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ANTIBIOTIC TREATMENT IN EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

PATRICIA VAN VELZEN

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Antibiotic treatment in exacerbations of chronic obstructive pulmonary disease

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Chapter 1

General introduction

COPD

Chronic obstructive pulmonary disease (COPD) is a common disease: worldwide, in 2016 the prevalence of COPD was estimated at 251 million and 5.48 million people died of COPD.[1,2] It is predicted that the annual number of global deaths will exceed 7 million by 2060.[2] In the Netherlands, 613.800 patients were registered in primary care with a diagnosis of COPD in 2018, and more than 6800 patients died that year of COPD.[3]

COPD is characterized by respiratory symptoms (dyspnea, cough and sputum production) and an irreversible airflow limitation.[4] The diagnosis is easy to make: an individual with exposure to harmful gases (e.g. smoke), respiratory symptoms and a forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of less than 0.7 after bronchodilation has COPD. However, the disease is complex and heterogeneous. It is complex because many COPD patients suffer from systemic manifestations of this lung disease and the disease is heterogeneous because patients with the same severity of COPD have different symptoms, and in a single patient symptoms vary over time.[5]

Although smoking is the most important risk factor in the developed world, COPD is not always self-inflicted. Other causes include biomass fuel exposure, air pollution, alfa-1 antitrypsin deficiency, abnormal lung development and asthma.[6] This is important to acknowledge, as patients with different COPD aetiology might benefit from different therapy. Most research, including this thesis, has been done in smoking-induced COPD.

Treatment of stable COPD is mainly symptomatic and consists of bronchodilator therapy, with or without anti-inflammatory therapy: inhaled corticosteroids, oral corticosteroids (OCS), phosphodiesterase-4 inhibitors and antibiotics.[4,7,8]

COPD exacerbations

An exacerbation is defined by a change in dyspnoea, cough, or sputum beyond day-today variability, sufficient to warrant a change in management.[4] Most patients with COPD experience exacerbations and mean number of exacerbations in primary care in the Netherlands is 0.54 per year.[9] Patients with two or more exacerbations are considered frequent exacerbators and

represent a distinctive phenotype.[10] Exacerbations are classified as mild (treated with short acting bronchodilators), moderate (treated with short acting bronchodilators in combination with OCS and/or antibiotics) or severe (requires hospitalisation). Exacerbations are events that have a mean time to recovery of 7 to 10 days, however some patients do not fully recover.[11,12] Exacerbations also have major long-term consequences for the individual patient: accelerated lung function decline,[13,14] increased mortality[15] and reduced quality of life.[16] For society, exacerbations pose a large economic burden.[17] Therefore, reduction of number of exacerbations is a key outcome in clinical trials.

Exacerbations are triggered by bacteria and viruses (50-70%) and air pollution (10%); in 30% the cause is unknown.[18] How the presence of bacteria is linked to exacerbations is difficult to assess. The most common bacterial pathogens that are encountered during exacerbations, *S. pneumoniae* and *H. influenzae*, are also isolated in stable state.[19] In 2002, Sethi *et al*[20] concluded that the appearance of a new bacterial strain, and not a new bacterial species, was associated with exacerbation, but not all changes in strains resulted in an exacerbation and not all exacerbations were associated with a new strain. Also, changes in lung microbiome are associated with COPD exacerbations.[21]

Viruses are identified in up to 64% of the COPD exacerbations. The most common are rhinovirus, influenza virus A and respiratory syncytial virus.[22] Viruses can be demonstrated in 5-45% of stable COPD patients, and during an exacerbation in 39.4-64% of patients. For bacteria, the same bacterial species are detected in patients with stable COPD (25–86%) and during exacerbations (58.8–81%).[22] Therefore, bacteria might be a secondary infectious hit after a viral infection and not the primary cause of an exacerbation.

Treatment of exacerbations

The vast majority of exacerbations is treated ambulatory. Treatment of an exacerbation of COPD consists of a short course of OCS, with or without antibiotics.[4] Two reviews concluded that OCS reduce short term treatment failure and improve lung function,[23] and showed a trend toward fewer hospital admissions.[7] OCS use was associated with more adverse events,[23] but international guidelines concluded that benefits outweigh potential risks and advise a short course of OCS in outpatients.[4,7,24] Some data indicate that

in patients with a blood eosinophil count above 2% OCS reduced treatment failure, but not in patients with a blood eosinophil count below 2%.[25]

The benefit of antibiotics is less clear. As previously described, bacteria can be identified in only approximately 50% of the exacerbations[22] and even if bacteria are identified, the relation with the exacerbation is unclear. In 2012, a systematic review including five randomized controlled trials showed that treatment failure rates were not reduced in outpatients treated with antibiotics compared to placebo.[26] In contrast, antibiotics did reduce treatment failure in hospitalized patient (three studies).[26] International guidelines however advise the use of antibiotics in outpatients treated for an exacerbation, particularly in case of sputum purulence.[4,7] The NICE guideline advise to weigh risks and benefits in each individual patient.[27]

In the Netherlands, guidelines for general practitioners advise to treat an exacerbation with a short course of OCS. Antibiotics are prescribed in addition to a course of OCS in patients with a FEV1 less than 30% predicted. In patients with a FEV1 between 30 and 50% predicted, antibiotics are advised if a patients has fever and clinical signs of infection. In patients with a FEV1 of more than 50% predicted, antibiotics are indicated if a patient has signs of infection, in combination with insufficient improvement after 2 to 4 days of treatment with OCS. In the latter, CRP can be used to guide antibiotic prescription: in case of a CRP value below 20 mg/L, no antibiotics are indicated. Antibiotics are indicated if CRP is more than 100 mg/L. Between 20 and 100 mg/L, prescription depends on clinical signs and symptoms.[28] Guidelines for pulmonologists advise to prescribe antibiotics in outpatients in case of signs of infection, including fever, or an FEV1 of less than 30% of predicted.[8]

Despite these stringent guidelines, antibiotics are prescribed more frequently than indicated in primary care in the Netherlands.[29,30] In Europe, almost 80% of patients with an exacerbation are treated with antibiotics.[31] For the individual patient, unwarranted use of antibiotics poses a risk of adverse events. For society, inappropriate prescription of antibiotics fuels the development of antibiotic resistance.[32]

Apart from potential short-term benefits, some data suggested that a short course of antibiotics could be beneficial on the long term. In two retrospective cohort studies,[33,34] antibiotic use was associated with a prolonged time to the next exacerbation and reduced mortality. Time to the next exacerbation was also increased in a randomized controlled trial that included time to the next exacerbation as a secondary outcome.[35]

At this moment, an exacerbation is usually diagnosed on symptoms reported by the patient, in combination with physical examination. Other diagnoses like acute heart failure or pulmonary embolism can be difficult to distinguish from an exacerbation of COPD. No biomarkers are currently available to objectively diagnose an exacerbation.

Nowadays, the most important trigger to prescribe antibiotics is sputum purulence.[31] Anthonisen *et al*[36] divided exacerbations in three types: type 1 exacerbations present with three criteria (increased dyspnoea, increased sputum volume and sputum purulence); type 2 exacerbations with two criteria and type 3 exacerbations with only one criterion. They concluded that patient with type 1 exacerbations had significantly less treatment failure rates if they were treated with antibiotics compared to placebo. Since publication of this trial, sputum purulence combined with increased dyspnoea and/or increased sputum volume is the most important trigger to prescribe antibiotics. This finding was confirmed in one randomized controlled trial[37] but could not be demonstrated in other trials.[38,39] The decision to prescribe antibiotics would also benefit from a biomarker that differentiates exacerbations that are caused by bacteria from non-bacterial exacerbations.

Conclusion

COPD is a very prevalent disease with significant health implications for patients and economic consequences for the society. Exacerbations are heterogeneous events, for which currently 'one size fits most' care is provided, and antibiotics are widely prescribed for this indication despite limited short-term effects. Long-term benefits have not yet been demonstrated in prospective, randomized trials. Who benefits from antibiotic treatment remains unclear. Biomarkers that are able to identify patients that benefit from antibiotic treatment would be

useful to optimize treatment and reduce unnecessary antibiotic prescriptions. An appealing option for this would be non-invasive assessment of the molecular profile of exhaled air, which had been reported to be associated with exacerbations and bacterial infections in COPD.[40]

The corresponding research questions are therefore:

1. Do antibiotics prolong time to the next exacerbation in exacerbations of COPD?
2. Do antibiotics reduce short-term treatment failure rates in exacerbations of COPD in outpatients?
3. Is antibiotic treatment cost-effective in the treatment of COPD exacerbations?
4. Which clinical characteristics or biomarkers might be helpful to identify patients who benefit from antibiotic therapy?

Outline of this thesis

In **chapter 2** we report the results of a randomized controlled trial comparing doxycycline to placebo in addition to oral corticosteroids in outpatients with an exacerbation of COPD. The primary outcome was time to the next exacerbation. In **chapter 3**, we present the results of a systematic review and meta-analysis of randomised controlled trials that compared antibiotics to placebo in outpatients that are treated for an exacerbation of COPD. **Chapter 4** describes the economic evaluation that we performed alongside this randomised controlled trial. We compared costs per quality-adjusted life year in the doxycycline group versus the placebo group. In **chapter 5**, we performed subgroup analyses based on clinical variables with the aim to identify in which patients antibiotics reduce short-term treatment failure rates. Finally, in **chapter 6**, we report the results of a prospective, observational follow-up study. Exhaled volatile organic compounds before, during and after recovery from an exacerbation were analysed by gas chromatography-mass spectrometry and electronic nose to test if exhaled breath analysis qualifies as a non-invasive composite biomarker of COPD exacerbations.

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Chapter 2

Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind, placebo-controlled trial

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Summary

Background

Antibiotics do not reduce mortality or short-term treatment non-response in patients receiving treatment for acute exacerbations of COPD in an outpatient setting. However, the long-term effects of antibiotics are unknown. The aim of this study was to investigate if the antibiotic doxycycline added to the oral corticosteroid prednisolone prolongs time to next exacerbation in patients with COPD receiving treatment for an exacerbation in the outpatient setting.

Methods

In this randomised double-blind placebo-controlled trial, we recruited a cohort of patients with COPD from outpatient clinics of nine teaching hospitals and three primary care centres in the Netherlands. Inclusion criteria were an age of at least 45 years, a smoking history of at least 10 pack-years, mild-to-severe COPD (Global Initiative of Chronic Obstructive Lung Disease [GOLD] stage 1–3), and at least one exacerbation during the past 3 years. Exclusion criteria were poor mastery of the Dutch language, poor cognitive functioning, known allergy to doxycycline, pregnancy, and a life expectancy of shorter than 1 month. If a participant had an exacerbation, we randomly assigned them (1:1; with permuted blocks of variable sizes [ranging from two to ten]; stratified by GOLD stage 1–2 vs 3) to a 7 day course of oral doxycycline 100 mg daily (200 mg on the first day) or placebo. Exclusion criteria for randomisation were fever, admission to hospital, and current use of antibiotics or use within the previous 3 weeks. Patients in both groups received a 10 day course of 30 mg oral prednisolone daily. Patients, investigators, and those assessing outcomes were masked to treatment assignment. The primary outcome was time to next exacerbation in all randomly allocated patients except for those incorrectly randomly allocated who did not meet the inclusion criteria or met the exclusion criteria. This trial is registered with the Netherlands Trial Register, number NTR2499.

Findings

Between Dec 22, 2010, and Aug 6, 2013, we randomly allocated 305 (34%) patients from the cohort of 887 patients to doxycycline (152 [50%]) or placebo (153 [50%]), excluding four (1%) patients (two [1%] from each group) who were incorrectly randomly allocated from the analysis. 257 (85%) of 301 patients had

a next exacerbation (131 [87%] of 150 in the doxycycline group vs 126 [83%] of 151 in the placebo group). Median time to next exacerbation was 148 days (95% CI 95-200) in the doxycycline group compared with 161 days (118-211) in the placebo group (hazard ratio 1·01 [95% CI 0·79-1·31]; p=0·91). We did not note any significant differences between groups in the frequency of adverse events during the first 2 weeks after randomisation (47 [31%] of 150 in the doxycycline group vs 53 [35%] of 151 in the placebo group; p=0·54) or in serious adverse events during the 2 years of follow-up (42 [28%] vs 43 [29%]; p=1).

Interpretation

In patients with mild-to-severe COPD receiving treatment for an exacerbation in an outpatient setting, the antibiotic doxycycline added to the oral corticosteroid prednisolone did not prolong time to next exacerbation compared with prednisolone alone. These findings do not support prescription of antibiotics for COPD exacerbations in an outpatient setting.

Funding: Netherlands Organization for Health Research and Development.

Introduction

Most patients with COPD have exacerbations, characterised by an increase in dyspnoea, cough, sputum, or sputum purulence.[1] Exacerbations have a major, negative impact on patients' wellbeing,[2] quality of life,[3] COPD-associated health-care costs,[4] lung function,[5] and survival.[6] As a consequence, exacerbations are an important outcome in clinical research, and prevention of exacerbations is a key target for intervention. Treatment of exacerbations consists of systemic corticosteroids alone or in combination with antibiotics.[1,7] Systemic corticosteroids improve lung function and COPD symptoms and decrease the rate of relapses of exacerbations.[8] By contrast, use of antibiotics is still controversial.

Findings from a systematic review[9] showed that antibiotics for acute exacerbations of COPD reduced treatment non-response and mortality in patients admitted to hospital, but not in outpatients receiving treatment for mild-to-moderate exacerbation, including Anthonisen type 1 exacerbations[10] (presence of three criteria: increased dyspnoea, increased sputum volume, and sputum purulence). These findings are related to short-term clinical outcomes only, as most studies focus on clinical cure at the end of therapy. However, investigators of two retrospective cohort studies[11,12] of outpatients suggested that time to next exacerbation is significantly extended if exacerbations are treated with antibiotics in addition to oral corticosteroids (OCS). Moreover, mortality was significantly lower in the group given both OCS and antibiotics in these studies. Time to next exacerbation was a secondary endpoint in one randomised trial,[13] findings from which also suggested that antibiotic treatment prolonged time to next exacerbation by a median of 73 days. Therefore, antibiotics for mild-to-moderate exacerbations of COPD might have long-term rather than short-term clinical benefits. We did a randomised controlled trial to test the hypothesis that antibiotics added to OCS prolong time to next exacerbation in patients with COPD treated for an exacerbation in the outpatient setting.

Methods

Study design and participants

In this randomised double-blind placebo-controlled trial, we recruited participants with a confirmed diagnosis of COPD from the outpatient clinics of nine teaching hospitals and three primary care centres in the Netherlands. All patients entered a prospective cohort. If cohort participants had an exacerbation, they were enrolled in this trial. We entered patients into a prospective cohort first to enable collection of baseline characteristics data and spirometry confirmation of COPD before exacerbations occurred. Patients were eligible for inclusion in the cohort if they were 45 years or older; had a smoking history of at least 10 pack-years; had a clinical diagnosis of mild-to-severe COPD, defined as a postbronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity ratio of 0·7 or lower and a postbronchodilator FEV1 of at least 30%, according to Global Initiative of Chronic Obstructive Lung Disease (GOLD) and American Thoracic Society and European Respiratory Society criteria (GOLD stage 1–3);[1,7] and had at least one documented or self-reported exacerbation during the past 3 years, with the restriction that the last exacerbation had ended at least 4 weeks before inclusion and symptoms had returned to patients' baseline levels. Exclusion criteria were poor mastery of the Dutch language, poor cognitive functioning, known allergy to doxycycline, pregnancy, and a life expectancy of shorter than 1 month. We obtained written informed consent from all participants. The study protocol was approved by the ethics review board at the Academic Medical Centre at the University of Amsterdam (Amsterdam, the Netherlands).

Randomisation and masking

We randomly assigned patients to doxycycline or an identical placebo, in a 1:1 ratio. Randomisation was done with an automated and centralised randomization service, stratified by GOLD stage 1–2 versus GOLD stage 3. To ensure equal assignment to treatment groups and concealed randomisation, we used permuted blocks with variable sizes (ranging from two to ten). Patients, investigators, and those assessing outcomes were masked to treatment assignment.

Procedures

We identified patients with a diagnosis of COPD in the primary care setting for inclusion in the cohort using the International Classification of Primary Care code R95 and in pulmonology outpatient clinics using the Diagnosis Treatment Combination code. All patients fulfilling the inclusion criteria received an invitation letter from their own general practitioner (GP) or pulmonologist in which they were asked to participate. We instructed GPs and pulmonary physicians to contact the study team if an exacerbation occurred in cohort participants. We defined an exacerbation of COPD as an event characterised by a change in patients' baseline dyspnoea, cough, or sputum beyond day-today variability, sufficient to warrant a change in management other than optimisation of bronchodilator therapy.[1,7] We did not consider respiratory symptoms caused by an evidently non-pulmonary cause an exacerbation. Patients with fever (body temperature of >38·5˚C) were not eligible for randomisation as they met the criterion for treatment with antibiotics according to Dutch guidelines.[14,15] Other exclusion criteria for randomisation were admission to hospital, current use of antibiotics (including maintenance therapy), or use of antibiotics for a respiratory tract infection in the previous 3 weeks. We randomly allocated patients between doxycycline and placebo within 48 h of the change in management. We followed up patients for 2 years after randomisation. Patients in the doxycycline group received a 7 day course of oral doxycycline 100 mg daily (200 mg on the first day).[16] We chose doxycycline as it is recommended in US,[7] British,[17] Dutch,[14,15] and the international GOLD[1] guidelines as one of the first-choice antibiotics for treating exacerbations in outpatients. We purchased doxycycline and matching placebo from TioFarma (Oud-Beijerland, the Netherlands). Patients in both groups received a course of OCS (30 mg oral prednisolone daily for 10 days). If patients had known OCS intolerance, we prescribed inhaled steroids or increased their dose. Other medication was modified by the treating physician if deemed necessary. If subsequent exacerbations occurred during follow-up, patients remained in the same study group and received the same randomly allocated study medication. Therefore, during the 2 years of follow-up, in each patient all exacerbations were treated with either doxycycline or placebo.

At the time of inclusion in the cohort, patients were seen at the outpatient clinic or primary care practice by a dedicated research nurse. Baseline data,

including demographics, GOLD stage, self-reported comorbidities, self-reported health status, self-reported exacerbation rate, smoking history, and medication use, were recorded in standardised electronic case report forms (Oracle Clinical, Redwood Shores, CA, USA). COPD-specific health status was measured with the St George's Respiratory Questionnaire (SGRQ).[18] Scores of the SGRQ range from 0 to 100, with lower scores indicating better function and a minimal clinically important difference of 4.[19] If no recent (within the past 2 years) lung function data were available, we did postbronchodilator spirometry according to standardised European guidelines[20] at inclusion in the cohort. At the time of enrolment in the trial (first exacerbation) and during follow-up at week 1, week 2, week 3, week 4, month 3, and every 3 months thereafter until month 24, we collected data for respiratory symptoms, exacerbations, fever, use of antibiotics, steroids, and inhalation medication. We administered the SGRQ at inclusion in the trial and during follow-up until month 24. We repeated postbronchodilator spirometry at the end of follow-up. We calculated the difference in lung function between baseline (entry into the cohort) and end of follow-up, divided by the number of days between the two measurements, and multiplied it by 365 to get an annual decline in lung function. After 2 years of follow-up, we collected all pharmacy dispensing records for each patient and compared them with our data collected during follow-up. In cases for which a prescription of OCS or antibiotics was not consistent with the data that we had collected, we contacted the treating GP or pulmonologist and retrieved the indication. Also, at the end of follow-up, we collected data for mortality by contacting the patient. If a patient could not be reached, we contacted the patient's GP or the Municipal Personal Records Database to ensure complete assessment of mortality.

Outcomes

The primary endpoint was time between the first exacerbation (entry into the trial) and the next exacerbation. To avoid counting a long-lasting exacerbation not responding to initial therapy as a next exacerbation, we defined a minimum interval of 3 weeks between subsequent exacerbations.[21] A secondary outcome was treatment non-response at day 21 (3 weeks after the first exacerbation) and day 84 (late follow-up). We based treatment non-response on the definition by Chow and colleagues:[22] absence of any resolution in the magnitude of respiratory symptoms as reported by the patient, prescription of open-label

antibiotics, prescription of a new course of OCS, admission to hospital for an exacerbation, or death. Other secondary outcomes were mortality, number of exacerbations, COPD-specific health status, decline of lung volumes (postbronchodilator FEV1 and forced vital capacity) at the end of follow-up, and total antibiotic use. Cultured microorganisms and economic costs per exacerbation will be reported separately. We asked patients for adverse events possibly related to the study medication during the first 2 weeks after randomisation and serious adverse events during the 2 years of follow-up.

Statistical analysis

We estimated that 468 patients would need to be randomly allocated to ensure at least 251 second exacerbations to provide the study with a power of 80%. We based this calculation on the following assumptions: a constant hazard ratio for a second exacerbation of 0·73,[11] a 52% cumulative exacerbation proportion in the control group after 12 months and a 64% proportion after 24 months, equal group sizes, use of an unweighted logrank test, a one-sided α level of 0·05, and a 5% dropout in both groups. As the annual exacerbation rate was estimated to be at least 0·5 exacerbations per patient per year, we calculated that the cohort should consist of 1000 participants to enable us to randomly allocate 468 patients with eligible exacerbations. The exacerbation rate turned out to be higher than expected. Therefore, after reaching the a-priori defined number of 251 second exacerbations, we decided to stop inclusion in the trial.

