THE ROLE OF ANTIBIOTICS IN THE MANAGEMENT OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE OUTPATIENT SETTING

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is an illness characterized by progressive respiratory symptoms and frequent exacerbations. Acute exacerbations of COPD (AECOPD) are mostly treated in the outpatient setting and the use of antibiotics for this patient population remains controversial.

This thesis aimed to explore the role of antibiotics in the outpatient management of AECOPD through two studies. The first study was a systematic review of randomized controlled trials examining the impact of antibiotics on the outcome of treatment failure in outpatients with AECOPD. Meta-analysis was conducted using both frequentist random effects and Bayesian analyses. The second study was a secondary analysis of a prospective cohort of patients with AECOPD discharged from the emergency department. The association between antibiotic treatment and the outcome of rehospitalization within 14 days of discharge was examined using logistic regression and propensity score matched analyses.

In the systematic review and meta-analysis, both frequentist random effects and Bayesian analyses revealed a high likelihood of benefit for antibiotics. In the secondary analysis, there was no association between treatment with antibiotics and rehospitalization however due to a small sample size and a low event rate, there was considerable risk of Type II error. Overall, when considering the results of these two studies in the context of previous literature, treatment with antibiotics likely provides a modest benefit in the outpatient management of AECOPD.

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ABBREVIATIONS USED IN THE TEXT

COPD – chronic obstructive pulmonary disease

AECOPD – acute exacerbation of chronic obstructive pulmonary disease

GOLD – Global Initiative for Chronic Obstructive Lung Disease

HIV – human immunodeficiency virus

FEV_1 – forced expiratory volume in one second

FVC – forced vital capacity

mMRC – modified Medical Research Council

ICU – intensive care unit

SABA – short-acting $beta_2$-agonist

LABA – long-acting $beta_2$-agonist

SAMA – short-acting muscarinic antagonist

LAMA – long-acting muscarinic antagonist

ICS – inhaled corticosteroid

CPAP – continuous positive airway pressure

BPAP – bilevel positive airway pressure

MDI – metered dose inhaler

CRP – C-reactive protein

RCT – randomized controlled trial

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RoB2 – Cochrane Risk-of-Bias Tool Version 2

RR – risk ratio

CI – confidence interval

CrI – credible interval

OR – odds ratio

ED – emergency department

OCRS – Ottawa COPD Risk Scale

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation. This disorder is caused by abnormalities of the airway and alveoli resulting from exposure to noxious particles or gases or abnormal lung development. The natural course of this disease is chronic and progressive, often punctuated by episodes of increasing respiratory symptoms known as exacerbations (1).

Acute exacerbations of COPD (AECOPD) are defined as worsening respiratory symptoms requiring additional therapy (1). The most common respiratory symptoms of AECOPD include dyspnea, cough, and sputum production. Exacerbations of COPD are heterogenous in etiology and presentation and can be precipitated by disease progression, viral or bacterial infections, and environmental pollutants (2). Management of AECOPD comprises of respiratory support such as supplemental oxygen and positive pressure ventilation as well as pharmacologic therapies including bronchodilators, oral corticosteroids, and antibiotics. COPD is the third leading cause of death worldwide and effective management of exacerbations is crucial to limiting the progression and burden of disease (1).

1.2 Rationale for Thesis

COPD is an important public health challenge that is both preventable and treatable. Acute exacerbations of COPD serve as key markers of disease progression and, consequently, effective treatment and prevention of AECOPD represent important targets for intervention in preventing the morbidity and mortality of COPD.

The majority of patients with AECOPD are managed in the outpatient setting (1). While treatments such as bronchodilators and oral corticosteroids are well established in demonstrating benefit, the use of antibiotics in this patient population remains controversial. Antibiotic overuse may result in harmful medication side effects, drug-drug interactions, polypharmacy, increased costs, and promote resistant organisms (3). Therefore, it is imperative to determine the role of antibiotics in the management of AECOPD in the outpatient setting.

1.3 Objective of Thesis

The objective of this thesis is to examine the impact of antibiotics on patient outcomes in the management of AECOPD in the outpatient setting.

1.4 Overview of Thesis

Chapter One: *Introduction*

This chapter serves as a brief introduction to the thesis topic and provides an overview of its rationale, objective, and contents.

