Effectiveness and safety of medicines used in COPD patients

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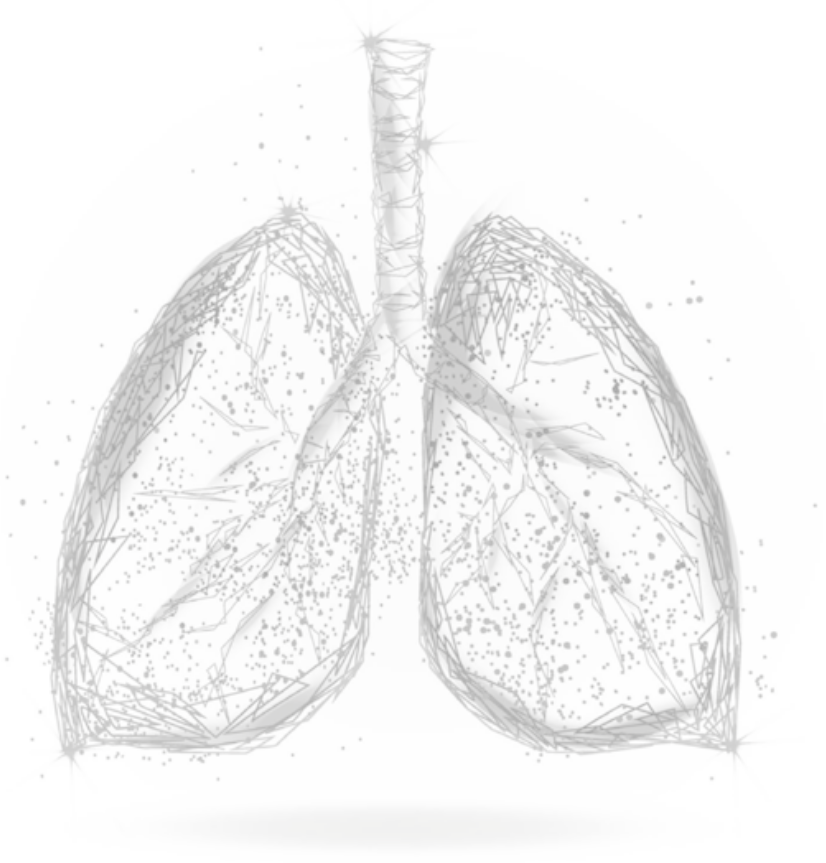
CHAPTER 4



Real-world short- and long-term effects of antibiotic therapy on acute exacerbations of COPD in outpatients: a cohort study under the PharmLines Initiative

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ABSTRACT

Introduction

Although antibiotic treatment is recommended for acute exacerbations of COPD (AECOPD) under specific circumstances, the treatment's value in an outpatient setting is unclear. We aim to evaluate the real-world short- and long-term effects of antibiotic treatment on AECOPD outpatients.

Methods

This retrospective inception cohort study was conducted under the PharmLines Initiative that linked the Lifelines cohort study database with IADB.nl, the University of Groningen's medication prescription database during the period 2005-2017. We included participants with a first recorded diagnosis of COPD who underwent systemic glucocorticoids treatment for an AECOPD episode. The exposed and reference group was defined as patients who received and not received any antibiotic prescriptions during AECOPD treatment. The short-term outcome was AECOPD treatment failure within 14-30 days after the index date. The long-term outcome was the time to the next exacerbation within a one-year follow-up period. Binary logistic regression analysis combined with propensity scores (PS) were used to estimate the association between antibiotic use and treatment failure. The risk of another exacerbation was assessed using Kaplan-Meier survival and Cox regression analyses. Several subgroup and sensitivity analyses were also performed.

Results

We analyzed linked data for 1,105 AECOPD patients. Antibiotics were prescribed for 518 patients (46.9%) while 587 patients (53.1%) received no antibiotics. The overall antibiotic use was associated with a significant relative risk reduction of AECOPD treatment failure by 33%-37% compared with the risk for the reference group (adjusted odds ratio [aOR]: 0.67 [95% CI: 0.42-1.04] and 0.63 [95% CI: 0.40-0.99] by regression and PS analyses, respectively). Similar protective effects were observed for doxycycline, macrolides and co-amoxiclav, but not for amoxicillin, and only the effects of doxycycline were statistically significant (aOR 0.53 [95% CI: 0.28-0.99] by PS analysis). There was no difference between the exposure and reference groups regarding the risk of and time to the next exacerbation, irrespective of the follow-up duration.