We based the analysis on all randomly allocated patients except for those incorrectly randomly allocated who did not meet the inclusion or met the exclusion criteria. We used Kaplan-Meier analysis and Cox proportional hazards analysis, accounting for death as a competing risk, including the following confounders: number of previous exacerbations in the 3 years before randomisation, GOLD stage (1 or 2 vs 3), hospital or primary care, and self-reported current smoking. We checked and confirmed the assumption of proportional hazards. We analysed secondary outcomes using appropriate regression models, such as logistic regression for death and negative binomial regression for number of exacerbations on the basis of one or more exacerbations per patient. In all analyses, we controlled for the same confounders as for the primary outcome, with the following exceptions: we added SGRQ scores to the analysis of COPD-specific health-related quality of life and added FEV1 and age

(as a continuous variable) to the analysis of lung function decline. Additionally, we did predefined subgroup analyses for age, sex, GOLD stage, smoking status, number of previous exacerbations in the past 3 years, and treatment setting. For subgroup analyses, we did tests for interaction. In all analyses, we quantified statistical uncertainties via corresponding 95% CIs. An independent data and safety monitoring board oversaw the study and qualitatively assessed all-cause mortality in the two treatment groups after 235 patients had completed 2 years of follow-up. This trial is registered with the Netherlands Trial Register, number NTR2499.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

887 patients were enrolled in the cohort between Dec 1, 2010, and Sept 15, 2012 (figure 1). Between Dec 22, 2010, and Aug 6, 2013, 305 (34%) patients that were included in the cohort had an exacerbation fulfilling the predefined criteria. Of those, 152 (50%) were randomly assigned to doxycycline and 153 (50%) were randomly assigned to placebo. Four (1%) patients, two (1%) in each group, were incorrectly randomly allocated because they did not meet the inclusion criteria or met the exclusion criteria and so were excluded from the analysis. 296 other exacerbations occurred in the cohort in 207 (68%) patients, but those exacerbations did not fulfil the inclusion criteria for the trial. Baseline characteristics at the time of inclusion in the cohort are summarised in table 1. The two groups were well balanced for baseline patient and exacerbation-related characteristics, but more women were included in the placebo group than in the doxycycline group. We noted no relevant differences between patients enrolled in the trial and the cohort (see appendix).

After randomisation, 136 (91%) patients in the doxycycline group versus 135 (89%) in the placebo group completed 2 years of follow-up. We prescribed study medication in 561 first and subsequent exacerbations: 292 (52%) exacerbations in the doxycycline group and 269 (48%) exacerbations in the placebo group.

257 (85%) of 301 patients had a next exacerbation: 131 (87%) of 150 patients in the doxycycline group and 126 (83%) of 151 patients in the placebo group. Median time to next exacerbation was 148 days (95% CI 95-200) in the doxycycline group compared with 161 days (118-211) in the placebo group (hazard ratio 1·01 [95% CI 0·79-1·31]; p=0·91; figure 2). The adjusted incidence rate ratio in the negative binomial regression analysis also incorporating repeated exacerbations was 0·98 (0·81-1·17; p=0·79). We noted no significant between-group differences in any of the subgroup analyses either (figure 3). A post-hoc analysis also revealed no differences in exacerbations with (84 [88%] of 95 patients with a second exacerbation in the doxycycline group *vs* 70 [80%] of 87 in the placebo group; hazard ratio 1·14 [0·83-1·57]) or without (47 [85%] of 55 *vs* 56 [88%] of 64; 0·83 [0·55-1·24]) sputum purulence (p=0·23). Before having a next exacerbation, 55 (36%) patients in the placebo group and 41 (27%) in the doxycycline group were prescribed at least one course of open-label antibiotics for exacerbations or other indications. If open-label antibiotics were prescribed for the first exacerbation of COPD after randomisation, we still counted this exacerbation as the next exacerbation. Limiting of the primary analysis to patients who were not prescribed open-label antibiotics reduced the time to next exacerbation, but the difference between the two study groups was still not significant: median time to next exacerbation was 123 days (IQR 46-363) in the doxycycline group compared with 143 days (56-336) in the placebo group (hazard ratio 1·01 [95% CI 0·74-1·37]; p=0·95).

The proportion of patients not responding to treatment at day 21 or day 84 was not significantly different between groups (table 2; number needed to treat to prevent treatment non-response in one patient at day 21 of 10·9). We noted no difference either in the proportion of patients not responding to treatment if we restricted the analysis to exacerbations with sputum purulence. Treatment non-response in the doxycycline group at day 21 in patients with sputum purulence was 22 (23%) of 95 and in the placebo group was 24 (28%) of 87 (odds ratio 0·8 [95% CI 0·41-1·60]; p=0·54). At day 84, in the doxycycline group, treatment non-response in those with sputum purulence was 39 (41%) of 95 and in the placebo group was 33 (38%) of 87 (1·07 [0·58-2·0]; p=0·82). During follow-up, patients assigned to the doxycycline group were prescribed more courses of antibiotics than were those in the placebo group. The median number of antibiotic courses excluding study medication was the same for both groups.

After randomisation, 241 (80%) patients received open-label antibiotics for exacerbations and other indications: 123 (82%) in the doxycycline group and 118 (78%) in the placebo group. We did not observe significant differences in the number of deaths, total number of exacerbations, COPD specific health status, or decline of lung volume after 2 years of follow-up (table 2, see appendix). We did not note any significant differences in the frequency of adverse events during the first 2 weeks after randomization or in serious adverse events during the 2 years of follow-up (table 3). Musculoskeletal pain was the most common adverse event. None of the serious adverse events were directly related to use of study medication.

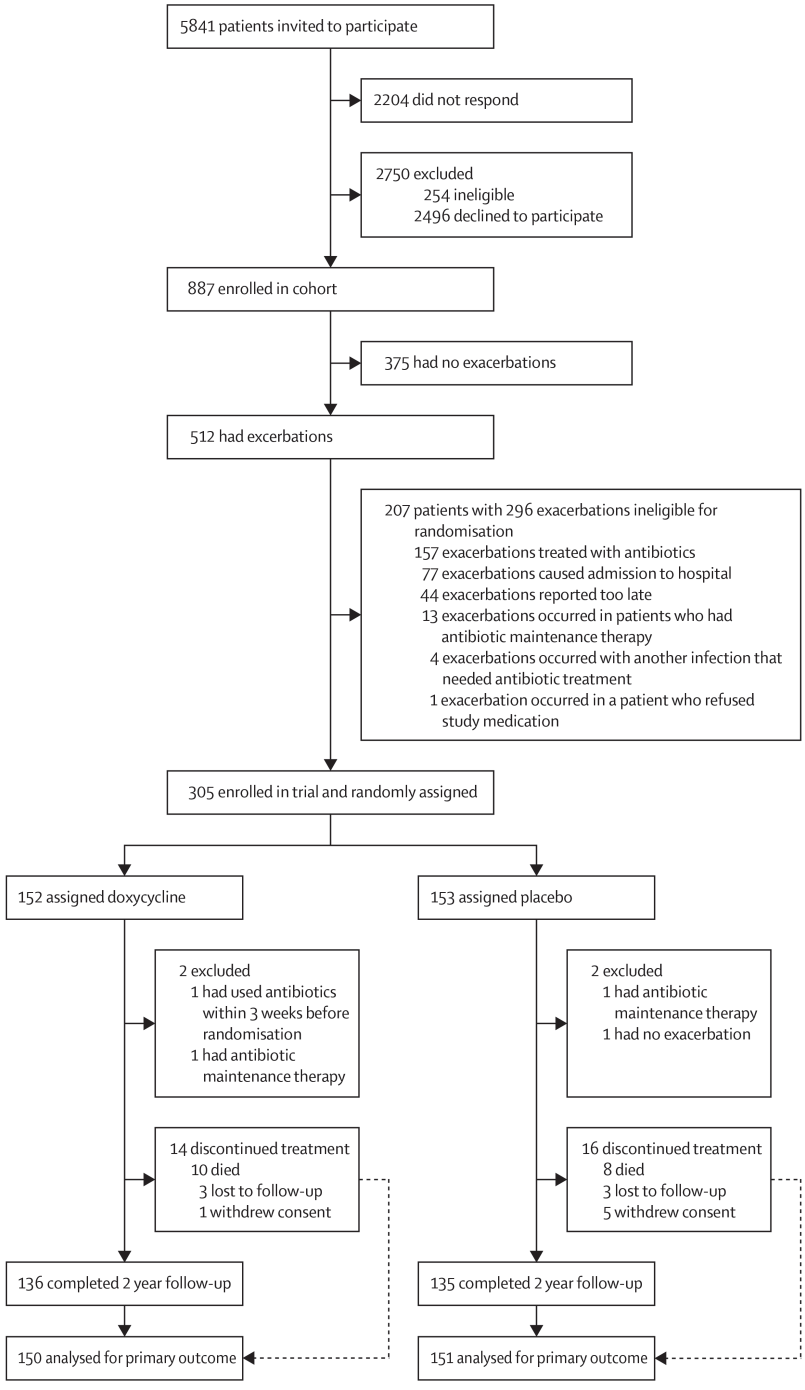
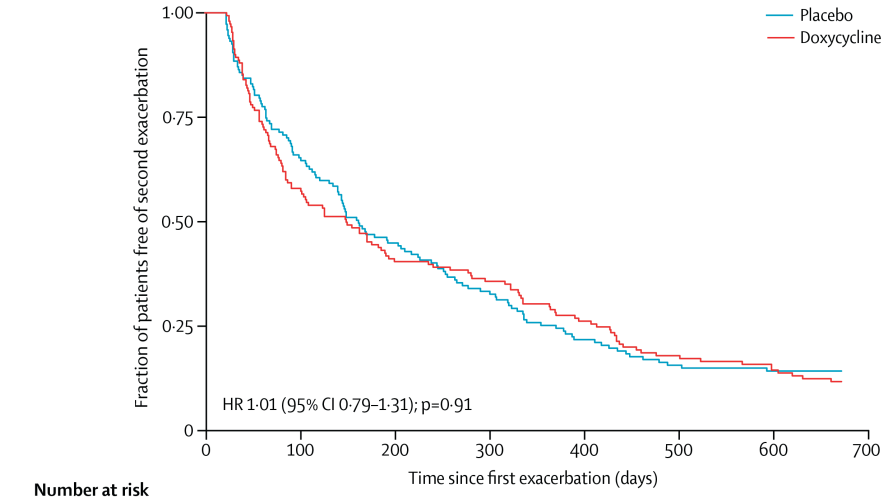


Figure 1: Trial profile

Table 1: Baseline characteristics

Patient characteristics*	Doxycycline (n=150)	Placebo (n=151)
Age – yr	65·8±9·3	66·4±9·5
Female sex – no. (%)	52 (35)	70 (46)
Comorbidities – no. (%)†		
Cardiac disorders		
Myocardial infarction	24 (16)	32 (21)
Heart failure	12 (8)	9 (6)
Cerebrovascular disorders	9 (6)	14 (9)
Diabetes mellitus	16 (11)	15 (10)
Smoking history – pack-years	47·2±36·8	50·8±31·7
Current smoker- no. (%)‡	49 (33)	65 (43)
Medication for COPD - no. (%)		
LAMA	112 (74)	107 (71)
LABA	18 (12)	19 (13)
ICS	21 (14)	20 (13)
ICS/LABA combination	111 (74)	118 (78)
GOLD stage – no. (%)		
- GOLD 1	21 (14)	19 (13)
- GOLD 2	81 (54)	84 (56)
- GOLD 3	48 (32)	48 (32)
Baseline lung function		
- FEV1 – litres	1·75±0·6	1·63±0·6
- FEV1 – % predicted	61·1±18·0	60·5±17·7
- FVC – litres	3·62±1·01	3·36±1·11
- FVC – % predicted	98·3±22·2	94·6±26·5
- FEV1/FVC	0·49±0·1	0·49±0·1
Number of exacerbations/year in previous 3 years†	1·3 (0·67-2·3)	1·3 (0·67-2·0)
St. George's Respiratory Questionnaire score§	46·3 ±18·4	48·0±17·7
Time from inclusion in cohort to inclusion in RCT –days	123 (53-250)	116 (49-281)
Exacerbation characteristics		
Diagnosis of exacerbation by pulmonologist – no. (%)	101 (67)	87 (58)
Prescription of oral corticosteroids – no. (%)	143 (95)	143 (95)
Increased sputum purulence – no. (%)	95 (63)	87 (58)
Type of exacerbation– no. (%)		
- type 1‖	89 (59)	77 (51)
- type 2**	30 (20)	44 (29)
- type 3††	31 (21)	30 (20)

Data are n (%), mean (SD), or median (IQR). LAMA=long-acting muscarinic antagonist. LABA=long-acting β agonist. ICS=inhaled corticosteroid. GOLD=Global Initiative for Chronic Obstructive Lung Disease. FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Collected at the time of inclusion in the cohort. †Self-reported. ‡All patients were current or former smokers. §St George's Respiratory Questionnaire scores range from 0 to 100; higher scores indicate worse quality of life. ¶Collected at the time of inclusion in the trial. ‖Three Anthonisen criteria10 present: increased dyspnoea, increased sputum, and sputum purulence. **Two Anthonisen criteria present. ††One Anthonisen criterion present.



Number at risk (number censored)								
Placebo	151 (0)	96 (9)	66 (10)	49 (11)	32 (11)	23 (11)	20 (12)	0 (13)
Doxycycline	150 (0)	86 (8)	60 (9)	53 (9)	38 (11)	26 (11)	21 (11)	0 (11)

Figure 2: Proportion of patients free of a second exacerbation
HR=hazard ratio.

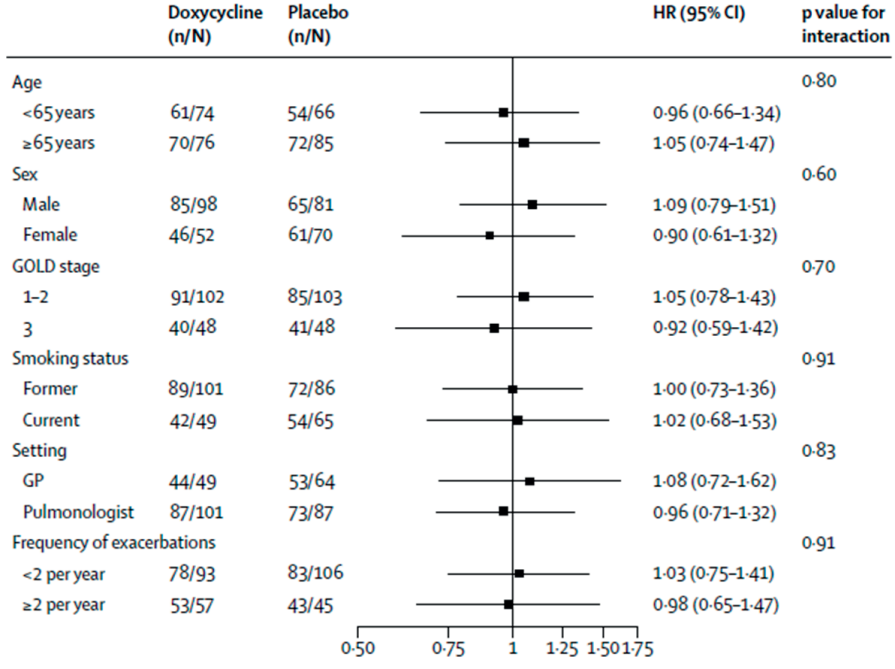


Figure 3: Subgroup analyses for patients who had a second exacerbation
We calculated HRs with Cox regression with terms for treatment. HR=hazard ratio. GOLD=Global Initiative of Chronic Obstructive Lung Disease. GP=general practitioner.

Table 2: Secondary endpoints

	Doxycycline (n=150)	Placebo (n=151)	Relative Risk (95% CI)*	P Value
Treatment failure				
day 21 – no. (%)	32 (21)	46 (31)	0·70 (0·47-1·03)	0·07
type 1 exacerbations††	19 (21)	19 (25)	0·86 (0·49-1·51)	0·61
Treatment failure				
day 84 – no. (%)	59 (39)	61 (40)	0·97 (0·74-1·3)	0·85
type 1 exacerbations†	35 (39)	28 (36)	1·08 (0·73-1·6)	0·70
Deaths during follow-up	10 (7)	8 (5)	1·25 (0·51- 3·1)	0·62
Number of exacerbations during follow-up	2 (1-4)	2 (1-4)		0·91
Decline of lung volume per year				
FEV1, ml	53·0±104·6	60·7±108·2		0·57
FEV1, % predicted	1·46±3·9	1·92±5·5		0·45
FVC, ml	73·6±231·3	77·0±212·0		0·90
FVC, % predicted	1·59±7·69	0·37±19·1		0·28
Total number of antibiotic courses during follow-up				
Including study medication	4 (2-6)	2 (2-6)		< 0·0001
Excluding study medication	2 (1-4)	2 (1-4)		0·87

Data are n (%), n/N (%), median (IQR), or mean (SD). FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity.
*The placebo group is the reference. †Three Anthonisen criteria10 present: increased dyspnoea, increased sputum, and sputum purulence.

Discussion

In patients with mild-to-severe COPD (GOLD stage 1–3) receiving treatment for an exacerbation without fever in an outpatient setting, doxycycline added to the OCS prednisolone did not prolong time to next exacerbation compared with prednisolone alone. This finding was consistent across all subgroups tested, although the study was not powered for these subgroup analyses. Additionally, we did not observe significant effects of doxycycline on any of the secondary outcomes, including treatment non-response at day 21 and day 84, mortality, quality of life, and lung function decline. Total antibiotic use over the 2 years of follow-up, however, was twice as high in patients randomly allocated to doxycycline as in those randomly allocated to placebo.

In this trial, treatment non-response at day 21 was not different between patients given doxycycline or placebo. These results are in line with those from a systematic review[9] that showed that in outpatients, treatment nonresponse 1 month after

treatment initiation was not different between patients receiving antibiotics or placebo, with a risk ratio of 0·80 (95% CI 0·63-1·01). However, if the results from this study are added to those from this systematic review, short-term treatment nonresponse is significantly lower in the doxycycline group than in the placebo group, with a risk ratio of 0·77 (0·63-0·94; p=0·01; see appendix).

The number needed to treat to prevent treatment nonresponse in one patient at day 21 was 10·9. By contrast with other studies that focused on short-term outcomes, we primarily designed our trial to examine the long-term effects of antibiotics in COPD exacerbations. Notably, our trial does not substantiate the findings from two retrospective cohort studies[11,12] that suggested that time to next exacerbation was extended and mortality reduced in patients with COPD given antibiotics and OCS compared with OCS alone. This discrepancy shows the need for our trial, which actually challenges the hypothesis generated by these retrospective studies.

Randomised, placebo-controlled trials[10,13,23] of the effects of antibiotics on exacerbations in patients with well defined COPD are scarce and only two published trials[10,13] have been done in patients treated in the outpatient setting. Only one of these trials[13] considered time to next exacerbation, including it as a secondary outcome. In that trial, patients with mild-to-moderate COPD were randomly allocated to amoxicillin and clavulanate or placebo. Median time to next exacerbation was significantly longer in the amoxicillin and clavulanate group (233 days) than in the placebo group (160 days).

This trial is, to our knowledge, the first randomised controlled trial primarily designed to examine the long-term effects of antibiotics added to OCS for COPD exacerbations. The trial design produced a well defined cohort of patients with COPD, and if they had subsequent exacerbations, they remained in the same study group and received the same randomised study medication. An exacerbation was diagnosed by the patient's own physician (GP or pulmonologist), with no direct involvement of the study team. Before randomisation, however, patients were contacted by the study team to verify if the inclusion criteria were met. This contact ensured a diagnosis of an exacerbation according to predefined criteria. OCS therapy was required and regulated by the protocol, as guidelines state that after optimisation of inhalation therapy, OCS are the next step in treatment of exacerbations.[11,7,15]

Despite being recommended by international guidelines,[1,7] only one previous trial,[23] of patients admitted to hospital, regulated OCS by protocol.

Our study has several limitations. First, during follow-up, most patients received open-label antibiotics for exacerbations and other indications from their own physicians. Hence, long-term effects of antibiotics might have been underestimated. However, exclusion of such patients from the primary analysis did not change the results. Second, we included patients with mild-to-severe COPD and a history of at least one exacerbation in the 3 years before inclusion. Therefore, whether or not our long-term results apply to patients with fewer or less severe COPD exacerbations than those included in this trial is unknown. However, we did not find differences in the predefined subgroup analyses for COPD severity and previous exacerbation history. Finally, we chose doxycycline for the antibiotic treatment since resistance of common pathogens causing COPD exacerbations, like *Haemophilus influenzae* and *Streptococcus pneumoniae*, to this antibiotic is rare.[24] Moreover, doxycycline is administered once a day and is generally well tolerated. Therefore, doxycycline is recommended as the first choice for treating exacerbations in outpatients in the Netherlands[14,15] and by international guidelines.[1,7,17] We cannot therefore be sure that our findings can be extrapolated to other antibiotics. However, the short-term effects in this trial were similar to those seen in studies[9] of β lactams or co-trimoxazole, and in a study[25] assessing antibiotic maintenance regimens, no differences in bacterial load were observed between doxycycline, moxifloxacin, azithromycin, or placebo after 3 months of treatment. By contrast with other antibiotics, azithromycin might have additional non-antibiotic effects, explaining the benefits of azithromycin as maintenance therapy in patients with severe COPD and a history of frequent exacerbations.[26,27]

Antibiotic resistance is a major public health problem and is fuelled by antibiotic use. Reduction of unnecessary antibiotic use is one of the most important strategies to contain resistance. Despite few short-term benefits,[9] we previously found that GPs often prescribe antibiotics for COPD exacerbations.[28] We have now provided evidence that in patients without fever treated for an exacerbation in an outpatient setting, antibiotics do not have long-term benefits. This finding applies to exacerbations with and without sputum purulence. Therefore, given increasing antibiotic resistance, insufficient scientific rationale exists to prescribe antibiotics for exacerbations treated in an outpatient setting.

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Supplementary Appendix

Assessments during follow-up

At time of enrolment in the randomised clinical trial (RCT) (first exacerbation) and during subsequent follow-up, at weeks 1, 2, 3, 4, month 3 and every 3 months thereafter until month 24, data covering respiratory symptoms, exacerbations, fever, use of antibiotics, steroids and inhalation medication were collected by telephone and documented in the standardised electronic case report form (eCRF).

The Saint George's Respiratory Questionnaire[1] (SGRQ) was administered during the first exacerbation (inclusion in the RCT), and during follow-up at week 4, month 3, 12 and 24. At inclusion in the cohort questionnaires were filled in under direct supervision; after randomisation questionnaires were administered by telephone or by mail. Post-bronchodilator spirometry was repeated at the end of follow-up (month 24). If a patient had another exacerbation during follow-up, data regarding this event were documented during an additional exacerbation visit and followed up for four weeks, including the SGRQ.

After two years of follow up, all pharmacy dispensing records were collected for each patient and compared with our data collected during follow-up. In case of a prescription of oral corticosteroids and/or antibiotics that was not consistent with our collected data, the treating general practitioner or pulmonologist was contacted and the indication retrieved.

Table S1: Baseline Characteristics of All Patients Included in RCT and Cohort.