Chapter Two: Background

This chapter provides a background literature review of the current understanding of COPD as well as clinical context for the thesis.

Chapter Three: Antibiotics for acute exacerbations of chronic obstructive pulmonary disease managed in the outpatient setting: A systematic review and meta-analysis

This chapter presents a systematic review and meta-analysis of randomized controlled trials that examine the impact of antibiotics on the outcome of treatment failure for outpatients with AECOPD.

Chapter Four: Association between antibiotics and rehospitalization in patients with acute exacerbations of chronic obstructive pulmonary disease discharged from the emergency department

This chapter presents a secondary analysis of data from a prospective cohort of patients with AECOPD discharged from the emergency department. The analysis examines the impact of antibiotic treatment on the outcome of rehospitalization in this patient cohort.

Chapter Five: Discussion

This chapter summarizes the studies presented in this thesis and interprets the results in the context of existing literature. Strengths and limitations of the studies as well as clinical and research implications are also discussed.

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CHAPTER TWO: BACKGROUND

2.1 Introduction and Definitions

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by progressive, incompletely reversible airflow obstruction resulting in persistent respiratory symptoms (1). The most common symptoms that characterize this illness are dyspnea, cough, and sputum production (2). These symptoms are chronic and progressive and a result of lung parenchymal destruction and abnormalities in the small airways (1). There are various contributing factors that can lead to these changes such as noxious environmental particles and gases—with the most prominent cause being tobacco smoke—as well as infections and abnormal lung development (1,3).

The terms "emphysema" and "chronic bronchitis" have often been associated with COPD. These terms, however, can be misleading and are not included in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD (1). Emphysema is a term used to describe the pathologic destruction of alveoli and only describes one of many abnormalities in patients with COPD. Chronic bronchitis refers to clinical symptoms and is usually defined as the presence of cough and sputum production for at least three months in each of the last two consecutive years, which may not necessarily be associated with airflow limitations. Thus, the label of chronic bronchitis does not accurately capture all patients who have the airflow limitations and structural changes that are consistent with COPD (1).

2.2 Epidemiology

COPD is a common condition with a high global burden of disease. It is estimated that COPD affects over 300 million people globally. From 1990 to 2017, the prevalence of COPD

has increased by almost 40% (4). As of 2017, COPD has become the third leading cause of death worldwide (5). In 2019, COPD resulted in approximately 3.3 million deaths globally (4).

Estimates of COPD prevalence and mortality, however, vary widely between studies and are limited by study methodology. Studies that estimate prevalence using patient self-reported diagnosis are consistently prone to underestimation (2,6). Moreover, underdiagnosis and inaccuracy of diagnostic codes in administrative health databases may result in further underestimation of COPD prevalence and mortality (7,8). Finally, the diagnosis of COPD currently depends on spirometry to determine the degree and reversibility of airflow limitation. Spirometry, however, is not widely available in many low- and middle- income countries and thus reliable data regarding the true prevalence and burden of disease is lacking (5).

Comparing 2017 to 2007, deaths from COPD increased by 17.5% (5). The prevalence of COPD is expected to continue to rise over the next 40 years and by 2060, there may be over 5.4 million deaths annually from COPD (1). This prediction is related to the increasing prevalence of cigarette smoking in developing countries as well as the aging population of high-income countries. Advances in many other chronic diseases have prolonged survival and life expectancy resulting in much larger elderly populations in many countries (1).

While rates of tobacco smoking are directly related to the prevalence of COPD, in many countries, outdoor, indoor, and occupational air pollution are major contributing risk factors (1). Previous studies have shown that 20 to 30% of patients with COPD have never smoked. Instead, major contributing factors are air pollution such as smoke from biomass fuel, asthma, infections such as human immunodeficiency virus (HIV) and tuberculosis, and impaired lung growth (9). While the prevalence and mortality of COPD varies across countries and groups within

countries, the burden of disease disproportionally affects low- and middle- income countries, where the majority of deaths due to COPD occur (5).

2.3 Pathophysiology

The unifying mechanism by which COPD develops is chronic inflammation causing changes to the airways, lung parenchyma, and pulmonary vasculature (10). While lung inflammation can be a normal process in response to noxious substances, there is an abnormal inflammatory response that results in the development of COPD. Mediators of inflammation leading to COPD include oxidative stress, pro-inflammatory cells and cytokines, and protease-antiprotease imbalance (11).