Conclusion

Our finding that antibiotics treatment supplementing systemic glucocorticoids treatment reduces short-term AECOPD treatment failure in real-world settings concurs with those of clinical trials. Larger studies of high quality are needed to confirm the beneficial effects for specific classes of antibiotics. Our results after controlling for confounding suggest that in observational studies on AECOPD, unmeasured confounding may induce underestimated beneficial antibiotic treatment effects.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is characterized by persistent respiratory symptoms and airflow limitation is one of the leading causes of morbidity and mortality worldwide.[1,2] COPD patients frequently experience acute exacerbations of COPD (AECOPD), defined as acute worsening of respiratory symptoms, necessitating additional therapy.[3] AECOPD has major impacts on patients' health status, accelerates the disease progression and increases health-care costs.[4,5] Therefore, reducing the symptoms of current exacerbations and preventing further exacerbations are essential aspects of sound pharmaceutical management of AECOPD. Because AECOPD is associated with increased airway inflammations, systemic glucocorticoids treatment is recommended to shorten the recovery time, improve lung function and promote oxygenation, given its proven beneficial effects.[3,6]

The majority of AECOPD episodes are caused by respiratory infections, especially bacterial infections, which account for around 50% of all exacerbations.[7,8] The most widely reported bacteria associated with exacerbations are *S. pneumoniae, H. influenza, P. aeruginosa*, *M. catarrhalis, A. baumannii,* and *S. aureus*.[7,9,10] Accordingly, antibiotics have been recommended for the management of AECOPD when signs of bacterial infection are present.[3] However, the beneficial effects of antibiotic treatment in addition to oral glucocorticoids for AECOPD are still uncertain among outpatients. The pooled results from five randomized controlled trials (RCTs) examined in a Cochrane meta-analysis conducted in 2012 did not show a significant reduced risk of treatment failure associated with currently prescribed antibiotics among outpatients.[11] However, an updated (2018) version of this Cochrane review that included two new RCTs, presented statistically significant beneficial effects of current prescribed antibiotics among outpatients.[12,13] Especially the RCT conducted by van Velzen et al in 2017 contributed a large proportion (24%) of the updated pooled results.[13] This RCT itself was not statistically significant. The limited external validity of RCTs prompts questions about the effects of antibiotics treatment for AECOPD in real-world settings.

Primary care of patients with COPD is mostly managed on an outpatient basis. This population from real-world setting is more heterogeneous than those of RCTs.[14] Additionally, antibiotic treatment for AECOPD is often not in accordance with current guidelines.[15,16] Therefore, the real-world treatment effects of antibiotics for AECOPD may differ from those obtained from clinical trials and merit further investigation. So far, only few observational studies were conducted to evaluate the treatment effects of antibiotics for AECOPD. Two of these studies focused exclusively on the long-term effects of antibiotics used for AECOPD and lacked any adjustments for potential differences in lung function and smoking history.[17,18] Two other cohort studies were conducted among inpatients.[19,20] The PharmLines Initiative presented a unique opportunity to retrieve precise information on many previously unmeasured confounders. Using an

inception cohort design, we assessed the short- and long-term effects of antibiotics used in addition to systemic glucocorticoids treatment for AECOPD in outpatients.

METHODS

Study setting and data sources

This retrospective cohort study was conducted as part of the PharmLines Initiative,[21] which linked the Lifelines Cohort Study database (https://www.lifelines.nl) and the IADB.nl prescription database (http://www.iadb.nl) affiliated to the University of Groningen. Individuals included in these two databases are representative for the population in the northern Netherlands.[22,23]

Lifelines is a multi-disciplinary prospective population-based cohort study involving 167,729 participants across three generations from 2006 to 2017. A broad range of investigative procedures were used to assess the biomedical, socio-demographic, behavioural, physical and psychological factors contributing to the health and disease status of the general population, with a particular focus on multi-morbidity and complex genetics.[24,25] Following baseline assessments, participants underwent physical examinations at the Lifelines location every 5 years and completed extensive questionnaires every 1.5 years. IADB.nl is an evolving drug prescription database since 1996 that currently covers prescription data for 730,000 participants from 72 community pharmacies.[23] Each patient is individually tracked throughout the database's operational period and their prescription records contain information on the date of dispensing, the quantity of medication dispensed, the dose regimen, the number of days for which the prescription is valid, the prescribing physician and the anatomical therapeutic chemical code (ATC code). Each patient, whose date of birth and gender are recorded, is assigned a unique anonymous identifier. Because of the strong patient-pharmacy commitment in the Netherlands, the medication records for each patient are virtually complete, except for over the counter drugs and medication dispensed during hospitalization.

The Lifelines cohort study was approved by the medical ethical committee of the University Medical Center Groningen, and all participants signed informed consent forms confirming their permission for their (anonymized) data and material to be used for scientific purposes. IADB.nl data are collected in accordance with the national and European guidelines on privacy requirements for handling human data.

Study population

Patients with a first recorded diagnosis of COPD who took systemic glucocorticoids for an acute exacerbation were selected for this study according to the following inclusion criteria: (1) patients were entered in both the Lifelines and IADB.nl databases. (2) Patients had spirometrically-confirmed COPD with a forced expiratory volume in 1

second/forced volume capacity (FEV1/FVC) < 70% according to lung function test or had general practitioner (GP)-confirmed COPD according to the self-reported questionnaire in the Lifelines Cohort Study. The date of first recorded COPD diagnosis was set as enrolment date of this study. (3) Patients had the first recorded acute exacerbation after enrolment date, which was indicated by the prescription of prednisone or prednisolone push treatments (3-4 defined daily doses for 3-14 days) recorded in the IADB.nl database in line with Dutch College of GPs guideline for COPD management.[26] The date of the first prescriptions for acute exacerbation was set as the index date. (4) Patients were 18 years or older on the index date.

