis* produce β-lactamases, with large geographical differences. Worldwide, the overall prevalence of penicillin non-susceptibility among strains of *S. pneumoniae* is around 30–40%, with geographical variations between 2% and 60%. The geographical differences can at least in part be attributed to differences in overall antibiotic consumption. A shorter duration of treatment might help contain these growing resistance rates, but shorter treatment can only be recommended if this is equally efficacious.

We performed a systematic review and meta-analysis of published randomised double-blind studies to determine whether a short course of antibiotic treatment is as effective as a long course in patients with a type 1 or 2 exacerbation of COPD/chronic bronchitis.
Methods

Criteria for considering studies for this review and primary outcomes
Studies considered eligible for inclusion were randomised trials of antibiotic intervention involving adult patients >18 years of age with a diagnosis of COPD or chronic bronchitis. Studies not published in the English language were excluded.

The primary outcome was clinical cure at early follow-up (as defined by the authors of the studies), defined as resolution or improvement of the clinical symptoms of the exacerbation. Treatment failure included lack of clinical resolution or improvement and indeterminate outcome: clinical response to the study drug could not be assessed for any reason. Secondary outcomes were: (1) the rate of clinical cure reported from the time of diagnosis to the final evaluation point (late follow-up): treatment failures included recurrences, relapses and indeterminate cases; and (2) the bacteriological cure rate. Bacteriological failure included persistence of the causative pathogen, presumed persistence (if no material was available for culture in a patient considered a clinical failure), and indeterminate outcome (if the bacteriological response to the study drug was not evaluable for any reason).

Search strategy for identification of studies
We searched the Cochrane central register of controlled trials on the Cochrane Library (Issue 2, 2006), Medline (1966–July 2006) and Embase (1988–July 2006) using the following search terms: chronic bronchitis or COPD, antibiotic treatment and clinical trials (see appendix A for details of the search strategy). We also searched the reference lists of included studies for additional studies.

Data extraction
Studies were included in the meta-analysis if they satisfied the following criteria: (1) adult patients >18 years of age; (2) clinical diagnosis of exacerbation of COPD, chronic bronchitis or pulmonary emphysema; (3) no antimicrobial therapy at the time of diagnosis; (4) random assignment to antibiotic treatment for ≤5 days versus treatment for >5 days; (5) study design with double blinding. Double-blind studies with azithromycin in the short arm were excluded. This antibiotic has a very long half-life and 3 days of treatment with azithromycin can therefore not be regarded as a short therapy.

Two authors independently rated abstracts identified by the electronic searches for inclusion in the meta-analysis. Inter-rater reliability for trial selection was assessed with Cohen’s κ. In cases of disagreement between raters, the full original article was retrieved for data extraction. Differences in opinion over inclusion of studies were resolved through discussions and consensus.
Hard copies of the full article of all potentially eligible studies were obtained. Two reviewers independently extracted the following data from each study: author, year of publication, sample size, mean age of subjects, percentage of smokers, hospitalised or outpatient status of the subjects, antibiotic regimen used, antibiotic treatment duration, criteria used to define exacerbation of chronic bronchitis or COPD and the major outcome measure(s) for each study.

**Assessment of study quality**
The internal validity of included trials was assessed by the same reviewers using the Jadad scale.\(^\text{18}\) The scale assigns scores from 0 to 5 (best quality trial) based on the following items: (1) the study is randomised; (2) the intervention is double blind; (3) an accounting and description of study withdrawals is done; (4) the randomisation procedure is adequately performed using an appropriate method such as computer generated random numbers; and (5) the blindness is also adequately performed using identical-looking placebo.

Concealment of treatment allocation was also evaluated for adequacy: if trialists were unaware of each participant’s allocation when they were recruited, the allocation was said to be adequately concealed.

**Statistical analysis**
Meta-analyses were performed with the Cochrane collaboration’s Revman 4.1 program (Cochrane Collaboration, Oxford, UK). From each study the clinical and bacterial cure rates were calculated and the chance of cure with a short course of antibiotics (≤5 days) compared with a longer course (>5 days) was expressed as an odds ratio (OR) with 95% confidence intervals (CIs). An OR of <1 indicates a lower number of cured cases with the short course of antibiotics and superiority of the long course of antibiotics.

Summary ORs were calculated based on the individual trial outcomes using the fixed-effect model. In additional analyses, studies were grouped by the class of antibiotic used in the short-course arm: cephalosporins, macrolides (other than azithromycin) and fluoroquinolones. Statistical heterogeneity among trials was assessed by \(\chi^2\) analysis. The presence of publication bias was assessed by a funnel plot.

Sensitivity analyses were conducted to assess the robustness of the study by comparing summary ORs among groups redefined by (1) excluding trials of a lower methodological quality (Jadad score < 4); (2) excluding trials with inadequate or unknown concealment; and (3) excluding trials of comparisons between different antibiotics.
Figure. 1 Flow diagram of stages in the systematic review of shorter duration antibiotic therapy in exacerbations of chronic obstructive pulmonary disease (COPD) or chronic bronchitis. RCT, randomised clinical trial.
Table 1. Details of studies comparing short antibiotic treatment with conventional treatment (7–10 days) in patients with acute exacerbations of chronic bronchitis and COPD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Quality score</th>
<th>Concealment</th>
<th>Study size</th>
<th>Mean age of subjects</th>
<th>Out- or inpatients</th>
<th>Treatment</th>
<th>Duration (days)</th>
<th>Early follow-up (days)</th>
<th>Late follow-up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorenz[46]</td>
<td>1998</td>
<td>4</td>
<td>unknown</td>
<td>222</td>
<td>56.0</td>
<td>unknown</td>
<td>Cefixime</td>
<td>5</td>
<td>10-13</td>
<td>27-33</td>
</tr>
<tr>
<td>Langan[21]</td>
<td>1999</td>
<td>5</td>
<td>adequate</td>
<td>544</td>
<td>56.8</td>
<td>Outpatients</td>
<td>Grepafloxacin</td>
<td>5</td>
<td>11-13</td>
<td>31-38</td>
</tr>
<tr>
<td>Wodzicki [a][22]</td>
<td>1999</td>
<td>5</td>
<td>adequate</td>
<td>499</td>
<td>52.0</td>
<td>Outpatients</td>
<td>Dirithromycin</td>
<td>5</td>
<td>10-12</td>
<td>17-21</td>
</tr>
<tr>
<td>Wodzicki [b][22]</td>
<td>1999</td>
<td>5</td>
<td>adequate</td>
<td>558</td>
<td>52.0</td>
<td>Outpatients</td>
<td>Dirithromycin</td>
<td>5</td>
<td>10-12</td>
<td>17-21</td>
</tr>
<tr>
<td>Wilson[47]</td>
<td>1999</td>
<td>4</td>
<td>unknown</td>
<td>750</td>
<td>60.0</td>
<td>unknown</td>
<td>Moxifloxacin</td>
<td>5</td>
<td>14</td>
<td>28-35</td>
</tr>
<tr>
<td>Wasilewski[19]</td>
<td>2000</td>
<td>5</td>
<td>adequate</td>
<td>600</td>
<td>64.2</td>
<td>Outpatients</td>
<td>Moxifloxacin</td>
<td>5</td>
<td>10-16</td>
<td>17-27</td>
</tr>
<tr>
<td>File[48]</td>
<td>2000</td>
<td>4</td>
<td>unknown</td>
<td>458</td>
<td>54.0</td>
<td>unknown</td>
<td>Clarithromycin</td>
<td>5</td>
<td>17-21</td>
<td>28-42</td>
</tr>
<tr>
<td>Paster[26]</td>
<td>2000</td>
<td>5</td>
<td>adequate</td>
<td>586</td>
<td>54.0</td>
<td>Outpatients</td>
<td>Clarithromycin</td>
<td>5</td>
<td>12-19</td>
<td>26-40</td>
</tr>
<tr>
<td>Gotstall[23]</td>
<td>2001</td>
<td>2</td>
<td>unknown</td>
<td>349</td>
<td>52.0</td>
<td>Outpatients</td>
<td>Clarithromycin</td>
<td>5</td>
<td>14-21</td>
<td>28-35</td>
</tr>
<tr>
<td>Masterton[49]</td>
<td>2001</td>
<td>3</td>
<td>unknown</td>
<td>532</td>
<td>59.5</td>
<td>Outpatients</td>
<td>Telithromycin</td>
<td>5</td>
<td>14-21</td>
<td>28-35</td>
</tr>
<tr>
<td>Author[50]</td>
<td>2002</td>
<td>4</td>
<td>unknown</td>
<td>325</td>
<td>61.5</td>
<td>Outpatients</td>
<td>Telithromycin</td>
<td>5</td>
<td>17-21</td>
<td>31-36</td>
</tr>
<tr>
<td>Soler[51]</td>
<td>2003</td>
<td>3</td>
<td>unknown</td>
<td>282</td>
<td>61.1</td>
<td>Inpatients</td>
<td>Gemifloxacin</td>
<td>5</td>
<td>11-14</td>
<td>31-38</td>
</tr>
<tr>
<td>Zarros[52]</td>
<td>2003</td>
<td>5</td>
<td>adequate</td>
<td>376</td>
<td>57.0</td>
<td>Unknown</td>
<td>Telithromycin</td>
<td>5</td>
<td>17-24</td>
<td>31-45</td>
</tr>
<tr>
<td>Seth[33]</td>
<td>2004</td>
<td>5</td>
<td>adequate</td>
<td>360</td>
<td>51.6</td>
<td>Unknown</td>
<td>Telithromycin</td>
<td>5</td>
<td>14-21</td>
<td>28-35</td>
</tr>
<tr>
<td>Seth[53]</td>
<td>2005</td>
<td>4</td>
<td>unknown</td>
<td>893</td>
<td>60.3</td>
<td>Both</td>
<td>Amoxi-clav 2000/125</td>
<td>5</td>
<td>14-21</td>
<td>28-35</td>
</tr>
<tr>
<td>Alvarez-Sala[27]</td>
<td>2006</td>
<td>3</td>
<td>unknown</td>
<td>541</td>
<td>61.1</td>
<td>Unknown</td>
<td>Cefitoren-Pivoxil</td>
<td>5</td>
<td>10-12</td>
<td>25-35</td>
</tr>
</tbody>
</table>
Chapter 4

Results

Literature search and trial inclusion
The search strategy identified 885 studies. A total of 30 full hard copies were selected for further data extraction (Figure 1). There was 94% agreement about which abstracts to include for retrieval of hard copies ($\kappa=0.79$, 95% CI 0.66 to 0.92).

Of these potentially eligible studies, 21 met the criteria for inclusion in the meta-analysis. Details of studies comparing short antibiotic treatment with conventional treatment (7–10 days) in patients with acute exacerbations of chronic bronchitis and COPD are shown in Table 1.

Three trials had three treatment arms.\(^{19-21}\) In these cases the comparison of the short and long duration with the same antibiotic was chosen above the comparison between different antibiotics. Two trials were reported in a single paper.\(^{22}\) As sufficient information could be extracted from this paper, they were included in the meta-analysis.

Methodological quality
The mean (SD) quality score for the trials was 3.9 (0.9) on the Jadad scale; 71% were of very high quality (Jadad score $\geq 4$; table 1). Substantial inter-rater agreement for assignment of this score was reached ($\kappa=0.75$, 95% CI 0.60 to 0.90). Seventeen studies (81%) described the reasons for patient withdrawal. Six trials (29%) were judged as having adequate allocation concealment (Table 1); the remaining studies did not describe the concealment of treatment allocation.

Description of trials
The 21 included studies included a total of 10,698 patients (Table 1), of which 5,348 patients were allocated to short treatment groups and 5,350 to long treatment groups. Four trials did not specify how exacerbation was defined.\(^{20-22}\) All other trials included only patients satisfying at least two of the following criteria: increased cough and/or dyspnoea, increased sputum volume and increased purulence (i.e. a type 1 or 2 exacerbation as defined by Anthonisen et al\(^8\)). The mean (SD) age of study patients was 57.4 (4.3) years in the short treatment groups and 58 (4.4) years in the long treatment groups. The mean (SD) percentage of smokers in the short treatment and long treatment groups was 71.8 (16.3)% and 71.8 (16.3)%, respectively. Most of the studies included outpatients. The mean (SD) duration of treatment was 4.9 (0.4) days in the short treatment groups and 8.3 (1.5) days in the long treatment groups (Table 1).
Short-course Antibiotic Treatment in Acute Exacerbations of Chronic Bronchitis and COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Short-course n/M</th>
<th>Conventional course n/M</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allers-Jara 2009</td>
<td>211 / 254</td>
<td>228 / 277</td>
<td>-</td>
<td>5.2</td>
<td>0.60 (0.54, 0.68)</td>
</tr>
<tr>
<td>Arras 2002</td>
<td>130 / 190</td>
<td>129 / 130</td>
<td>-</td>
<td>2.7</td>
<td>1.22 (1.06, 1.39)</td>
</tr>
<tr>
<td>Chiodo 2000</td>
<td>274 / 269</td>
<td>289 / 281</td>
<td>1.5</td>
<td>1.3 (0.85, 2.0)</td>
<td></td>
</tr>
<tr>
<td>Fie 2000</td>
<td>247 / 304</td>
<td>247 / 295</td>
<td>-</td>
<td>5.4</td>
<td>0.56 (0.51, 0.62)</td>
</tr>
<tr>
<td>Fiozzi 2000</td>
<td>317 / 226</td>
<td>329 / 270</td>
<td>-</td>
<td>5.1</td>
<td>1.25 (0.84, 1.88)</td>
</tr>
<tr>
<td>Fiozzi 2005</td>
<td>226 / 270</td>
<td>239 / 282</td>
<td>4.6</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Goffin 2005</td>
<td>195 / 218</td>
<td>172 / 235</td>
<td>5.3</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Langen 1988</td>
<td>273 / 340</td>
<td>261 / 344</td>
<td>5.8</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Langen 1989</td>
<td>141 / 275</td>
<td>149 / 285</td>
<td>1.2</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Lorenz 1988</td>
<td>273 / 340</td>
<td>261 / 344</td>
<td>1.2</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Londres 2004</td>
<td>197 / 256</td>
<td>207 / 262</td>
<td>6.4</td>
<td>0.74 (0.62, 0.90)</td>
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</tr>
<tr>
<td>Landers 2004</td>
<td>38 / 156</td>
<td>139 / 170</td>
<td>2.4</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Landers 2005</td>
<td>156 / 172</td>
<td>141 / 179</td>
<td>3.6</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Landers 2006</td>
<td>195 / 192</td>
<td>139 / 179</td>
<td>2.4</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Landers 2007</td>
<td>382 / 443</td>
<td>389 / 450</td>
<td>7.1</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Landers 2008</td>
<td>273 / 340</td>
<td>261 / 344</td>
<td>5.8</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Landers 2009</td>
<td>141 / 275</td>
<td>149 / 285</td>
<td>1.2</td>
<td>0.56 (0.51, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Zerwas 2005</td>
<td>229 / 255</td>
<td>209 / 259</td>
<td>5.3</td>
<td>0.30 (0.24, 0.38)</td>
<td></td>
</tr>
<tr>
<td>Total (95%)</td>
<td>4080 / 5261</td>
<td>4079 / 5270</td>
<td>1.0</td>
<td>0.99 (0.96, 1.02)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity (chi-square): 13.24 df=19 p=0.6
Test for overall effect: z=0.20 p=0.8

Figure 2. Clinical cure at early follow-up.