The degree of inflammation and, consequently, the risk of disease development and progression varies from person to person. A number of factors have been shown to affect the prognosis of COPD, including age, sex, comorbidities, genetics, infections, lung growth, socioeconomic status, and continued exposure to noxious particles and gases (1).

Numerous causes of chronic inflammation in COPD have been described. The most common cause is tobacco smoke from cigarettes. Traditionally COPD has been viewed as a "self-inflicted" disease caused by cigarette smoking. But this notion has now been expanded to acknowledge that COPD is a complex disease that is affected by many risk factors throughout life. At least one in five cases of COPD globally occurs in patients who have never smoked (9). Indoor and outdoor air pollution, occupational exposures, and infections are other well-documented causes of chronic inflammation that leads to COPD (12).

Chronic inflammation leads to many structural changes within the lungs. Inflammation and narrowing of small airways lead to decreased airflow and gas trapping during exhalation

(13). Gas trapping is commonly referred to as hyperinflation, which can be static (constant over time) or dynamic (progressively increasing over time). Hyperinflation in the lungs leads to decreased inspiratory capacity and causes dyspnea and decreased exercise tolerance (14). Clinically, the degree of airway limitation is commonly described using spirometry by measuring the forced expiratory volume in one second (FEV_1).

Destruction of lung parenchyma, or emphysema, also leads to decreased airflow as well as impaired gas exchange. Abnormal gas exchange of carbon dioxide and oxygen leads to ventilation-perfusion mismatch, resulting in hypoxemia. Increased dead space ventilation and reduced ventilatory drive also causes retention of carbon dioxide and leads to hypercapnia (15). Chronic hypoxemia leads to vasoconstriction of pulmonary arteries, which can cause pulmonary hypertension and right-sided heart failure (16).

Mucus hypersecretion is another characteristic feature of COPD but may not be seen in all patients. When present, mucus hypersecretion is mediated by activation of epidermal growth factor receptor causing an increased number of goblet cells and enlarged submucosal glands (17). Clinically, this results in a chronic productive cough, sometimes termed chronic bronchitis, which may or may not be associated with airflow limitation (1).

2.4 Risk Factors

There are several well-known risk factors for the development of COPD. From an epidemiologic perspective, the diagnosis of COPD is more prevalent in men compared to women, in people who smoke compared to people who do not, and in older patients (over 40 years of age) compared to younger patients (under 40 years of age) (18–20).

2.4.1 Tobacco smoking

Tobacco smoking is the most well-documented risk factor for the development of COPD. People who smoke cigarettes have a higher prevalence of respiratory symptoms, greater annual decline in FEV_1, and higher mortality from COPD compared to people who do not smoke (21). In addition to cigarettes, smoking tobacco using cigars and pipes are also associated with COPD (22). Marijuana smoking has also been associated with COPD (23).

Approximately half of COPD cases worldwide are due to non-tobacco-related risk factors (9). While smoking significantly contributes to COPD prevalence in high-income countries, smoking is less of a contributor in countries with lower socioeconomic index where non-tobacco exposures are higher. In general, non-tobacco-related risk factors for COPD become more prominent as wealth decreases (9).

2.4.2 Occupational exposures

Occupational exposures such as dust, chemicals, and fumes have been shown to be risk factors for COPD (1). Occupations such as sculptors, gardeners, and warehouse workers have been shown to be associated with an increased risk of COPD among people who have never smoked (9). Based on a large population-based study in the US, the proportion of COPD attributable to occupational exposures was approximately 30% among people who have never smoked and 20% overall (24).

2.4.3 Indoor air pollution

Indoor air pollution such as biomass fuel used for cooking and heating in enclosed spaces is an important risk factor for COPD. In women who cook at home using biomass fuel, it is

estimated that 2 hours of exposure per day for 13 years is equivalent to 10 pack-years of cigarette smoking (9). In many tropical countries, another potential source of indoor air pollution is from mosquito coils made from coconut husk and pyrethrum. They are burned indoors in the night to kill mosquitos but produce significant concentrations of particulate matter. People exposed to mosquito coils have a higher prevalence of dyspnea, cough, and wheeze (9).