Exposure and outcomes

During the treatment for first recorded acute exacerbation with systemic corticosteroid treatment, patients who also received antibiotics (ATC code: J01) within 3 days before and 7 days after the index date were defined as the exposed group. Those patients who were not prescribed any antibiotics during the same period were defined as the reference group. The short-term outcome was treatment failure defined as any new prescription of prednisolone, prednisone or antibiotics between 14 and 30 days after index date. The long-term outcome was the time to the next exacerbation defined as a new prescription of prednisone or prednisolone within a one-year follow-up period. As the first exacerbation may last for a long time, to avoid counting its following treatment as a second exacerbation, we restricted the minimum time from the first to the second exacerbation to 21 days.[27] The study design for the exposure and outcome measurements is described in Figure 1.

Data collection and covariates

Age was calculated as the difference in years between the date of birth and the index date. On the enrolment date, the following information was extracted as covariates from the Lifelines database to describe the characteristics of cohort members with AECOPD: smoking history, the global initiative for chronic obstructive lung disease (GOLD) stages of COPD, lung function parameters and related comorbidities including cardiovascular diseases, diabetes, depression and other disorders. If information concerning the risk status of AECOPD (e.g., smoking history and chronic comorbidities) was not documented on the enrolment date, we used information from the closest follow-up assessment in the Lifelines, if available. Additionally, information on the frequency of AECOPD and maintenance drugs for COPD in the previous year before the index date was retrieved as covariates from the IADB.nl database.

Subgroup and sensitivity analysis

Given that different antibiotics may have different effects on AECOPD, we conducted a subgroup analysis to explore the effects of four most frequently used antibiotics (doxycycline, macrolides, co-amoxiclav and amoxicillin). As COPD patients with an

asthma component may respond differently to antibiotics, we conducted a sensitivity analysis by excluding these patients to verify the robustness of our study.

Statistical analysis

Continuous variables were presented as means with standard deviations (SDs) or median with interquartile ranges (IQRs) and Student's *t*-test or Mann-Whitney U Test was performed, as appropriate, to examine their difference between the two patient groups. Categorical variables were presented as percentages with 95% confidence intervals (95% CI) and compared using a Chi-square test or Fisher's exact test, as appropriate. Binary logistic regression was performed to estimate the odds ratio (OR) with a 95% CI for treatment failure and adjusted for possible covariates. To better control the differences of characteristics between groups, propensity score (PS) analysis was also conducted by including the PS as a single covariate in the binary logistic regression model. A Kaplan-Meier survival analysis and log-rank test were conducted to compare the times to the next exacerbations between exposure and reference groups. A cox proportional hazards regression was performed to estimate the hazard ratio (HR) and 95% CI for the risk of the next exacerbation. A p-value < 0.05 was considered as statistically significant. All analyses were performed using the IBM SPSS statistics version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

The linkage of the IADB.nl and Lifelines database provided 7,760 adults who were prescribed a prednisone or prednisolone treatment (Figure 2). Of these adults, 2,614 (34%) had a diagnosis of COPD. Of these COPD patients, 1,105 with a first acute exacerbation recorded after their enrolment dates according to pre-set definitions were eligible for our study. In all, 518 patients were enrolled in the exposed group, receiving both systemic glucocorticoids and an antibiotic. 587 patients were enrolled in the reference group, only receiving systemic glucocorticoids. The baseline characteristics of the study population are summarized in Table 1. Overall, the measured covariates were very similar for both exposed and reference groups. The number of previous exacerbations and antibiotic courses as well as the prevalence of heart failures were higher in the exposure group compared with the reference group.

Short-term outcome

Within 14-30 days after treatment of the index exacerbation, 56 (10.8%) patients in the antibiotic exposed group versus 62 (10.6%) patients in the reference group experienced treatment failure (crude OR: 1.03 [95% CI: 0.70-1.50], Table 2). After adjusting for potential confounders through regression and PS analysis, the OR decreased in the direction of a beneficial effect of antibiotics (aOR: 0.67 [95% CI: 0.42-