Patient characteristics	RCT N=301	All patients N=887
Age – yr	66.1±9.5	67.1±9.6
Female sex – no. (%)	122 (40.5)	359 (40.5)
Comorbidities – no. (%) *		
Cardiac disorders		
- myocardial infarction	56 (18.6)	151 (17.0)
- heart failure	21 (7.0)	74 (8.3)
Cerebrovascular disorders	23 (7.6)	65 (7.3)
Diabetes mellitus	31 (10.3)	104 (11.7)
Smoking history – pack-years	49.0±34.3	48.0±33.7
Current smoker- no. (%) †	114 (37.9)	328 (37.0)
Medication for COPD - no. (%)		
LAMA	220 (73.1)	659 (74.3)
LABA	32 (10.6)	103 (11.6)
ICS	41 (13.6)	94 (10.6)
ICS/LABA combination	229 (76.1)	653 (73.6)
GOLD stage – no. (%)		
- GOLD 1	40 (13.3)	119 (13.4)
- GOLD 2	165 (54.8)	497 (56.0)
- GOLD 3	96 (31.9)	271 (30.6)
Baseline lung function		
- FEV1 – liters	1.69±0.6	1.71±0.6
- FEV1 – % predicted	60.6± 17.8	61.7±17.7
- FVC – liters	3.49±1.1	3.44±1.0
- FVC – % predicted	60.6±17.6	61.7±17.7
- FEV1/FVC	0.49±0.1	0.49±0.1
Number of exacerbations/year in previous 3 years, median (IQR)	1.3 (0.67-2.0)	1.0 (0.33-2.0)
St. George's Respiratory Questionnaire score ‡	47.3 ±18.0	44.5±19.1

Patient characteristics were collected at the time of inclusion in the cohort. Plus-minus values are means ±SD.

COPD denotes chronic obstructive pulmonary disease, LAMA long-acting muscarinic antagonist, LABA long-acting β-agonist, ICS inhaled corticosteroids, GOLD Global Initiative for Chronic Obstructive Lung Disease, FEV1 forced expiratory volume in 1 second, FVC forced vital capacity, IQR interquartile range.

* Comorbidities were self-reported.

† All patients were current or former smokers.

‡ St. George's Respiratory questionnaire scores range from 0 to 100; higher scores indicate worse quality of life.[1]

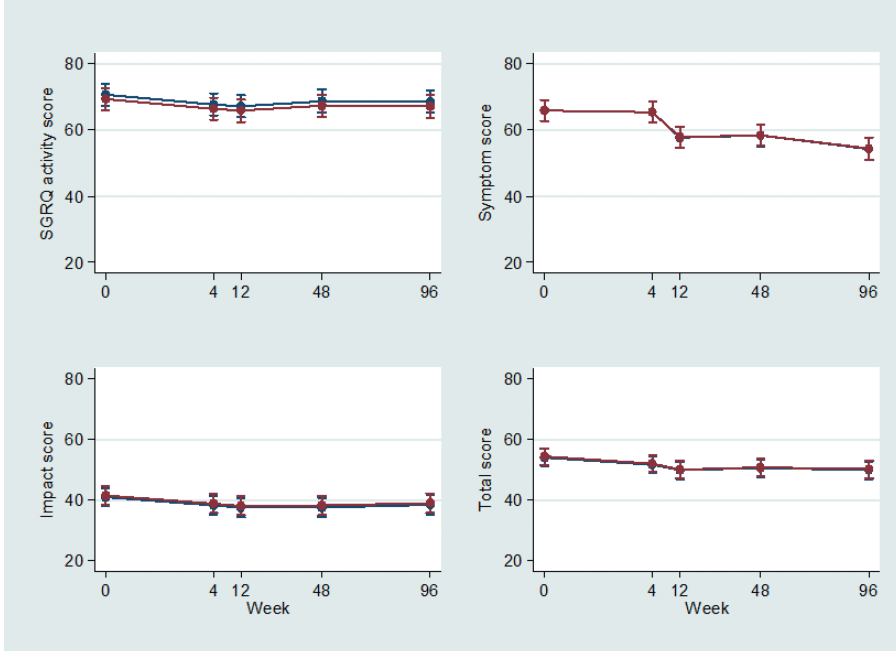

Figure S2. Scores of the St. George's Respiratory Questionnaire during Inclusion in the RCT, and during Follow-Up.

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthonisen 1987	19	57	28	59	25.7%	0.70 [0.45, 1.11]
Brusse-Keizer 2014	3	18	3	17	2.9%	0.94 [0.22, 4.05]
Llor 2012	15	158	30	152	28.6%	0.48 [0.27, 0.86]
Van Velzen 2017	32	150	46	151	42.8%	0.70 [0.47, 1.03]
Total (95% CI)		**383**		**379**	**100.0%**	**0.65 [0.50, 0.84]**
Total events	69		107			

Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.001)

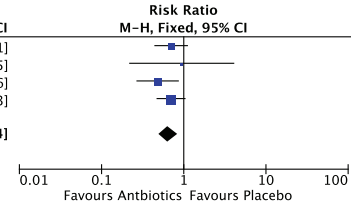

Figure S3: Forest plot of comparison: Antibiotics versus placebo, outcome: Treatment failure within 4 weeks - current drugs only.[2]

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Author contributions:

GR, PBre, PS, and JP designed the study.
PV, PBre, JJB, BTJvdB, JWKvdB, JWFD, JMAD, DRGLG-T, REJ, CvK, FHK, KP, and AR collected data.
PV, GR, and PBri analysed data.
PV, GR, PS, and JP interpreted data.
PV, GR, PS, and JP wrote the manuscript.
PBre, JJB, BTJvdB, JWKvdB, PBri, JWFD, JMAD, DRGLG-T, REJ, CvK, FHK, KP, and AR reviewed the manuscript.
PV and GR created the figures.
All authors approved the final manuscript.

Chapter 3

Antibiotics for COPD exacerbations in an outpatient setting: a systematic review and meta-analysis

P. van Velzen, G. ter Riet, R. Spijker, P.J. Sterk, J.M. Prins

Manuscript in preparation

Abstract

Introduction

Antibiotics are frequently prescribed for COPD exacerbations that are treated in an outpatient setting, as antibiotics reduce short-term treatment failure rates. The question is whether this also applies to patients with exacerbations that are concurrently treated with oral corticosteroids (OCS). The primary objective of this review was to investigate the effect of antibiotics on short-term treatment failure rate in COPD exacerbations, in particular in patients without sputum purulence and in patients that are concurrently treated with OCS.

Methods

We searched for randomized controlled trials (up to May 12, 2020) comparing antibiotics with placebo in the treatment of COPD exacerbations. Trials were eligible if they included outpatients and compared treatment for an exacerbation of COPD with antibiotics *versus* placebo. We performed predefined subgroup analyses in patients without sputum purulence and in patients that were concurrently treated with OCS. We calculated summary risk ratios (RRs) with corresponding 95% confidence intervals (CIs). To assess heterogeneity, we used the chi^2 and I^2 statistics. Risk of bias of each included study was assessed and certainty of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results

We identified 5269 records of which 4 trials including 762 patients were eligible for inclusion. Two trials protocolized treatment with OCS. Overall, treatment failure rate up to one month was lower in patients treated with antibiotics (RR 0.65, 95%CI 0.50-0.84, high-certainty evidence). The risk ratios for treatment failure in patients without sputum purulence and in those treated with OCS were in the same range, but with the 95% CI crossing the null hypothesis (1) (RR 0.78, 95%CI 0.30-2.06 and 0.72, 95% CI 0.49-1.04, low and moderate-certainty evidence respectively). The risk ratio for adverse events with antibiotics was 1.21, 95% CI 0.59-2.46 (low-certainty evidence).

Conclusion

In outpatients treated for an exacerbation of COPD, antibiotics reduced short-term treatment failure rates with high certainty. For outpatients without sputum purulence and in patients that are concurrently treated with OCS the effect of antibiotic treatment was less certain.

Introduction

Chronic obstructive pulmonary disease (COPD) is a very prevalent, progressive chronic respiratory disease, characterized by persistent respiratory symptoms and airflow limitation.[1] Exacerbations of COPD are acute events that present with worsening of respiratory symptoms.[1,2] Most exacerbations are treated in an outpatient setting and treatment consist of bronchodilation therapy and oral corticosteroids (OCS), with or without antibiotics.[1]

The use of antibiotics is controversial. The presence of bacteria, especially new strains, has been associated with exacerbations[3] but it is estimated that less than 50% of the exacerbations are caused by bacterial infection.[4]

The most recent systematic review[5] on the use of antibiotics in exacerbation COPD was published in 2018. The reported effect in outpatients (7 studies) was a 28% reduction of the treatment failure rate: risk ratio (RR) 0.72, 95% confidence interval (CI) 0.56 to 0.94. Evidence of moderate quality showed that currently used antibiotics reduce the risk of treatment failure among inpatients by 35%, but the upper limit of the 95% CI is also compatible with the absence of effect (RR 0.65, 95% CI 0.38-1.12). There tended to be more side effects in the group (combined in- and outpatients) treated with antibiotics, RR 1.20, 95% CI 0.89 to 1.63. Since then, no randomized controlled trials (RCTs) have been published.

In line with this evidence, current guidelines advise the prescription of antibiotics in outpatients with an exacerbation, particularly in the case of sputum purulence.[1,2,6,7] However, the diagnosis of COPD was not well established in all studies included in the review,[5] and in only two[8,9] of the trials, the prescription of OCS was protocolized. This is remarkable, as all international guidelines[1,2,7] advise the prescription of OCS. OCS improve symptoms, lung function and reduce treatment failure rates.[10]

Taken together, current international clinical guidelines advise the prescription of antibiotics in addition to OCS in outpatients treated for an acute exacerbation of COPD, despite limited evidence on its effect, potentially more adverse events and the increasing problem of antimicrobial resistance.

The aims of this systematic review were to examine the effect of antibiotics in COPD exacerbations on short-term treatment failure rate, hospitalization and mortality rates, adverse events and time to the next exacerbation in ambulatory patients with an established diagnosis of smoking-induced COPD. We specifically performed subgroup analyses in patients with sputum purulence and in patients that were concurrently treated for the exacerbation with OCS.

Methods

Data sources and study selection

In collaboration with a clinical librarian, we searched Embase, Web of Science, Ovid MEDLINE and the Cochrane Central Register of Controlled Trials (Central) on randomized controlled trials comparing antibiotics with placebo in the treatment of COPD exacerbations. Details of the search strategy are provided in the appendix.

Reference lists of randomized controlled trials and systematic reviews were browsed for additional randomized controlled trials. Studies up to May 11, 2020 were included. Search results were imported in the Rayyan web application[11] and duplicates were removed. All titles and abstracts were screened by one member of the study team (PV) to identify studies that potentially met the inclusion criteria, and 10% were independently screened by another author (JP). Differences in opinion were resolved by discussion. If after discussion the difference would remain greater than 2·5%, all titles and abstracts would be reviewed by JP. Next, the full texts of all potentially relevant articles were retrieved and assessed for eligibility by PV and JP. Any disagreement on inclusion or exclusion of studies was resolved through discussion.

Inclusion criteria

We included randomized controlled trials comparing treatment of an acute exacerbation of COPD in outpatients with antibiotics *versus* placebo, with a follow-up duration of at least 1 month. We included trials if an exacerbation had been defined as an increase in at least one of the following symptoms: dyspnoea, cough, sputum volume, or sputum purulence and this increase in

symptoms was more than the day to day variability.[1,2] Trials were eligible if more than 90% of the patients had a doctor's diagnosis or a spirometrically confirmed diagnosis of COPD, had an age of 40 years and older and had a smoking history. Only studies that used antibiotics that are currently available for prescription were included.

Exclusion criteria

We excluded studies that had included patients with asthma, pneumonia, acute bronchitis or bronchiectasis, studies that included patients younger than 18 years old and studies including patients on antibiotic maintenance therapy. Data that were published as conference abstract only and studies that were published in another language than English, German, French or Dutch were also excluded.

Data extraction and statistical analysis

A standard form was used to extract data from included studies. We extracted title, year, authors, antibiotics used, treatment failure rates up to 1 month, treatment failure in patients without sputum purulence, treatment failure in patients concurrently treated with OCS, adverse events up to 1 month, and information necessary to assess risk of bias. Extracted data were entered in review manager 5.3. Risk of bias of each of the included studies was assessed with the Revised Cochrane risk-of-bias tool for randomised trials, version 2.0.[12] Data extraction and assessment of risk of bias was done by PV and fully checked for accuracy by JP. In case data were missing for a secondary outcome, authors were not contacted for additional information.

Data were pooled and outcomes are reported as risk ratios (RR) with 95% confidence interval (95% CI). We used the chi^2 test (significance level: 0.1) and the I^2 test to test for heterogeneity. We used the Mantel-Haenszel method for fixed effect models if I^2 was less than 50%. If I^2 was equal or more than 50%, a random effects model was used. We conducted the following prespecified subgroup analyses when the subgroup was reported in at least two studies: patients reporting sputum purulence and concurrent therapy with OCS. Certainty of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Each outcome was calculated using review manager 5.3. We adhered to the PRISMA checklist

for systematic reviews.[13] Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID= 42018099458.

Results

We identified 5269 studies: 1432 in Medline,1252 in Embase, 1615 in Cochrane and 970 in web of Science. Removal of duplicates resulted in 3439 studies. After screening titles and abstracts, 3425 studies were excluded. Another 7 studies were removed after full-text screening (figure 1).

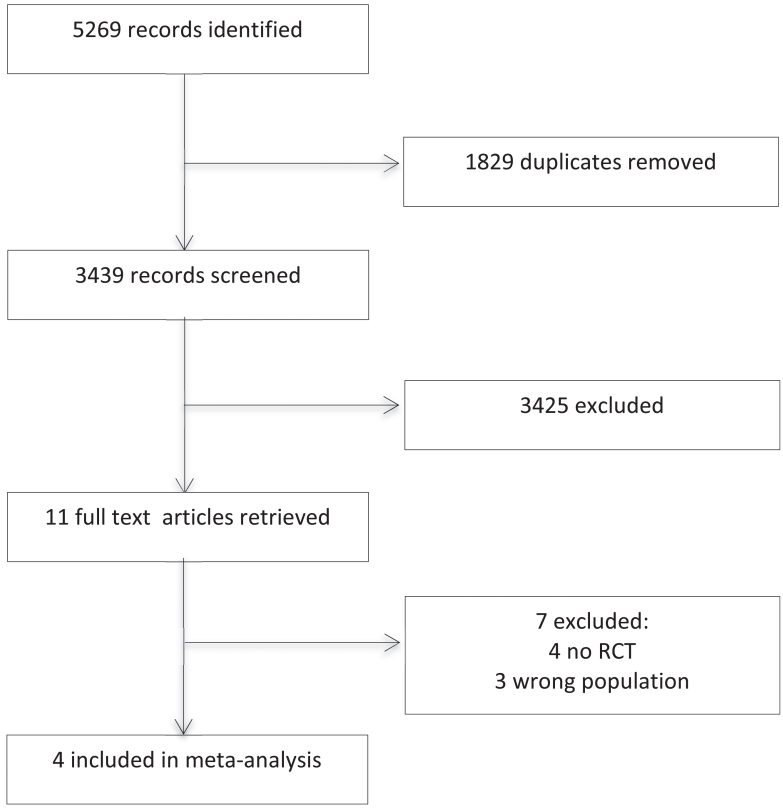

Figure 1: study flow diagram

Studies included in meta-analysis

We included 4 randomized controlled trials.[8,9,14,15] Studies were published between 1987 and 2017 and included 762 patients: 383 in the antibiotic group and 379 in the placebo group. The antibiotics used in the trial were trimethoprim/sulphamethoxazole,[15] amoxicillin,[15] doxycycline[8,15] and amoxicillin/clavulanic acid.[9,14] If reported, patients had mild to very severe COPD and all studies included patients with Anthonisen exacerbations types 1, 2 and 3. In two trials,[8,9] patients received treatment with OCS in addition to antibiotics. Included trials had a low risk of bias.

We excluded three trials that were included in the systematic review by Vollenweider.[5] 15% of the patients included in the trial by Sachs *et al*[16] had a diagnosis of asthma and at most 80% of the patients classified as having COPD was a current or former smoker. Jørgensen *et al*[17] included patients with chronic bronchitis and less than 75% had a smoking history. Finally, only 80% of the patients in the trial by Hassan *et al*[18] were current or former smokers.

Treatment failure up to 1 month

Treatment failure was defined as no improvement in symptoms or the need for hospitalization, additional medication or death due to COPD. Treatment failure was established between day 21 and day 28. The pooled data for treatment failure, treatment failure in patients without sputum purulence, treatment failure in patients concurrently treated with OCS and adverse events are shown in figures 2-5, with the data summarized in table 1.

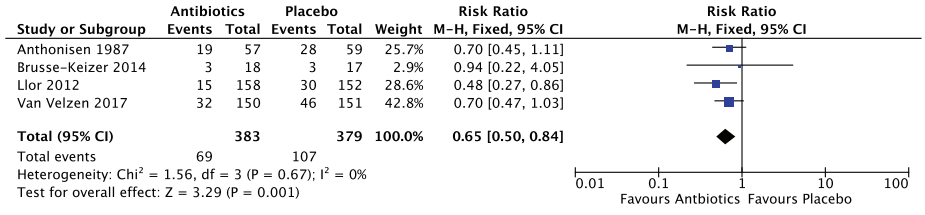

Figure 2: Treatment failure up to 1 month

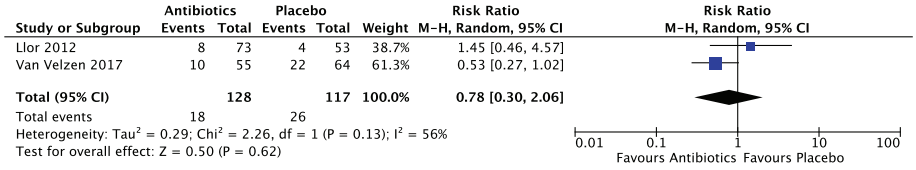

Figure 3: Treatment failure in patients without sputum purulence up to 1 month

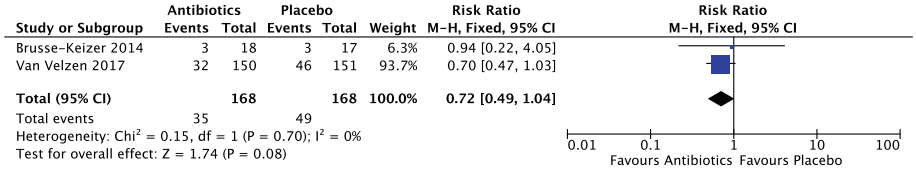

Figure 4: Treatment failure in patients concurrently treated with OCS up to 1 month

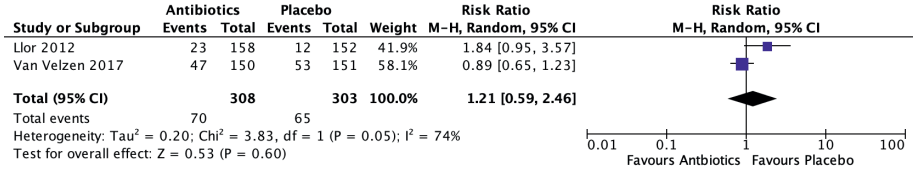

Figure 5: Adverse events up to 1 month

Overall, treatment failure rate was lower in patients treated with antibiotics (RR 0.65, 95% CI 0.50-0.84, high-certainty evidence). The risk ratios for treatment failure in patients without sputum purulence and in those treated with OCS were in the same range, but with the 95% CI crossing the null hypothesis (1) (RR 0.78, 95% CI 0.30-2.06 and 0.72, 95% CI 0.49-1.04) respectively, low and moderate-certainty evidence respectively). The risk ratio for adverse events with antibiotics was 1.21, 95% CI 0.59-2.46 (low-certainty evidence).

Two trials reported time to next exacerbation. Llor *et al*[14] followed patients for one year and reported a median time to next exacerbation of 233 days (interquartile range (IQR) 110-365) compared to 160 days (IQR 66-365) in the placebo group. P=0.015. In our own study,[8] we found a median time to next exacerbation of 148 days (95% CI 95-200) in the antibiotic group vs 161 days (95% CI 118-121) in the placebo group (hazard ratio 1.01; 95% CI 0.79–1.31; p=0.91). As definitions differed between these studies, we did not pool the

data. In none of the studies hospitalization rates were reported, and only one study[8] provided mortality data, precluding pooling of data.

Discussion

In outpatients treated for an exacerbation of COPD, antibiotics reduced short-term treatment failure rates. In outpatients without sputum purulence and in patients that are concurrently treated with OCS, antibiotics showed a comparable trend towards reduced treatment failure rates, but the certainty of the observed effect was only low to moderate, respectively. The effect of antibiotic treatment on the risk of adverse events was uncertain.

We could find only four trials in which all patients had spirometrically confirmed COPD and a relevant smoking history. Outcomes were not specified for COPD severity and we cannot be sure that patients with more severe COPD benefit most from antibiotic treatment. In addition, trials included patients with Anthonisen type 1, 2 and 3 exacerbations, but because data are not specified for exacerbation type, we cannot confirm that patients with type 1 exacerbations benefit more from antibiotic treatment than patients with type 3 exacerbations. Our data suggest that patients without sputum purulence may also benefit from antibiotics. This is in accordance with our recently published data,[19] in which we concluded that sputum characteristics do not identify those patients with an exacerbation that benefit from antibiotic treatment.

This is the first meta-analysis to report treatment failure rates in patients that are concurrently treated with OCS. Although OCS are advised by all international guidelines,[1,2,7] only two trials protocolized simultaneous treatment with OCS. Although the RR of 0.72 (CI 0.49-1.04) is not different than that of all trials together, due to low numbers the effect of antibiotics in these patients is less certain.

Our results considering short-term treatment failure confirm the results of the review by Vollenweider *et al*.[5] Regarding adverse events, Vollenweider pooled data of outpatients and hospitalized patients and found that patients that

received antibiotics had more side effects, although this was not statistically significant (OR 1.20, 95% CI 0.89 to 1.6). Limiting the analysis of adverse events to outpatients, we identified two trials[8,14] that reported this outcome and found a comparable risk ratio, but the effect was uncertain.