2.4.4 Outdoor air pollution

Outdoor air pollution as measured by levels of particulate matter and nitrogen dioxide (NO_2) has been shown to be associated with COPD in multiple countries (9). Short-term exposure to ambient particulate matter is associated with increased COPD hospitalizations and mortality (25). However, the impact of outdoor air pollution is relatively small when compared to cigarette smoking and the association may be mediated by the effects of outdoor air pollution on lung maturation and development in childhood. Indeed, impaired lung growth in early life has also been shown to be a prominent risk factor for COPD (1).

2.4.5 Asthma

In high-income countries, asthma appears to be the most common risk factor for COPD in people who have never smoked (9). Chronic airway inflammation and airway remodelling are believed to be the underlying mechanisms of how asthma could precipitate COPD. Among people with COPD, almost 25% have a history of asthma. Additionally, asthma also increases the probability that a person who smokes will develop COPD (9). A subset of patients will have asthma-COPD overlap, which is a heterogenous condition that contains features of both asthma and COPD such as airflow limitation and hyperinflation. While there is a lack of consensus

regarding the definition and a corresponding lack of understanding of the prevalence, asthma-COPD overlap appears to be a different entity when compared to COPD in people who have never smoked (26).

2.4.6 Infections

Infections such as pulmonary tuberculosis and HIV have been shown to be associated with COPD (9). Pulmonary tuberculosis infection likely causes endobronchial and lung tissue destruction, resulting in emphysema and small airway obstruction. The link between HIV and COPD is believed to be mediated by immune and inflammatory mechanisms. Not only is COPD more common in HIV-positive patients when compared to HIV-negative patients, lower CD4 cell counts have also been associated with higher COPD prevalence in patients with HIV (9).

2.4.7 Socioeconomic status

As with many chronic illnesses, the role of socioeconomic status is of major importance in the development and progression of COPD. Poverty is consistently associated with airflow obstruction at individual and community levels (27). It is likely that lower socioeconomic status increases the risk of COPD through increased occupational exposures, malnutrition, living conditions that are prone to exposure to indoor air pollution, reduced access to health care and screening, and lower health literacy regarding the risks to lung health (9).

2.5 Diagnosis

The diagnosis of COPD should be made on the basis of symptoms, risk factors, and spirometry that demonstrates persistent airflow obstruction (12). COPD should be considered in

any patient with the symptoms of dyspnea, chronic cough, or sputum production, especially if there is a history of any COPD risk factors such as cigarette smoking. A detailed history and physical examination should be performed as part of the initial assessment, followed by appropriate investigations and spirometry.

2.5.1 Clinical history

Dyspnea is a hallmark symptom of COPD and can cause significant disability and anxiety (28). Chronic cough in COPD may be productive or non-productive and airflow limitation may be present without cough (29). Sputum production can be difficult to evaluate as it can be intermittent and patients may not always expectorate the sputum (30). Other symptoms that can be associated with COPD include wheezing, chest tightness, fatigue, anorexia, and weight loss.

On past medical history, conditions such as asthma, allergy, sinusitis, nasal polyps, childhood respiratory infections, HIV, and tuberculosis would be important potential risk factors for the development of COPD. Comorbidities such as heart disease, osteoporosis, malignancies, and anxiety and depression are important as they may contribute to restrictions in daily activities and overall disability (1).

The pattern of symptom development is important to elicit on medical history. It may reveal episodes of intermittent worsening of symptoms consistent with exacerbations, even if these episodes were not identified as COPD exacerbations. The impact of symptoms on the patient's life is another crucial aspect of the medical history. COPD can result in significant limitations in activity, missed work, and feeling of anxiety and depression. Furthermore, social

and family support as well as potential opportunities to discuss risk factor mitigation such as smoking cessation should also be explored on history (1).

2.5.2 Physical examination

On physical examination, vital signs may reveal tachypnea (increased respiratory rate) or hypoxia (low oxygen saturation). Evidence of hyperinflation such as increased anteroposterior chest diameter and increased resonance to percussion may be evident in severe disease. In the setting of an exacerbation, patients may have decreased air entry and wheezing on auscultation as well as signs of respiratory distress such as use of accessory muscles, tripod positioning, and cyanosis. While physical signs may provide helpful clinical information, physical examination has relatively low sensitivity and specificity with respect to diagnosing COPD and the absence of these signs does not rule out the diagnosis (1).