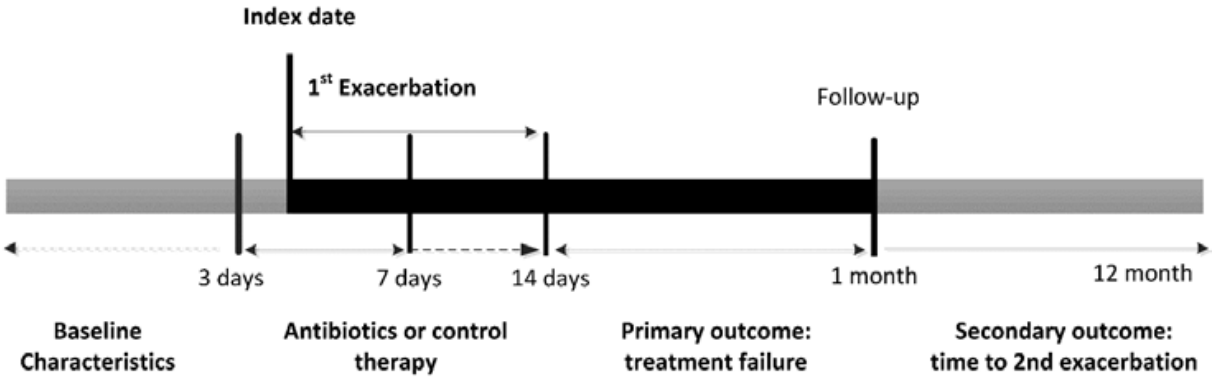

Figure 1. Retrospective cohort study design.

1.04] in the regression analysis), which was statistically significant in the PS analysis (aOR 0.63 [95%CI: 0.40-0.99]).

Long-term outcome

Within a year of follow-up after the index date, 153 (29.5%) patients in the exposure group and 147 (25.0 %) patients in the reference group experienced a next exacerbation (crude HR: 1.19 [95% CI: 0.95-1.49], see Table 3). After adjusting for confounders, the point estimate of the HR for subsequent exacerbation did not change substantially (adjusted HR 1.14 [95% CI: 0.87-1.49]). There was also no difference between the two comparison groups for the time to the next exacerbation (Figure 3), which applied to the short follow-up period of 3 and 6 months (Table 3).

Subgroup and sensitivity results

The findings of both the logistic regression and PS analyses indicated that the risk of treatment failure was reduced significantly by 47% by doxycycline compared to the reference treatments (aOR 0.53 [95% CI: 0.28-1.00] and 0.53 [95% CI: 0.28-0.99] by regression and PS analyses, respectively, Table 1). Although not statistically significant, similar beneficial trends were seen for the macrolides exposed group (aOR 0.49 [95% CI: 0.22-1.11] and 0.58 [95% CI: 0.26-1.29] by regression and PS analyses, respectively) and co-amoxicillin exposed group (aOR 0.50 [95% CI: 0.19-1.32] and 0.46 [95% CI: 0.17-1.24] by regression and PS analyses, respectively) compared to the results in the reference group. No statistical difference was observed between the amoxicillin exposed group and the reference group (aOR 1.56 [95% CI: 0.81-3.00] and 1.49 [95% CI: 0.78-2.84] by regression and PS analyses, respectively) and the point estimate of aOR was in the opposite direction.

Even when we excluded self-reported COPD and focused only on spirometrically-confirmed COPD, the protective effect of antibiotics on treatment failure continued (aOR 0.56 [95% CI: 0.32-0.97] and 0.52 [95% CI: 0.29-0.90] by regression and PS analyses,