<table>
<thead>
<tr>
<th>Study</th>
<th>Short-course n/M</th>
<th>Conventional course n/M</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiodo 2002</td>
<td>274 / 269</td>
<td>205 / 120</td>
<td>-</td>
<td>5.2</td>
<td>1.00 (0.22, 2.3)</td>
</tr>
<tr>
<td>Goffin 2005</td>
<td>150 / 215</td>
<td>172 / 220</td>
<td>-</td>
<td>2.4</td>
<td>0.30 (0.24, 0.38)</td>
</tr>
<tr>
<td>Langen 1988</td>
<td>141 / 272</td>
<td>149 / 280</td>
<td>-</td>
<td>2.7</td>
<td>0.30 (0.24, 0.38)</td>
</tr>
<tr>
<td>Lorenz 1989</td>
<td>77 / 140</td>
<td>72 / 120</td>
<td>-</td>
<td>2.2</td>
<td>0.12 (0.09, 0.15)</td>
</tr>
<tr>
<td>Maitland 2001</td>
<td>187 / 202</td>
<td>205 / 200</td>
<td>-</td>
<td>4.1</td>
<td>0.30 (0.24, 0.38)</td>
</tr>
<tr>
<td>Sivin 2005</td>
<td>382 / 443</td>
<td>389 / 450</td>
<td>-</td>
<td>1.2</td>
<td>0.30 (0.24, 0.38)</td>
</tr>
<tr>
<td>Total (95%)</td>
<td>1283 / 1559</td>
<td>1258 / 1586</td>
<td>-</td>
<td>1.00</td>
<td>0.30 (0.24, 0.38)</td>
</tr>
</tbody>
</table>

Test for heterogeneity (chi-square): 9.3 df=5 p=0.08
Test for overall effect: z=0.42 p=0.6

Figure 3. Clinical cure at early follow-up in trials with the same antibiotics in both study arms.

All trials defined clinical cure as the disappearance of acute exacerbations of chronic bronchitis and COPD-related signs and symptoms, return to the pre-infection state, or sufficient improvement such that additional or alternative antimicrobial therapy was not required. The mean (SD) time of early follow-up evaluation was after 15 (3.5) days and the mean (SD) time of late evaluation was at day 31 (5.3). In all but one trial clinical cure rates
at early follow-up could be extracted or calculated.\(^20\) Four studies did not report clinical cure rates at late follow-up.\(^{20,23-25}\) Three studies did not report bacteriological cure rates.\(^{23,26,27}\)

### Figure 4. Bacteriological cure at early follow-up.

#### Outcome of clinical and bacteriological cure rates

The primary outcome analysed was the clinical cure rate at early follow-up in an intention-to-treat (ITT) analysis. Early follow-up was before day 25 in all studies. Tests for statistical heterogeneity were performed for all analyses. Statistically significant heterogeneity was not observed in the primary outcome of early clinical cure (\(p=0.8\)) or in the secondary outcomes of late clinical cure (\(p=0.34\)) and bacteriological cure (\(p=0.2\)). A funnel plot did not suggest any form of publication bias.

The summary OR for early treatment cure was 0.99 (95% CI 0.90 to 1.08) (Figure 2). In trials with the same antibiotic in both arms, the summary OR was 0.93 (95% CI 0.78 to 1.11) (Figure 3). The summary OR for cured cases at late follow-up was 1.0 (95% CI 0.91 to 1.10) and for bacteriological cure was 1.05 (95% CI 0.87 to 1.26) (Figure 4).

Similar summary ORs were observed for early clinical cure in studies grouped by the antibiotic class used in the short arm. The summary OR was 1.04 (95% CI 0.87 to 1.24) for cephalosporins, 0.96 (95% CI 0.80 to 1.16) for macrolides and 0.94 (95% CI 0.81 to 1.09) for fluoroquinolones (Figure 5).

<table>
<thead>
<tr>
<th>Study</th>
<th>Short course</th>
<th>Conventional course</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
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</thead>
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<tr>
<td>Auber 2002</td>
<td>29 / 96</td>
<td>19 / 44</td>
<td></td>
<td>5.4</td>
<td>0.96 (0.90 to 1.00)</td>
</tr>
<tr>
<td>Chokshi 2001</td>
<td>142 / 152</td>
<td>168 / 166</td>
<td></td>
<td>4.4</td>
<td>0.92 (0.82 to 1.03)</td>
</tr>
<tr>
<td>Fite 2001</td>
<td>40 / 84</td>
<td>35 / 144</td>
<td></td>
<td>1.4</td>
<td>2.57 (0.73 to 8.80)</td>
</tr>
<tr>
<td>Foggarty 2006</td>
<td>70 / 96</td>
<td>76 / 91</td>
<td></td>
<td>6.3</td>
<td>0.72 (0.32 to 1.62)</td>
</tr>
<tr>
<td>Ofek 2001</td>
<td>85 / 97</td>
<td>78 / 100</td>
<td></td>
<td>0.0</td>
<td>2.03 (0.50 to 8.04)</td>
</tr>
<tr>
<td>Ofek 2005</td>
<td>83 / 105</td>
<td>91 / 111</td>
<td></td>
<td>0.6</td>
<td>0.76 (0.40 to 1.52)</td>
</tr>
<tr>
<td>Langan 1998</td>
<td>74 / 102</td>
<td>74 / 100</td>
<td></td>
<td>0.6</td>
<td>0.70 (0.50 to 1.01)</td>
</tr>
<tr>
<td>Langan 1989</td>
<td>78 / 108</td>
<td>78 / 106</td>
<td></td>
<td>4.3</td>
<td>0.75 (0.39 to 1.49)</td>
</tr>
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<td>Lennox 1990</td>
<td>25 / 26</td>
<td>16 / 17</td>
<td></td>
<td>2.4</td>
<td>0.54 (0.32 to 0.93)</td>
</tr>
<tr>
<td>Meselton 2001</td>
<td>92 / 112</td>
<td>64 / 101</td>
<td></td>
<td>2.4</td>
<td>0.95 (0.45 to 2.00)</td>
</tr>
<tr>
<td>Siter 2004</td>
<td>33 / 84</td>
<td>48 / 60</td>
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<td>0.0</td>
<td>0.70 (0.36 to 1.40)</td>
</tr>
<tr>
<td>Siter 2005</td>
<td>162 / 141</td>
<td>94 / 116</td>
<td></td>
<td>1.9</td>
<td>1.10 (0.78 to 1.54)</td>
</tr>
<tr>
<td>Siter 2003</td>
<td>55 / 63</td>
<td>63 / 67</td>
<td></td>
<td>2.9</td>
<td>1.02 (0.70 to 1.50)</td>
</tr>
<tr>
<td>Waksman 1998 A</td>
<td>79 / 103</td>
<td>95 / 110</td>
<td></td>
<td>0.0</td>
<td>0.94 (0.33 to 2.85)</td>
</tr>
<tr>
<td>Waksman 1998 B</td>
<td>163 / 125</td>
<td>82 / 108</td>
<td></td>
<td>7.2</td>
<td>2.01 (1.56 to 2.56)</td>
</tr>
<tr>
<td>Wilcox 1989</td>
<td>89 / 115</td>
<td>71 / 114</td>
<td></td>
<td>1.1</td>
<td>0.76 (0.49 to 1.20)</td>
</tr>
<tr>
<td>Wilson 2002</td>
<td>43 / 57</td>
<td>46 / 56</td>
<td></td>
<td>4.2</td>
<td>1.76 (0.78 to 3.93)</td>
</tr>
<tr>
<td>Zerwe 2003</td>
<td>19 / 25</td>
<td>22 / 26</td>
<td></td>
<td>2.4</td>
<td>0.99 (0.48 to 2.06)</td>
</tr>
</tbody>
</table>

Test for heterogeneity df=15 \(\chi^2=51\) \(p=0.2\)

Test for overall effect \(z=4.40\) \(p=0.8\)
**Figure 5.** Clinical cure at early follow-up of studies grouped by antibiotic class.

### Sensitivity analysis

Sensitivity analyses were conducted for the primary outcome (ie, clinical cure rate at the early follow-up). Treatment cure rates were not significantly more likely with shorter duration in very high quality trials (summary OR 1.02, 95% CI 0.91 to 1.13), trials with adequate concealment (summary OR 1.04, 95% CI 0.87 to 1.24) or in trials with the same antibiotic in both arms (summary OR 0.93, 95% CI 0.78 to 1.11).
Discussion

In this systematic review of randomised double-blind studies we found that short courses of antibiotic therapy (≤5 days) are as effective as the conventional courses of >5 days in the treatment of mild to moderate acute exacerbations of chronic bronchitis and COPD. The clinical cure rates at both early and late follow-up as well as the bacteriological cure rates were comparable for both treatment strategies. Similar summary ORs were found for early cure in trials with the same antibiotic in both arms.

The overall methodological quality of studies in our systematic review was found to be high or very high, with 71% of the studies having a Jadad score of at least 4. Sensitivity analyses showed no differences between both treatment groups, enhancing the statistical robustness of the overall analysis and strengthening the appropriateness of combining all studies into a single meta-analysis. Statistically significant heterogeneity was not present.

A potential weakness of meta-analyses is the incorporation of existing biases and the introduction of new biases. To minimise bias during trial selection we used predetermined inclusion criteria. Language bias must be considered since this meta-analysis included only trials published in the English language. No signs of publication bias were detected.

Different antibiotic classes are represented, but new agents were often used in the short treatment arm. Studying amoxicillin-clavulanic acid (co-amoxiclav) and tetracyclin/doxycyclin in the short arm would be relevant. However, on microbiological or pharmacological grounds, there are no reasons to believe the results are different for these agents. Most of the studies included in the meta-analysis were conducted in the community, although at least four studies also included hospital inpatients. Although almost all exacerbations were classified as Anthonisen type 1 or 2, we feel some caution is necessary when applying our findings to patients with severe exacerbations who are admitted to hospital with respiratory failure.

Antibiotics are widely prescribed for respiratory tract infections, which account for 75% of community prescriptions. Tonsillopharyngitis is the most frequent indication, followed by bronchitis. It has already been demonstrated that a short course (4–5 days) of treatment with a cephalosporin is at least as effective as 10 days of penicillin treatment in patients with group A streptococcal tonsillopharyngitis, and that a short course (5 days) of short-acting antibiotics is an effective treatment for uncomplicated acute otitis media in children. Studies investigating the effectiveness of shorter courses in community-acquired pneumonia show promising results.

According to most guidelines on the treatment with COPD, antibiotic treatment is only indicated in patients with acute exacerbations of COPD characterised by increased sputum
volume and purulence. The issue of the appropriate duration of antibiotic therapy, however, is not addressed in any of these guidelines.

Shorter courses of antibiotic treatment have several potential advantages compared with long courses of treatment. Poor compliance appears to be more common with longer treatment courses, so shorter courses of antibiotics may enhance compliance. The compliance rate in tonsillopharyngitis, in which penicillin therapy is typically prescribed for 10 days, is inversely related to the duration of treatment and has been observed to be as low as 8% by the ninth day of treatment. It is to be expected that a short course of treatment will also reduce antibiotic costs.

More important is the effect of unnecessarily lengthy courses on the development of resistant organisms. On a population level, there is a clear relationship between total antibiotic consumption and resistance rates of pathogens. Decreasing the duration of antibiotic courses in respiratory tract infections might contribute to a decrease in these resistance rates.

Our meta-analysis supports the effectiveness of short-course treatment in mild to moderate exacerbations of COPD or chronic bronchitis characterised by at least two of the following criteria: increased cough and/or dyspnoea, increased sputum volume and increased purulence. Based on the included studies, it seems that the duration of antibiotic treatment can be safely reduced. We therefore propose that the guidelines for COPD should recommend antibiotic treatment duration of no longer than 5 days, regardless of antibiotic class, in mild to moderate exacerbations of COPD or chronic bronchitis.