2.5.3 Investigations

While chest radiography is not, on its own, useful for diagnosing COPD, it may be helpful in assessing for other alternative diagnoses such as congestive heart failure. Chest x-ray may also reveal concomitant respiratory disease such as pneumonia, pulmonary fibrosis, or bronchiectasis. Signs of COPD on chest x-ray may include flattening of the diaphragm, hyperlucency of lungs, and rapid tapering of vascular markings (1).

Spirometry remains the cornerstone of diagnosing COPD. It is a non-invasive, reproducible, and objective measurement of airflow limitation. Spirometry is indicated for any patient with symptoms or risk factors of COPD and likely not necessary for asymptomatic individuals (1). The most important measurements for the diagnosis of COPD are forced vital capacity (FVC) and the FEV_1. Persistent airflow limitation is defined as a post-bronchodilator

FEV_1/FVC ratio of less than 0.70. Given that the FEV_1/FVC ratio declines with age, the fixed value of 0.70 may result in more frequent COPD diagnoses in the elderly. As a result, an alternative threshold of using the fifth percentile lower limit of normal of the FEV_1/FVC ratio has been proposed (31). Controversy exists regarding which threshold to use but the lower limit of normal has not been shown to be better than the fixed value in terms of discriminative accuracy and prognosis (32). Considering the simplicity and consistency of the fixed value and the lack of evidence to demonstrate superiority of the lower limit of normal, the fixed value of 0.70 is recommended by GOLD (1).

2.5.4 Classification of disease severity

The severity of airflow limitation is classified using FEV_1 (Table 1). However, this measurement is only weakly correlated with symptom severity. To classify symptom severity, the most widely used tool is the Modified British Medical Research Council Questionnaire, which has been found to correlate well with health status and mortality risk (Table 2). Another important aspect of COPD assessment is history of exacerbations, which predicts the risk of future exacerbations. Therefore, the "ABCD" classification system was created by GOLD in 2011, which combines symptom severity and exacerbation history. The "ABCD" classification utilizes clinical information, independent of spirometry, to help guide therapeutic management for individual patients (Table 3). It has been shown to be similar to spirometry measurements of airflow limitation in terms of predicting mortality and other important COPD outcomes (1).

Table 1: GOLD classification of airflow limitation in COPD (1)

FEV_1	Airflow limitation	GOLD classification
≥ 80% predicted	Mild	1
≥ 50% and < 80% predicted	Moderate	2
≥ 30% and < 50% predicted	Severe	3
< 30% predicted	Very severe	4

GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second

Table 2: Modified Medical Research Council Dyspnea Scale (1)

mMRC Grade	Symptoms
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight hill.
2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
3	I stop for breath after walking about 100 meters or after a few minutes on the level.
4	I am too breathless to leave the house or I am breathless when dressing or undressing.

mMRC, Modified Medical Research Council

Table 3: GOLD "ABCD" assessment tool for COPD (1)

		Symptoms	
		mMRC 0-1	mMRC ≥ 2
Moderate or severe exacerbation history	0 or 1 (not leading to hospital admission)	A	B
	≥ 2 or ≥ 1 leading to hospital admission	C	D

GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified Medical Research Council

2.6 Management of Stable COPD

2.6.1 Smoking cessation

Smoking cessation has the greatest potential to influence the natural course of COPD. Among COPD patients, approximately 40-50% smoke (33). Behavioural or pharmacologic therapies or a combination of both—without preference for any particular form of therapy—have been shown to be effective in helping people who smoke with COPD to quit smoking (34).

2.6.2 Vaccinations

Vaccinations against viral and bacterial respiratory infections have been shown to reduce morbidity and mortality in patients with COPD. The influenza vaccine significantly reduces COPD exacerbations as well as hospitalizations and death in elderly patients (35,36). The pneumococcal 13-valent polysaccharide conjugate vaccine (PCV13) has been shown to reduce pneumococcal community-acquired pneumonia and invasive pneumococcal disease among older adults (37). Pneumococcal vaccination has also been shown to reduce the rates of COPD exacerbation (38). Vaccination against coronavirus disease 2019 (COVID-19) has been shown

to be highly effective in reducing hospitalization and intensive care unit (ICU) admission and patients with COPD should receive the COVID-19 vaccination in accordance with international guidelines (1,39).