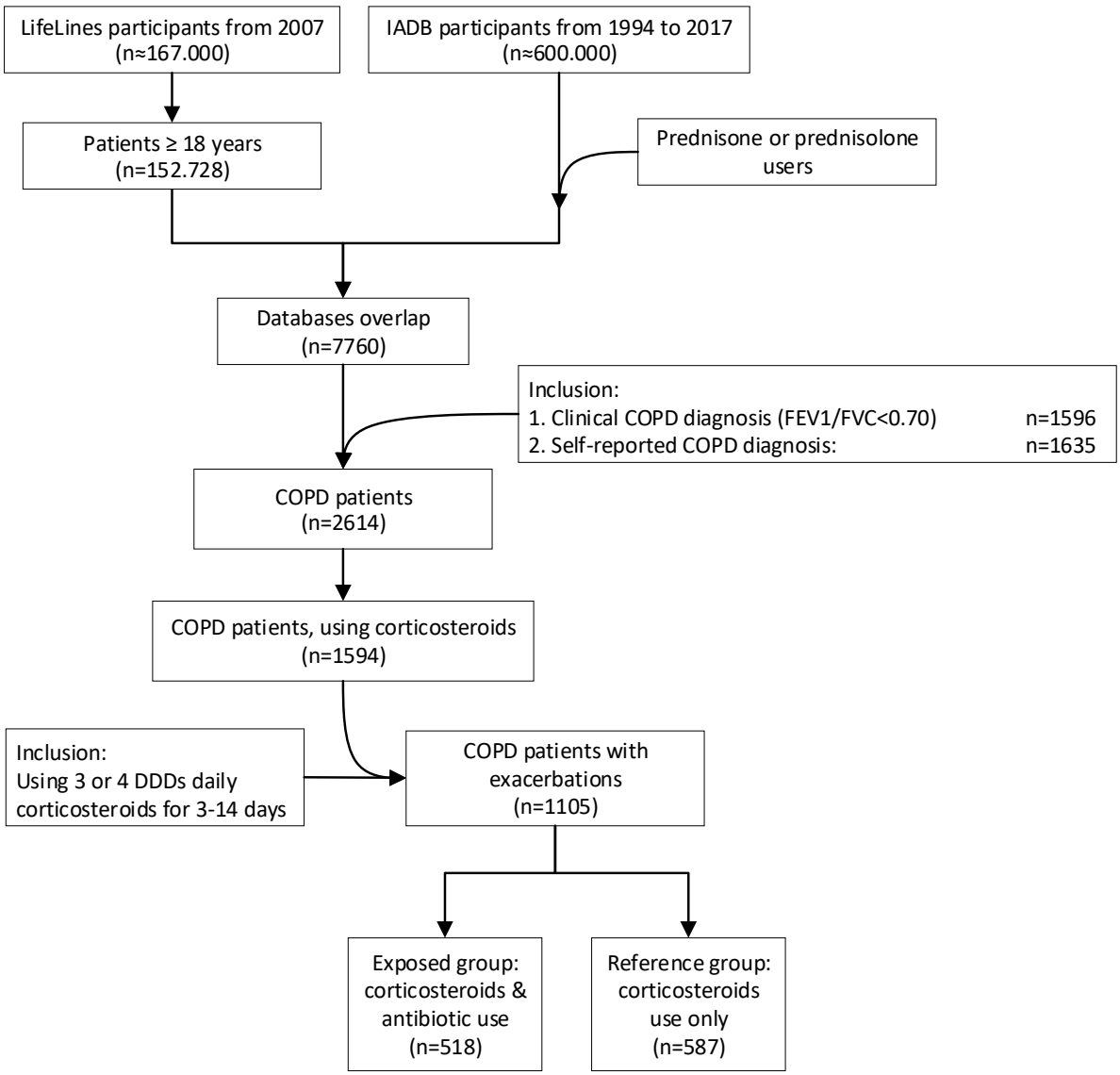

Figure 2. Flow chart of study subject selection.

respectively; Table 4). Similarly, after excluding COPD patients with asthma, the aOR (exposure vs reference) for treatment failure was further reduced towards a protective effect (aOR 0.58 [95% CI: 0.32-1.01] and 0.57 [0.32, 1.02] by regression and PS analyses) with a boundary statistical significance.

DISCUSSION

Primary findings

In this study of COPD outpatients with mostly mild to moderate GOLD stages, antibiotics prescription, notably doxycycline, in addition to systemic prednisone or prednisolone therapy, appeared to reduce the treatment failure of AECOPD substantially. The supplementation of antibiotic treatment to systemic glucocorticoids did not prolong the time to the next exacerbation for up to one follow-up year compared with

Table 1. Baseline characteristics of COPD patients included in this study (N=1,105).

Patient characteristics	Exposed (n=518) N (%)	Reference (n=587) N (%)	P-value
Age (yr.)			
Median	55 (18)	54 (18)	0.24
<= 50	185 (35.7)	222 (37.8)	0.77
50-65	189 (36.5)	208 (35.4)	
>=65	144 (27.8)	157 (26.7)	
Gender			0.68
Male	211 (40.7)	232 (39.5)	
Female	307 (59.3)	355 (60.5)	
BMI (kg/m^2)			
Median	26.85 (6.5)	26.40 (5.9)	0.24
<= 24.9	171 (33.0)	203 (34.6)	0.35
25.0-29.9	195 (37.6)	239 (40.7)	
>= 30	152 (29.3)	145 (24.7)	
Lung function			
FEV1 (L)	2.59 (1.0)	2.68 (1.0)	0.24
FEV1 (% predicted)	83.91 (23.25)	84.28 (22.29)	0.76
FVC (L)	3.86 (1.0)	3.96 (1.0)	0.13
FVC (% predicted)	65.54 (18.72)	66.45 (17.16)	0.72
FEV1 to FVC ratio	0.68 (0.11)	0.67 (0.09)	0.77
GOLD stage			0.43
I: Mild	266 (59.1)	307 (59.4)	
II: Moderate	160 (35.6)	193 (37.3)	
III and IV: Severe/very severe	24 (5.4%)	17 (3.3)	
Smoking status			0.25
Current smoker	169 (35.6)	167 (30.8)	
Former smoker	190 (40.0)	227 (41.9)	
Non smoker	116 (24.4)	148 (27.3)	
No. of AECOPD in previous yr.			0.01
0	472 (91.1)	557 (94.9)	
1	17 (3.3)	17 (2.9)	
2 or more	29 (5.6)	13 (2.2)	
No. of antibiotics prescription in previous yr.			<0.01
0	20 (3.9)	322 (54.9)	
1	228 (44.0)	139 (23.7)	
2 or more	270 (52.1)	126 (21.5)	
Comorbidities			
A. Cardiovascular diseases			
Heart failure	22 (4.2)	12 (2.0)	0.03
Heart attack	23 (4.4)	18 (3.1)	0.23
Stroke	< 10	11 (1.9)	0.87
Arrhythmia	74 (14.4)	78 (13.3)	0.63
Hypertension	165 (31.9)	180 (30.7)	0.67