**Acknowledgements**
The authors thank Heleen C Dyserinck for her support with the search strategy.

**Funding**
References

Short-course Antibiotic Treatment in Acute Exacerbations of Chronic Bronchitis and COPD


49. Masterton RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day


Appendix A

Electronic search strategy using Medline: ("Pulmonary Disease, Chronic Obstructive"[MeSH]) OR (chronic bronchitis) OR (pulmonary emphysema) OR (chronic obstructive bronchitis*) OR (chronic airflow limitation*) OR (chronic airflow obstruction*) OR (obstructive airways disease*) OR (chronic obstructive lung disease*)
AND
("Anti-Bacterial Agents"[MeSH] OR “Anti-Bacterial Agents”[Pharmacological Action]) OR (antibiotic*)
AND
Electronic search strategy using Ovid
1. exp Chronic Obstructive Lung Disease/
2. exp Chronic Bronchitis/
3. exp lung emphysema/
4. chronic bronchitis.tw.
5. lung emphysema.tw.
6. chronic obstructive lung disease.tw.
7. pulmonary emphysema.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Antibiotic Agent/
10. 8 and 9
11. random$.tw.
12. 10 and 11
13. limit 12 to (human and English language)
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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Chapter 5

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 -2.0 to 20). After 3 months, 13 (62%) of 21 patients were cured, compared with 14 (56%) of 25 (difference 5.9%; 95% CI -2.3 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.
Three vs 10 Days of Amoxicillin-clavulanic acid for Type 1 Acute Exacerbations of COPD

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 guidelines8 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 days9 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 telithromycin13 or ceftibuten,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 (<1.0×10⁹/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\(^\text{16}\) (Table 1).

Table 1. Definitions of clinical response according to criteria given by Chow et al.\(^\text{18}\)

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>TOC</th>
<th>Late follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test of Cure</strong></td>
<td><strong>Cure</strong></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>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td></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>
</tr>
<tr>
<td><strong>Indeterminate</strong></td>
<td></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>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td><strong>Cure</strong></td>
<td>Continued resolution or improvement of acute symptoms and signs to a baseline level or reduction of dyspnoea, cough, sputum production and, if elevated at enrolment, resolution of fever.</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td><strong>Cure</strong></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><strong>Indeterminate</strong></td>
<td></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...
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>Gender</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>Age, years</td>
<td>69 (59–76)</td>
<td>66 (61–71)</td>
</tr>
<tr>
<td>Classification of COPD by severity*</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>Daily used medication</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>No daily used medication</td>
<td>3 (14)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>β2 agonists/ anticholinergics</td>
<td>6 (29)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Ics (+/- β2 agonists/ anticholinergics)</td>
<td>11 (52)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Underlying disease¶</td>
<td>12 (57)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3 (14)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>9 (43)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (48)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Temperature &gt; 37.5 °C</td>
<td>11 (52)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Symptom scores, median (IQR)+</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>Detected pathogen at study entry$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>S. pneumoniae</td>
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<td>2</td>
</tr>
<tr>
<td>M. catarrhalis</td>
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<td>2</td>
</tr>
<tr>
<td>E. coli</td>
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<td>0</td>
</tr>
<tr>
<td>Candida albicans</td>
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</tr>
<tr>
<td>Influenza A/ B</td>
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<td>3</td>
</tr>
<tr>
<td>RS virus</td>
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<td>1</td>
</tr>
<tr>
<td>M. pneumoniae</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 theofylline.
¶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.4–6 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.12–14

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.20–24 To address this problem, new antimicrobial agents have been tested and have been found to be clinically and bacteriologically effective.25–27 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.

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References

Antibiotic Treatment is Associated with Reduced Risk of a Subsequent Exacerbation in Obstructive Lung Disease: An Historical Population based Cohort Study

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Abstract

Objectives
The risk of a subsequent exacerbation after treatment of an exacerbation with oral corticosteroids without (OS) or with antibiotics (OSA) was evaluated in a historical population based cohort study comprising patients using maintenance medication for obstructive lung disease.

Methods
The Pharmo database includes drug dispensing records of more than 2 million subjects in the Netherlands. Eligible were patients ≥ 50 years who in 2003 were dispensed ≥ 2 prescriptions of daily used inhaled β2-agonists, anticholinergics, and/or corticosteroids, and experienced at least one exacerbation before 1 January 2006. Exacerbation was defined as a prescription of OS or OSA. We compared the times to the second and third exacerbations using Kaplan-Meier survival analysis. Independent determinants of new exacerbations were identified using multivariable Cox recurrent event survival analysis.

Results
Of 49,599 patients using maintenance medication, 18,928 patients had at least one exacerbation; in 52% antibiotics had been added. OS and OSA groups were comparable for potential confounding factors. The median time to the second exacerbation was 321 days in the OS group and 418 days in the OSA group (p< 0.001); and between the second and third exacerbation 127 vs. 240 days (p<0.001). The protective effect of OSA was most pronounced during the first three months following treatment (hazard ratio (HR) 0.62; 99%CI 0.60 – 0.65). In the OSA group mortality during follow-up was lower (HR 0.82; 99% CI 0.66-0.98).

Conclusion
Treatment with antibiotics in addition to oral corticosteroids was associated with a longer time to the next exacerbation, and a decreased risk of developing a new exacerbation.
Introduction

The mainstay of treatment of exacerbations of COPD consists of oral corticosteroids and antibiotics. The use of corticosteroids in this situation is well-accepted, but the role of antibiotics in exacerbations of COPD is still under debate. Patients with severe exacerbations, characterised by severe symptoms, and/ or patients with a low baseline expiratory flow rate are considered to benefit from antibiotic treatment. A recent Cochrane review supports the use of antibiotics for short term benefits in patients with an exacerbation with increased cough and sputum purulence who are moderately or severely ill. Studies conducted in general practice showed no advantage of antimicrobial treatment. Given the inconclusive results from the literature, guidelines differ in their recommendations. The main concern with antibiotic use is a rise of antimicrobial resistance, which correlates well with the overall antibiotic use in the community.

The Dutch Pharmo database contains extensive data on pharmacy dispensing records from community pharmacies and hospital discharge records of more than two million residents of the Netherlands. This gave us the unique opportunity to evaluate the long-term effects of treatment of exacerbations in a large patient group using maintenance medication for obstructive lung disease. In particular, we compared the risk of a subsequent exacerbation after treatment with oral corticosteroids without or with antibiotics.

Methods

Data sources

Data for this study were obtained from the PHARMO database. This population-based database includes pharmacy dispensing records from community pharmacies and hospital discharge records of more than two million residents of 50 regions scattered over the Netherlands. Data are representative for the Netherlands. Both prescriptions from General Practitioners and outpatients are registered. For all residents, the drug-dispensing histories are linked to the hospital discharge records of the same patient, using a probabilistic algorithm, based on characteristics such as date of birth, gender, and a code for the GP. The computerised drug-dispensing histories contain data concerning the dispensed drug and dispensing date. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The hospital records include information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification).

For this study, ethical approval was not relevant because data were anonymised before entering the PHARMO database.
Patient selection
We included patients who in 2003 were dispensed at least two prescriptions of daily used respiratory drugs with ATC-code R03, i.e. inhaled beta-2-agonists, inhaled anticholinergics, inhaled corticosteroids, oral theophylline, or a combination of these agents. We included patients aged 50 years or older, in order to exclude patients with uncomplicated asthma.

Furthermore, patients using leukotriene receptor antagonists (LTRAs) (montelukast, ATC-code R03DC03) or cromoglycates (R03BC) and patients who had been hospitalised with a diagnosis of asthma (ICD-9-CM) in the previous 2 years or during follow-up were excluded.

The cohort entry date was the date of first dispensing of any R03 drug in 2003. Patients were followed until 31 December 2005. If patients had died before that date, they were censored at the date of death. Apart from age, sex, and respiratory drugs, also data on co-medications for cardiovascular disease and diabetes mellitus, as well as previous hospitalisations for COPD and pneumonia were collected.

Definition of exacerbation
To address the study question, we identified those patients who experienced one or more exacerbations. Our assumption is that, in these patients who are on respiratory drugs, a short course of oral corticosteroids is almost exclusively prescribed in case of an exacerbation. Therefore, we defined an exacerbation as a documented dispensing of a short course of oral corticosteroids, with or without antibiotics. We documented the date of dispensing of oral corticosteroids (ATC code: H02AB06/ H02AB07), with or without antibiotics. We scored the antibiotics doxycyclin (ATC-code: J01AA02), amoxicillin (J01CA04), amoxicillin-clavulanate (J01CR02), azithromycin (J01FA10), clarithromycin (J01FA09), ciprofloxacin (J01MA02), moxifloxacin (J01MA14), levofloxacin (J01MA12), and erythromycin (J01FA01), because, in the Netherlands, these cover almost all antibiotics dispensed for exacerbations of COPD.17 We did not include episodes treated only with antibiotics, because information on the coinciding diagnosis was unavailable.

As symptoms, increased at the onset of exacerbation, are usually substantially improved after three weeks,18 we presumed that a second prescription for steroids within 3 weeks suggested an exacerbation not well responding to the initial therapy. To avoid counting these prescriptions as a “next exacerbation”, we introduced a minimum interval between steroid courses of three weeks. If the time between two dispensings exceeded three weeks, we considered the second episode as a new exacerbation. As a consequence, until three weeks after the first course was dispensed, patients were considered not to be at risk for a new exacerbation. Patients dispensed oral corticosteroids or antibiotics for more than 21 days at regular intervals, for a period of three months or longer, were excluded from the analysis, because they are likely to be patients on maintenance treatment with oral corticosteroids or antibiotics, respectively.
**Statistical analysis**

We assessed the first exacerbation after cohort entry (first course of oral corticosteroids) and calculated the time to the second exacerbation (second course of oral corticosteroids). Similarly, we calculated the time between second and the third exacerbation. We compared these time periods between patients treated with oral corticosteroids only, and those treated with oral corticosteroids combined with antibiotics using Kaplan-Meier survival analysis. Patients were censored for exacerbation free survival. The effect of the variable of primary interest, oral corticosteroid (coded as 0) or oral corticosteroid with antibiotic (coded as 1), was analysed in a Cox proportional hazards model. All exacerbations from each patient were used, and time was set back to zero after each exacerbation (gap-time unrestricted model). Hence, each exacerbation was treated as a separate record and time since last exacerbation as principal time scale. A correction for recurrent exacerbation events from the same individual was made by including a frailty term in the model. The Schoenfeld residuals as obtained from the model of time to first exacerbation suggested the difference in treatment effect be highly nonproportional. Therefore, we allowed the difference in treatment effect to change at three months, six months and one year. The data were coded so that hazard ratios below unity indicated a preventative effect of adding an antibiotic to the oral corticosteroids. Potential confounding by the following factors was controlled for: sex, age, number of dispensings of respiratory drugs, including inhaled corticosteroids, co-medication for cardiovascular disease (yes/no) or for diabetes (yes/no), and previous hospitalisation for COPD and pneumonia (yes/no). Dispensing of antibiotics unrelated to exacerbations were also treated as a time-dependent covariate, and assumed to be of influence for a period of three months. This means that three months after dispensing this antibiotic, the variable was again coded as no antibiotic. All-cause mortality of both treatment groups was analyzed using Kaplan-Meier survival analysis and Cox regression analysis. We calculated 99% confidence intervals. Analyses were performed using Stata software, version 9.2 (StataCorp, College Station Texas, USA), R-2.6.0 (R Development Core Team (2007): R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org) and SPSS v. 14.0.2 software (SPSS Inc., Chicago, IL, USA).

**Results**

**Patients**

From the PHARMO database we identified 52 753 patients, 50 years and older, fulfilling the prespecified criteria on respiratory drug use. In total, 3114 patients who had been hospitalised with a diagnosis asthma or used LTRAs or cromoglycates were excluded, and 40 patients were excluded because of administrative errors, leaving 49 599 patients. Of these patients, 19 882 (40%) had had at least one exacerbation as previously defined. 715 patients were excluded from further analysis because they were likely to be on maintenance treatment with oral corticosteroids (n=349), or with antibiotics (n=366). 239
patients were not at risk for a next exacerbation, as they had only one exacerbation within the 3 weeks before the end of follow-up, leaving 18,928 patients for further analysis.

We found that 1053 patients (6%) died during the follow-up period. For 894 patients the cause of death was unknown, 159 patients died during hospitalization for COPD. This was counted as an event, and not right-censored. After the first exacerbation, 2341 hospital admissions for COPD occurred; 1636 within one month of a documented exacerbation and 546 independently from a registered exacerbation. These 546 hospital admissions were considered as an event; instead of 'time to the next exacerbation', time to hospital admission was counted. As information on in-hospital treatment was not available, they were not analyzed further.