2.6.3 Bronchodilators

Bronchodilators are medications that affect airway smooth muscle tone and widen airways to increase expiratory flow. Specifically, these medications act as agonists of $beta_2$-adrenergic receptors in airway smooth muscle. $Beta_2$-agonists can be short-acting or long-acting. Short-acting $beta_2$-agonists (SABAs) typically last 4 to 6 hours while long-acting $beta_2$-agonists (LABAs) have a duration of action of 12 or more hours. In COPD, bronchodilators increase FEV_1 and reduce dynamic hyperinflation (40,41). For stable COPD, regular and as-needed use of SABAs improves FEV_1 and symptoms (42).

Antimuscarinics are medications that act on muscarinic receptors expressed in airway smooth muscle to block the bronchoconstrictor effects of acetylcholine. Antimuscarinics can be short-acting muscarinic antagonists (SAMAs) or long-acting muscarinic antagonists (LAMAs). For stable COPD, SAMAs such as ipratropium bromide used alone does not seem to be better than LABAs alone in terms of COPD symptoms and exercise tolerance, however the combination of SAMA and LABA seems to confer a modest benefit in quality of life and reduced requirements for SABAs (43). Treatment with LAMAs such as tiotropium significantly improves quality of life and risk of exacerbation (44).

Combining bronchodilators with different mechanisms in thought to increase bronchodilation while minimizing the risk of side effects. For patients with symptoms from moderate to severe airflow limitation, combination LABA/LAMA treatment has been shown to

be superior to inhalers with individual components in terms of quality of life, rescue medication use, and exacerbation risk (45). Additionally, in symptomatic patients with low exacerbation risk not receiving inhaled corticosteroids, combination LABA/LAMA treatment has also been shown to improve lung function and symptoms when compared to long-acting bronchodilator monotherapy (46).

2.6.4 Inhaled corticosteroids

Inhaled corticosteroids (ICS) as monotherapy has not been shown to be effective in slowing the decline in FEV_1 or decreasing mortality in patients with COPD (47). In addition, ICS use has been associated with higher rates of oral candidiasis, hoarse voice, skin bruising, and pneumonia (47). For patients with moderate to severe COPD, however, an ICS combined with a LABA is more effective than ICS alone with respect to improving lung function, exacerbation risk, and mortality (48). There is also evidence to suggest that patients with higher blood eosinophil are more likely to benefit more from ICS therapy (49).

Triple therapy for stable COPD consists of LABA, LAMA, and ICS. Two recent large randomized controlled trials compared triple therapy with LABA/LAMA and LABA/ICS (50,51). Both trials enrolled symptomatic patients with a history of frequent exacerbations. In the ETHOS trial, triple therapy was shown to result in significantly lower rates of moderate or severe exacerbations when compared to LABA/LAMA or LABA/ICS (50). In the IMPACT trial, triple therapy resulted reduced risk of all-cause mortality compared to LABA/LAMA, but there was no difference when compared to LABA/ICS (51).

2.6.5 Prophylactic antibiotics

Macrolide antibiotics such as azithromycin and erythromycin have been shown to reduce the risk of exacerbation when compared to usual care (52–54). However, prolonged macrolide use may be associated with bacterial resistance, prolonged QT interval (increasing the risk of life-threatening arrhythmias), and hearing impairment (54). Pulsed moxifloxacin has also been shown to reduce the risk of exacerbation compared to placebo in patients with stable COPD, with the moxifloxacin group experiencing more drug-related adverse events, mostly in the form of gastrointestinal symptoms (55).

2.6.6 Pulmonary rehabilitation

Pulmonary rehabilitation is an important non-pharmacologic aspect of the management of stable COPD. It is defined as "a comprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, self-management intervention aiming at behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (56). The optimum duration of pulmonary rehabilitation programs is about six to eight weeks and they should be delivered by a multidisciplinary team. Pulmonary rehabilitation has been shown to improve dyspnea, quality of life, and exercise capacity (57).

2.6.7 Oxygen therapy

Domiciliary oxygen therapy has been shown to improve survival for COPD patients with severe resting hypoxemia, defined as arterial P_aO_2 less than 55 mmHg (58). This benefit was not seen for patients with mild to moderate hypoxemia or those with only desaturation at night (58).