Table 1. (continued)

Patient characteristics	Exposed (n=518) N (%)	Reference (n=587) N (%)	P-value
B. other major disorders			
Asthma	169 (32.6)	200 (34.1)	0.62
Pulmonary fibrosis	< 10	< 10	0.99
Diabetes	28 (5.4)	34 (5.8)	0.78
Cancer	< 10	< 10	0.79
Osteoporosis	27 (5.2)	21 (3.6)	0.18
Renal impairment	16 (3.1)	22 (3.7)	0.55
Depression	83 (16.0)	87 (14.8)	0.58
Anxiety	< 10	< 10	0.26
Anemia	72 (13.9)	78 (13.3)	0.77
C. other minor disorders			
Ulcerative colitis	< 10	< 10	0.03
Stomach ulcer	24 (4.6)	23 (3.9)	0.56
Irritable bowel syndrome	61 (11.8)	62 (10.6)	0.52
Hepatic impairment	13 (2.5)	10 (1.7)	0.35
COPD maintenance medications in previous yr.			
SABA	169 (32.6)	183 (31.2)	0.61
LABA	22 (4.2)	31 (5.3)	0.42
SAMA	12 (2.3)	14 (2.4)	0.94
LAMA	72 (13.9)	61 (10.4)	0.07
ICS	67 (12.9)	70 (11.9)	0.61
LABA/ICS	190 (36.7)	194 (33)	0.21
Theophylline	< 10	< 10	0.67

Note: Data are presented as mean (standard deviation [SD]) or median with interquartile range (IQR) or numbers with percentage. Due to privacy protection of patients according to contract, the number below 10 was not permitted to present. Abbreviations: BMI: body mass index; SABA: short-acting β agonist; SAMA: short-acting muscarinic antagonist; LABA: long-acting β agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; GOLD: global initiative for chronic obstructive lung disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; AECOPD: acute exacerbation of chronic obstructive pulmonary disease;

treatment with only glucocorticoids. Our results, after limiting to the COPD patients to those who had spirometrically-confirmed COPD, were robust. Similar robust results were also obtained after excluding COPD patients with self-reported asthma.

The beneficial treatment effects of antibiotic use for AECOPD observed in this study were consistent with the updated pooled results by Vollenweider et al. for outpatients.[12] The finding that additional antibiotic treatment for AECOPD did not produce long-term beneficial effects is also consistent with results of a previous RCT conducted in COPD outpatients.[13] Conversely, two previous observational studies reported that antibiotic treatment is associated with a reduced risk of a subsequent exacerbation.[17,18] However,

Table 2. Odds ratio for treatment failure of index exacerbation among COPD outpatients with adjustment by logistic regression and propensity score weighted analysis.

Treatment groups (No.)	Treatment failure No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	PS adjusted OR (95% CI)[b]
Reference (587)	56 (10.8)	1	1	1
All antibiotics (518)	56 (10.8)	1.03 (0.70-1.50)	0.67 (0.42-1.04)	0.63 (0.40-0.99)*
Doxycycline (214)	19 (8.9)	0.83 (0.48-1.42)	0.53 (0.28-1.00)*	0.53 (0.28-0.99)*
Macrolides (102)	11 (10.8)	1.02 (0.52-2.02)	0.49 (0.22-1.11)	0.58 (0.26-1.29)
Amoxicillin (100)	18 (18.0)	1.86 (1.05-3.30)	1.56 (0.81-3.00)	1.49 (0.78-2.84)
Co-amoxicillin (87)	< 10	0.74 (0.33-1.68)	0.50 (0.19-1.32)	0.46 (0.17-1.24)

Abbreviation: OR: odds ratio; CI: confidence interval; PS: propensity score weighted analysis; No.: number; [a]Adjusted result by logistic regression; [b]Adjusted result by propensity score weighted analysis; *P<0.05;

Tables 3. Hazard ratio for next exacerbation with follow-up of 1 year among COPD outpatients.

Follow-up time	Antibiotics group	Reference group	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
3 months	57 (11.0)	60 (10.2)	1.10 [0.76, 1.58]	1.11 [0.71, 1.71]
6 months	109 (21.0)	119 (20.3)	1.06 [0.81, 1.37]	1.05 [0.77, 1.42]
12 months	153 (29.5)	147 (25.0)	1.19 [0.95, 1.49]	1.14 [0.87, 1.49]

Abbreviation: HR: hazard ratio; CI: confidence interval; [a]Adjusted baseline characteristics by using cox hazard logistic regression.

insufficient information in these studies on, for example, lung function, smoking history and related comorbidities, which are important risk factors associated with exacerbation events, could have accounted for these discrepancies.[28]