Table 1. Characteristics of patients according to treatment of first exacerbation

|                          | Total n=18,928 | Oral corticosteroids n=9,074 | Oral corticosteroids and antibiotics n=9,854 | p²
|--------------------------|---------------|-----------------------------|---------------------------------|---
| Gender                   |               |                             |                                 |   
| Male                     | 9,395 (50)    | 4,536 (50)                  | 4,859 (49)                      |   
| Female                   | 9,533 (50)    | 4,538 (50)                  | 4,995 (51)                      |   
| Age (years)*             | 70 (61-77)    | 70 (61-77)                  | 70 (61-77)                      | 0.60
| No of respiratory dispensings in 2003 | 8 (4-13) | 8 (4-13) | 8 (4-13) | <0.01
| ICS§ (maintenance medication)* | 16,771 (89) | 8 (4-13) | 8 (4-13) | <0.01
|                           | 7,883 (87)    | 8,888 (90)                  |                                 |   
| Co-medication|                |                             |                                 |   
| Cardiovascular Diabetes  | 12,995 (69)   | 6,245 (69)                  | 6,750 (68)                      | 0.63
|                           | 2,682 (14)    | 1,264 (14)                  | 1,418 (14)                      |   
| Hospitalisation† for COPD| 1,925 (10)    | 994 (11)                    | 931 (9)                         | <0.01
| Pneumonia               | 651 (3)       | 325 (4)                     | 326 (3)                         | 0.30
| Follow-up characteristics|               |                             |                                 |   
| Follow-up time (days)*   | 754 (437-974) | 786 (472-988)               | 739 (404-957)                   |   
| Number of exacerbations* | 2 (1-4)       | 2 (1-4)                     | 2 (1-3)                         |   

Data are n (%), unless otherwise stated. *Median (Interquartile range). §ICS: Inhaled corticosteroids. †Once or more in previous 2 years. ‡Diagnosis: chronic bronchitis, emphysema or chronic obstructive pulmonary disease. *Chi-square or Mann-Whitney test, where appropriate. The oral corticosteroids and antibiotics group had a significant higher number of respiratory dispensings, but the 25th, 50th and 75th percentiles for both treatment groups were similar.

The median follow-up time after the first exacerbation was 754 days [interquartile range (IQR) 437-974]. In total, 18,928 patients were followed for 36,104 person years. GPs
prescribed 72% of all antibiotics, oral corticosteroids and respiratory maintenance medication, 24% came from pulmonologists and 5% from other or unknown prescribers. Antibiotics used in the treatment of first exacerbations were doxycyclin (n=4011, 41%), penicillins (amoxicillin-clavulanate and amoxicillin, n=3597, 37%), macrolides (azithromycin and clarithromycin, n=1916, 20%), and fluoroquinolones (ciprofloxacin, moxifloxacin and levofloxacin, n=260, 3%). 53 cases could not be assigned to a treatment group.

**Time to second exacerbation**

Of 18,928 patients having had at least one exacerbation, the first exacerbation after cohort entry was treated with oral corticosteroids only in 48% (9,074 patients) and with oral corticosteroids and antibiotics in 52% (9,854 patients). These two groups of patients were similar with respect to age, gender, use of co-medication for diabetes and cardiovascular disease, and the number of previous hospitalisations for pneumonia. However, more patients in the oral corticosteroids with antibiotics group were dispensed prescriptions of respiratory maintenance drugs and inhaled corticosteroids over time (p<0.01). On the other hand, this group had had fewer hospital admissions for COPD in the previous two years compared to patients in the oral corticosteroids only group (p<0.01) (Table 1).

**Kaplan-Meier estimates of the cumulative incidence of developing a second or third exacerbation stratified according to treatment type (oral corticosteroids with or without antibiotics)**

The time to the second exacerbation was much shorter in the oral corticosteroids only group than in the oral corticosteroids with antibiotics group (Figure 1A). The median time between the first and the second exacerbation in the oral corticosteroids only group was 321 days (99% CI 297-345) compared to 418 (99% CI 393-443) days in the oral corticosteroids with antibiotics group. Six months after the first exacerbation, 60% in the oral corticosteroids only group had no new exacerbation compared to 70% in the oral corticosteroids with antibiotics group. Twelve months after the first exacerbation this was 48% and 54% respectively. There were no differences between antibiotic treatment groups with respect to time to the second exacerbation. The median time to the second exacerbation was 414 (99% CI 377-451) days for doxycyclin, 415 (371-458) days for penicillins, 431 (376-486) days for macrolides and 329 (189-469) days for fluoroquinolones (p=0.14).

During follow-up, 472/9,854 (4.8%) patients died in the oral corticosteroid and antibiotic group versus 581/9,074 (6.4%) in the corticosteroid only group (p<0.01, Figure 2). In a univariate Cox regression model the Hazard Ratio (HR) of mortality after treatment with oral corticosteroids and antibiotics compared to corticosteroids only was 0.78 (99% CI 0.62-0.94). In a multivariable Cox model, adjusting for potential confounders (sex, age, number of dispensings of respiratory drugs, including inhaled corticosteroids, co-
Figure 1. Kaplan-Meier estimates of the cumulative incidence of developing a second (Fig 1A) or third exacerbation (Fig 1B) stratified according to treatment type (oral corticosteroids and antibiotics compared with oral corticosteroids).
Antibiotics Associated with Reduced Risk Subsequent Exacerbation in Obstructive Lung Disease

medication for cardiovascular disease or for diabetes, previous hospitalisation for COPD and pneumonia, and exposure to antibiotics unrelated to exacerbation), the HR was 0.82 (99% CI 0.66-0.98).

**Time to third exacerbation**

Of the 18 928 patients with a first exacerbation, 10 588 had had a second exacerbation. Of these exacerbations, 5420 (51%) were treated with oral corticosteroids and 5168 (49%) with oral corticosteroids and antibiotics. After the second exacerbation the difference between the two treatment groups with respect to the time to the next (third) exacerbation was even more pronounced than after the first exacerbation (Figure 1B). The median time between the second and the third exacerbation was 127 (99% CI 117-137) days in the oral corticosteroids only group and 240 (99% CI 222-258) days in the oral corticosteroids with antibiotics group. Six months after the second exacerbation, 42% of patients treated with oral corticosteroids had not had a third exacerbation compared to 57% of patients treated with oral corticosteroids and antibiotics; after one year this was 30% and 39% respectively.

**Figure 2.** Kaplan-Meier estimates of the cumulative survival stratified according to treatment type (oral corticosteroids and antibiotics compared with oral corticosteroids).
Cox recurrent event survival analysis of developing new exacerbations: effect of treatment type

In a univariate Cox regression model the Hazard Ratio (HR) of a new exacerbation after treatment with oral corticosteroids and antibiotics compared to corticosteroids only was 0.63 (99% CI 0.61–0.66) in the first three months following treatment. In a multivariable Cox model adjusting for potential confounders, the HR of a new exacerbation after treatment with corticosteroids with antibiotics was 0.62 (99% CI 0.60–0.65) in the first three months following treatment, but the effect difference decreased in subsequent time periods. Exposure to antibiotics unrelated to exacerbations decreased the risk of a new exacerbation [HR 0.82 (99% CI 0.78–0.87)]. Hospitalisation for COPD in the previous two years increased the risk [HR 1.45 (99% CI 1.35–1.57)]. The variables ‘age’ and ‘number of respiratory drugs dispensings in 2003’ were included in the Cox model, but were not fitted linearly, therefore HR are not presented. The risk of a new exacerbation increased with age until 80 years and with a higher number of respiratory drugs dispensings in 2003 up to a number of 50 dispensings, but decreased after these values.

Table 2. Hazard Ratio’s of determinants of developing a next exacerbation after oral corticosteroids with antibiotics - compared to oral corticosteroids only - treatment in a multivariable Cox model

<table>
<thead>
<tr>
<th>HR of new exacerbation</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Antibiotics added to treatment with oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td>0-3 months following treatment</td>
<td>0.62</td>
</tr>
<tr>
<td>3-6 months &quot; &quot; &quot;</td>
<td>0.68</td>
</tr>
<tr>
<td>6-12 months &quot; &quot; &quot;</td>
<td>1.03</td>
</tr>
<tr>
<td>&gt; 12 months &quot; &quot; &quot;</td>
<td>1.31</td>
</tr>
<tr>
<td>Exposure to antibiotics after previous exacerbation</td>
<td>0.82</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.95</td>
</tr>
<tr>
<td>Inhaled corticosteroids as maintenance medication</td>
<td>0.91</td>
</tr>
<tr>
<td>Co-medication cardiovascular</td>
<td>1.16</td>
</tr>
<tr>
<td>Co-medication for diabetes</td>
<td>1.05</td>
</tr>
<tr>
<td>Hospitalisation’ for COPD¹</td>
<td>1.45</td>
</tr>
<tr>
<td>Hospitalisation for pneumonia</td>
<td>1.19</td>
</tr>
</tbody>
</table>

CI, Confidence interval. ¹Diagnosis: chronic bronchitis, emphysema or chronic obstructive pulmonary disease. The variables ‘age’ and ‘number of respiratory drugs dispensings in 2003’ were included in the Cox model, but were not fitted linearly, therefore HR are not presented.
Checking the assumption that a short course of oral corticosteroids in patients who are on respiratory drugs, is dispensed in case of an exacerbation of COPD.

We defined an exacerbation as a course of oral corticosteroids (with or without antibiotics), assuming that (in the Netherlands) a course of oral corticosteroids in this population of patients on maintenance respiratory drugs is almost exclusively prescribed because of an exacerbation of COPD. We checked this assumption by investigating data based on the Second Dutch National Survey of General Practice (DNSGP-2), carried out by The Netherlands Institute for Health Services Research (NIVEL). This registration database gives a representative impression of morbidity and prescribing habits in Dutch general practice. From 01 January 2002 to 31 December 2002, from 1037 patients with COPD defined according to the international classification of primary care (ICPC) code R95, we analysed 1355 prescriptions of oral corticosteroids. Twelve hundred and fifty-four prescriptions (92%) were COPD-related. Forty prescriptions (3%; upper limit of the 95% CI: 4.0) were prescribed for ‘other musculoskeletal/connective disorders’ (ICPC-code L99). In addition, sixty-one prescriptions (4%; upper limit of the 95% CI: 5.7) were prescribed for other indications. Extrapolating these findings to the present study, we think our definition of exacerbation was appropriate, and this small percentage of misclassified patients would cause bias towards the null.

Discussion

In this historical follow-up study among 18,928 patients with an exacerbation of obstructive lung disease, and focusing on relapse and not on short-term recovery, we showed that treatment with oral corticosteroids and antibiotics compared to treatment with oral corticosteroids alone was associated with a longer time to the next exacerbation, and a decreased risk of developing a new exacerbation. Exposure to antibiotics between exacerbations was also associated with a lower risk of a subsequent exacerbation. In addition, in the group also treated with antibiotics, mortality during follow-up was significantly lower. As in the majority of cases the cause of death was unknown, we are cautious to claim a survival benefit, but this finding is important and certainly warrants confirmation in a prospective study.

Deriving the data from a pharmacy database enabled us to measure actually dispensed medication in a very large number of patients treated with maintenance treatment for obstructive lung disease. Prescriptions both from general practitioners and pulmonologists were documented. A limitation of observational studies might be the presence of treatment selection bias, due to unknown, potentially prognostic important differences among patients. In our study, clinical information on patients was not available. However, patients treated with antibiotics and oral steroids are likely to have more severe exacerbations compared to patients treated with oral steroids only. Therefore, we suspect
that any treatment selection bias, if present, would cause bias towards the null, thus underestimating the effect of adding antibiotics.

We found the effect of treatment was strongest in the first three months following treatment and then gradually decreased, and even reversed after one year. Apparently the protective effect of antibiotics wanes over time, which is to be expected. Patients could not be selected based on a diagnosis of COPD or chronic bronchitis. Therefore, we selected patients who used maintenance respiratory drugs used in the treatment of obstructive lung disease. We included patients aged 50 years or older, in order to exclude patients with uncomplicated asthma. Furthermore, we excluded patients who had been hospitalised with a diagnosis of asthma and those using LTRAs or cromoglycates. Nevertheless, a small proportion of patients with asthma may still have been included in this study.

Recent studies stress the benefits from antibiotic treatment in exacerbations of COPD, and a recent Cochrane review reports reduction of mortality and treatment failure, although in community-based studies no differences were found between antibiotic and placebo. Most studies so far have been conducted in clinical settings, frequently in hospitalised patients, with merely severe exacerbations. For patients treated in general practice, studies showed no advantage of antimicrobial treatment on short-term outcome. In the population we studied, GPs were responsible for 72% of all dispensings. In general, these COPD patients can be classified as GOLD 2 (moderate COPD). So, also in patients with less severe exacerbations, antibiotic treatment added to treatment with oral corticosteroids seems advantageous. The differences we found with respect to time from the first to the second exacerbation and from the second to the third exacerbation, suggest that in patients with frequent exacerbations the benefits of antibiotic treatment added to treatment with oral corticosteroids may be greater.

Most randomised trials have follow-up durations of not more than six weeks. Benefits from antibiotic treatment may become more apparent in the long-term follow-up compared to short-term evaluations, possibly due to antibiotic treatment decreasing bacterial load. The finding that exposure to antibiotics for any indication also decreased the risk of a next exacerbation may suggest that some COPD patients carrying bacteria in a stable state could benefit from antibiotics.

There is sufficient evidence for the contributory role of bacteria in exacerbations. During bacterial exacerbations bacteria are present in the lower airways, associated with airway inflammation, and in sufficient concentrations (>1000 cfu/ml) to cause invasive infections. Inflammatory changes are also related to recurrent exacerbations. Immune responses to bacteria play an important role, and especially nontypeable H. influenzae is known for its role in the process of colonisation and infection. Isolation of new strains of bacterial pathogens increases the risk of an exacerbation. Increased sputum purulence is the main sign of a new or increased significant bacterial stimulus. In addition, patients with severe exacerbations are known to benefit most from antibiotic treatment.
We showed that treatment with oral corticosteroids and antibiotics compared to treatment with oral corticosteroids alone was associated with a longer time to the next exacerbation, and a decreased risk of developing a new exacerbation. On the other hand, treating all exacerbations with antibiotics will significantly increase overall antibiotic consumption, which might fuel the increasing rates of resistance among respiratory pathogens. Therefore, future prospective studies should explore for which exacerbations with respect to patient profiles and clinical symptoms in particular antibiotics are indicated.