Vollenweider *et al* also investigated treatment failure rates in patients hospitalized for an exacerbation (4 trials, 576 patients) and concluded that the evidence does not support antibiotic prescription for inpatients: whereas the risk ratio was comparable, the upper limit of the 95% CI crossed the null hypothesis (1): RR 0.65, 95% CI 0.38-1.12. In contrast, a systematic review by Puhan *et al*[20] (4 trials,475 patients) did find a reduction of treatment failure rate (odds ratio 0.25, 95% CI 0.16–0.39), but they included a trial that used antibiotics that are currently unavailable[21] and used data from a trial that included patients requiring mechanical ventilation.[22] From a pathophysiological perspective, it is unlikely that antibiotics have an effect in outpatients, but not in hospitalized patients with more severe exacerbations.

The most important limitation of this review is that only 683 patients were included. Data that might influence the effect of antibiotic treatment such as sputum purulence and concurrent treatment with OCS were inconsistently reported. In addition, not all studies reported other important clinical outcomes (hospitalization, mortality).

Considering the huge number of patients with COPD exacerbations that are prescribed antibiotics, the number of randomized controlled trial is disappointingly low. Most antibiotic trials in COPD have been head-to-head trials, comparing one antibiotic to another, without evidence of a benefit from antibiotics in the first place.[23] To prevent unnecessary antibiotic prescription, more randomized placebo controlled trials are needed to confirm that patients benefit from antibiotic treatment. In particular, future trials should standardize treatment with OCS and report on other important outcomes as well, such as adverse events and hospital admission rates.

Table 1: GRADE Summary of findings and quality of evidence

Antibiotics compared to placebo for COPD exacerbations

		Certainty assessment			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**
Treatment failure up to 1 month					
762 (4 RCTs)	not serious	not serious	not serious	not serious	none
Treatment failure - patients without sputum purulence up to 1 month					
245 (2 RCTs)	not serious	serious [a]	not serious	serious [b]	none
Treatment failure - patients concurrently treated with oral corticosteroids up to 1 month					
336 (2 RCTs)	not serious	not serious	not serious	serious [b]	none
Adverse events up to 1 month					

In conclusion, our results show that antibiotics reduce short-term treatment failure rates in outpatient (number needed to treat: 9.8), but if OCS are concurrently prescribed, as the guidelines advise, the treatment effect is less certain. Our data also suggested that patients without sputum purulence may also benefit from antibiotics. It would be helpful if we could identify those patients who do benefit from antibiotic treatment, but in our own large RCT[8] we did not find clinical characteristics, in particular not sputum characteristics, that identify those who benefit from antibiotic treatment. To reduce unnecessary antibiotic use, an important first step might be, as shown by Butler et a,[24] biomarker guided prescription. This turned out to be safe while substantially reducing the antibiotic prescription rate.

Summary of findings

Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
	With placebo	With antibiotics		Risk with placebo	Risk difference with antibiotics
⊕⊕⊕ HIGH	107/379 (28.2%)	69/383 (18.0%)	**RR 0.65** (0.50 to 0.84)	282 per 1.000	**99 fewer per 1.000** (from 141 fewer to 45 fewer)
⊕⊕◯◯ LOW	26/117 (22.2%)	18/128 (14.1%)	**RR 0.78** (0.30 to 2.06)	222 per 1.000	**49 fewer per 1.000** (from 156 fewer to 236 more)
⊕⊕⊕◯ MODERATE	49/168 (29.2%)	35/168 (20.8%)	**RR 0.72** (0.49 to 1.04)	292 per 1.000	**82 fewer per 1.000** (from 149 fewer to 12 more)

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Appendix:

S1. Search strategy

Ovid MEDLINE

"Lung Diseases, Obstructive"/ or "Pulmonary Disease, Chronic Obstructive"/ or "Bronchitis, Chronic"/ or "Pulmonary Emphysema"/ or (emphysema* or (chronic* adj3 bronchiti*) or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or COPD or COAD or COBD or AECB).ti,ab,kf.
("Anti-Bacterial Agents" or antibacterial or anti-bacterial or antibiotic* or penicillin* or amoxycillin or ampicillin or cefalosporin* or cefaclor or cefalexine or cephalotin or cefazolin or cefixime or cefotaxime or cefpodoxime or cephradine or ceftizoxime or ceftriaxone or cefuroxime or tetracyclin* or demeclocycline or doxycycline or minocycline or oxytetracycline or macrolides or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin or fluoroquinol* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem* or Flucloxacillin).ti,ab,hw,kw,rn.
1 and 2
("Randomized controlled trial" or "controlled clinical trial").pt. or (random* or placebo or groups).ti,ab. or "clinical trials as topic".sh. or trial.ti.
3 and 4
exp animals/ not humans/
5 not 6

Embase

obstructive airway disease/ or chronic obstructive lung disease/ or chronic bronchitis/ or lung emphysema/ or (emphysema* or (chronic* adj3 bronchiti*) or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or COPD or COAD or COBD or AECB).ti,ab,kw.
exp antibiotic agent/ or ("Anti-Bacterial Agents" or antibacterial or anti-bacterial or antibiotic* or penicillin* or amoxycillin or ampicillin or cefalosporin* or cefaclor or cefalexine or cephalotin or cefazolin or cefixime or cefotaxime or cefpodoxime or cephradine or ceftizoxime or ceftriaxone or cefuroxime or tetracyclin* or demeclocycline or doxycycline or minocycline or oxytetracycline or macrolides or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin or fluoroquinol* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem* or Flucloxacillin).ti,ab,hw,kw,dy.
(Randomized controlled trial/ not ((exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/)) or ((((((((((Controlled clinical study/ or Random$.ti,ab. or randomization/ or intermethod comparison/ or placebo.ti,ab. or (compare or compared or comparison).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (open adj label).ti,ab. or ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. or double blind procedure/ or parallel group$1.ti,ab. or (crossover or cross over).ti,ab. or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. or (assigned or allocated).ti,ab. or (controlled adj7 (study or design or trial)).ti,ab. or (volunteer or volunteers).ti,ab. or human experiment/ or trial.ti.) not Randomized controlled trial/ not (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or Cross-sectional study/) not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or (((case adj control$) and random$) not randomi?ed controlled).ti,ab. or (Systematic review not (trial or study)).ti. or (nonrandom$ not random$).ti,ab. or "Random field$".ti,ab. or (random cluster adj3 sampl$).ti,ab. or (review.ab. and review.pt.)) not trial.ti.) or "we searched".ab.) and (review.ti. or review.pt.)) or "update review".ab. or (databases adj4 searched).ab. or (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.) and animal experiment/) or Animal experiment/) not (human experiment/ or human/))
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Web of Science

# 5	941	#4 AND #3
	5,674,270	ts=(random* or rct or trial or placebo or groups)
# 4		
	1.99	#2 AND #1
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	506.314	ts=((“Anti-Bacterial Agents” or antibacterial or anti-bacterial or antibiotic* or penicillin* or amoxycillin or ampicillin or cefalosporin* or cefaclor or cefalexine or cephalotin or cefazolin or cefixime or cefotaxime or cefpodoxime or cephradine or ceftizoxime or ceftriaxone or cefuroxime or tetracyclin* or demeclocycline or doxycycline or minocycline or oxytetracycline or macrolides or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin or fluoroquinol* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem* or Flucloxacillin))
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Cochrane Central Register of Controlled Trials

#1	obstructive airway disease:mh OR “Pulmonary Disease, Chronic Obstructive”:mh or “Bronchitis, Chronic”:mh or “Pulmonary Emphysema”:mh or “obstructive airway disease”:eh or “chronic obstructive lung disease”:eh or “chronic bronchitis”:eh or “lung emphysema”:eh or (emphysema* or (chronic* NEAR3 bronchiti*) or (obstruct* NEAR3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or COPD or COAD or COBD or AECB):ti,ab,kw
#2	MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES
#3	(antibacterial or anti-bacterial or antibiotic* or penicillin* or amoxycillin or ampicillin or cefalosporin* or cefaclor or cefalexine or cephalotin or cefazolin or cefixime or cefotaxime or cefpodoxime or cephradine or ceftizoxime or ceftriaxone or cefuroxime or tetracyclin* or demeclocycline or doxycycline or minocycline or oxytetracycline or macrolides or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin or fluoroquinol* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem* or Flucloxacillin):ti,ab,kw,eh,mh
#4	#2 OR #3
#5	#1 AND #4

Chapter 4

Doxycycline added to prednisolone in outpatient-treated acute exacerbations of COPD: a cost-effectiveness analysis alongside a randomised controlled trial

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Abstract

Background

Most patients with mild to severe chronic obstructive pulmonary disease (COPD) experience exacerbations, which are also associated with increased healthcare costs. Despite limited evidence of antibiotics' benefits for exacerbations in outpatients, antibiotics are frequently prescribed. The aim of this study was to investigate whether doxycycline added to prednisolone is cost-effective compared to placebo plus prednisolone for the treatment of COPD acute exacerbations.

Methods

An economic evaluation from the societal perspective was performed alongside a 2-year randomised trial in 301 COPD patients in the Netherlands. The primary outcome was cost per quality-adjusted life year (QALY). The secondary outcome was cost per exacerbation prevented. Healthcare utilisation and loss of productivity were measured using retrospective questionnaires and clinical report forms. Missing data were imputed using multiple imputations by chained equations. Bootstrapping was employed to estimate statistical uncertainty surrounding cost-effectiveness outcomes. A sensitivity analysis from the healthcare perspective was performed.

Results

On average, costs in the doxycycline group were €898 higher than in the placebo group [95% confidence interval (CI) – 2617 to 4409] for the 2 years of follow-up. QALY values were higher in the doxycycline group (0.03; 95% CI – 0.00 to 0.06), but patients in this group suffered 0.01 more exacerbations than patients in the placebo group (95% CI – 0.14 to 0.11). Cost-effectiveness acceptability curves showed that the probability of doxycycline being cost-effective compared to placebo was 61% and 43% at a willingness-to-pay threshold of €34,000 per QALY and per exacerbation avoided, respectively. The sensitivity analysis showed similar results from the healthcare system perspective.

Conclusions

In patients with mild to severe COPD treated for exacerbations in an outpatient setting, doxycycline added to prednisolone is not cost-effective compared to prednisolone plus placebo over a 2-year period.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent disease, characterised by non-fully reversible airflow limitation.[1, 2] According to recent estimates, 65 million people are affected by COPD worldwide, and the disease is predicted to become the third most common cause of death by 2020.[3] Most patients with COPD experience exacerbations, which are characterised by an acute worsening of respiratory symptoms. [1,4] Exacerbations have a major impact on patients' physical and psychological wellbeing,[5] and are associated with a reduced quality of life,[6] a faster decline in lung function,[7] and increased mortality.[8] Exacerbations are one of the most important drivers of the total COPD costs on the healthcare system, especially when hospitalisation is necessary, and impose a large economic burden on society.[9] In the Dutch context in particular, exacerbations are the main cost driver, together with medications.[10]

Most exacerbations are treated in an outpatient setting. Treatment of exacerbations consists of oral corticosteroids with or without antibiotics.[1,4] Despite limited short-term benefits,[11] antibiotics are frequently prescribed. Two retrospective studies[12,13] and one randomised controlled trial[14] suggested that antibiotics prolong time to the next exacerbation. However, evidence on the cost-effectiveness of antibiotics for the treatment of COPD exacerbations in an outpatient setting is scarce.[15]

Recently, a randomised controlled trial conducted by the current research group investigated the long-term clinical effectiveness of doxycycline versus placebo added to prednisolone for the treatment of COPD exacerbations in an outpatient setting.[16] Differently from what it was hypothesised, it found that treatment with antibiotics did not prolong time to the next exacerbation. However, the randomised controlled trial could not exclude the possibility that short-term treatment nonresponse was lower in patients treated with antibiotics, which might result in lower total costs in this group. Hence, despite not being clinically effective, treatment with doxycycline might still be cost-effective. To assess whether this was the case, we conducted a cost-effectiveness analysis alongside the previously reported randomised controlled trial, the results of which are presented here.

Methods

Trial Design

An economic evaluation from the societal perspective was conducted alongside the TEXACOLD study in The Netherlands. This was a randomised, double-blind, controlled trial investigating the long-term clinical and cost-effectiveness of doxycycline plus prednisolone versus placebo plus prednisolone for the treatment of COPD exacerbations in an outpatient setting. The trial protocol was approved by the ethics committee of the Academic Medical Centre at the University of Amsterdam, and patients gave their written informed consent. Participants, investigators and those assessing outcomes were blinded to intervention assignment. Full details of the trial are available in Van Velzen *et al*.[16]

Participants

Participants were recruited from nine teaching hospitals and three primary care practices in The Netherlands. Patients were eligible for inclusion if they were 45 years or older, had a clinical diagnosis of mild-to-severe COPD, defined as a post-bronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio of ≤ 0.7 and a post-bronchodilator FEV1 of ≥ 30%, according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) and American Thoracic Society and European Respiratory Society criteria,[1,2] had a smoking history of at least 10 pack-years, and had suffered one or more exacerbations during the previous 3 years, with the limitation that the last exacerbation ended less than 4 weeks before recruitment. Patients were not eligible if they did not speak Dutch, had poor cognitive abilities, were pregnant, had a known allergy to doxycycline, or had a life expectancy shorter than 1 month.

All patients entered a prospective cohort. In the case of an exacerbation, cohort participants were randomly assigned to a 7-day course of doxycycline 100 mg (first day 200 mg) or to a control group, in a 1:1 ratio. An exacerbation of COPD was defined as an event characterised by a change in the patient's baseline dyspnoea, cough, or sputum beyond day to-day variability, sufficient to warrant a change in management other than optimising bronchodilator therapy.[1,2]

Patients in both groups were administered oral corticosteroids, i.e. prednisolone 30 mg daily for 10 days. If further exacerbations occurred during the 2-year

follow-up period, patients received the same medications as by treatment allocation.

Procedures

Baseline data, including demographics, GOLD stage, smoking history and medication use, were collected at the time of inclusion in the prospective cohort and recorded in a standardised electronic case record form (eCRF, Oracle Clinical).

Health status was measured using the Dutch version of the EQ-5D-3L. The EQ-5D-3L consists of two parts: a questionnaire and a visual analogue scale (VAS). The questionnaire self-reported health status ranges from 11111 (no problems in any of the five dimensions) to 33333 (extreme problems in all the five dimensions). The VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health).[17] The EQ-5D-3L was administered at randomisation, at month 1 after randomisation, month 3, and every 3 months thereafter until month 4.

Resource Use and Unit Costs (€, 2017)

Information on resource use was collected retrospectively at month 1 after randomisation, month 3, and every 3 months thereafter until month 24; patients were asked to respond to selected questions of the Trimbos/iMTA Labour and Health questionnaire.[18] Given the societal perspective employed in this economic evaluation, all-cause resource use was collected, i.e. not only resource use related to COPD. Each patient self-reported hospitalisation was verified by contacting the hospital where hospitalisation took place and requesting a hospital discharge letter. Healthcare costs included intervention costs, i.e. doxycycline and prednisolone; primary care costs, e.g. general practitioner (GP) and physiotherapist visits; secondary care costs, e.g. hospital admissions and intensive care unit admissions; diagnostics costs, e.g. computed tomography (CT) scans, X-rays and blood tests; support equipment costs, e.g. ventilators, wheelchairs and walkers; and other costs, e.g. nursing home residency. Patient and family costs included informal care and unpaid help. Costs were estimated multiplying the units of resource use by their standard cost according to the Dutch guidelines for economic evaluation.[19] These standard costs take into account labour, overhead and material costs.

The drug prescription costs were obtained from the Royal Dutch Society of Pharmacy.[20] Loss of productivity due to absenteeism and presenteeism was calculated using the friction cost method. Differently from the human capital method, the friction cost method assumes that after a given period of absence from employment, the sick employee is replaced.[21] This study used a friction period of 85 days. Hence, productivity losses are generated only during that time period. Absenteeism was assessed by asking responders how many days of paid work they missed due to health problems. Presenteeism was assessed by asking responders how many hours they would need to work to make up for the time lost while at work due to health problems. Costs of absenteeism and presenteeism were calculated based on gender-specific income values of the Dutch population.[19] All costs were inflated to the year 2017 using consumer price indexes. The main unit costs used for the cost calculation are presented in Table 1.

Table 1: Main unit costs used for cost calculation

Resources	€ (2017 values)	Source
Direct costs		
Intensive care unit (day)	2041.19	(19)
Hospitalisation (day)	448.75	(19)
Accident and emergencies admission	262.36	(19)
GP office visit	33.42	(19)
GP home visit	50.65	(19)
GP phone call	17.22	(19)
Specialist visit	113.45	(19)
Nurse (h)	21.27	(19)
Help at home (day)	73.94	(19)
Nursing home (day)	170.18	(19)
Rehabilitation (day)	154.98	(19)
CT scan	136.75	(19)
X-ray chest	46.04	(19)
Blood tests	106.35	(19)
Wheelchair/walker	455.85	(19)
Oxygen concentrator	2039.16	(19)
Productivity losses		
Absenteeism from paid labour woman (h)	32.01	(19)
Absenteeism from paid labour man (h)	38.39	(19)
Presenteeism from paid labour woman (h)	32.01	(19)
Presenteeism from paid labour man (h)	38.39	(19)
Interventions		
Prednisolone + doxycycline	38.47	(20)
Prednisolone alone	31.52	(20)

Outcome Measures

As recommended by the Zorginstituut in The Netherlands[22] and the National Institute for Health and Care Excellence in the UK,[23] the primary outcome for this cost-effectiveness study was quality-adjusted life years (QALYs). QALYs are an index that multiplies the time patients spend in a given health state with a utility value that represents the health-related quality of life (HRQoL) associated with that health state. Transitions between health states were considered to be linear. Utility values were obtained using the Dutch version of the EQ-5D-3L with the Dutch tariff.[24] The EQ-5D-3L was chosen as it is the most widely used measure for economic evaluations worldwide[25] and it has been deemed valid for COPD populations.[26] The number of exacerbations during the 2 years after randomisation was the secondary outcome. This was chosen as clinical studies have shown that prescribing antibiotics for exacerbations might reduce their frequency.[12-14] A minimum interval of 3 weeks between subsequent exacerbations was defined,[27] to avoid counting an exacerbation not responding to treatment as a next exacerbation

Analysis

The study sample size (n = 301) was calculated to ensure at least 251 s exacerbations, with a statistical power of 80% for the outcome occurrence of a second exacerbation. The economic evaluation was conducted according to the intention-to-treat principle. Missing costs and effectiveness data were imputed using multiple imputations by chained equations, stratified by treatment group.[28] The imputation model included all outcome variables, characteristics differing between groups at baseline, variables related to missing data and variables related to outcome variables. The model was used to create 25 complete datasets, after which the loss of efficiency was 1%.[28] Non-normal distribution of costs was accounted for by using predictive mean matching in the multiple imputation by chained equations procedure.[29] Rubin's rules were used to pool effects and costs from the imputed datasets.[30]

Seemingly unrelated regressions were employed to estimate differences in costs and effects, adjusting for baseline HRQoL. Seemingly unrelated regressions were chosen as they take into account the covariance between costs and effects in estimating the error terms.[31] For the second year of the randomised clinical trial, 4% discounting was employed for costs, and 1.5%

discounting was employed for effects.[22] Seemingly unrelated regression analysis assumes bivariate normality, an assumption that is clearly violated by the distribution of costs and QALYs. Therefore, joint uncertainty around costs and effects was estimated using bias-corrected and accelerated bootstrapping with 5000 replications.[32] Bootstrapped costs and effects were plotted on a cost-effectiveness plane (CE plane) to graphically present the uncertainty surrounding the incremental cost-effectiveness ratio (ICER).[33] In addition, a cost-effectiveness acceptability curve (CEAC) was estimated in order to present the probability that the treatment is cost-effective compared to the control at different ceiling ratios, i.e. the amount society is willing to pay to gain one unit of effect.[34] In order to interpret the CEAC for QALYs, the commonly used threshold of £20,000–30,000 per QALY (€22,000–34,000 per QALY) was employed.[23] Analyses were performed using Stata/MP 14.1®.

Sensitivity Analysis

The primary analysis was based on costs from a societal perspective. In addition, a sensitivity analysis was performed with the objective of assessing the cost-effectiveness for the primary and secondary outcomes from the healthcare system perspective. This choice was made as health technology assessment bodies such as the National Institute for Health and Care Excellence request economic evaluations to be performed from this perspective.[23]

Results

Participants

Between 1 December 2010 and 15 September 2012, 887 patients were enrolled in the cohort, of whom 305 had an exacerbation and were randomly allocated to the doxycycline (152 participants) or the placebo group (153 participants). Four participants, two in each arm, were incorrectly randomly allocated because of failed eligibility criteria and were excluded. A flow-chart of the allocation process is provided in Fig. 3 in "Appendix". As shown in Table 2, background characteristics of the included participants did not differ between treatment arms, except for the placebo group comprising a higher percentage of women (46% vs 35% in the doxycycline group).

Complete follow-up data for the EQ-5D-3L were obtained from 24% of the participants. Data on the EQ-5D-3L was missing for 20% of participants at baseline and 1 month follow-up, 22% at 3 and 6 months, 31% at 9 months, 30% at 12 months, 28% at 15 months, 29% at 18 months and 36% at 21 and 24 months. All participants had complete follow-up data for the secondary outcome, number of exacerbations during the 2 years after randomisation. Background characteristics did not differ between participants with and without complete follow-ups, except for the FVC percentage, which was statistically significantly higher for the complete cases.