2.6.8 Positive pressure ventilation

For stable COPD, non-invasive positive pressure ventilation in the form of continuous positive airway pressure (CPAP) can improve survival and decrease hospitalization for patients with both COPD and obstructive sleep apnea (59).

2.6.9 Interventional therapies

Lung volume reduction surgery is a procedure where parts of the lungs are resected to reduce hyperinflation and improve the efficiency of respiratory muscles. In patients with severe emphysema, lung volume reduction surgery improved survival when compared to medical treatment (60). Endobronchial valve placement is a less invasive approach to reducing lung volumes and improve respiratory muscle mechanics and has been shown to have similar benefits with fewer complications when compared to lung volume reduction surgery (61).

2.6.10 Palliative care

Palliative care is a crucial aspect in the management of patients with COPD. Palliative care expands the goals of treatment from modifying disease to alleviating symptoms and improving quality of life and should be integrated concurrently with COPD-directed therapies (62). For many patients, COPD results in gradual decline in health status and progressively

increasing symptoms. A multitude of symptoms can result from advanced COPD including fatigue, dyspnea, depression, anxiety, and insomnia (1). For patients approaching end-stage disease, these symptoms should be addressed and consideration should be made early on for consultation with palliative care specialists (62).

2.7 Acute Exacerbations of COPD

The natural course of COPD is characterized by progressive decline in lung function and acute episodes of increasing symptoms known as exacerbations. Acute exacerbations of COPD (AECOPD) are defined clinically as an acute worsening of respiratory symptoms requiring additional therapy (1).

AECOPD should be diagnosed and treated early. Many COPD exacerbations are underreported by patients and can have a negative impact on health status (63). Symptoms of COPD exacerbation typically last 7 to 10 days. At 8 weeks, up to 20% of patients will not have recovered to their pre-exacerbation state (64). Early treatment of AECOPD is associated with faster recovery and higher health-related quality of life (65). Prolonged symptomatic COPD exacerbation is associated with accelerated decline in lung function (66).

The best predictor of exacerbations is a history of previous exacerbations (67,68). Exacerbations become more frequent as the severity of COPD increases and has also been shown to be associated with gastroesophageal reflux, poorer quality of life, and elevated white blood cell count (68). Frequent exacerbations are associated with faster decline in lung function, lower quality of life, reduced exercise capacity, increased airway and systemic inflammation, and increased mortality (69–73).

2.7.1 Clinical evaluation of AECOPD

Clinical evaluation of AECOPD should include a focused medical history, physical examination, and relevant investigations. It is crucial to assess for any other potential causes of the patient's presenting symptoms as many other conditions mimic those of AECOPD (Table 4). Inappropriately attributing the patient's symptoms to AECOPD may lead to negative outcomes (74).

Table 4: Differential diagnosis of AECOPD

Asthma
Pneumonia
Pneumothorax
Pleural effusion
Pulmonary embolism
Cardiogenic pulmonary edema (e.g. congestive heart failure)
Non-cardiogenic pulmonary edema (e.g. acute respiratory distress syndrome)

AECOPD, acute exacerbation of chronic obstructive pulmonary disease

The main clinical symptoms of COPD exacerbation are increased dyspnea, increased sputum production, and increased sputum purulence. Dyspnea is thought to be caused by airway narrowing and increased ventilation/perfusion (V/Q) mismatch. Airway narrowing is a consequence of multiple processes including mucosal damage, inflammatory cell infiltration, airway edema, and increased airway secretions. Increased sputum production is caused by mucous gland hypertrophy and goblet cell hyperplasia and degranulation while recruitment of eosinophils and neutrophils is thought to cause increased sputum purulence (75).

The most commonly cited clinical criteria used to characterize AECOPD presentations are those described by Anthonisen and colleagues: Type 1 exacerbations are characterized by the presence of all three cardinal symptoms of increased dyspnea, increased sputum volume, and new or increased sputum purulence. Type 2 exacerbations are defined as the presence of any of

the two cardinal symptoms. Type 3 exacerbations are defined as the presence of only one of the cardinal symptoms with at least one of upper respiratory infection symptoms (sore throat, nasal discharge), fever, wheezing, cough, or increased heart rate or respiratory rate by 20% compared to baseline (76).