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**References**

Antibiotics Associated with Reduced Risk Subsequent Exacerbation in Obstructive Lung Disease

Reduced Risk of Next Exacerbation and Mortality Associated with Use of Antibiotics in COPD

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Abstract

The long-term risk of a subsequent exacerbation of COPD after treatment with oral corticosteroids without (OS) or with antibiotics (OSA) was compared in a historical general practice-based cohort.

Eligible were patients ≥ 50 years with a registered diagnosis of COPD on maintenance respiratory drugs, who experienced at least one exacerbation defined as a prescription OS or OSA. Times to second and third exacerbations were assessed using Kaplan-Meier survival analysis, the risk of a subsequent exacerbation in a Cox proportional hazards analysis, and all cause mortality.

842 patients had one or more exacerbations. The median time from first to second exacerbation was comparable for the OS group and the OSA group, but the time from second to third exacerbation differed: 189 versus 258 days. The protective effect of OSA was most pronounced during the first three months following treatment (hazard ratio 0.72; 95%CI 0.62–0.83). Exposure to antibiotics unrelated to a course of oral corticosteroids almost halved the risk of a new exacerbation. Mortality during follow-up was considerably lower in the OSA group.

Adding antibiotics to oral corticosteroids was associated with a reduced risk of a subsequent exacerbation, especially in patients with recurrent exacerbations, and a reduced risk of all cause mortality.
Introduction

Patients with an acute exacerbation of COPD are often treated with a combination of antibiotics and corticosteroids. However, in fact, only patients with severe symptoms, and/or patients with a low baseline expiratory flow rate appear to benefit from antibiotic treatment.\textsuperscript{1-3} A recent Cochrane review\textsuperscript{4} supports the use of antibiotics for exacerbations of COPD with increased cough and sputum purulence in patients who are moderately or severely ill. An analysis restricted to community-based studies, however, did not demonstrate a difference between antibiotic and placebo.\textsuperscript{4} In addition, most studies on the use of antibiotics in exacerbations of COPD focused on the evaluation of short term recovery from exacerbation, with a follow-up period of a few weeks only.

In a previous population-based cohort study using pharmacy dispensing records,\textsuperscript{5} we demonstrated that treatment of an exacerbation with antibiotics in addition to oral corticosteroids was associated with an increased time to a subsequent exacerbation and an improved survival. Extrapolation of our results to patients diagnosed with COPD, however, must be done with caution: we studied a heterogeneous population defined by the use of respiratory drugs used for the maintenance treatment of obstructive lung disease.\textsuperscript{6}

Therefore, the aim of the present study was to extend our observations to a well-defined COPD population using the Second Dutch National Survey of General Practice.\textsuperscript{7}

Methods

Data sources
The data were derived from the Second Dutch National Survey of General Practice (DNSGP-2), carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001,\textsuperscript{7} and completed with data from the National Information Network of General Practice (LINH).\textsuperscript{8} DNSGP-2 was performed in 104 general practices in the Netherlands, comprising 195 GPs and including 400,911 patients, and it provides a representative impression of the morbidity and prescribing habits in Dutch general practice.\textsuperscript{7} The patients in these practices are representative for the Dutch general population with respect to age, gender and type of health care insurance. LINH, connected with NIVEL, is a computerized network of 85 general practices with almost 340,000 registered patients, providing representative information with respect to care delivered by Dutch General Practitioners (GPs), based on data from electronic medical records. In the DNSGP-2 data were collected for one year; LINH collects data continuously. We selected general practices participating both in the DNSGP-2 as well as in the LINH registration network.
Patient selection
From the DNSGP-2 and LINH databases we selected those practices that provided complete data on morbidity and prescriptions from the cohort entry date, the date of the general practice entering the DNSGP-2 in 2001, until 31 December 2005. We included patients who in the first year of participating in the DNSGP-2 were registered with COPD, according to International Classification of Primary Care code (ICPC) R95 and in addition in the first year of participating in the DNSGP-2 had at least two prescriptions of maintenance respiratory drugs, coded ATC (Anatomical Therapeutic Chemical) R03. These prescriptions included inhaled beta-2-agonists, inhaled anticholinergics, inhaled corticosteroids, oral theophylline, or a combination of these agents. Since we aimed to minimize the number of patients with asthma, only patients aged 50 years or older were included. For the same reason, patients using leukotriene receptor antagonists (LTRAs), montelukast (ATC-code R03DC03) or cromoglycates (R03BC) were also excluded. Patient characteristics (age, gender, maintenance medication for obstructive lung disease, co-medication for cardiovascular disease and diabetes mellitus) were derived from the DNSGP-2 database.

Definition of Exacerbation
We selected COPD patients who experienced one or more exacerbations during the follow-up period. An exacerbation was defined as 'a prescription of a short course of oral corticosteroids, with or without antibiotics'. The date of prescription of oral corticosteroids (ATC code: H02AB06/ H02AB07), with or without antibiotics was recorded. The following antibiotics were selected: doxycyclin (ATC-code: J01AA02), amoxicillin (J01CA04), amoxicillin-clavulanate (J01CR02), erythromycin (J01FA01), azithromycin (J01FA10), clarithromycin (J01FA09), ciprofloxacin (J01MA02), moxifloxacin (J01MA14), and levofloxacin (J01MA12). In the Netherlands, these antibiotics cover almost all antibiotics prescribed for exacerbations of COPD in primary care.11 When more than one course of oral corticosteroids was prescribed within a period of three weeks, this episode was considered as a single exacerbation. If the time between two prescriptions exceeded three weeks, we considered this second episode a new exacerbation, as in the majority of patients three weeks after the onset of an exacerbation symptoms are usually considerably improved.12 Patients prescribed oral corticosteroids or antibiotics for more than 21 days at regular intervals, for a period of three months or longer, were excluded from the analysis, since these patients cannot be discriminated from patients on maintenance treatment.

Statistical analysis
Treatment groups were compared at time of first exacerbation with respect to age, gender, use of inhaled respiratory drugs, including inhaled corticosteroids, and co-medication for cardiovascular disease or diabetes. We assessed the first exacerbation after cohort entry and calculated the time to the second exacerbation. The date of prescribing the exacerbation medication was considered to be the start of the second exacerbation. We also calculated the time between the second and the third exacerbation. We compared
these time periods between patients treated with oral corticosteroids only (OS) and those treated with oral corticosteroids and antibiotics (OSA) using a Kaplan-Meier survival analysis. Patients were censored for exacerbation free survival.

The effect of the variable of primary interest, treatment of exacerbation, OS (coded as 0), or OSA (coded as 1), was analysed in a Cox proportional hazards model. All exacerbations from each patient were used, and time was set back to zero after each exacerbation (gap-time unrestricted model).13 Hence, each exacerbation was treated as a separate record and time since last exacerbation as principal time scale. A correction for recurrent exacerbation events from the same individual was made by including a frailty term in the model.14 The Schoenfeld residuals as obtained from the model of time to next exacerbation suggested the difference in treatment effect to be highly nonproportional. Therefore, we allowed the difference in treatment effect to change at three months, six months and one year. The data were coded so that hazard ratios (HRs) below unity indicated a preventive effect of adding an antibiotic to the oral corticosteroids. Potential confounding by the following patient characteristics was controlled for: age, gender, number of prescriptions of respiratory drugs, including inhaled corticosteroids, co-medication for cardiovascular disease (yes/no) or for diabetes (yes/no).15 Prescriptions of antibiotics without oral corticosteroids were also treated as a time-dependent covariate, and assumed to be of influence for a period of three months; three months after this antibiotic was prescribed, the variable was again coded as 'no antibiotic'.

All-cause mortality of both treatment groups was analyzed using Kaplan-Meier and Cox proportional hazards analysis.

We calculated 95% confidence intervals. Analyses were performed using R-2.6.016 and SPSS v. 14.0.2 software (SPSS Inc., Chicago, IL, USA).

Results

Patients
From the DNSGP-2/LINH database, 54 practices, comprising 216,455 patients, provided complete data on morbidity and prescriptions in the selected time period. 63,721 patients were aged over 50 years, and we identified 1841 patients diagnosed with COPD (2.9%). In total 999 of these patients were excluded: 356 did not meet the prespecified criteria on the use of maintenance respiratory drugs, 532 patients did not experience a single exacerbation, as they were never prescribed oral corticosteroids, and 52 patients used LTRAs or cromoglycates, leaving 901 patients with one or more exacerbations. Of these patients, 30 were excluded because the oral corticosteroids were prescribed for other indications than COPD, 10 were on maintenance treatment with oral corticosteroids for COPD, 13 were on maintenance treatment with antibiotics, and 6 patients were not ‘at
risk’ for a next exacerbation (only one exacerbation less than 21 days before the end of follow-up), leaving 842 patients for the final analysis (Figure 1).

Of these 842 patients, 144 (17%) died during the follow-up period. The cause of death in 23 patients was reported not to be related to COPD. 13 patients died as a result of COPD; this was counted as an event, and not right-censored. In the remaining 108 patients the cause of death could not be retrieved from the database. The median follow-up time after
the first exacerbation was 1353 [interquartile range (IQR) 791-1649] days (3 years and 8.5 months). In total, 842 patients were followed for 2723 person years in total.

Of 842 patients having had at least one predefined exacerbation, 404 patients were at first exacerbation treated with oral corticosteroids (OS), and 438 with oral corticosteroids and antibiotics (OSA). These groups were similar with respect to age, gender, respiratory medication, and use of co-medication for diabetes and cardiovascular disease (Table 1).

**Table 1. Characteristics of patients according to treatment of first exacerbation**

<table>
<thead>
<tr>
<th></th>
<th>Oral corticosteroids n=404</th>
<th>Oral corticosteroids and antibiotics n=438</th>
<th>p-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>70 (62-78)</td>
<td>71 (63-77)</td>
<td>0.30</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>217 (54)</td>
<td>231 (53)</td>
<td>0.78</td>
</tr>
<tr>
<td>Number respiratory prescriptions**</td>
<td>8 (4-12)</td>
<td>8 (4-13)</td>
<td>0.35</td>
</tr>
<tr>
<td>Using ICS§</td>
<td>313 (77)</td>
<td>360 (82)</td>
<td>0.88</td>
</tr>
<tr>
<td>Co-medication#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>301 (74)</td>
<td>323 (74)</td>
<td>0.80</td>
</tr>
<tr>
<td>Diabetes</td>
<td>53 (13)</td>
<td>50 (11)</td>
<td>0.45</td>
</tr>
<tr>
<td>Follow-up time (days)*</td>
<td>1322 (750-1627)</td>
<td>1375 (832-1657)</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise stated. *Median (Interquartile range). **In the first year of participating in the DNSGP-2.  §ICS: Inhaled corticosteroids. ‡Chi-square, T-test or Mann-Whitney test, where appropriate.

Of all 4038 exacerbations (median 3 (IQR 1-6) per patient), GPs prescribed OS in 54% and OSA in 46%. Antibiotics used in the treatment of first exacerbations were doxycyclin (n=218, 50%), penicillins (amoxicillin-clavulanate and amoxicillin, n=141, 32%), macrolides (azithromycin, clarithromycin, and erythromycin, n=68, 16%), and fluoroquinolones (ciprofloxacin, moxifloxacin and levofloxacin, n=11, 3%).

**KM estimates of developing a second exacerbation according to treatment type (OS or OSA)**

Overall, 595 patients (71%) experienced a second exacerbation. The median time to the second exacerbation was 331 (95% CI 258-404) days in the OS group compared to 312
(95% CI 265.359) days in the OSA group (p=0.31) (Figure 2A). Six months after the first exacerbation, 27% of patients treated with oral corticosteroids had experienced a second exacerbation compared to 23% of patients treated with oral corticosteroids and antibiotics; after one year this was 52% and 54% respectively.

![Figure 2A](image)

**Figure 2A.** Kaplan-Meier estimates of the fraction of patients that is free of a second exacerbation stratified according to treatment type.
The calculated median differences between both treatment groups, 19 days; p=0.31 by log-rank.

**KM estimates of developing a third exacerbation according to treatment type (OS or OSA)**
Of the 595 patients having a second exacerbation, 308 (52%) were treated with oral corticosteroids only (OS) and 287 (48%) with oral corticosteroids and antibiotics (OSA). 450 patients had a third exacerbation during follow up. The time between the second and the third exacerbation was much shorter in the OS group than in the OSA group, median time 189 (95% CI 149-229) days compared to 258 (95% CI 198-318) days (p<0.01) (Figure 2B). Six months after the second exacerbation, 50% of patients treated with oral corticosteroids had experienced a third exacerbation compared to 41% of patients treated with oral corticosteroids and antibiotics; after one year this was 69% and 61% respectively.
Reduced Risk of Next Exacerbation and Mortality Associated with Use of Antibiotics in COPD

Figure 2B. Kaplan-Meier estimates of the fraction of patients that is free of a third exacerbation stratified according to treatment type. The calculated median differences between both treatment groups, 69 days; p<0.01 by log-rank.