Table 2: Background characteristics of participants by treatment group

Characteristics	Doxycycline (*n* = 150)	Control (*n* = 151)
Age (years)	65.8 (9.3)	66.4 (9.5)
Female (sex)	52 (35%)	70 (46%)
Comorbidities	24 (16%)	32 (21%)
Myocardial infarction		
Heart failure	12 (8%)	9 (6%)
Cerebrovascular disorder	9 (6%)	14 (9%)
Diabetes mellitus	16 (11%)	15 (10%)
Smoking history (pack years)	47.2 (36.8%)	50.8 (31.7%)
Current smoker‡	49 (33%)	65 (43%)
GOLD stage	21 (14%)	19 (13%)
1		
2	81 (54%)	84 (56%)
3	48 (32%)	48 (32%)
Baseline lung function FEV1 (L)	1.75 (0.6)	1.63 (0.6)
FEV1 (% predicted)	61.1 (18.0)	60.5 (17.7)
FVC (L)	3.62 (1.01)	3.36 (1.11)
FVC (% predicted)	98.3 (22.2)	94.6 (26.5)
FEV1 to FVC ratio	0.49 (0.1)	0.49 (0.1)
Number of exacerbations per year in previous 3 years	1.3 (0.67–2.3)	1.3 (0.67–2.0)
St George's Respiratory Questionnaire†	46.3 (18.4)	48.0 (17.7)
Time from inclusion in cohort to inclusion in the trial (days)	123 (53–250)	116 (49–281)
Prescription of oral corticosteroids	143 (95%)	143 (95%)

Data are *n* (%), mean (SD), or median (IQR). Data are based on Van Velzen *et al*.[16] *GOLD* Global Initiative for chronic obstructive lung disease, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *IQR* interquartile range, *SD* standard deviation. ‡ All patients were current or former smokers. † Higher scores represent worse quality of life

Costs and Effects

Table 3 reports the mean costs and effects per patient for the doxycycline and placebo groups over the 2 years of follow-up, and their bootstrapped mean differences. Total costs amounted to €11,840 for the doxycycline group and €10,942 for the control group: difference €898 [95% confidence interval (CI) – 2617 to 4409]. Higher costs in the doxycycline arm were mainly due to higher absenteeism (€648; 95% CI – 561 to 2060) and tertiary care costs (€390; 95% CI – 2474 to 3648). The costs for support equipment, e.g. respirators, wheelchairs, etc., was higher in the control group (– €226; 95% CI – 450 to 2). Costs in all remaining cost categories were similar across treatment arms. QALYs were 1.44 in the doxycycline group and 1.41 in the control (mean difference 0.03; 95% CI – 0.00 to 0.07). However, patients treated with doxycycline tended to suffer an average of 0.01 exacerbations more than those treated with placebo (95% CI – 0.14 to 0.11). None of these differences were statistically significant.

Table 3: Mean costs (€ for 2017) and effectiveness per participant in the doxycycline and placebo groups for the 2-year follow-up

Cost category	Doxycycline (*n* = 150) mean (95% CI)	Control (*n* = 151) mean (95% CI)	Mean difference (95% CI)
Intervention	139 (125 to 152)	113 (102 to 125)	26 (8 to 42)
Primary care	54 (39 to 68)	85 (59 to 110)	– 31 (– 5 to – 61)
Secondary care	571 (458 to 683)	546 (434 to 657)	25 (– 135 to 182)
Tertiary care and accident and emergencies	5236 (2824 to 7648)	4846 (2892 to 6800)	390 (– 2474 to 3648)
Diagnostics	383 (307 to 459)	387 (317 to 459)	– 4 (– 104 to 103)
Other costs, e.g. nursing homes	287 (15 to 556)	365 (76 to 652)	– 78 (– 461 to 327)
Support equipment, e.g. ventilators, wheelchairs, etc.	1473 (1309 to 1635)	1699 (1532 to 1865)	– 226 (– 450 to 2)
Paid or unpaid help	1132 (921 to 1339)	1081 (903 to 1308)	51 (– 218 to 332)
Productivity losses: absenteeism	1664 (596 to 2732)	1016 (255 to 1775)	648 (– 561 to 2060)
Productivity losses: presenteeism	901 (761 to 1041)	804 (676 to 930)	97 (– 90 to 286)
Total cost from societal perspective	11840 (9196 to 14490)	10942 (8601 to 13291)	898 (– 2617 to 4409)
Total cost from healthcare system perspective	6670 (4222 to 9121)	6342 (4313 to 8375)	328 (– 2791 to 4409)
Quality-adjusted life years	1.44 (1.37 to 1.50)	1.41 (1.33 to 1.47)	0.03 (– 0.00 to 0.07)
Number of exacerbations	2.71 (2.35 to 3.06)	2.70 (2.33 to 3.07)	0.01 (– 0.14 to 0.11)

CI confidence interval

Cost-Effectiveness Analysis

Table 4 reports the results of the cost-effectiveness analysis. For QALYs, the ICER was 32,482, meaning that 1 QALY gained in the doxycycline group was associated with an extra cost of €32,482 compared to the control group. Figure 1a graphically presents the distribution of cost and effect pairs in the CE plane. As can be seen, 70% of pairs were located in the north quadrants, showing that doxycycline is likely to be more expensive than placebo. Pairs were mostly located in the east quadrants (76% vs 24%), highlighting that there is a higher probability of doxycycline being more effective than placebo. Figure 1b reports the CEAC for the primary outcome QALYs. It shows that at a willingness-to-pay threshold of €0 per QALY, the probability that doxycycline is cost-effective is 26%, while at a willingness-to-pay threshold of €34,000 per QALY this increases to 61%. For the number of exacerbations avoided, an ICER of – 60,194 was found. This meant that one additional exacerbation in the doxycycline group was associated with an increased cost of €60,194 in comparison with the control. Once again, cost–effect pairs were mostly concentrated in the north quadrants, i.e. 70%, and approximately equally distributed between the eastern and western quadrants, i.e. 47% versus 53% (Fig. 1c). Hence, doxycycline is most likely to be more expensive and has an equal probability of being less or more effective. Figure 1d reports the CEAC for the number of exacerbations. It shows that at a willingness-to-pay threshold of €0 per exacerbation avoided, the probability of doxycycline being cost-effective is 26%, and that this probability increases to 43% at a willingness-to-pay threshold of €34,000 per exacerbation avoided.

Table 4: Difference in costs (€ for 2016) and effectiveness, ICER and distribution in the CE plane, adjusted for baseline HRQoL

Analysis		Outcome	ΔC (95%CI) (€)	ΔE (95%CI) (Points)	ICER (€/point)	Distribution CE-plane (%)			
Perspective	Type of analysis					NE[1]	SE[2]	SW[3]	NW[4]
Societal	**Main analysis**	QALYs (Range: 0 - 1)	939 (-40 to 1839)	0.03 (-0.00 to 0.06)	32,066	0.52	0.24	0.06	0.18
Societal	**Main analysis**	Number of exacerbations (0 - ∞)	939 (-40 to 1839)	-0.01 (-0.14 to 0.11)	-59,442	0.30	0.17	0.13	0.40
Healthcare system	**Sensitivity Analysis I**	QALYs (Range: 0 - 1)	357 (-448 to 1163)	0.03 (-0.00 to 0.06)	12,200	0·42	0.33	0.08	0.17
Healthcare system	**Sensitivity Analysis II**	Number of exacerbations (0 - ∞)	357 (-448 to 1163)	-0.01 (-0.14 to 0.11)	-22,616	0·25	0.23	0.19	0.33

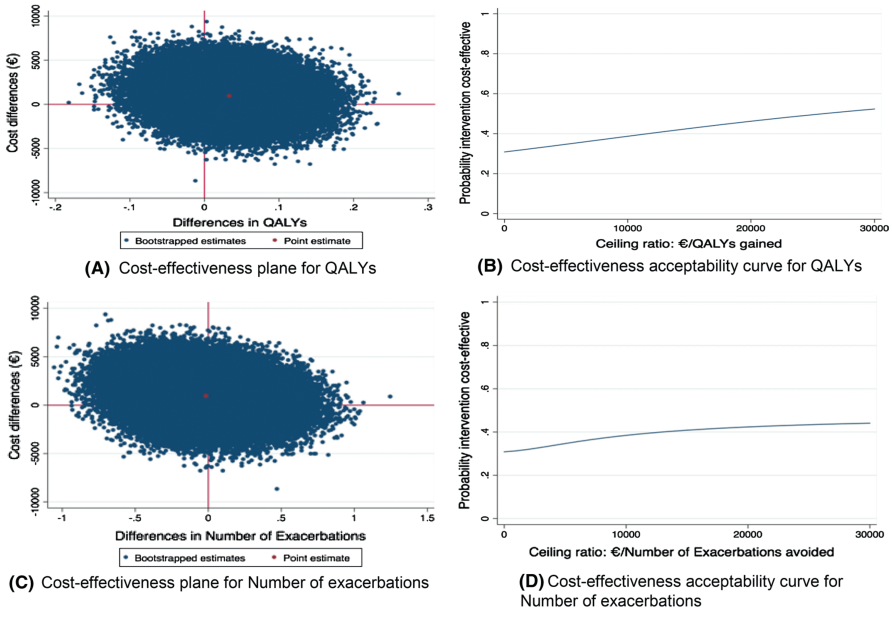
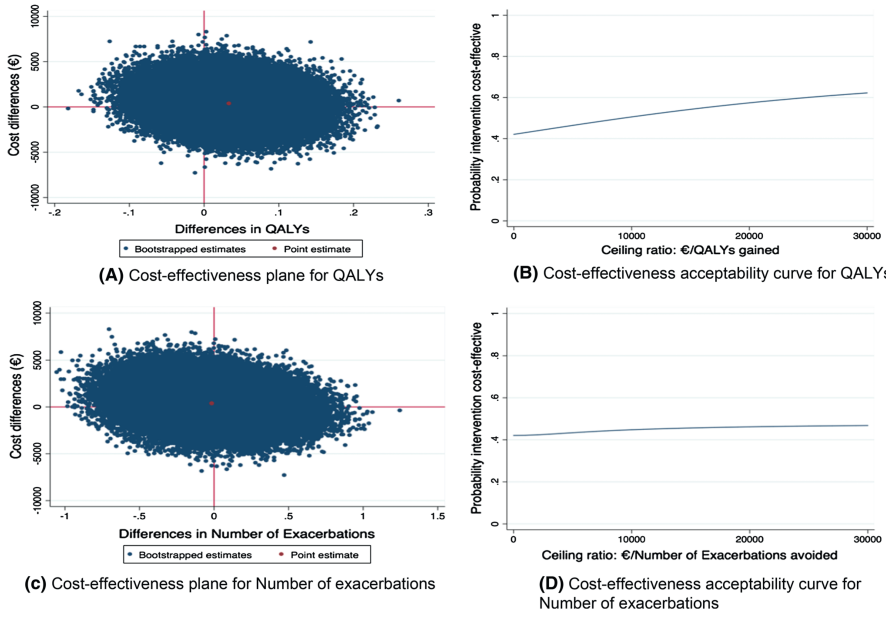


Figure 1: Main analysis cost-effectiveness plane and cost-effectiveness acceptability curve for QALYs and number of exacerbations. QALY quality-adjusted life year

Sensitivity Analysis

Results of the sensitivity analysis are reported in Table 4. From the healthcare system perspective, total costs still tended to be higher for the doxycycline group compared to the placebo group, but the difference between arms was smaller (i.e. €328; 95% CI – 2791 to 4409). The smaller difference decreased the ICER to €12,358 per QALY, and increased the number of pairs located in the southern (fewer costs) and eastern (more effective) quadrants of the CE plane to 41% and 75%, respectively (Fig. 2a). Hence, the probability of doxycycline being cost-effective increased to 42% at a willingness-to-pay threshold of €0 per QALY and 61% at a willingness-to-pay threshold of €34,000 per QALY (Fig. 2b). Also, the ICER for the number of exacerbations avoided was lower from the healthcare system perspective, i.e. – €22,905 per exacerbation avoided, and the percentage of pairs located in the northern (more expensive) quadrants decreased to 58% (Fig. 2c). Despite this, the probability of doxycycline being cost-effective in comparison with placebo was only 42% and 43% at willingness-to-pay ratios of €0 and €34,000 per exacerbation avoided, respectively.



(A) Cost-effectiveness plane for QALYs

(B) Cost-effectiveness acceptability curve for QALYs

(c) Cost-effectiveness plane for Number of exacerbations

(D) Cost-effectiveness acceptability curve for Number of exacerbations

Figure 2. Sensitivity analysis cost-effectiveness plane and cost-effectiveness acceptability curve for QALYs and number of exacerbations. QALY quality-adjusted life year

Discussion

This study evaluated the cost-effectiveness of treating COPD exacerbations with doxycycline in addition to prednisolone as compared to prednisolone plus placebo from a societal perspective. Total costs in the doxycycline group were higher than in the placebo group, but the difference was not statistically significant. Differences in QALYs and number of exacerbations between arms were small and not statistically significant. The ICER was €32,482 per QALY gained. Although this is potentially within the commonly accepted thresholds of €22,000–34,000 per QALY, the probability of doxycycline being cost-effective at a willingness-to-pay threshold of €34,000 was only 61%. For the number of exacerbations avoided, the results showed that doxycycline was less effective and more costly than placebo, and thus, was dominated by placebo. Based on these results, we concluded that using doxycycline in addition to prednisolone is not cost-effective compared to prednisolone plus placebo. To assess the robustness of our findings, we conducted a sensitivity analysis from the healthcare system perspective, confirming that doxycycline

was not cost-effective in comparison with prednisolone alone from this perspective. The rationale for performing this economic evaluation was that in retrospective studies, fewer subsequent exacerbations were observed in patients treated with antibiotics during exacerbations,[12,13] and we hypothesised that total costs might be lower in the doxycycline group as compared to the placebo group. In addition, although we found a non-statistically significant difference in short-term treatment failure rates in previous research (odds ratio 0.8; 95% CI 0.41–1.60),[16] we speculated that doxycycline might reduce the number of hospitalisations. As hospitalisations are the key drivers of costs in exacerbations,[35] doxycycline would still be cost-effective and therefore justify antibiotic prescription. However, our analysis does not lend strong support for that idea.

The finding that doxycycline is not cost-effective compared to placebo differs from a previous cost-effectiveness analysis on the use of antibiotics versus no antibiotics for the treatment of COPD exacerbations, in which antibiotics were associated with lower costs and better outcomes.[15] There are multiple explanations for this difference, among which are the designs of the studies, i.e. an experimental design versus an observational design, the outcome measures covered, i.e. QALYs versus GP visits, hospital admissions and infections, and the healthcare systems investigated, i.e. The Netherlands versus UK.

This study has a number of important strengths. It represents, to the best of our knowledge, the first cost-effectiveness analysis investigating the long-term effects of doxycycline administered in conjunction with prednisolone versus prednisolone alone for the treatment of COPD acute exacerbations in an outpatient setting. All patients included had COPD confirmed by spirometry. It was conducted alongside a pragmatic randomised controlled trial, which implied prospective collection of cost and effect data and a long-term evaluation of the intervention in a setting generalisable to actual clinical practice. The study employed a societal perspective, meaning that detailed measurements of all costs regardless of the payers were performed, which allows for identifying shifting of costs between different budgets. Finally, the EQ-5D-3L for measuring QALYs was used, which allows cross-programme comparison for health technologies assessment decisions in the Dutch setting, and possibly other settings as well.

Despite these strengths, this study does not come without limitations. First, this study only used Dutch unit costs and the Dutch EQ-5D-3L tariff. As unit costs and tariffs are country specific, this might have limited the generalisability of our findings to different healthcare systems or populations. In addition, differences in costs might also exist, as resource utilisation might differ between countries. Second, only a minority of responders had complete observations for the EQ-5D-3L. This might have affected the quality of our effectiveness estimates. However, baseline differences between complete and non-complete cases were mostly non-significant and the percentage of missing values at each follow-up was generally small. Also, missing data were imputed using multiple imputation by chained equations, which is generally considered the most valid method to account for missing data in economic evaluations.[35,36] Third, while the EQ-5D-3L is generally considered valid for use in COPD populations,[26] evidence also exist that the measure might miss important generic and specific items of relevance for COPD populations, among which are breathing,[38] cough and dyspnoea.[39,40] Moreover, the EQ-5D-3L was measured at month 1 after randomisation, month 3 and every 3 months thereafter until month 24. Although COPD exacerbations greatly influence quality of life, COPD exacerbations may have occurred at random moments. This might have reduced the ability of this study to detect differences of relevance for the investigated population. Fourth, this study was based on a randomised controlled trial powered to detect differences in time to the next exacerbation and not QALYs. Although this might be one explanation for doxycycline's lack of effectiveness, the consistency between our results and the clinical results reported in van Velzen *et al*[16] suggests that this is unlikely.

This study provides evidence for the lack of cost-effectiveness of doxycycline in the treatment of acute COPD exacerbations in an outpatient setting, despite the possibly lower short-term failure rate. As antibiotic resistance is a major concern for public health systems and it is worsened by the inappropriate use of antibiotics, this lack of cost-effectiveness discourages their use for COPD exacerbations treated in an outpatient setting.

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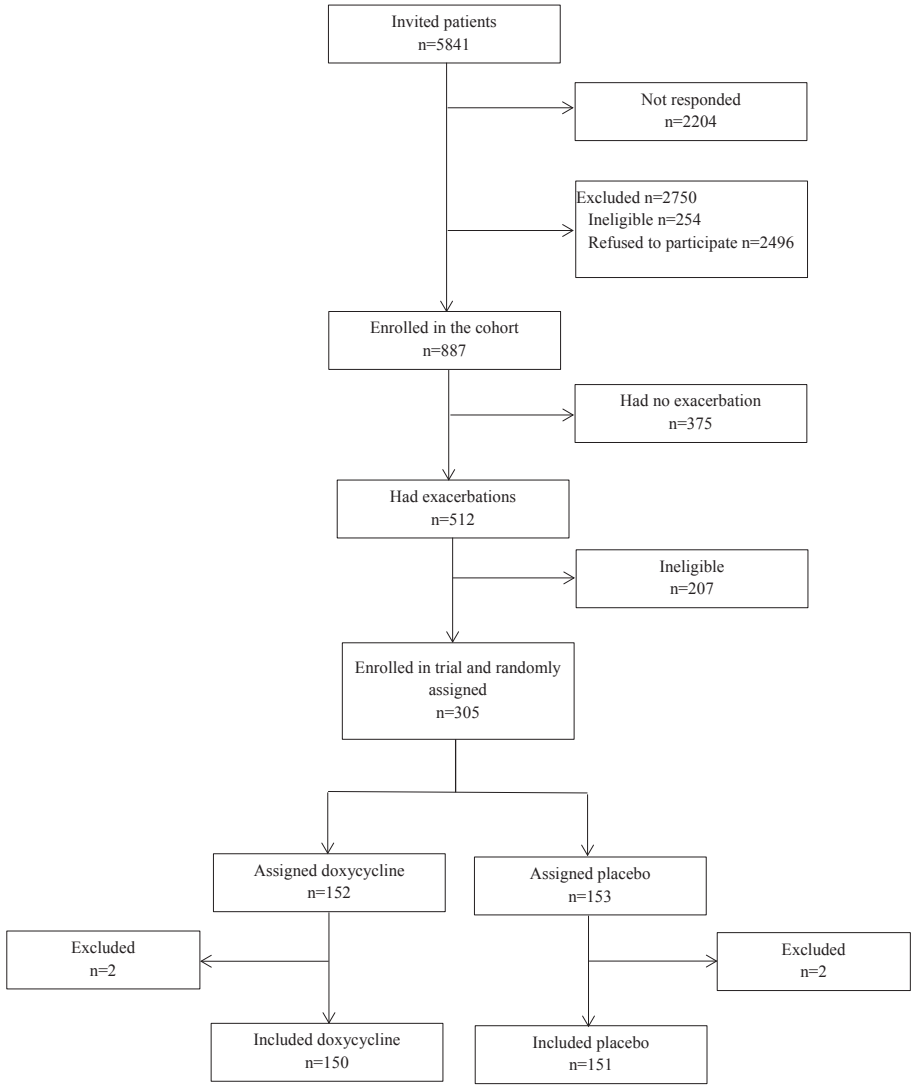

Figure 3: TEXACOLD trial recruitment flowchart

Author contributions

AF conducted the analyses and wrote the methods, results and discussion sections of the article.

PV collected data, wrote the introduction, methods and discussion sections and reviewed the first and second draft of the manuscript.

JB provided comments on the first and second draft of the manuscript.

GR, PS and JP provided comments on the first draft of the introduction and the second draft of the manuscript.

Chapter 5

Doxycycline for exacerbations of chronic obstructive pulmonary disease in outpatients; who benefits?

P. van Velzen, G. ter Riet, P. Brinkman, P.J. Sterk, J.M. Prins, on behalf of the TEXACOLD study group.

ERJ Open Research 2020; 6: 00099-2020

To the Editor,

Most patients with chronic obstructive pulmonary disease (COPD) experience exacerbations.[1] More than 80% of the exacerbations are treated ambulatory. Treatment consists of inhaled bronchodilator therapy and oral corticosteroids, whereas the contribution of antibiotics is less clear. A meta-analysis[2] recently reported less treatment failure within 4 weeks in outpatient exacerbations treated with antibiotics: 21.2% in the group treated with antibiotics vs 29.2% in the placebo group. This means that 12-13 patients have to be treated with antibiotics to prevent one treatment failure (number needed to treat = 12.5).

It remains unclear who benefits from antibiotic treatment. Restricting antibiotic treatment to those who benefit is important to prevent antibiotic overuse, the key driver of antibiotic resistance. A randomised trial by Anthonisen *et al*[3] showed that patients with increased dyspnoea, increased sputum volume and increased sputum purulence had statistically significantly less treatment failure within 21 days when they were treated with antibiotics compared to placebo. There were no statistically significant differences in treatment failure rates in patients with only one symptom. This could not be confirmed in a more recent study.[4] Current guidelines reflect this uncertainty. The European Respiratory Society and American Thoracic Society recommend antibiotics for all ambulatory patients.[5] Guidelines by the Global Initiative of Chronic Obstructive Lung Disease (GOLD) recommend treating outpatients with antibiotics if they have three major symptoms (increase in dyspnoea, sputum volume, and sputum purulence) or 2 if increased sputum purulence is one of them.[1] In contrast, the National Institute for Health and Care Excellence guideline advises weighing risks and benefits of antibiotics in each individual case.[6]

The use of biomarkers however might be helpful: C-reactive protein (CRP)-guided prescribing of antibiotics for exacerbations of COPD in primary care resulted in lower antibiotic use, with no evidence of harm,[7] and in another study primary care patients without sputum purulence, and a CRP value below 40 mg/L could be safely treated without antibiotics.[4] Also a procalcitonin-guided antibiotic strategy has been associated with fewer antibiotic prescriptions.[8] As these tools are not always available, additional research is needed to identify those outpatients that benefit from antibiotic therapy. The aim of the present

study was to identify clinical characteristics that could guide the decision to prescribe or withheld antibiotic treatment.