GOLD guidelines recommend amoxicillin with clavulanic acid, macrolide and tetracycline as the first-line antibiotics treatment for AECOPD.[3] The Dutch primary care guidelines recommend amoxicillin or doxycycline as first-line antibiotics in AECOPD treatment.[26] The combined results of seven RCTs examined in the updated Cochrane review showed that the antibiotics were generally effective in treating AECOPD in outpatients.[12] However, three of these studies examined combined antibiotics[29-31] and only four focused on the specific antibiotics recommended in the above-mentioned guidelines: one on doxycycline, two on co-amoxiclav and one on amoxicillin.[13,32-34] Therefore, no scientifically sound conclusion could be drawn about the effects of these specific antibiotics used for AECOPD. Regarding specific antibiotics in our study, doxycycline had significant beneficial treatment effects on AECOPD, we observed similar trends towards beneficial effects for macrolides and amocillin-clavunalate, though non-significant, which may be due to the limited power of our study size to detect effects in subgroup analysis, or there were no effects at all, and more qualified studies are needed

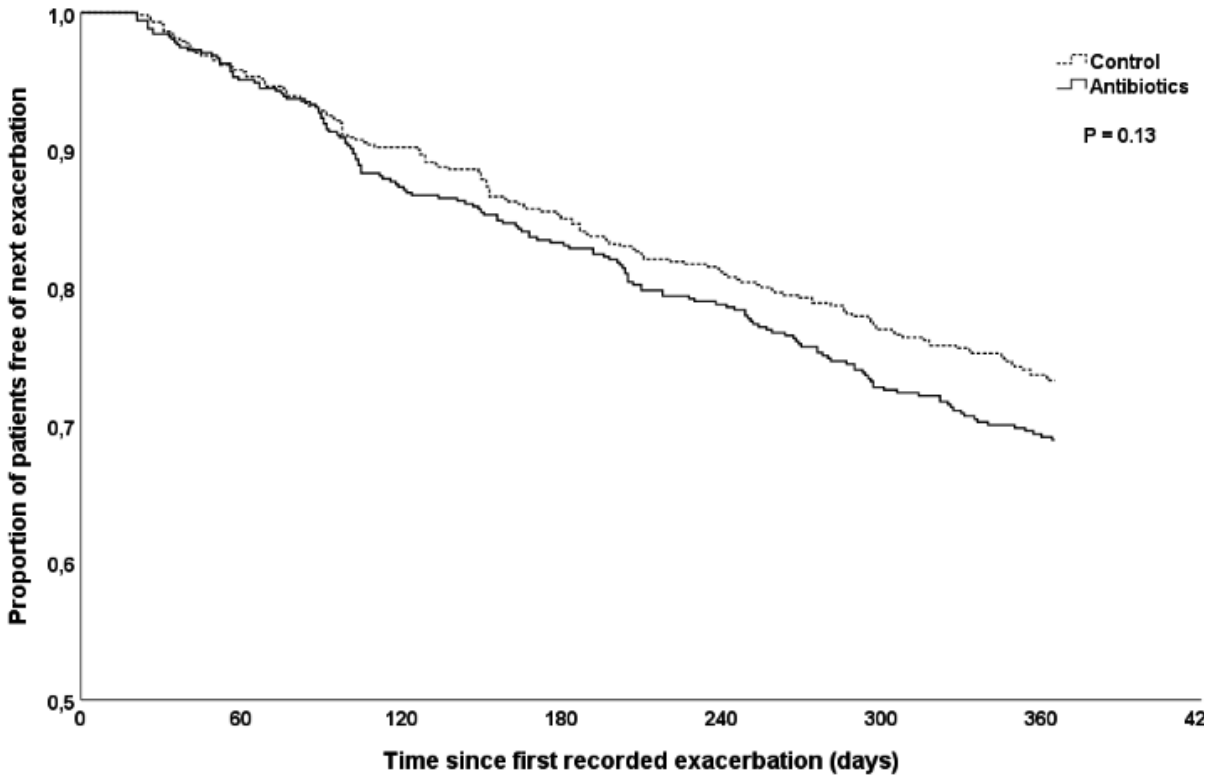

Figure 3. Kaplan-Meier curves showing the proportion of patients free of next exacerbation in COPD outpatients up to follow-up of 1 year.

to explore these effects further. Regarding the short-term effects of doxycycline, the resistance of common pathogens for AECOPD like *Haemophilus influenzae* and *Streptococcus pneumonia* to doxycycline is reported to be rare in the Netherlands,[35] this may contribute to its successful short-term treatment effects.