Cox analysis of developing a new exacerbation according to treatment type

In a univariate Cox regression model the Hazard Ratio (HR) of a next exacerbation after treatment with oral corticosteroids and antibiotics (OSA) compared to oral corticosteroids only (OS) was 0.73 (95% CI 0.63–0.84). In a Cox proportional hazards model, adjusting for potential confounding factors, the HR of a next exacerbation after treatment with OSA was 0.72 (95% CI 0.62-0.83) in the first three months following treatment, but the effect was not significant in subsequent time periods. In addition, the use of antibiotics prescribed without a course of oral corticosteroids, irrespective of the indication, almost halved the risk of a next exacerbation (HR 0.56; 95% CI 0.48-0.71) (Table 2).
Table 2. HR of developing a subsequent exacerbation, in a Cox proportional hazards model

<table>
<thead>
<tr>
<th></th>
<th>HR of next exacerbation</th>
<th>95% CI HR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics and oral corticosteroids, vs steroids only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 months following treatment</td>
<td>0.72</td>
<td>0.62</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>0.85</td>
<td>0.70</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td>1.02</td>
<td>0.80</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>1.22</td>
<td>0.89</td>
<td>1.66</td>
<td></td>
</tr>
<tr>
<td>Exposure to antibiotics after previous exacerbation</td>
<td>0.56</td>
<td>0.45</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.91</td>
<td>0.75</td>
<td>1.10</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids as maintenance medication#</td>
<td>0.87</td>
<td>0.68</td>
<td>1.12</td>
<td></td>
</tr>
<tr>
<td>Co-medication cardiovascular#</td>
<td>1.37</td>
<td>1.10</td>
<td>1.73</td>
<td></td>
</tr>
<tr>
<td>Co-medication for diabetes#</td>
<td>0.90</td>
<td>0.68</td>
<td>1.19</td>
<td></td>
</tr>
</tbody>
</table>

HR, Hazard Ratio. CI, Confidence interval. #In the first year of participating in the DNSGP-2. The variables ‘age’ and ‘number of respiratory drugs prescriptions’ were included in the Cox model, but were not fitted linearly, therefore HRs are not presented. The risk of a new exacerbation increased significantly with age and with a higher number of prescriptions of respiratory drugs.

Figure 3. Kaplan-Meier estimates of the cumulative survival stratified according to treatment type. Difference between both treatment groups, p = 0.02, by log-rank.
Mortality of both treatment groups during follow-up
After the first exacerbation, during follow-up 62/438 (14%) patients died in the OSA group compared to 82/404 (20%) in the OS only group (p=0.02) (Figure 3). The HR of all-cause mortality after treatment with oral corticosteroids and antibiotics compared to corticosteroids only was 0.67 (95% CI 0.48-0.93) in a univariate Cox regression model. In a Cox proportional hazards model, adjusting for the potential confounders, the HR was 0.62 (95% CI 0.45–0.87).

Discussion
In COPD patients treated by general practitioners and using maintenance respiratory medication, we compared the long-term risk of a subsequent exacerbation after treatment with oral corticosteroids with or without antibiotics. The results show that treatment of exacerbations with antibiotics in addition to oral corticosteroids, and also the use of antibiotics without oral corticosteroids is associated with a reduced risk of a subsequent exacerbation. Moreover, we show a survival benefit in the oral corticosteroid and antibiotics group. As far as we know, the demonstrated effect of antibiotic treatment on the risk of a subsequent exacerbation as well as the associated survival benefit was not reported before in an extensive population-based COPD cohort.

Strengths and limitations of this study
The DNSGP.2/ LINH database provided a selection of COPD patients according to International Classification of Primary Care code (ICPC) R95.9 One limitation of using a registration database is that available data were not collected for the specific aim of this study, and therefore relevant information, such as lung function data, may be lacking. In addition, no clinical information on the severity of the exacerbation was present, and this may have caused treatment selection bias. However, relevant baseline characteristics of the treatment groups were similar. Furthermore, patients treated with antibiotics and oral corticosteroids are likely to have more severe exacerbations compared to patients treated with oral corticosteroids only. Therefore, we suspect that bias at this point, if present, would be associated with an underestimation of the effect of treatment.

An antibiotic course without steroids seemed to work even better than antibiotics combined with oral corticosteroids in preventing subsequent exacerbations. However, unfortunately, it could not be derived from the database whether the antibiotic courses were in all cases prescribed for an exacerbation of COPD. Nevertheless, this finding is remarkable, and appears in support of the conclusion that antibiotics are beneficial in the prevention of exacerbations.

The exacerbation rate of the selected patients was 1.5 per patient per year, indicating that we selected patients with more severe COPD, as the exacerbation rate in general practice in the Netherlands is usually < 1 per patient yearly.17 Exacerbations in patients with more
severe COPD are more likely to benefit from antibiotic treatment.\textsuperscript{2,3,4,18} The stronger treatment effect we found in time to the third exacerbation compared with the time to the second exacerbation suggests that the conclusions of this study may be especially applicable for patients with recurrent exacerbations.

**Comparison with existing literature**

Most studies evaluate short-term outcomes: acute resolution rates and early relapse rates. It has been noticed earlier that the use of time to the next exacerbation as primary outcome measure is especially suitable in evaluating COPD exacerbations.\textsuperscript{19-21} As hypothesized, effective antibiotic treatment that results in bacterial eradication may prevent recurrence.\textsuperscript{19,21} One study demonstrated for the first five months after antibiotic treatment a significant difference between two antibiotics in the recurrence rate of exacerbations, related to differences in induced bacterial eradication.\textsuperscript{22} These effects of antibiotic treatment may become apparent in long-term evaluations, while short-term outcomes may not show these differences, as is the case in community-based studies of exacerbations comparing antibiotic and placebo.\textsuperscript{4,23}

The present results extend, in a well-defined COPD population, the results of our previous PHARMO study, where we selected patients on the basis of prescribed medication.\textsuperscript{6} The annual rate of exacerbations, treatment of first exacerbation (OS versus OSA), and the use of respiratory maintenance medication were comparable in both studies. A significant difference between both studies was the effect of treatment on time between the first and second exacerbation, which was present in PHARMO but not in this study. In the PHARMO database also prescriptions by other prescribers were included, but selecting patients treated by general practitioners (74%) resulted in smaller, but still significant difference between treatment groups. An explanation for the difference might be the difference between pharmacy- and GP-based data, in that GPs’ prescriptions are not always redeemed from the pharmacy. This may account for about 10\% of prescriptions in the DNSGP-2/ LINH study, resulting in a diminished treatment effect.

Bacteria are of influence in inducing exacerbations. Superadded bacterial infection after viral infections occur frequently, and both bacteria and viruses may interact in a complex inflammatory process.\textsuperscript{26-28} The beneficial effect of antibiotics that is described could be attributed to the fact that antibiotics may cause bacterial eradication. Airway inflammation is increased at the time of an exacerbation,\textsuperscript{29,31} as is systemic inflammation.\textsuperscript{32,33} Even more, also in clinically stable, chronically \textit{H. influenzae}-infected COPD patients airway inflammation is more pronounced as compared to non-infected patients.\textsuperscript{34} Systemic inflammation contributes substantially to the overall mortality in COPD patients.\textsuperscript{35,36} It can be hypothesized that the observed survival benefit of added antibiotics is related to a stronger effect on systemic inflammation than treatment with oral corticosteroids alone. Recently bacterial colonisation was found to be related to a higher frequency of exacerbations in patients with moderate to severe COPD, suggesting the clinical relevance of the presence of bacteria in the lower airways.\textsuperscript{37} Our finding of the beneficial role of antibiotics on the long-term recurrence rate is in line with these observations.
Conclusion
Until now, studies only showed a significant short-term effect of antibiotic treatment in more severe and in hospitalised patients\textsuperscript{1-4}, but this study now also shows (long-term) benefits for patients treated by general practitioners. However, due to the retrospective character of this study and the limitations with regard to the availability of characteristics of patients and exacerbations, the results presented here cannot be seen as a definitive proof of the long-term effects of antibiotics, but should be confirmed in randomized clinical trials.

Even one exacerbation can have a large and sustained effect on health status. Although the initial recovery can be fast, the period to full recovery may be long.\textsuperscript{38} A number of patients even does not recover to baseline symptoms,\textsuperscript{12,39} and a decline in FEV\textsubscript{1} as a result of the exacerbations might contribute to this process.\textsuperscript{40,42} Early re-exacerbation is more common in patients with a deteriorated health status after an exacerbation and in patients with severe COPD, and delays the course of recovery.\textsuperscript{37} Patients with frequent exacerbations have a lower quality of life, an increased risk of hospital admission and greater mortality, and generate more costs than patients with less frequent exacerbations. Postponing the next exacerbation can contribute to delaying this process of deterioration.

In this study in primary care COPD patients, who used respiratory maintenance treatment, addition of antibiotics to oral corticosteroids in the treatment of an exacerbation was associated with a reduced risk of a subsequent exacerbation; in particular, this goes for patients with recurrent exacerbations. Moreover, during follow-up we demonstrated a survival benefit in the patients treated with antibiotics next to corticosteroids. If confirmed in future prospective studies, these observations may have a major impact on exacerbation management in COPD patients. Before general implementation, however, the pros and cons of antibiotic use, in particular the risk of increasing rates of resistance among respiratory pathogens, should be weighed against each other.

Acknowledgment
We thank Ronald B. Geskus for his support in the data-analysis.
References


Summary and General Comments
Summary

This thesis addressed three different aspects of the treatment of COPD exacerbations, resulting in three sets of chapters. The chapters 2 and 3 presented the results of studies on the treatment of COPD exacerbations in the primary care setting in the Netherlands: the study in chapter 2 explored how currently exacerbations are treated in daily practice, and in chapter 3 standardized treatment with a high-dose oral corticosteroid course and antibiotic treatment strictly in accordance with the Dutch guidelines for COPD was compared with current usual care. The chapters 4 and 5 dealt with the shortening of duration of antibiotic therapy in the treatment of acute exacerbations. Chapters 6 and 7, with results derived from two large community-based datasets, evaluated the long-term effects of treatment of COPD exacerbations; in particular the additional value of adding antibiotics to a treatment with oral corticosteroids was studied.

In Chapter 2 we determined how general practitioners (GPs) treated exacerbations of COPD, in particular whether short courses of oral corticosteroids and antibiotics were prescribed in accordance with the Dutch guidelines for COPD. Medical records of patients registered at four primary healthcare centres in the Netherlands were retrospectively analysed. Of 35,589 patients, 458 were registered with a diagnosis of COPD (1.3%). Within 2 years follow-up, 47% of the patients had no exacerbation, 35% had one or two exacerbations, and 18% had three or more exacerbations. In 536 exacerbations, GPs prescribed a short course of oral corticosteroids in 30% of cases, antibiotics in 29%, steroids combined with an antibiotic in 23%, and in 18% maintenance medication for COPD was adapted. Prescriptions in patients with one or two exacerbations during follow-up differed significantly from those in patients with three or more; in the latter group oral corticosteroid courses were prescribed more often, either as monotherapy or combined with antibiotics. We concluded that treatment was often not in accordance with current guidelines; in particular, antibiotics were prescribed more often than recommended.

Chapter 3 presented the results of the randomized trial originating from the conclusions of the previous study, investigating whether patient outcomes in exacerbations of COPD or chronic bronchitis could be improved through optimizing the treatment regimen. Primary health care centres and general practices were randomly assigned to either the control arm (usual care) or the intervention study arm. The objective was to compare usual care with a standardized treatment regimen comprising a high-dose oral corticosteroid course, and antibiotics only prescribed strictly in accordance with the Dutch guideline for COPD. In order to discuss and refine the study protocol, a meeting was organised before the start of the study between the study team, the GPs in the intervention arm, and the pulmonologists of the referral hospitals involved. In the final analysis 89 patients were included, 53 in the intervention and 36 in the usual care (control) group. Oral corticosteroid courses were prescribed in 90% (48/53) of the exacerbations in the intervention group and in 75% (27/36) in the control group, and antibiotics in 19%
(10/53) and 44% (16/36), respectively. The health status of the patients was evaluated using the Clinical COPD Questionnaire (CCQ). This validated 10-item questionnaire is divided into three domains: symptoms, functional state and mental state. It utilises a seven-point Likert scale where 0 = asymptomatic/no limitations and 6 = extremely symptomatic/total limitation. The final score is the mean of all items. At three weeks, the mean CCQ scores did not return to baseline levels in both study groups. The rates of cure, improvement and failure, based on the CCQ scores, did not differ (p=0.94) between both groups. The CCQ-scores improved compared to the score at enrolment in 46/53 (87%) patients in the intervention arm compared to 32/36 (89%) patients in the control arm. In 7/53 (13%) and in 4/36 (11%) patients respectively the total CCQ score did not improve. At three months, 23% of patients in the intervention group and 25% of the control group had a recurrence of their exacerbation. We concluded that the study protocol was effectively implemented; however, compared to the current usual care, the standardized treatment regimen with a high-dose oral corticosteroid course did not improve short term outcomes of exacerbations in general practice. The number of antibiotic prescriptions, however, was reduced significantly without affecting patients’ short term outcome.

Chapter 4 was concerned with short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD and presents a meta-analysis of double-blind studies. Antibiotic treatment for up to five days versus longer than five days was compared in 21 studies with a total of 10 698 patients. At early follow-up (<25 days), the summary odds ratio (OR) for clinical cure with short treatment versus conventional treatment was 0.99 (95% CI 0.90 to 1.08). At late follow-up (≥ 17 and ≤ 45 days) the summary OR was 1.0 (95% CI 0.91 to 1.10) and the summary OR for bacteriological cure was 1.05 (95% CI 0.87 to 1.26). Similar summary ORs were observed for early cure in trials with the same antibiotic in both arms and in studies grouped by the antibiotic class used in the short-course arm. We concluded that a short course of antibiotic treatment is as effective as the traditional longer treatment in patients with mild to moderate exacerbations of chronic bronchitis and COPD.