For this study, we used data of all 301 patients participating in a randomised placebo-controlled trial comparing doxycycline with placebo for the treatment of COPD exacerbations in an outpatient setting.[9] Trial design, participants and procedures have been described previously.[9] In short, we recruited a cohort of patients with COPD from outpatient clinics of nine teaching hospitals and three primary care centres in the Netherlands. In case of an exacerbation, patients were randomly assigned to doxycycline or placebo. An exacerbation was defined as an event characterised by a change in patients' baseline dyspnoea, cough, or sputum beyond day-to-day variability, sufficient to warrant a change in management other than optimising bronchodilator therapy.[1,5] All patients received a course of oral corticosteroids (OCS). Fever at the time of exacerbation was the most important exclusion criterion. At randomisation, clinical data, including respiratory symptoms and sputum characteristics were collected. Treatment failure was defined as the need for a new course of OCS and/or the prescription of open-label antibiotics, hospitalisation or death.[10] The presence of treatment failure was established at day 21.

We performed 33 subgroup analyses in which we compared treatment failure rates. Six were predefined in our previous publication:[9] age, sex, GOLD stage, smoking status, number of previous exacerbation in the past 3 years and treatment setting. The other were exploratory. Subgroups were based on clinical variables available at baseline or during exacerbation, including exacerbation characteristics, spirometry data, medical history, inhalation medication and health-related quality of life.

Continuous data were dichotomised; split was based on literature or mean/median. We repeated analyses with continuous data grouped in tertiles. For all subgroups, stratum-specific odds ratios (ORs) with 95% confidence interval (CI) and tests for interaction were calculated. For statistical analyses, we used the Mantel-Haenszel odds ratio (mhor) function from the epiDisplay package in R (v3.6.1) and RStudio (v1.2.1.335). We used a significance level of 0.05; therefore, given the number of comparisons at least 1 interaction test is expected to be statistically significant based on chance alone.[11]

301 patients were included in the trial, 150 in the doxycycline group and 151 in the placebo group. Clinical and exacerbation characteristics were generally well balanced.[9] Treatment failure rates at day 21 were 24 out of 150 (16%) in the doxycycline group and 40 out of 151 (26.5%) in the placebo group (p=0.03). Reasons for treatment failure were a new course of OCS in 12 patients in the doxycycline group and in 7 patients in the placebo group (p=0.28), open label antibiotics in 5 vs 15 patients (p=0.04), and both OCS and open label antibiotics in 7 vs 10 patients (p=0.62). No patients were admitted to the hospital in the doxycycline group vs 8 in the placebo group (p=0.007). There were no deaths in either group.

Former smokers were more likely to fail without antibiotics than current smokers: OR 3.33, 95% CI 1.45-8.09, p value for interaction 0.02. We found no other subgroup effects (figure 1).

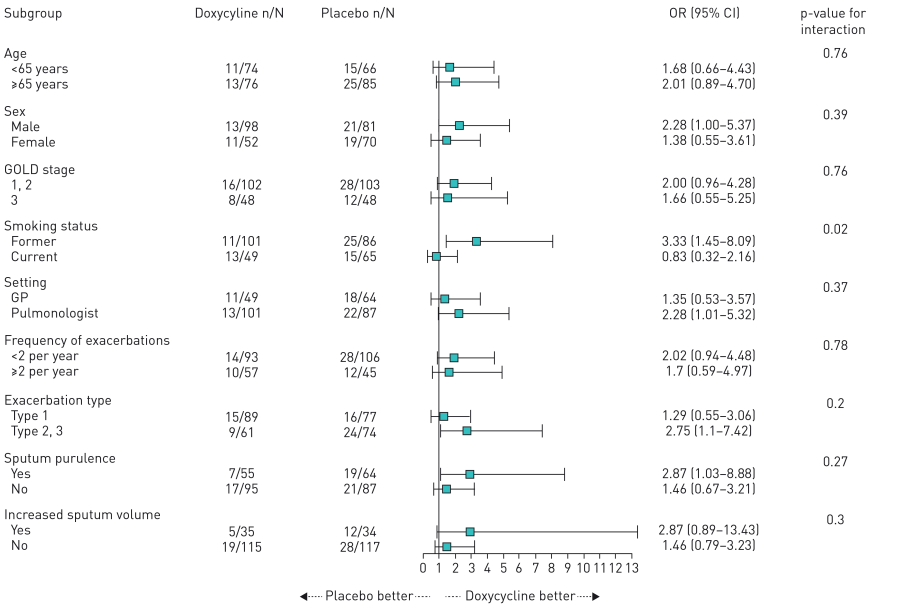

Figure 1: Subgroup analyses for patients who had treatment failure at day 21. Type 1: three Anthonisen criteria [3] present (increased dyspnoea, increased sputum and sputum purulence). Type 2: two Anthonisen criteria present. Type 3: one Anthonisen criterion present. For exacerbation type, sputum purulence and sputum volume, odds ratios differ by an amount that seems clinically relevant. The 95% confidence intervals show that a type II error may be responsible for the large p-value for interaction. GOLD: Global Initiative for Chronic Obstructive Lung Disease; GP: general practitioner.

Former smokers had a greater risk of treatment failure at day 21 without antibiotics than current smokers. This is an unexpected and previously unpublished finding, which we should therefore interpret with caution. There were no additional benefits of antibiotic treatment in any of the other predefined and exploratory subgroups. Notably, presence of sputum purulence was not associated with less treatment failure if treated with antibiotics. Sputum purulence is associated with bacterial presence[12,13] and is often used as a justification to prescribe antibiotics. Two randomised trials reported that sputum purulence is associated with treatment failure if not treated with antibiotics[3,14], but this finding was not confirmed in our trial: failure rates did not differ in type 1 vs. type 2/3 exacerbations and exacerbations with or without sputum purulence treated with or without antibiotics. This might be explained by differences in study design and study population. First, concomitant treatment with OCS was regulated per protocol and was prescribed in 95% of the patients, in contrast with the two previously mentioned trials,[3,14] OCS are recommended in all current guidelines as OCS improve lung function and might reduce treatment failure.[15] Second, fever was an exclusion criterion. Third, patients with very severe COPD were excluded.

A strength of this study is the use of data from one of the largest randomised trials in this field. Limitations of an exploratory study are that this does not allow for power calculations. Therefore, negative results may represent type II error. An analysis in which we partitioned our data in tertiles to enhance contrast between the lowest and the highest tertiles did also not demonstrate subgroup effects. Another limitation is that patients with very severe COPD were excluded. As most patients have mild to severe COPD, we think that our results can be extrapolated to most outpatients. Finally, in all cases, the antibiotic was doxycycline. We cannot therefore be sure that our findings can be extrapolated to other antibiotics.

In conclusion, doxycycline has some effect on treatment failure rates at day 21. However, we did not find clinical characteristics, in particular not sputum characteristics, in patients with mild to severe COPD with an exacerbation without fever that identify those who benefit from antibiotic treatment.

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Author contributions:

PV and GR analysed data.

PV, GR, PS, and JP interpreted data.

PV wrote the manuscript.

GR, PS and JP reviewed the manuscript.

Chapter 6

Exhaled breath profiles before, during and after exacerbation of COPD: a prospective follow-up study

P. van Velzen, P. Brinkman, H.H. Knobel, J.W.K. van den Berg, R.E. Jonkers, R.J. Loijmans, J.M. Prins, P.J. Sterk

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Abstract

Many patients with chronic obstructive lung disease (COPD) experience exacerbations. The diagnosis of an exacerbation is solely based on symptoms. We hypothesized that exhaled breath profiles, measured by Gas Chromatography-Mass Spectrometry (GC-MS) or electronic nose (eNose), are different between stable disease and exacerbations and may therefore have the potential to serve as biomarkers for COPD exacerbations. In this prospective follow-up study, patients with mild-to-severe COPD were recruited from two teaching hospitals in the Netherlands. Breath samples were taken during clinically stable COPD, during a subsequent exacerbation and after recovery. Samples were analyzed by GC-MS and eNose. CCQ symptom scores were associated with univariate outcomes of GC-MS and eNose using analysis of covariance (ANCOVA). After multivariate modelling by Principal Component Analysis (PCA), paired student t-tests were performed to compare means between repeated measures. 68 patients were included, 31 had an exacerbation and 16 patients had breath sampled at all three time points. Significant differences were found in breathprints taken during exacerbation as compared to baseline and recovery for both GC-MS and eNose. Breath profiles obtained by GC-MS as well as by eNose showed a correct classification of 71% (10/14) for baseline *vs* exacerbation and of 78% (11/14) for exacerbation *vs* recovery. When monitoring patients with COPD, breathprints obtained by two distinct technologies (GC-MS and eNose) differ between exacerbations and clinically stable episodes. These results provide proof of principle that exhaled breath can serve as a non-invasive biomarker for the diagnosis of COPD exacerbations.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent lung disease, characterized by non-fully reversible airflow limitation.[1] Most patients with COPD experience exacerbations defined as an acute increase in respiratory symptoms.[1,2] Exacerbations are mostly driven by viral or bacterial airway infection,[1,2] have a negative impact on patients' quality of life,[3] accelerate lung function decline,[4] increase mortality[5] and are representing a huge economic burden to society.[6] Despite having those major negative consequences, at least half of the exacerbations is not reported.[7-9] Objective assessment of an exacerbation might allow for early intervention, thereby improving patient related outcomes and reducing costs.[10]

At this moment, there is no diagnostic test or biomarker to confirm the presence of an exacerbation of COPD. The diagnosis of an exacerbation is based on the patient's history and clinical findings, such as increased dyspnoea, cough, sputum volume and sputum purulence.[1] However, these symptoms are non-specific and may lead to the wrong treatment, over-treatment or non-treatment. A biomarker that identifies exacerbations of COPD would be useful for diagnosis and monitoring of individual patients, whilst representing an objective endpoint in clinical trials. The need for a biomarker for COPD exacerbations is endorsed by the Global Initiative of Chronic Obstructive Lung Disease (GOLD) and the American Thoracic Society (ATS) and European Respiratory Society (ERS).[11-13]

Volatile organic compounds (VOCs) in exhaled air may be used as non-invasive biomarkers in the diagnosis and phenotyping of lung diseases.[14] Measuring these metabolites in breath can in general be carried out by analytical chemistry methods such as gas chromatography-mass spectrometry (GC-MS) or by cross-reactive gas-sensor technology also called electronic nose or eNose. GC-MS allows identification of exhaled molecular compounds,[15] which contributes by unraveling pathophysiology mechanisms. A recent cross-sectional pilot study showed that VOCs captured by GC-MS can accurately discriminate stable COPD patients from those with exacerbations.[16] However, GC-MS analyses requires specialized laboratories and are therefore not suitable as a rapid point of care test.

Alternatively, eNose technology allows pattern recognition of entire mixtures of VOCs.[15] This provides a real-time breathprint and can potentially be used as a point of care test. Two recent studies have shown that eNose technology is able to discriminate COPD patients with and without airway infection with moderate good accuracy.[17,18] This suggests that eNose technology may also be able to identify the presence of an exacerbation as such.

GC-MS and eNose techniques are both needed to make biomarker identification based on exhaled VOCs suitable for clinical practice, as eNose sensor arrays can then specifically be tailored for exacerbations by using metabolite-specific sensor arrays derived from GC-MS data. This requires longitudinal studies using both technologies similar to those performed in asthma, in which GC-MS and eNose signals appeared to be discriminative when measured before, during and after recovery of an exacerbation.[19]

We performed a prospective, observational follow-up study alongside a published randomized controlled trial on the treatment of COPD exacerbations in an outpatient setting.[20] We hypothesized that exhaled breath metabolomics by GC-MS and eNose differ between stable disease and exacerbations, and we therefore compared exhaled breath profiles before, during and after recovery from an exacerbation in patients with COPD.

Methods

Trial design

This prospective, observational study was performed in an unselected subgroup of patients participating in the randomized controlled trial on the treatment of COPD exacerbations[20] from December 2011 until December 2014. In the present study, exhaled breath samples were obtained before, during and after an exacerbation of COPD. An exacerbation was defined as an event characterized by a change in patients' baseline dyspnea, cough, or sputum beyond day-to-day variability, sufficient to warrant a change in management other than optimising bronchodilator therapy.[2,13] Respiratory symptoms originating from an evidently non-pulmonary cause were not considered an exacerbation.

Participants

Participants were recruited from the Isala Clinics, Zwolle and the Amsterdam UMC, Amsterdam, two teaching hospitals in the Netherlands. Inclusion criteria were an age of 45 years or older, a clinical diagnosis of mild-to-severe COPD, defined as a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio ≤ 0·7 and a post-bronchodilator FEV1 ≥ 30%, according to GOLD and ATS/ERS criteria,[2,13] a smoking history of at least 10 pack-years and one or more exacerbations during the previous three years, with the limitation that the last exacerbation ended more than 4 weeks before recruitment and symptoms had returned to baseline level.[20] Patients were not eligible if they did not speak Dutch, had poor cognitive abilities, or had a life expectancy shorter than one month. The study was carried out in accordance with the Declaration of Helsinki. All patients gave written informed consent. The trial protocol was approved by the ethics committee of the Amsterdam UMC at the University of Amsterdam.

Procedures

All participants fulfilling inclusion criteria entered a prospective cohort. At baseline, breath samples were collected and characteristics, including demographics, lung function data, smoking history and medication were recorded in a standardized electronic case record form (eCRF, Oracle Clinical). Patients were instructed to contact their treating physician (general practitioner or pulmonologist) if they experienced an increase in respiratory symptoms. When the diagnosis of an exacerbation was confirmed, as part of the main project, the patient was randomly assigned to a 7-day course of oral doxycycline or placebo.[20] Patients in both arms received a 10-day course of oral corticosteroids (OCS). Next, within 48 hours after the diagnosis of an exacerbation, breath samples were taken for the exacerbation visit and data concerning respiratory symptoms, fever, use of antibiotics, steroids and inhalation medication were recorded. After 12 weeks, when symptoms had returned to baseline level, this procedure was repeated for breath sampling at the recovery visit.

Clinical control was measured by the symptom score of the Clinical COPD Questionnaire (CCQ).[21] The CCQ is a self-administered questionnaire that consists of 10 questions in 3 domains (symptoms, functional state and

mental state). Scores for each of the questions and the total score range from 0 (very good control) to 6 (extremely poor control), with a minimal clinically important difference of 0.4.[22] The symptom score is calculated by adding up the scores of questions 1, 2, 5 and 6 and dividing the total score by 4. The CCQ was administered at baseline, during exacerbation and 12 weeks after the exacerbation.

Exhaled breath sampling

All participants were instructed to refrain from smoking, eating and drinking at least 2 hours prior to breath sampling to minimize the influence of exogenous compounds. Exhaled breath was collected as previously described.[19] First, patients breathed for 5 minutes at tidal volume through a two-way non-rebreathing valve and an inspiratory carbon VOC-filter (A2, North Safety, Middelburg, NL) to clean the inspired air. Second, the subject exhaled a single vital capacity volume into a 10 liter Tedlar bag (SKC Inc, Eighty Four, PA, USA). Within 30 minutes after breath collection, two thermal desorption tubes (Tenax GR SS 6mm x 7", Gerstel, DaVinci BV, Rotterdam, NL) were connected to the Tedlar bag for collection, transportation and storage of the expired VOCs. Each tube was sampled with 500 mL exhaled air at a flow of 250 mL/min using a peristaltic pump. VOCs present in exhaled breath were thereby captured onto the Tenax GR sorbent mesh in the tubes. Tubes were send to Philips Research (Eindhoven, the Netherlands) for GC-MS analysis and to the Amsterdam UMC, location AMC, University of Amsterdam (Amsterdam, the Netherlands) for analysis by the electronic eNose platform.[23] This eNose platform has been validated[24] and was used in 2 recently published clinical studies.[19,25]

Breath sample measurement by GC-MS

For desorption, the Tenax tubes containing the VOCs were heated using a Gerstel TDS3 desorption oven (Gerstel, Mülheim an der Ruhr, Germany) with helium as carrier gas. Next, the sample was transmitted to a packed liner, heated to 225°C for 3 minutes and transferred to a Tenax TA cold trap at 150°C, which was heated after 2 minutes to 280°C at 20°C/s and splitless injected onto the chromatographic column. Subsequently, VOCs were separated by capillary gas-chromatography with helium as a carrier gas at 1.2 mL/min (7890 N GC, Agilent, Santa Clara, CA, USA) on a VF1-MS column (30 m, diameter 0.25 mm, film thickness 1 µm, 100% dimethylpolysiloxane, Varian Chrompack, Middelburg,

the Netherlands). The column oven temperature was programmed as follows: isothermal at 40°C for 5 minutes, increased until 300°C with 25°C/min and held isothermal for 2 minutes. Finally, a Time of Flight mass spectrometer (Pegasus 4D system, LECO, St. Joseph, Mi, USA), in electron impact ionization mode at 70 eV, was used for charging the compounds and detection of resulting individual ions (ranging from 29 to 400 Dalton).

Breath sample measurement by eNose platform

VOCs were released from the tubes through thermal desorption in a Gerstel TDS3 desorption oven, using nitrogen as carrier gas and subsequently captured in a Tedlar bag. Obtained samples were used for further analysis by the eNose platform,[23] which consists of four instruments, all using unique sensor technologies: Common Invent eNose (metal oxide semiconductor sensors; 8 sensors),[26] Owlstone Lonestar (FAIMS, Field Assymetric Ion Mobility Spectrometry; 110 datapoints),[27] Cyranose C320 (carbon black-polymer sensors; 32 sensors)[28] and Tor Vergata eNose (quartz crystal microbalances covered with metalloporphyrins; 8 sensors).[29]

Data processing and statistical analysis

R version 3.1.2 through the R studio interface was used for data processing and statistical analyses. Both were extensively described in a recent publication.[19] In summary, GC-MS data processing, consisting of denoising, peak detection and alignment, was performed using the XCMS package[30] (Scripps Center for Metabolomics, La Jolla, CA). The derived ion fragment peak table served as source for further analysis. Next, fragments were transformed into compounds by running a principal component analysis (PCA) on all fragments within a retention time frame of 5 seconds. Finally, the data of the individual eNose sensors and the GC-MS compounds were normalized by adjusting their average values and standard deviations to, respectively, 0 and 1.

As exacerbations of COPD are solely defined by symptoms, the CCQ symptom scores at baseline, exacerbation and recovery visits were associated with univariate outcomes of eNose (sensor level) and GC-MS (compound level) using analysis of covariance (ANCOVA). eNose sensors or GC-MS compounds with a Pearson $r \geq 0.4$ and $p < 0.05$ were retained. During the next step, PCA was performed using baseline and exacerbation visit data to merge the remaining

variables into two multivariate datasets. Subsequently, Principal Components (PCs) for exacerbation + recovery visit and baseline + recovery visit data sets were calculated based on the loading factors of the baseline + exacerbation PCA. Next, paired student t-tests on the obtained PCs were performed to compare the means between the repeated measures: baseline *vs* exacerbation, exacerbation *vs* recovery and baseline *vs* recovery. P-values <0.05 were considered significant (Figure 1). To validate the results, leave-one-out cross validation was performed using the jackknife leave-one-out strategy from the r package bootstrap. Logistic regression analysis were done to derive details on sensitivity and specificity. Spectra of GC-MS compounds retaining after univariate analysis were identified based on NIST-library (v.2.0a) matching.

Results

In the 2 participating hospitals, 84 patients were invited to participate. 68 patients gave informed consent and entered the prospective cohort. Of these patients, 31 reported exacerbations and 18 exacerbations fulfilled the pre-defined criteria (Figure 2). From 18 patients breath samples were successfully captured during exacerbation and from 16 patients after recovery. 14 participants had complete data for GC-MS analysis, and 14 had complete date for eNose analysis; of these, 12 had complete data for both analyses. 4 patients could not be sampled for both methods because of logistic reasons. After 12 weeks, in all but one patient, symptoms had returned to baseline level and 15 follow-up breath samples were taken. One patient had multiple exacerbations and was completely recovered in week 25 at which moment breath samples were collected. Baseline characteristics are shown in table 1.

All but one patient reported the use of the same inhalation medication in the same dosage at baseline, exacerbation and recovery; one patient used formoterol/budesonide within 2 hours before sampling. One patient started OCS the day before sampling, both during an exacerbation. All other patients started treatment with OCS and/or study medication after breath sampling. No patient used antibiotics at time of sampling. Six (37.5%) of the exacerbations were type 1 exacerbations (all 3 Anthonisen criteria present: increased dyspnea, increased sputum and sputum purulence). All exacerbations were

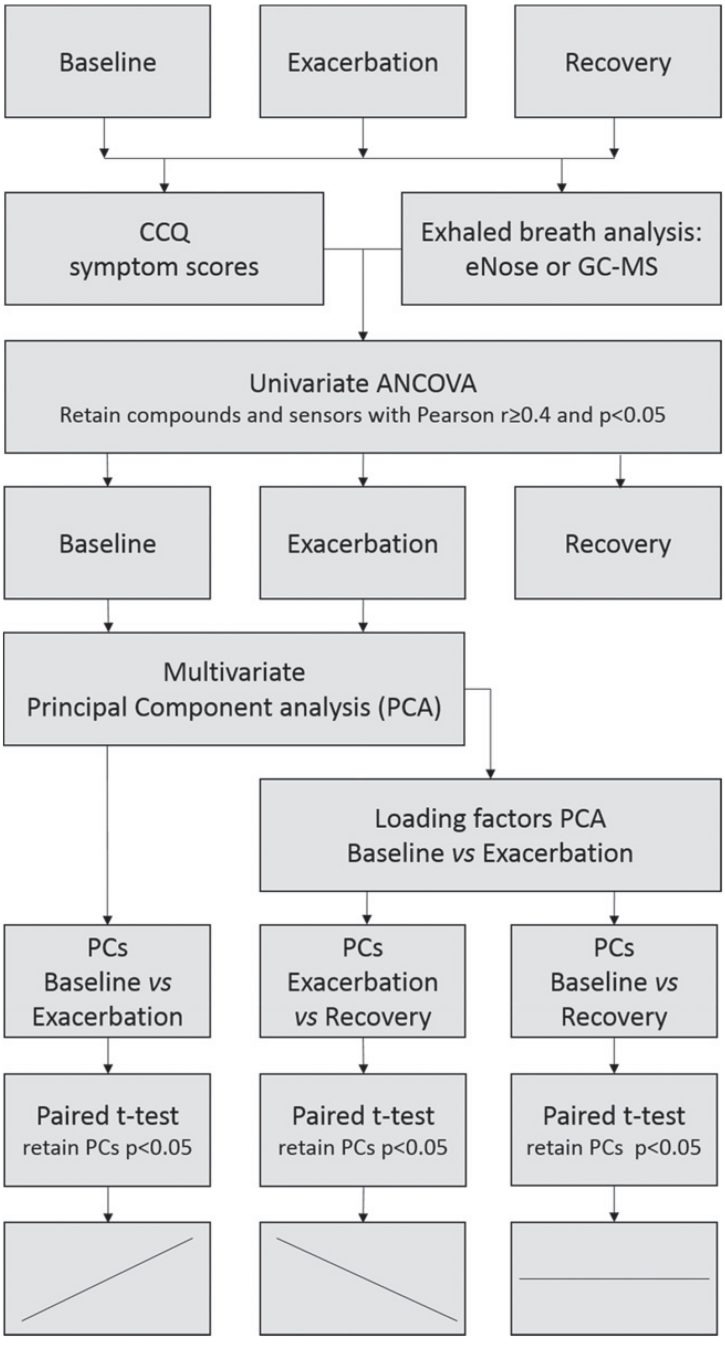

Figure 1: Statistical analysis.

treated ambulatory. CCQ symptom scores were significantly different between baseline and exacerbation (2.57 *vs* 3.65, p 0.001) and between exacerbation and recovery (3.65 *vs* 2.57, p<0.001), but not between baseline and recovery (2.57 *vs* 2.57, p=1).