There is a general consensus that exacerbation frequency increases with COPD severity.[36] Because the COPD severity of patients in our study was generally mild (around 60%) compared with that of patients in previous studies (10%-20%),[12,13] the rate of next exacerbations in our study was relatively low. About 30% of patients experienced re-exacerbation after index exacerbation within one year of follow-up. After adjusting for possible confounders, we observed similar rates of next exacerbations between antibiotic users and non-antibiotic users, a finding that is consistent with that of a previous RCT report.[13]

Although the presence of purulent sputum is widely deemed to be the sole determinant of antibiotic treatment of AECOPD,[3] its accuracy and reproducibility as an indicator of bacterial infection is limited,[37] especially for outpatients. Consequently, guidelines on antibiotics prescriptions are not stringently adhered to for treating AECOPD.[15] Moreover, antibiotics were unusually overprescribed for patients, notably for patients between 18 and 65 years of age in general practice.[16,38] Accordingly, we could not exclude

Table 4. Sensitivity analyses: odds ratio for treatment failure of index exacerbation among COPD outpatients.

Limited study population (Number)	Treatment failure No. (%)		Crude OR (95% CI)	Adjusted OR[a] (95% CI)	PS adjusted OR[b] (95% CI)
	Antibiotics	Reference			
COPD without asthma (736)	36 (10.3))	39 (10.1)	1.03 [0.64, 1.66]	0.58 [0.32, 1.01]	0.57 [0.32, 1.02]
COPD with asthma (369)	20 (11.8)	23 (11.5)	1.03 [0.55, 1.95]	0.81 [0.39, 1.67]	0.71 [0.35, 1.48]
Spirometrically confirmed COPD (707)	30 (9.4)	43 (1.1)	0.83 [0.51, 1.36]	0.56 [0.32, 0.97]	0.52 [0.29, 0.90]
Self-reported COPD (398)	26 (13.1)	19 (9.5)	1.42 [0.76, 2.67]	1.03 [0.46, 2.32]	0.94 [0.43, 2.06]

Abbreviation: OR: odds ratio; CI: confidence interval; PS: propensity score weighted analysis; No.: number; [a]adjusted result by logistic regression; [b]Adjusted result by propensity score weighted analysis; *P<0.05;

the possibility that antibiotic treatment for some of patients were improperly prescribed. The general implication of our finding is that contrasting with an ideal situation in which all patients' prescriptions adhere to the guidelines, effects of antibiotics for a bacterially caused AECOPD were underestimated in our study.

Clinical implications

Although improper use of antibiotics may occur within the COPD outpatient population in a real-world setting, our findings supported the beneficial effect of antibiotics used for AECOPD. Valid antibiotics prescription could further improve the effects of antibiotic treatments on AECOPD. According to the latest GOLD guideline, the sputum colour can be used to avoid unnecessary antibiotic therapy safely with cream, white or clear sputum indicating very low bacterial infections.[3,14] If applicable, a procalcitonin-guided algorithm or C-reactive protein (CPR) test can also be considered before making decisions for GP to reduce the unnecessary administration of antibiotics .[39,40]

Given significant variability between GP practices of prescribing antibiotics to COPD patients experiencing exacerbations,[41] we recommend doxycycline as the mainstay based on our findings that are consistent with the Dutch guidelines.[26] Though estimates indicate similar beneficial effects for some specific antibiotics, larger studies of high quality with extensive control for potential confounders are needed to explore their role in AECOPD management. Importantly, the final antibiotic choice should also be based on the local bacterial resistance patterns, and sputum cultures of high-risk patients with frequent exacerbations and severe airflow limitations should be performed, given the possible presence of resistant pathogens.[3]

Strengths and limitations

Our study had several strengths. Firstly, the population included in this study was representative of COPD outpatients. Hence our findings reflect the real-world effects of antibiotic treatment for AECOPD. Secondly, properly diagnosed COPD patients and their complete background information , for example, lung function, smoking status and related comorbidities that were lacking in previous observational studies were included in this study. Moreover, the outcomes were adjusted for possible confounders using both logistic regression and PS analyses. Sensitivity analyses by further narrowing study population by excluding different sources of uncertainty were also conducted to test the robustness of the results.

There were, however, several limitations. Firstly, an acute exacerbation was defined by the prescriptions of systemic glucocorticoids as a proxy according to Dutch guideline for AECOPD and this may have led to some misclassifications. In addition, we lacked clinical information on the severity of AECOPD at the time of diagnosis. Moreover, the severity of exacerbations may not have been evenly distributed between the two comparison

groups. Secondly, antibiotics may have been prescribed improperly in the absence of confirmed bacterial infections, this could lead to an underestimated effect of antibiotics on AECOPD. Thirdly, the low power of subgroup analyses in this study hindered us to make a definitive conclusion regarding the effects of some specific antibiotics on AECOPD. Finally, the IADB.nl did not include prescriptions during a hospitalization. However, given the relatively mild outpatient group, we expect only few patients to have such a serious outcome in our study.

CONCLUSION

The results of this study support the use of antibiotic therapy, notably doxycycline, for AECOPD in addition to systematic glucocorticoids treatment among outpatients. Further larger qualified studies with prospective designs and extensive control of confounders are required to explore the effects of other specific antibiotics in a real-world settings. No further long-term beneficial effects of antibiotics treatment on AECOPD were found for subsequent exacerbations.

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