In Chapter 5 the outcome of treatment with amoxicillin–clavulanic acid for three versus ten days was evaluated in hospitalised patients with a type 1 exacerbation of COPD. 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. 56 patients were enrolled in the study. Cure rates of both treatment groups at three weeks and three months were comparable, although not confirmed statistically, due to the low number of included patients. Microbiological success, symptom recovery, the use of corticosteroids, the duration of oxygen therapy and the length of hospital stay were similar in both treatment groups. It was concluded that 3-day treatment with amoxicillin–clavulanic acid seemed to be a safe and effective alternative to the standard 10-day treatment for hospitalised patients with Acute Exacerbation of COPD (AECOPD) who have improved after initial therapy for 3 days.
In Chapter 6 we evaluated the risk of a subsequent exacerbation after treatment of an exacerbation with oral corticosteroids without or with antibiotics, in a historical population-based cohort comprising patients, aged 50 years or older, using maintenance medication for obstructive lung disease. The Pharmo database includes drug-dispensing records of more than 2 million subjects in the Netherlands. In 18,928 patients had at least one exacerbation, defined as a prescription of oral corticosteroids with or without antibiotics. At time of first exacerbation, treatment groups were comparable for potential confounding factors. Kaplan-Meier analysis showed a median time to the second exacerbation of 321 (99% CI 297-345) days in the oral corticosteroid group and 418 (99% CI 393-443) days in the oral corticosteroid and antibiotics group (p< 0.001); and between the second and third exacerbation the median time was 127 (99% CI 117-137) vs. 240 (99% CI 222-258) days (p<0.001). Analyzing all exacerbations in a Cox proportional hazards model, the protective effect of oral corticosteroids and antibiotics was most pronounced during the first three months following treatment (HR 0.62; 99% CI 0.60–0.65). Exposure to antibiotics between exacerbations, irrespective of indication, was also associated with a lower risk of a subsequent exacerbation. Moreover, in the oral corticosteroids/antibiotics group mortality during follow-up was significantly lower (HR 0.82; 99% CI 0.66-0.98).

In Chapter 7 we extended the observations from the previous study to a well-defined COPD population using the Second Dutch National Survey of General Practice (DNSGP-2), carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001, completed with data from the National Information Network of General Practice (LINH). Eligible were patients aged 50 years or older with a registered diagnosis of COPD (according to the International Classification of Primary Care code R95), using maintenance respiratory drugs, who experienced at least one exacerbation, defined as a prescription of oral corticosteroids with or without antibiotics. The median follow-up time after the first exacerbation was 1353 (interquartile range 791-1649) days. 842 patients had one or more exacerbations. A Kaplan-Meier analysis showed that the median time from first to second exacerbation was comparable for the oral corticosteroid only group and the oral corticosteroid/antibiotics group, but the median time from second to third exacerbation differed: 189 versus 258 days (p<0.01). In a Cox proportional hazard analysis in which all exacerbations were included, the protective effect of treatment with oral corticosteroids and antibiotics was most pronounced during the first three months following treatment (HR 0.72; 95%CI 0.62–0.83). Exposure to antibiotics unrelated to a course of oral corticosteroids almost halved the risk of a new exacerbation (HR 0.56; 95% CI 0.48-0.71). All-cause mortality during follow-up was considerably lower in the oral corticosteroid and antibiotics group (HR 0.62; 95%CI 0.45–0.87). We concluded that adding antibiotics to oral corticosteroids was associated with a reduced risk of a subsequent exacerbation, especially in patients with recurrent exacerbations. Also a reduction in all-cause mortality was found in those patients treated with oral corticosteroids and antibiotics.
Consequences for daily practice, and further research

In the long-term follow-up, we showed that adding antibiotics to oral corticosteroids was associated with a reduced risk of a subsequent COPD exacerbation, especially in patients with recurrent exacerbations, and with a reduced risk of all-cause mortality. These observations are new and may have a major impact on the management of exacerbations in COPD patients. Reducing the frequency of exacerbations is clinically important, as exacerbations can have a large and sustained effect on health status, especially in patients with frequent exacerbations. Furthermore, exacerbations are associated with a lower quality of life, an increased risk of hospital admission, high costs and, moreover, greater mortality. On the other hand, treating all exacerbations with antibiotics might have a major impact on overall antibiotic use in the community, and this might fuel resistance rates among respiratory pathogens. Resistance should always be taken into account when antibiotics are prescribed. It is too early now to advise treatment with antibiotics and oral corticosteroids for exacerbations in all patients with recurrent exacerbations. A limitation of our observational studies, described in chapter 6 and 7, might be the presence of treatment selection bias, due to unknown, potentially prognostic important differences among patients. In these studies, clinical information on patients was not available, for example the severity of symptoms and baseline spirometry were unknown. Our results should therefore be confirmed in a prospective study, and profiles should be established of the patients that will benefit most from added antibiotics. These profiles should be based not only on classification according to GOLD criteria, but should also include patients history, present clinical symptoms, medication use, co-morbidity and newly developed markers or indices applicable or already in use in the primary care setting, like the BODE-index.

Our finding that the antibiotic prescription rate in general practice could be reduced by 25%, without affecting patient outcome, is in line with the studies conducted in this setting, showing no benefit of antibiotics above placebo in short term evaluations, with acute resolution rates and early relapse rates as principle endpoints. The value of antibiotic treatment in exacerbations of COPD has mainly been demonstrated in clinical settings, merely in patients with severe symptoms (Anthonisen type 1 or 2), diagnosed according to GOLD criteria. This population differs from the general practice population, in which 80% of COPD patients has mild or moderate disease (GOLD 1 or 2), and some patients having the diagnosis based on other criteria than deviating baseline spirometric values. However, in selected patients from general practice antibiotic treatment will have the same benefits on the short term as demonstrated in the clinical based studies. Based on our results, the dividing line between patients who will and who will not profit from antibiotic treatment in general practice can not be drawn yet. Maybe, having at least two of the following criteria: increased dyspnoea, increased sputum volume and increased sputum purulence
treatment decisions should be based on long term effects (relapse and mortality) as well, and not only on short term effects (resolution rate). Identification of the clinical profiles of those patients that will or will not benefit from additional antibiotic treatment should be subject for future studies. Until then, starting treatment with or without antibiotics in patients with an exacerbation of COPD will be a matter of cautious estimation.

When indicated, antibiotics should be prescribed for no longer than absolutely necessary. In most guidelines the duration of antibiotic therapy for exacerbations is not addressed,\textsuperscript{14,16} or a traditional period of 7-10 days is advised\textsuperscript{1}; only the recently updated GOLD guidelines mention a period of 3-7 days, although marked with the lowest level of evidence\textsuperscript{12}. Our studies have shown that in patients with exacerbations of COPD an antibiotic treatment duration of 5 days is equivalent to a traditional longer course. To our opinion there is sufficient evidence now to incorporate short-term antibiotic treatment in guidelines on treatment of COPD exacerbations in general practice.

Two more things can be learnt from the study described in chapter 3. First, the study protocol was effectively implemented. The proposed increase in oral corticostereoid course prescriptions for exacerbations and a reduction of antibiotic prescriptions was indeed achieved. So, prescribing behaviour of general practitioners appears amenable to guided change. This is important, since implementation of guidelines usually is a complex process with many barriers to pull down. Secondly, standardized treatment with oral corticosteroids did not improve short term patient outcomes of exacerbations in general practice. However, in the control arm there was already a high prescription rate of oral corticosteroids (75%). The Cochrane review on corticosteroids in COPD exacerbation, showing benefits of treatment with corticosteroids compared with placebo, was merely based on clinical studies, while no community-based studies were included. The research question which patient will benefit from treatment with oral corticosteroids in general practice remains unanswered. Oral corticosteroid courses may not be as beneficial in mild COPD as in severe COPD, or other characteristics than the GOLD classification might be essential to differentiate between patients who will benefit from oral corticosteroids and those who will not. Therefore, future research in general practice, where the majority of COPD patients is treated, should include placebo-controlled studies, with a focus on elucidation of relevant patient characteristics.
References


Chapter 8


Samenvatting

Dit proefschrift behandelt drie verschillende aspecten van de behandeling van exacerbatie (een toename van klachten) van COPD (chronisch obstructieve longaandoeningen). Deze aspecten zijn de korte termijn effecten van behandeling van COPD exacerbaties, de duur van antibiotische behandeling bij een exacerbatie en de lange termijn effecten van antibiotica op het optreden van een volgende exacerbatie. De hoofdstukken 2 en 3 geven de resultaten weer van studies naar de behandeling van exacerbatie van COPD in de eerste lijn in Nederland. In hoofdstuk 2 wordt onderzocht waaruit de behandeling van exacerbatie COPD in de dagelijkse huisartsenpraktijk bestaat. In hoofdstuk 3 wordt een gestandaardiseerde behandeling met een kuur orale corticosteroïden (Prednisolon) vergeleken met de gebruikelijke behandeling. Antibiotica worden alleen voorgeschreven wanneer dit volgens de Nederlandse richtlijnen voor behandeling van COPD nodig is. Hoofdstuk 4 en 5 gaan over verkorting van de duur van de antibiotische behandeling bij exacerbatie COPD. In hoofdstuk 6 en 7 wordt gekeken naar de lange termijn effecten van antibiotica wanneer ze worden toegevoegd aan een behandeling met een kuur (orale) corticosteroïden. De gegevens voor deze studies zijn afkomstig van twee grote Nederlandse gegevensbestanden; de eerste is gebaseerd op registraties van apotheken en de tweede op registraties van huisartsen.

In hoofdstuk 2 wordt onderzocht hoe huisartsen exacerbatie COPD in de dagelijkse praktijk behandelen en of dit in overeenstemming is met de Nederlandse richtlijnen.1 Medische dossiers van patiënten van vier 1e lijns gezondheidscentra in Nederland werden retrospectief geanalyseerd. Van 35.589 patiënten waren er 458 geregistreerd met de diagnose COPD (1,3%). Gedurende twee jaar follow-up had 47% van deze patiënten geen exacerbatie, 35% had een of twee exacerbaties en 18% had drie exacerbaties of meer. Bij 536 exacerbaties schreven huisartsen in 30% een kuur corticosteroïden voor, in 29% een kuur antibiotica, in 23% corticosteroïden plus antibiotica en in 18% werd de onderhoudsmedicatie aangepast. Prescripties voor patiënten met een of twee exacerbaties gedurende de follow-up verschillen significant met die van hen die drie of meer exacerbaties hadden. Bij de laatste werd vaker een kuur corticosteroïden voorgeschreven, alleen of samen met antibiotica. Onze conclusie luidde dat behandeling vaak niet in overeenstemming met de richtlijnen was en dat vooral antibiotica vaker werden voorgeschreven dan geadviseerd.

Hoofdstuk 3. Gebaseerd op de conclusies uit hoofdstuk 2 werd een gerandomiseerd onderzoek uitgevoerd, waarbij werd onderzocht of de resultaten van de behandeling voor de patiënt met exacerbatie COPD of chronische bronchitis konden worden verbeterd door de behandeling te optimaliseren. 1e lijns gezondheidscentra en huisartspraktijken werden toegewezen aan óf de controle óf de interventie studiegroep. Het doel was om de gebruikelijke behandeling te vergelijken met een gestandaardiseerde behandeling, bestaande uit een kuur orale corticosteroïden, waarbij antibiotica werden voorgeschreven
conform de Nederlandse richtlijnen voor COPD. Voor de start van de studie werd een onderzoeksbijeenkomst georganiseerd door het studieonderzoeksteam samen met de huisartsen van de interventiegroep en de longartsen van de ziekenhuizen die bij het onderzoek waren betrokken, om het studieprotocol te bespreken en te verfijnen. In de analyse zaten 89 patiënten, 53 in de interventiegroep en 53 in de controlegroep. Corticosteroïdkuren werden voorgeschreven in 90% (48/53) van de exacerbaties in de interventiegroep en in 75% (27/36) in de controlegroep en antibiotica in respectievelijk 19% (10/53) en 44% (16/36). De gezondheidstoestand van de patiënten werd beoordeeld met behulp van de CCQ vragenlijst (Clinical COPD Questionnaire). Deze gevalideerde 10-item vragenlijst is in drie domeinen verdeeld: symptomen, functioneren en mentaal. Er wordt gescoord op een 7-punts Likert schaal, waar “0” betekent “geen klachten of beperkingen” en “6” “extreme veel klachten of volledige beperking.” De eindscore is het gemiddelde van alle items. Na drie weken kwam de CCQ score in beide studiegroepen niet terug op het baseliniveau. Het aantal patiënten in beide studiegroepen dat was hersteld, verbeterd, of verslechterd verschilde niet. De CCQ score ten opzichte van de baselinescore was verbeterd in 46/53 (87%) van de patiënten in de interventiegroep vergeleken met 32/36 (89%) van de patiënten in de controlegroep. In 7/53 (13%) respectievelijk 4/36 (11%) patiënten verbeterde de totale CCQ score niet. Na drie maanden had 23% van de patiënten in de interventiegroep vergeleken met 25% uit de controlegroep een nieuwe exacerbatie doorgemaakt. Wij concludeerden dat het studieprotocol effectief was geïmplementeerd, maar dat in de eerste lijn de gestandaardiseerde behandeling met een kortere kweektijd de korte termijn resultaten niet verbeterde. Het aantal antibiotica voorschriften was wel significant verminderd, zonder nadelige uitkomsten voor de patiënten op korte termijn.