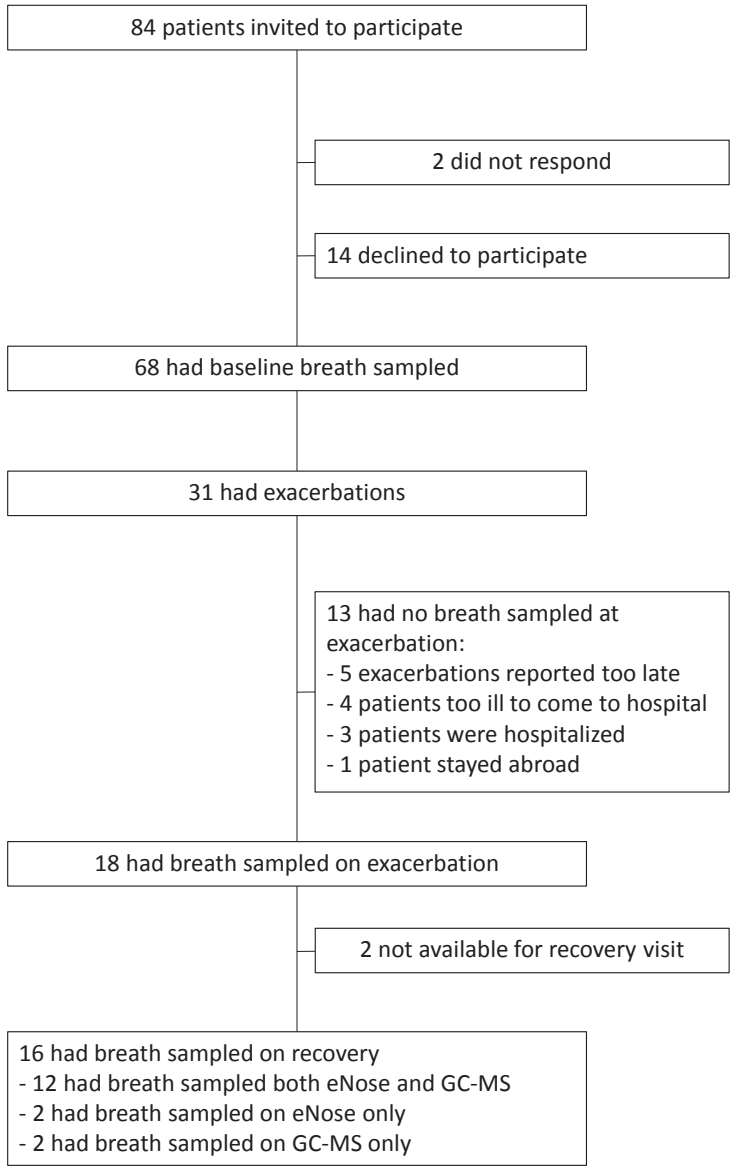

Figure 2: Study profile

Table 1: baseline characteristics

	N=16
Age (years)	65.9 (8.6)
Male sex	14 (87.5%)
Smoking history (pack-years)	43.0 (27.0-53.2)
Current smoker	6 (37.5%)
Medication for COPD	
LAMA	11 (68.8%)
LABA	2 (12.5%)
Combination LABA/ICS	14 (87.5%)
GOLD stage	
1	2 (12.5%)
2	8 (50.0%)
3	6 (37.5%)
Baseline lung function	
FEV1 (L)	1.73 (0.57)
FEV1 (% predicted)	56.6 (17.0)
FVC (L)	3.82 (1.02)
FVC (% predicted)	98.5 (22.09)
FEV1/FVC	0.45 (0.13)
CCQ symptom score at baseline	2.57 (0.5)
Exacerbation characteristics	
Type of exacerbation	
Type 1‖	6 (37.5%)
Type 2**	8 (50%)
Type 3††	2 (12.5%)
Increased sputum purulence	6 (37.5%)
CCQ symptom score at exacerbation	3.65 (0.36)

Data are n (%), mean (SD), or median (IQR). LAMA=long-acting muscarinic antagonist; LABA=long-acting ß agonist; ICS=inhaled corticosteroid; GOLD=Global Initiative for Chronic Obstructive Lung Disease; FEV1=forced expiratory volume in 1 s; FVC=forced vital capacity.

[a]Self reported.

[b]CCQ=Clinical COPD Questionnaire. Scores range from 0 to 6; higher scores indicate more symptoms.[21]

[c]Three Anthonisen criteria[35] present: increased dyspnea, increased sputum, and sputum purulence.

[d]Two Anthonisen criteria present.

[e]One Anthonisen criterion present.

GC-MS

Forty-two breath samples were analyzed by GC-MS and 5214 ion fragments were identified. These ion fragments corresponded with 276 volatile organic compounds. After optimization of data distribution and normalization, univariate ANCOVA between CCQ symptom scores and VOCs identified ten compounds of interest. These included: acetone, 1,2-pentadiene, toluene, butyrolactone, ethylbenzene, (Z)-2-decenal, limonene, 4,7-dimethyl-undecane, eicosane and 1-undecanol. PCA modelling resulted in four PCs with an

eigenvalue >1. For PC 2, 3 and 4, there were no significant differences between the visits.

PC 1 of the identified VOCs was significantly different between baseline *vs* exacerbation (p=0.03), exacerbation *vs* recovery (p=0.03) but not between baseline *vs* recovery (p=0.23). Accuracies based on differences resulted in a 71% (10/14) correct classification for baseline vs exacerbation and 78% (11/14) for exacerbation *vs* recovery, respectively (Figure 3). Leave-one-out cross validation had the following results: baseline *vs* exacerbation: p=0.04, 95% confidence interval (CI)±0.01, exacerbation *vs* follow-up: p=0.03, 95% CI±0.01 and baseline *vs* follow-up: p=0.26, 95% CI±0.05.

Logistic regression for baseline *vs* exacerbation resulted in an accuracy of 0.71, with a sensitivity and specificity of 0.71. For exacerbation *vs* follow up, accuracy was 0.75, with a sensitivity of 0.92 and a specificity of 0.57. For baseline *vs* follow-up, accuracy was 0.57, with a sensitivity of 0.64 and a specificity of 0.5.

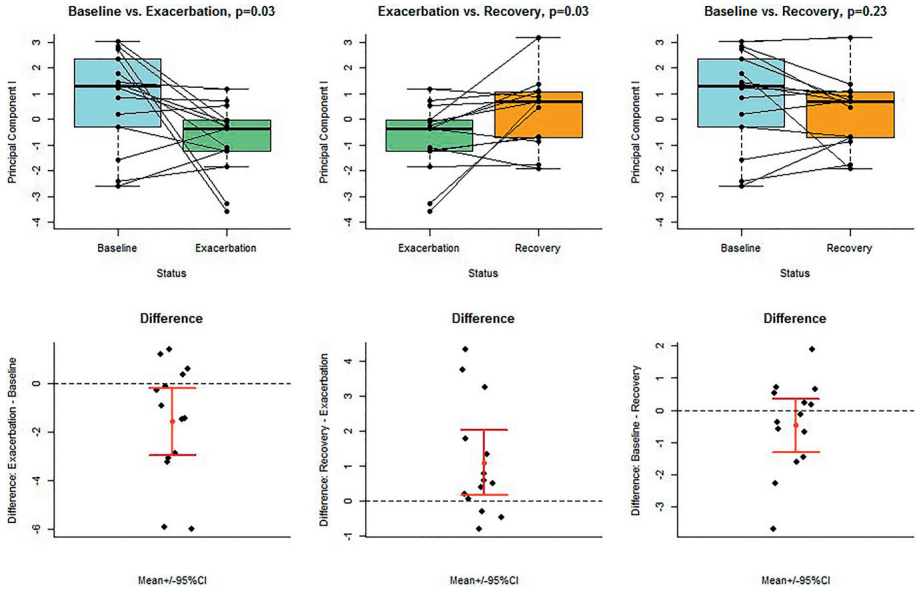

Figure 3: Exhaled breath profiles (principal components) obtained by GC-MS with mutual comparisons between baseline, exacerbation and recovery. Upper panel: boxplots of paired t-tests. Lower panel: difference plots, including means and 95% confidence intervals for the means.

eNose platform

After pre-processing, fourteen eNose sensors retained ANCOVA. This resulted in five PCs with an eigenvalue >1. For PC 2, 3, 4 and 5, there were no significant differences between the visits. For PC 1, there were significant differences: baseline *vs* exacerbation (p=0.03) and exacerbation *vs* recovery (p<0.001), but not baseline *vs* recovery (p=0.22). Accuracies for eNose analysis resulted in 71% (10/14) and 78% (11/14) correct classification for baseline *vs* exacerbation and exacerbation *vs* recovery (Figure 4). The instrument that most prominently drove the discriminative eNose signal with regard to exacerbation was the ion mobility spectrometer (with eleven out of fourteen retaining eNose variables).

Leave-one-out cross validation had the following results: baseline *vs* exacerbation: p=0.04, 95% confidence interval (CI)±0.01, exacerbation *vs* follow-up: p=0.01, 95% CI±0.00 and baseline *vs* follow-up: p=0.25, 95% CI±0.05. Logistic regression for baseline *vs* exacerbation and for exacerbation *vs* follow-up, resulted in an accuracy of 0.75, with a sensitivity 0.79 of and a specificity of 0.71. For baseline *vs* follow-up, accuracy was 0.61, with a sensitivity of 0.57 and a specificity of 0.64.

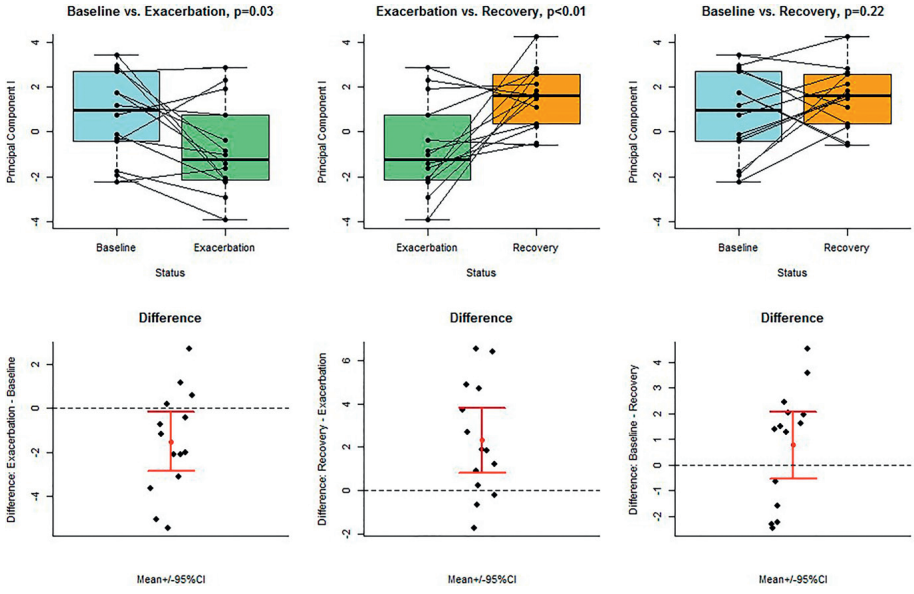

Figure 4: Exhaled breath profiles (principal components) obtained by eNose with mutual comparisons between baseline, exacerbation and recovery. Upper panel: boxplots of paired t-tests. Lower panel: difference plots, including means and 95% confidence intervals for the means.

Discussion

When monitoring COPD patients with ambulatory treated exacerbations of COPD, exhaled breath metabolomic profiles as measured by GC-MS and eNose were different during an exacerbation as compared to baseline and recovery. Therefore, exhaled breath has the potential to serve as a non-invasive biomarker for COPD-exacerbations.

To our knowledge, this is the first prospective follow-up study comparing VOCs, captured by both GC-MS and e-Nose before, during and after naturally occurring exacerbations in patients with COPD. These data confirm and extend similar longitudinal data in asthma, in which the exacerbation visit also could be distinguished from baseline and recovery.[19] For COPD mostly cross-sectional studies were reported, comparing exhaled breath VOCs during exacerbations and stable episodes. Using GC-MS, Pizzini *et al*[16] compared breathprints from patients with stable COPD with those having an exacerbation. Exacerbated and stable COPD could be discriminated by 4 VOCs (n-butane, 2-pentanone, cyclohexanone and 4-heptanone). The recent data by Gaugg *et al*[31] showed that metabolites identified by a real time breath analyzer (secondary electrospray ionization- high resolution mass spectrometry) differ during clinically stable episodes between COPD patients with frequent and non-frequent exacerbations. This suggests that not only the exacerbations themselves, but also the phenotype of frequent exacerbations is associated with distinguishable exhaled metabolomic profiles.

Thus far the only longitudinal VOC analysis during and after COPD exacerbations was published by Shafiek *et al*.[17] Comparing eNose-derived breathprints of patients (n=93) hospitalized for an exacerbation of COPD with breathprints of the same patients after recovery (n=61) showed a trend towards distinguishing the exacerbation of COPD from its recovery, with an accuracy of 70%, sensitivity of 72% and specificity of 67% (p=0.068).[17] In our study the latter comparison reached statistical significance with similar accuracies, even though we included milder exacerbations treated in an outpatient setting. This suggests that the observed accuracies are consistent over a broad range of exacerbation severities in COPD.

Our study has a few strengths. First, by combining GC-MS and eNose technologies, we are taking a necessary next step towards developing a non-invasive biomarker suitable for clinical practice. GC-MS and eNose both have their strengths and limitations. On the one hand, currently available GC-MS technology as the analytical chemistry standard is not suitable for clinical practice, as GC-MS does not allow real-time analysis, requires specialized laboratories and is expensive. Yet, GC-MS can identify individual compounds that are needed for the development of VOC-specific sensors in eNose-technology. On the other hand, eNose technology cannot identify individual VOCs, merely producing (powerful) pattern recognition of VOC-mixtures. Notably, in the present study GC-MS and eNose provided highly similar accuracies, which represents an internal validation. Second, the longitudinal study design allowed for follow-up of a well-defined cohort of patients with spirometry-confirmed COPD. Furthermore, as more than 80% of COPD exacerbations is treated ambulatory,[1] our cohort is representative for COPD patients in daily clinical practice. Finally, the GC-MS and eNose measurements were unlikely to be influenced by medication, as patients continued to use the same medication during this trial and all but one exacerbation samples were taken before the start of OCS and/or antibiotics.

Nevertheless, the study has limitations. First, the sample size was relatively small. This was due to the complexity of recruiting patients and capturing their breath samples during the acute clinical event of a COPD exacerbation. By including 68 patients with stable COPD and an estimated exacerbation rate of 0.5/patient/year we aimed to include 30 patients with an exacerbation. Indeed, 31 exacerbations occurred in this group, but 13 exacerbations were either missed or not suitable for adequate breath sampling (Figure 2). Still we observed significant differences in GC-MS and eNose signals over the course of the exacerbations that were statistically validated using the jackknife leave-one out strategy. Hence, limited statistical power does not seem to be a major restriction of the present study. Nevertheless, the present data should be considered as proof of principle. Second, the present study did not include an independent replication cohort. Hence, our findings need to be clinically validated in another cohort of COPD patients before VOCs can be used as a clinical tool for diagnosing COPD exacerbations. Finally, even though we identified 10 VOCs by GC-MS that were associated with CCQ scores during

the course of follow-up, we could not identify individual components that were significantly different before, during and after an exacerbation. Such significant differences were shown for PC 1, that combined information by GC-MS of multiple VOCs rather than relying on a single component. We believe that this finding is not unexpected given the biological complexity and clinical heterogeneity of COPD exacerbations.

Four of the compounds that were identified in the current study were previously reported in exhaled air in the literature,[32-34] even though we are the first to show an association with COPD exacerbations. Acetone is common in exhaled air but is also associated with pathogenic bacteria;[32] 1,2-pentadiene is also common in exhaled air,[34] whilst toluene is a potential marker for bacterial presence, being associated with *Pseudomonas* species and *Haemophilus influenzae*.[32,33] Limonene is also a potential marker for bacterial presence,[32] but can also be related to food ingestion. These findings suggest that bacterial infection is involved in providing at least part of the VOC signal during exacerbations of COPD. However, the presently observed VOCs do not correspond with those published in the cross-sectional studies by Pizzini *et al*[16] and Gaugg *et al*.[31] This is not surprising as there are important differences between the studies, including study design, data analysis and study populations (such as severity of COPD and severity of exacerbations). These differences between studies underline the call for standardization of methodologies in breath studies, which is currently ongoing.[14]

Conclusions

Our proof of principle data show that exhaled breath analysis by eNose as well as by GC-MS can distinguish an exacerbation from stable disease during follow-up of patients with COPD. Notably, breathprints at baseline and after clinical recovery did not differ, suggesting that there is complete recovery of metabolic activity as captured in exhaled air. Therefore, exhaled breath tests may qualify as a non-invasive biomarker of the acute episode of COPD exacerbations. If the present data can be replicated in a large COPD cohort, VOC analysis can be made applicable for the monitoring of patients with COPD. This has the potential of early intervention, leading to less symptoms, fewer hospitalizations and reduced costs.[10]

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Author contributions

PV, PB, RL, JP, and PS designed the study.

PV, RJ, and JvdB collected data.

PV, PB, and HK analyzed data.

PV, PB, JP, and PS interpreted data.

PV, PB, JP, and PS wrote the manuscript.

HK, RJ, JvdB, and RL reviewed the manuscript.

All authors approved the final manuscript.

Chapter 7

General discussion

General discussion

This thesis focused on the use of antibiotics during exacerbations of chronic obstructive pulmonary disease (COPD). Do antibiotics prevent exacerbations on the long term, and do antibiotics decrease short-term treatment failure rates? These questions will be addressed and discussed, based on the findings of this thesis and current literature. In addition, we will discuss biomarkers, in COPD and COPD exacerbations.

Do antibiotics prevent exacerbations on the long term?

The most recent guideline by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) advise to prescribe antibiotics in all exacerbations of COPD.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) advises to prescribe antibiotics in case of three key symptoms (increase in dyspnoea, sputum volume and sputum purulence), or two if sputum purulence is one of them.[2] ERS/ATS concluded that first, antibiotics reduce the risk of short-term treatment failure and second, antibiotics prolong time to the next exacerbation. The latter conclusion was based on one trial that had time to the next exacerbation as a secondary but pre-defined outcome.[3] The trial by Llor *et al*[3] reported a statistically significant difference in median time to next exacerbation: 233 days (interquartile range (IQR) 110-365) in the group treated with amoxicillin-clavulanic acid and 160 days (IQR 66-365) in the group treated with placebo; p=0.05. In our study[4] (chapter 2) we found no difference in time to the next exacerbation: median time to next exacerbation was 148 days (95% confidence interval (CI) 95–200) in the doxycycline group compared to 161 days (95% CI 118–211) in the placebo group; p=0.91.

How to explain this discrepancy? The two trials had important differences in population, design and statistical analyses.[3,4] For example, we also included patients with severe COPD, used doxycycline and all patients received concomitant therapy with oral corticosteroids (OCS). In contrast, the trial by Llor excluded patients with severe COPD, used amoxicillin-clavulanic acid and OCS were prescribed in only a minority of patients (17.1%). Finally, we calculated time to the next exacerbation in all randomized patients, with an interval of at least 3 weeks between subsequent exacerbations. In the trial by Llor, time to the next exacerbation was assessed only in patients with cure or improvement at day 10; no interval between exacerbations was defined.

Aforementioned trials[3,4] examined the long-term effect (time to the next exacerbation) of a single short course of antibiotics. In contrast, prevention of exacerbations has also been studied in trials comparing long-term antibiotic therapy with placebo. A systematic review[5] showed that the continuous or intermittent use of prophylactic antibiotics reduced the risk of an exacerbation compared to placebo. For continuous use, azithromycin, doxycycline and erythromycin have been studied. The odds ratio (OR) for the risk of one or more exacerbations was 0.53 (95% CI 0.36-0.79). For intermittent use with azithromycin (three studies) the OR was 0.39 (95% 0.19-0.77). There was no reduction shown for pulsed antibiotic therapy with moxifloxacin (two studies): the OR was 0.85 (95% 0.68-1.07). No such trial with azithromycin or another macrolide has been done.

The most influential and largest of these trials that compared continuous antibiotics therapy with placebo was the trial by Albert et al.[6] In this trial patients with COPD received azithromycin 250 mg daily or placebo during a year. Median time to the next exacerbation was 266 days (95% CI 227-313) in the azithromycin group *vs* 174 days (95% CI 143-215) in the placebo group (P<0.001). 73.5% of the included patients had severe or very severe COPD. Rates of COPD exacerbations were lower in the azithromycin-treated patients: 1.48 versus 1.83 (hazard ratio 0.73; 95% CI 0.63- 0.84; p=0.01).

Azithromycin has direct antibacterial, anti-inflammatory and immunomodulatory effects.[7] For example, azithromycin decreases the production of pro-inflammatory cytokines and reduces neutrophilic inflammation by reducing chemotactic responses to cytokines. This might explain why azithromycin does prolong time to the next exacerbation. At this moment, no studies have examined the long-term effect of a short course of azithromycin.

Prophylactic uses of azithromycin has some important adverse effects: ototoxicity, cardiac toxicity, interactions with other drugs and antibiotic resistance.[8] Azithromycin is not recommended in patients with cardiovascular disease, including patients with heart failure and cerebrovascular disorders.[8] Patients that are prescribed prophylactic azithromycin should be monitored for QTc prolongation and hearing loss. Effects of long-term azithromycin on development of antibiotic resistance are of major concern.

Conclusion

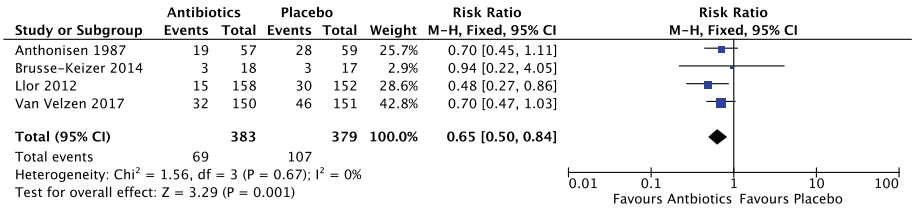
At this moment, there is insufficient evidence to prescribe a short course of antibiotics in order to prolong time to the next exacerbation. In patients with three or more moderate or severe exacerbations, prophylactic treatment with azithromycin daily or three times a week might be useful to prevent exacerbations. The ERS/ATS guideline indeed advises prophylactic treatment with macrolides but not fluoroquinolones in patients with moderate to very severe COPD that continue to have exacerbations despite optimal inhalation therapy. Cardiovascular risk factors should be assessed before prescription.[1] The guideline by the National Institute for Health and Care Excellence (NICE) [9] advises azithromycin in non-smokers that have optimised inhalation therapy and non-pharmacological management but continue to experience frequent exacerbations, or prolonged exacerbations with sputum production or exacerbations that require hospitalisation. ECG and liver function tests should be performed before starting azithromycin. GOLD[2] states that "azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (500 mg two times per day) for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care. Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests."

Do antibiotics prevent short-term treatment failure?

Despite short-term benefits were until recently not demonstrated in outpatients,[10] antibiotics are widely prescribed for exacerbations of COPD, in outpatient settings as well as in hospital settings. In our trial, we found that the treatment failure rate in patient treated with doxycycline was 32/150, vs 46/151 in patients that received a placebo (RR 0.70, 95% CI 0.47-1.03, p=0.07). A recent systematic review that included our Texacold trial[11] did show a statistically significant benefit of antibiotics on short-term treatment failure rate: RR 0.72 (0.56-0.94).

International guidelines advise the prescription of antibiotics in ambulatory treated exacerbations: ERS/ATS in all exacerbations[1] and GOLD in case of sputum purulence.[2] Antibiotic use fuels antibiotic resistance, and because COPD and COPD exacerbations are prevalent, prescribing antibiotics in all exacerbations might have a huge impact on resistance.

The aforementioned systematic review[11] included seven studies, but in our opinion, the diagnosis of COPD was not well established in all studies included. Therefore, we repeated this review of the literature (chapter 3) and included randomised controlled trials comparing treatment of an acute exacerbation of COPD in outpatients with antibiotics *versus* placebo, with a follow-up duration of at least one month. Trials were eligible if more than 90% of the patients had a doctor's diagnosis or a spirometry-confirmed diagnosis of COPD, patients had an age of 40 years and older and had a smoking history.



Our review confirmed that antibiotics have a statistically significant effect on short-term treatment failure rate in outpatients treated for an exacerbation of COPD. Of notice, in only two of the included trials OCS were routinely prescribed, as recommended by international guidelines.[1,2] If OCS are simultaneously prescribed, the treatment effect of antibiotics is less certain: RR 0.72, 95% CI 0.49-1.04. Should all outpatients with an exacerbation receive antibiotics in addition to OCS? At this moment, we need more randomized placebo controlled trials in which OCS are routinely prescribed to confirm that patients benefit from antibiotic treatment.

Should antibiotics be reserved for patients with certain clinical characteristics, such as sputum purulence? The subgroup analysis of our systematic review suggested that patients without sputum purulence may also benefit from antibiotics. So, which patients benefit from antibiotic treatment? In many guidelines,[2,13] sputum purulence is a trigger to prescribe antibiotics. Sputum purulence is associated with bacterial load[14] and one, often referenced randomised controlled trial showed in a post-hoc analysis that patients with sputum purulence, an increase in dyspnea and an increase in sputum volume (type 1 exacerbation) had less treatment failure when treated with antibiotics compared to placebo.[15] This was less clear in patients with type 2 exacerbations (two criteria present) and it was not shown for type 3 exacerbations (only one

criterion present). Sputum purulence was assessed by the physician and a nurse-practitioner. Sputum purulence was also a predictor of failure in a study by Miravitlles et al.[16] Sputum purulence was assessed by the primary care physician.

In chapter 5 we evaluated more than 30 clinical characteristics that might identify patients who benefit from antibiotic treatment, but we could not find a single one with adequate predictive value. In particular, treatment failure rates in patients with sputum purulence were not different in patients treated with and without antibiotics. An explanation for this difference might be that sputum purulence was reported by patients and not assessed by a physician. This is in accordance with a study by Daniels *et al*, who concluded that the sputum colour reported by patients was not reliable, whereas sputum colour assessed by a physician was related to bacterial load.[17]

Remarkable is that although sputum purulence is the most important trigger to prescribe antibiotics in daily practice, its definition is unclear. Different studies used different definitions,[17,18] and in many studies, including the Anthonisen trial,[15] purulence is not defined. In our trial, we did not specifically describe the definition of sputum purulence, but we used change in both thickness and in colour. Taking that into account, it is not surprising that trial results are inconsistent.

In conclusion, antibiotics reduce treatment failure rates in outpatients, but trials that protocolised the use of OCS are less certain of this effect.[4,19] Sputum purulence is a trigger to prescribe antibiotics, but the definition of sputum purulence is unclear and sputum colour reported by patients is unreliable. Therefore, antibiotics might be withheld for exacerbations in outpatients that do not have fever and are treated with OCS; sputum purulence should not be a reason to deviate from this.

Biomarkers in COPD and COPD exacerbations

An exacerbation is defined as a change in patients' baseline dyspnoea, cough, or sputum beyond day-today variability, sufficient to warrant a change in management.[2] This definition is entirely based on symptoms and relies on the recognition of symptoms by the patient and the physician. Because

unreported exacerbations have an impact on health-related quality of life[20] biomarkers that identify an exacerbation might be useful to better recognize less severe exacerbations. We showed that exhaled breath can serve as a noninvasive biomarker for the diagnosis of COPD exacerbations.[21] C-reactive protein (CRP) was also tested as an biomarker to distinguish stable COPD from exacerbations, but was sensitive nor specific enough (area under the receiver operating curve 0.73; 95% confidence interval, 0.66-0.80).[22] To date, no other biomarker is available to distinguish stable from exacerbated COPD.

For exacerbations, several biomarkers were tested with the goal to reduce antibiotic prescription rates, the most important being C-reactive protein and procalcitonin (PCT). In a randomised controlled trial that included 649 outpatients,[23] antibiotic prescription guided by CRP reduced antibiotic use during the first 4 weeks after diagnosis with 20.6%. In patients hospitalised for an exacerbation, antibiotic prescription guided by CRP reduced prescription rates with 14.5% compared to antibiotic prescription guided by GOLD-criteria: increased sputum purulence in combination with increased dyspnoea and/or increased sputum volume.[24] In both trials, a reduction in number of antibiotic prescriptions did not cause harm. A systematic review[25] that included 7 randomized controlled trials concluded that in patients hospitalised for an exacerbation of COPD, procalcitonin-guided antibiotic therapy was associated with less antibiotic prescriptions (RR 0.55; 95% CI 0.39-0.76); in outpatients the role of procalcitonin in COPD exacerbation has not been investigated.

In conclusion, there is need for biomarkers to objectively diagnose COPD exacerbations. Whereas clinical characteristics do not identify patients who benefit from antibiotic treatment in case of an exacerbation, CRP-guided antibiotic therapy can reduce antibiotic exposure in outpatients with an exacerbation of COPD. We showed in a proof of principle study[21] that volatile organic compounds in exhaled breath have the potential to be such a biomarker. It is possible that exhaled volatile organic compound could qualify as a composite biomarker for identification of responders to antibiotic treatment during or after an exacerbation of COPD. Our data merit examining this in subsequent prospective follow-up studies.

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Antibiotic treatment in exacerbations of chronic obstructive pulmonary disease

Summary

Chronic obstructive pulmonary disease (COPD) is a common disease that is characterized by respiratory symptoms and an irreversible airflow limitation. Most patients with COPD experience exacerbations. Exacerbations have major consequences, for the individual patient as well as for society. Therefore, reducing the number of exacerbations is a key outcome in clinical trials.

Exacerbations are caused by bacteria and viruses (50-70%) and air pollution (10%); in 30% the cause is unknown. Treatment of an exacerbation of COPD consists of a short course of oral corticosteroids, with or without antibiotics. Antibiotics might have short-term benefits, and some data suggested that a short course of antibiotics could be beneficial on the long term. However, the use of antibiotics poses a risk for adverse events for the individual patient, and fuels the development of antibiotic resistance for society.

This thesis aimed to answer the following research questions:

1. Do antibiotics prolong time to the next exacerbation in exacerbations of COPD?
2. Do antibiotics reduce short-term treatment failure rates?
3. Is antibiotic treatment cost-effective in the treatment of COPD exacerbations?
4. Which clinical characteristics or biomarkers might be helpful to identify patients who benefit from antibiotic therapy?

In **Chapter 2** we report the results of a randomized, placebo-controlled trial that examined the long-term effects of a short course of doxycycline added to oral corticosteroids in exacerbations of COPD. 301 patients with a mild to moderate exacerbation without fever were randomized and were followed for two years. Time to the next exacerbation was not prolonged in patients treated with doxycycline compared to placebo. Secondary outcomes, including mortality, lung function decline and treatment non-response at day 21 were also not significant different between the two groups. We concluded that

antibiotics can be withheld in outpatients without fever that are treated for an exacerbation of COPD.

Chapter 3 is a systematic review and meta-analysis of randomized controlled trials that compared antibiotic treatment *versus* placebo for COPD exacerbations that are treated in an outpatient setting. The primary outcome was treatment failure within one month. Four trials were included in the meta-analysis and we concluded that antibiotics statistically significantly reduce short-term treatment failure. For patients that were concurrently treated with OCS and for patients without sputum purulence the effect of antibiotic treatment was less certain.

Chapter 4 describes a cost-effectiveness analysis alongside the aforementioned randomized controlled trial. The primary outcome, cost-effectiveness, was calculated with quality-adjusted life years (QALYs). To determine QALYs, the time spend in a given health state is multiplied with a utility value that represents the health-related quality of life. Utility values were obtained during our trial using the Dutch version of the EQ-5D-3L. We demonstrated that in patients with mild to severe COPD treated in an outpatient setting, doxycycline added to prednisolone is not cost-effective compared to prednisolone plus placebo.

In **Chapter 5**, we performed 33 subgroup analyses in which we compared short-term treatment failure rates between the two study arms. Six subgroups were predefined and the other were exploratory. Subgroups were based on clinical variables available at baseline or during exacerbation. Data from our randomized controlled trial showed that short-term treatment failure rates were non-significantly lower in the doxycycline group compared to the placebo group. Treatment failure was defined as the need for a new course of OCS and/or the prescription of open-label antibiotics, hospitalisation or death. While doxycycline had some effect on treatment failure rates at day 21, we could not identify those patients who benefit from antibiotic treatment.

In **Chapter 6** we report the results a prospective follow-up study that studied breath samples from 16 patient with mild to severe COPD experiencing an exacerbation. Samples were taken during clinically stable COPD, during an exacerbation and after recovery. Samples were analyzed by

Gas Chromatography-Mass Spectrometry (GC-MS) and/or electronic nose (eNose). After multivariate modelling by Principal Component Analysis (PCA), paired student t-tests were performed to compare means between repeated measures. We found significant differences in breath samples taken during exacerbation as compared to baseline and recovery for both GC-MS and eNose. No differences were found between baseline and recovery. These results provide proof of principle that exhaled breath can serve as a non-invasive biomarker for the diagnosis of COPD exacerbations.

Finally, in **Chapter 7** we discuss the main findings of this thesis in the light of recent literature.

Antibiotische behandeling voor exacerbaties van COPD

Samenvatting

Chronische obstructieve longziekte (COPD) is een veel voorkomende ziekte die wordt gekenmerkt door klachten van de luchtwegen en een onomkeerbare verstoring van de luchtstroom. De meeste patiënten met COPD ervaren af en toe exacerbaties: een tijdelijke verergering van de klachten ("een longaanval"). Exacerbaties hebben grote gevolgen, zowel voor de individuele patiënt als voor de samenleving. Daarom is het verminderen van het aantal exacerbaties een belangrijke uitkomst in klinische onderzoeken.

Exacerbaties worden veroorzaakt door bacteriën en virussen (50-70%) en luchtverontreiniging (10%); in 30% is de oorzaak onbekend. Behandeling van COPD-exacerbatie bestaat uit een korte kuur prednison, met of zonder antibiotica. Antibiotica hebben mogelijk voordelen op korte termijn en eerdere studies suggereren dat een korte antibioticakuur ook op lange termijn gunstig kan zijn. Het gebruik van antibiotica geeft echter een risico op bijwerkingen voor de individuele patiënt en bevordert de ontwikkeling van antibioticaresistentie in de bevolking.

Het doel van dit proefschrift is om de volgende onderzoeksvragen te beantwoorden:

1. Verlengen antibiotica bij exacerbaties van COPD de tijd tot de volgende exacerbatie?
2. Reduceren antibiotica behandelfalen op korte termijn?
3. Is behandeling met antibiotica kosteneffectief bij de behandeling van een exacerbatie van COPD?
4. Welke klinische kenmerken of biomarkers kunnen patiënten identificeren die baat hebben bij antibioticatherapie?

In **hoofdstuk 2** rapporteren we de resultaten van een gerandomiseerde, placebo-gecontroleerde studie die de langetermijneffecten onderzocht van een korte kuur van het antibioticum doxycycline toegevoegd aan orale corticosteroïden (prednison) bij COPD-exacerbaties. 301 patiënten met een lichte tot matig ernstige exacerbatie zonder koorts werden gerandomiseerd

tussen doxycycline en placebo en gedurende twee jaar gevolgd. De tijd tot de volgende exacerbatie was niet verlengd bij patiënten die met doxycycline werden behandeld in vergelijking met placebo. Secundaire uitkomsten, waaronder sterfte, achteruitgang van de longfunctie en behandelfalen op dag 21 waren ook niet significant verschillend tussen de twee groepen. We concludeerden dat antibiotica niet geïndiceerd zijn bij patiënten zonder koorts die poliklinisch worden behandeld voor een exacerbatie van COPD.

Hoofdstuk 3 is een systematische review en meta-analyse van gerandomiseerde, placebo- gecontroleerde studies die antibiotische behandeling vergeleken met behandeling met placebo voor poliklinisch behandelde COPD-exacerbaties. De belangrijkste uitkomstmaat was behandelfalen binnen een maand. Vier onderzoeken werden opgenomen in de meta-analyse en we concludeerden dat antibiotica de kans op behandelfalen verminderde. Voor patiënten die gelijktijdig werden behandeld met prednison en voor patiënten zonder sputumpurulentie was het effect van behandeling met antibiotica minder zeker.

Hoofdstuk 4 beschrijft een kosteneffectiviteitsanalyse die parallel liep aan de bovengenoemde gerandomiseerde placebo-gecontroleerde studie. De primaire uitkomst, kosteneffectiviteit, werd berekend met voor kwaliteit gecorrigeerde levensjaren (QALY's). Om QALY's te bepalen, wordt de tijd die in een bepaalde gezondheidstoestand wordt doorgebracht vermenigvuldigd met een utiliteit (waardering) die de gezondheidsgerelateerde kwaliteit van leven vertegenwoordigt. Deze utiliteit werd verkregen met de Nederlandse versie van de EQ-5D-3L. We toonden aan dat doxycycline toegevoegd aan prednisolon bij patiënten met milde tot ernstige COPD die poliklinisch worden behandeld, niet kosteneffectief is in vergelijking met de behandeling met prednisolon en placebo.

In **hoofdstuk 5** hebben we 33 subgroepanalyses uitgevoerd waarin we de kans op behandelfalen op korte termijn tussen de twee onderzoeksarmen (antibiotica of placebo) vergeleken. Zes subgroepen waren vooraf gedefinieerd en de anderen waren exploratief. Subgroepen waren gebaseerd op klinische variabelen die we tot onze beschikking hadden bij aanvang van de studie of tijdens de exacerbatie. Gegevens van onze gerandomiseerde gecontroleerde

studie toonden aan dat de kans op therapiefalen op korte termijn lager was in de doxycycline-groep in vergelijking met de placebogroep, maar dit was statistisch niet significant. Hoewel doxycycline enig effect had behandelfalen op dag 21, konden we niet vaststellen welke patiëntkarakteristieken de kans op behandelfalen voorspelden.

Het objectief vaststellen of er een exacerbatie is of niet blijft lastig. In **hoofdstuk 6** rapporteren we de resultaten van een prospectieve studie die ademmonsters bestudeerde van 16 patiënten met milde tot ernstige COPD die een exacerbatie kregen. Ademmonsters werden afgenomen tijdens klinisch stabiele COPD, tijdens een exacerbatie en na herstel. Deze ademmonsters werden geanalyseerd met gaschromatografie-massaspectrometrie (GC-MS) en/of elektronische neus (eNose). We vonden significante verschillen in ademmonsters die tijdens exacerbatie werden genomen in vergelijking met baseline en herstel, voor zowel GC-MS als eNose. Er werden geen verschillen gevonden tussen baseline en herstel. Deze resultaten duiden er op dat uitgeademde adem kan dienen als een niet-invasieve biomarker voor de diagnose van COPD-exacerbaties.

Ten slotte bespreken we in **hoofdstuk 7** de belangrijkste bevindingen van dit proefschrift in het licht van de recente literatuur.

PhD portfolio

	Year	ECTS
General courses		
- Basis Course Legislation and Organization (BROK)	2010	0.9
- Practical Biostatistics	2011	1.4
- Re-registration BROK	2014, 2019	0.2
Seminars, workshops, symposia		
- NRS young investigators symposium	2011	0.1
- Lung Amsterdam	2012, 2013, 2014	0.3
- Infectieziekten symposium	2015	0.2
Presentations & conferences		
American Thoracic Society International Conference		
- *Antibiotics for treating COPD exacerbations in an out-of-hour setting*		
Oral presentation, 2011, Denver		1.5
- *Exhaled breath analysis during exacerbations and clinically stable episodes of COPD*		
Poster presentation, 2013, Philadelphia		1.5
- *Repeated electronic nose analysis of exhaled air identifies exacerbations of COPD*		
Poster presentation, 2014, San Diego		1.5
- *Long-term effects of antibiotics in COPD exacerbations: a randomized clinical trial*		
Oral presentation, 2016, San Francisco		1.5
- *ICU admissions among patients with mild to severe COPD*		
Poster discussion, 2017, Honolulu		1.5
European Respiratory Society International conference		
- *Clinical determinants for oral steroids during COPD exacerbations in primary care*		
Poster presentation, 2011, Amsterdam		1.5
- 2013, Barcelona		1
- 2015, Amsterdam		1
- 2017, Milan		1
- 2018, Paris		1
- 2019, Madrid		1
Infectieziekten symposium		
- *Antibiotica in exacerbaties van COPD*		
Oral presentation, 2015, Amsterdam		0.5
Other		
Journal club, weekly	2010-2012	5
Research meeting, weekly	2010-2012	5

Publications

P. van Velzen, G. ter Riet, P. Bresser, J.J. Baars, B.T.J. van den Berg, J.W.K. van den Berg, P. Brinkman, J.W.F. Dagelet, J.M.A. Daniels, D.R.G.L. Groeneveld-Tjiong, R.E. Jonkers, C. van Kan, F.H. Krouwels, K. Pool, A. Rudolphus, P.J. Sterk, J.M. Prins
Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind, placebo-controlled trial
The Lancet Respiratory Medicine. 2017 Jun;5(6):492-499

P. van Velzen, A.P. Finch, G. ter Riet, P.J. Sterk, J.M. Prins, J.E. Bosmans
Doxycycline added to prednisolone in outpatient-treated acute exacerbations of COPD: a cost-effectiveness analysis alongside a randomised controlled trial
Pharmacoeconomics. 2019 May;37(5):689-699

P. van Velzen, P. Brinkman, H.H. Knobel, J.W.K. van den Berg, R.E. Jonkers, R.J. Loijmans, J.M. Prins, P.J. Sterk
Exhaled breath profiles before, during and after exacerbation of COPD: a prospective follow-up study
COPD. Journal of Chronic Obstructive Pulmonary Disease. 2019 Dec;16 (5-6):330-337

P. van Velzen, G. ter Riet, P. Brinkman, P.J. Sterk, J.M. Prins, on behalf of the TEXACOLD study group.
Doxycycline for exacerbations of chronic obstructive pulmonary disease in outpatients; who benefits?
ERJ Open Research 2020; 6: 00099-2020

Curriculum vitae

Patricia van Velzen studeerde geneeskunde aan de Universiteit van Amsterdam. Daarna werkte ze als arts-assistent in het Rode Kruis Ziekenhuis in Beverwijk en in het Sint-Elisabeth Hospitaal in Willemstad, Curaçao.

In 2008 begon zij aan de opleiding longziekten en tuberculose in het Medisch Centrum Alkmaar (nu Noordwest Ziekenhuisgroep) en vanaf 2014 vervolgde zij haar opleiding als fellow intensive care in het Academisch Medisch Centrum in Amsterdam. Vanaf 2010 combineerde zij opleiding met promotieonderzoek.

Op dit moment werkt zij als longarts-intensivist in het Dijklander Ziekenhuis in Hoorn en Purmerend.

Dankwoord

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En Yennece, als research nurse heb je de studie in de lucht gehouden terwijl ik met mijn opleiding verder ging. Heel veel dank daarvoor.