**Hoofdstuk 4** behandelt de kortdurende antibiotische behandeling van exacerbatie COPD of chronische bronchitis en laat een meta-analyse zien van dubbelblinde studies. 21 studies met in totaal 10.698 patiënten werden geselecteerd. Antibiotische behandeling van maximaal vijf dagen werd vergeleken met een behandeling van langer dan vijf dagen. In de vroege follow-up (tot 25 dagen) werd geen verschil gevonden in de kans op klinisch herstel tussen de korte en conventionele behandeling [smallest odds ratio (OR) 0,99; 95% betrouwbaarheidsinterval (BI) 0,90 – 1,08]. Ook tijdens de late follow-up (17-45 dagen) en in het bacteriologische herstel werd geen verschil gevonden tussen beide behandelgroepen (smallest OR 1,0 [95% BI 0,91 – 1,10] en 1,05 [95% BI 0,87 – 1,26] respectievelijk). Evenmin werd er verschil gezien in de vroege follow-up in studies met hetzelfde antibioticum in beide studiearmen, noch wanneer de studies werden gegroepeerd naar antibiotische klasse in de korte arm. Wij concludeerden dat een korte antibiotische kuur even effectief is als de traditionele langere kuur bij patiënten met milde tot matig ernstige exacerbatie van chronische bronchitis en COPD.

In **hoofdstuk 5** wordt de behandeling met amoxicilline-clavulaanzuur gedurende drie dagen vergeleken met een behandelduur van 10 dagen bij patiënten die in het ziekenhuis zijn opgenomen met een COPD exacerbatie die wordt gekenmerkt door een toename van kortademigheid en een toename van volume en purulentie van het sputum...
Samenvatting

Patiënten die binnen 72 uur verbeterden werden gerandomiseerd naar een behandeling met amoxicilline-clavulaanzuur (625 mg) of placebo, vier maal daags gedurende zeven dagen. 56 patiënten werden in de studie geïncludeerd. Na drie weken én na drie maanden was het aantal patiënten dat was hersteld in beide behandelgroepen vergelijkbaar, hoewel dit door het lage aantal geïncludeerd patiënten niet statistisch bevestigd kon worden. Microbiologisch herstel, herstel van symptomen, het gebruik van corticosteroïden, de duur van zuurstof therapie en de duur van de ziekenhuisopname waren vergelijkbaar in beide behandelgroepen. De conclusie luidde dat een 3-daagse behandeling met amoxicilline-clavulaanzuur een veilig en effectief alternatief lijkt voor de standaard 10-daagse behandeling van patiënten die in het ziekenhuis zijn opgenomen met exacerbatie COPD, en die na drie dagen initiële therapie herstel laten zien.

In hoofdstuk 6 evalueerden we het risico op een volgende exacerbatie na behandeling van een exacerbatie met orale corticosteroïden zonder en met antibiotica, in een historische op de populatie gebaseerd cohort van patiënten van 50 jaar en ouder, die medicatie gebruikten voor obstructieve longaandoeningen. De Pharmo dataset bevat gegevens van uitgifte van medicijnen van meer dan twee miljoen personen in Nederland. 18.928 patiënten hadden tenminste één exacerbatie, gedefinieerd als een recept voor orale corticosteroïden, met of zonder antibiotica. Ten tijde van de eerste exacerbatie waren beide behandelgroepen vergelijkbaar wat betreft mogelijke vertekende factoren. Er was een significant verschil in (mediane) tijd tot de tweede exacerbatie van 321 dagen in de alleen orale corticosteroïden groep tegenover 418 dagen in de orale corticosteroïden en antibiotica groep; tussen de tweede en derde exacerbatie was dit 127 respectievelijk 240 dagen. Uit een analyse waarin alle exacerbaties werden betrokken bleek dat het beschermende effect van orale corticosteroïden en antibiotica het sterkst was in de eerste drie maanden na behandeling (hazard ratio 0,62). Gebruik van antibiotica tussen de exacerbaties, ongeacht de indicatie, was eveneens geassocieerd met een lager risico op een volgende exacerbatie. Bovendien was de sterfte in de orale corticosteroïden en antibiotica groep gedurende de follow-up significant lager (hazard ratio 0,82).

In hoofdstuk 7 worden de observaties van de studie beschreven in hoofdstuk 6 uitgebreid naar een goed gedefinieerde populatie van COPD patiënten, waarbij gebruik wordt gemaakt van gegevens van De Tweede Nationale Studie, uitgevoerd door het Nederlands Instituut voor onderzoek van de Gezondheidszorg (NIVEL) in 2001, vergeleken met gegevens van Het Landelijk Informatie Netwerk Huisartsen zorg (LINH). In aanmerking kwamen patiënten van 50 jaar en ouder met een geregistreerde diagnose "COPD" (volgens de Internationale Classificatie van 1e lijns zorg code R95), die respiratoire onderhoudsmedicatie gebruikten en die ten minste één exacerbatie doormaakten, gedefinieerd als een prescriptie orale corticosteroïden met of zonder antibiotica. De (mediane) follow-up duur was 1353 dagen. 842 patiënten hadden een of meer exacerbaties. De Kaplan-Meier analyse liet zien dat er geen verschil was tussen de tijd tot de tweede exacerbatie voor de groep patiënten behandeld met alleen corticosteroïden en de groep die daarnaast ook antibiotica had gekregen. De (mediane) tijd tot de derde exacerbatie was wel significant verschillend, 189 dagen versus 258 dagen. Uit de analyse waarin alle
Exacerbaties werden meegenomen (Cox proportional hazard analyse) bleek dat het beschermende effect van antibiotica gedurende de eerste drie maanden na behandeling het grootst was (HR 0,72). Gebruik van antibiotica zonder dat corticosteroïden werden voorgeschreven vermindere de kans op een volgende exacerbatie bijna de helft (HR 0,62). We concludeerden dat het toevoegen van antibiotica aan een kuur orale corticosteroïden geassocieerd was met een kleinere kans op een volgende exacerbatie, met name bij patiënten die meerdere exacerbaties hebben. Bovendien werd gedurende de follow-up een lagere “all-cause” mortaliteit gevonden bij patiënten die met orale corticosteroïden en antibiotica waren behandeld.

**Algemeen commentaar**

**Gevolgen voor de dagelijkse praktijk en verder onderzoek**

In de lange termijn follow-up hebben we aangetoond dat het toevoegen van antibiotica aan orale corticosteroïden geassocieerd was met een verlaagd risico op een volgende exacerbatie, vooral bij patiënten die vaker exacerbaties hebben; en verder met een verlaagd “all-cause” mortaliteitsrisico. Deze observaties zijn nieuw en kunnen grote impact hebben op de behandeling van exacerbaties van COPD patiënten. Het terugbrengen van de frequentie van exacerbatie is klinisch belangrijk, omdat exacerbaties een langdurig en aanhoudend effect op de gezondheidstoestand kunnen hebben, vooral bij patiënten met frequent exacerbaties. Bovendien worden exacerbaties geassocieerd met een lagere kwaliteit van leven, een verhoogde kans op ziekenhuisopname, hogere kosten en daarnaast meer sterfte. Daar staat tegenover dat –wanneer alle exacerbaties met antibiotica zouden worden behandeld- dit een grote impact heeft op het totale antibiotica gebruik in de bevolking, wat weer leidt tot toename van resistentie onder respiratoire ziekteverwekkers.

Antimicrobiële resistentie moet altijd in overweging worden genomen wanneer antibiotica worden voorgeschreven. Het is nog te vroeg om voor alle patiënten met frequent exacerbaties antibiotica en een kuur corticosteroïden te adviseren. Een beperking van onze observationele studies, beschreven in hoofdstuk 6 en 7, is de kans op selectie “bias” (vertekening van de resultaten) als gevolg van de behandeling, veroorzaakt door onbekende, mogelijk belangrijke prognostische verschillen tussen patiënten. In deze studies was klinische informatie van patiënten niet beschikbaar, bij voorbeeld de ernst van de symptomen en de spirometrische gegevens. Onze resultaten moeten daarom worden bevestigd in een prospectief opgezette studie, waarbij profielen worden benoemd voor patiënten die het meeste profijt hebben van toegevoegde antibiotica. Deze profielen moeten niet alleen zijn gebaseerd op classificatie van ernst van de longfunctiebeperkingen volgens GOLD-criteria, maar moeten ook informatie bevatten over ziekte geschiedenis, huidige klinische symptomen, medicijngebruik, co-morbiditeit en nieuw ontwikkelde markers of indicatoren toepasbaar of zelfs al in gebruik in de 1e –lijns setting, zoals de BODE-index.
Ons resultaat dat het aantal recepten voor antibiotica in de 1e lijn met 25% kon worden teruggebracht zonder dat dit van invloed was op de uitkomst voor de patiënt is in lijn met de studies die eerder in deze setting zijn gedaan en waarbij geen voordeel van antibiotica boven placebo aangetoond kon worden in de korte termijn evaluatie, met herstel en vroege exacerbatie als eerste eindpunten.\textsuperscript{9,11} De waarde van antibiotische behandeling van exacerbatie van COPD is vooral aangetoond in klinische settings, voornamelijk bij patiënten met ernstige symptomen (type 1 of 2 exacerbatie, dus 2 of 3 van de eerder genoemde symptomen) en gediagnosticeerd volgens GOLD-criteria.\textsuperscript{11,12} Deze populatie verschilt van die van de huisartspraktijk, waarvan bekend is dat van de COPD patiënten 80\% dit in een milde tot matig ernstige vorm heeft,\textsuperscript{13} terwijl bij sommige patiënten de diagnose is gebaseerd op andere criteria dan afwijkende spirometrie-waarden. In bepaalde patiënten uit de huisartspraktijk echter zal antibiotische behandeling dezelfde voordelen hebben op de korte termijn zoals aangetoond in klinische studies. Op grond van onze resultaten is de scheidslijn tussen patiënten die wel en die niet zullen profiteren van antibiotische behandeling moeilijk te trekken. Misschien moeten beslissingen over het al dan niet voorschrijven van antibiotica eveneens op de lange termijn effecten (re-exacerbatie en mortaliteit) worden gebaseerd en niet alleen op korte termijn effecten (herstel). De klinische profielen van patiënten die wel en die niet zullen profiteren van het tovoegen van antibiotica aan de behandeling van exacerbatie van COPD moet in toekomstige studies worden onderzocht. Tot dan zal het wel of niet antibiotisch behandelen van patiënten met exacerbatie COPD zorgvuldig moeten worden afgewogen.

Indien geïndiceerd, moeten antibiotica niet langer worden voorgeschreven dan strikt noodzakelijk. In de meeste richtlijnen wordt de duur van de antibiotische behandeling niet genoemd,\textsuperscript{14,16} of een traditionele periode van 7 tot 10 dagen wordt geadviseerd. Alleen de recent geüpdate GOLD richtlijnen vermelden een periode van 3 tot 7 dagen, hoewel gmarkeerd met het laagste bewijsniveau. Onze studies hebben laten zien dat voor patiënten met exacerbatie COPD een kuur van ten hoogste 5 dagen equivalent is aan een traditionele langere behandeling. Naar onze mening is er nu voldoende bewijs om kortdurende antibiotische behandeling op te nemen in de richtlijnen over behandeling van exacerbatie COPD in de eerste lijn.

Nog twee zaken kunnen worden geleerd van de studie die in hoofdstuk 3 is beschreven. In de eerste plaats was het studieprotocol effectief geïmplementeerd. De verwachte toename in het voorschrijven van corticosteroïden en de afname van antibiotica voorschriften werden inderdaad geëffectueerd. Ergo, voorschrijfgedrag van huisartsen is vatbaar voor begeleide verandering. Dit is belangrijk, omdat het implementeren van richtlijnen doorgaans als een complex proces wordt beschouwd, waarbij vele barrières geslecht moeten worden. In de tweede plaats, gestandaardiseerde behandeling met een kuur orale corticosteroïden heeft niet geleid tot verbetering van resultaten op de korte termijn voor de patiënt in de eerste lijn. In de controlearm echter was al een hoog percentage prescripties corticosteroïden van 75%. De Cochrane review over corticosteroïden voor COPD exacerbaties, waarin voordelen van corticosteroïden ten opzichte van placebo werden aangetoond, was voornamelijk gebaseerd op klinische studies, terwijl hierin geen in
De bevolking uitgevoerde studies waren geïncludeerd. De onderzoeksvraag welke patiënt in de eerste lijn zal profiteren van behandeling met corticosteroïden blijft onbeantwoord. Orale corticosteroïden hebben misschien minder voordeel bij patiënten met een milde vorm van COPD dan bij hen met een ernstiger vorm van COPD; of mogelijk zijn andere patiënt karakteristieken nodig om te onderscheiden welke patiënten hier baat bij hebben.

Toekomstig onderzoek in de eerste lijn, waar de meerderheid van de COPD patiënten wordt behandeld, zou placebo gecontroleerd moeten zijn, met het focus op het exploreren van relevante patiënt karakteristieken.

Referenties


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(Jullie zijn mijn aarde,
Tastbare werkelijkheid,
Zichtbaar groen en blauw,
Heerlijke zee van tijd,
Wanneer de zon jullie
In z’u licht zet
Voor altijd) (Vrij naar Hans Andreus)
Curriculum Vitae


In 2000 startte zij in het Academisch Medisch Centrum in Amsterdam, op de afdeling Inwendige Geneeskunde, onderafdeling Infectieziekten, Tropische Geneeskunde en AIDS (Prof. dr. P. Speelman). Zij werkte als onderzoeksverpleegkundige aan een multi-center RCT (Randomized Clinical Trial) naar kortere antibiotische behandeling bij luchtweginfecties. Deze studie vormde de basis voor het promotieonderzoek naar de behandeling van exacerbatie COPD in de 1e en 2e lijn.

Sinds mei 2008 werkt zij als sr. onderzoeker/ epidemioloog bij het CIb (Centrum Infectieziektebestrijding) van het RIVM (Rijks Instituut voor Volksgezondheid en Milieu) (Prof. dr. R.A. Coutinho) als coördinator van EARSS (European Antimicrobial Resistance Surveillance System) (Prof. dr. H. Grundmann).

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