COPD is complex and heterogenous condition (77). Exacerbations can be attributed to disease progression, viral or bacterial infections, environmental pollutants, and ambient temperature changes (74). The most common viral infection associated with COPD exacerbation is rhinovirus, which can be detected up to a week after exacerbation onset (75). Eosinophilia predominant exacerbations have been associated with viral infection and have also been proposed as a separate entity compared to bacterial exacerbations (78,79). These phenotypes have been noted to be indistinguishable based on clinical symptoms or Anthonisen criteria (78). Exacerbations associated with an increase in sputum or blood eosinophils may be more responsive to systemic steroids (80). A proportion of patients may also have bacterial and viral coinfection (79).

2.7.2 Management of AECOPD

The goals of treatment for AECOPD should be to mitigate the negative impacts of the current exacerbation and to prevent the development of subsequent exacerbations. More than 80% of AECOPD are managed in the outpatient setting using pharmacologic treatments including bronchodilators, oral corticosteroids, and antibiotics (1).

GOLD classifies AECOPD into three levels of severity corresponding to the indicated treatments: mild, moderate, and severe. Mild exacerbations are typically treated with short acting bronchodilators only. Moderate exacerbations are treated with short acting

bronchodilators with the addition of antibiotics and/or oral corticosteroids. Severe exacerbations require emergency department visit or hospitalization and may also be associated with acute respiratory failure (1).

2.7.3 Indications for hospitalization

Indications for hospitalization or inpatient management of AECOPD include acute respiratory failure, severe symptoms, presence of serious comorbidities, failure of initial outpatient treatment, and insufficient home support (1). Acute respiratory failure can be classified as hypoxemic, hypercapnic, or mixed and should be assessed based on respiratory rate, pulse oximetry, use of accessory muscles, presence of cyanosis or mental status changes, and blood gas analysis. Signs of respiratory failure clinically or blood gas analysis may necessitate inpatient management of AECOPD.

2.7.4 Respiratory support

Supplemental oxygen should be used to treat hypoxemia targeting an oxygen saturation of 88 to 92% (81). For patients with significantly increased work of breathing or severe respiratory acidosis, non-invasive positive pressure ventilation, usually in the form of bilevel positive airway pressure (BPAP) can be highly beneficial. Non-invasive ventilation decreases work of breathing, improves oxygenation, and improves respiratory acidosis (82–84). In addition, non-invasive ventilation reduces the need for endotracheal intubation, reduce length of hospital stay, and improve mortality (85). Patients with AECOPD who have decreased level of consciousness, persistent hypoxemia or hypercapnia, require endotracheal intubation, have hemodynamic instability, or fail initial emergency therapy require admission to the ICU (1).

2.7.5 Bronchodilators

Short-acting bronchodilators including inhaled beta$_2$-agonists and anticholinergics should be initiated as the first-line pharmacologic treatment for AECOPD. There are no differences in FEV_1 at one hour and safety outcomes whether the bronchodilators are delivered through metered dose inhalers (MDIs) or nebulizers (86).

2.7.6 Systemic corticosteroids

Systemic corticosteroids have been shown to improve oxygenation, decrease the risk of relapse and treatment failure, and reduce the length of hospitalization (87–89). A total of five days of corticosteroid treatment has been shown to be optimal duration of treatment and longer courses of corticosteroids may be associated with pneumonia and increased mortality (90,91). There is no difference in the outcome of treatment failure when comparing corticosteroids administered through intravenous and oral routes (92).

2.7.7 Antibiotics

The routine use of antibiotics in the management of AECOPD remains controversial (1). While bacterial infection can precipitate AECOPD and should be treated with antibiotics, many exacerbations are not caused by bacterial infection and using antibiotics in those cases may expose patients to the risks of antibiotics without the potential to derive any benefit.

2.7.7.1 Sputum assessment

Sputum colour and purulence is associated with positive bacterial cultures and may be indicative of patients with bacterial exacerbation requiring antibiotics (76,93). However, patient

reports of sputum colour and purulence may be unreliable and even sputum assessed by laboratory analysts demonstrates about 52% specificity for positive bacterial cultures (94).

2.7.7.2 Laboratory biomarkers

Given the difficulty of clinically distinguishing patients with bacterial exacerbations, laboratory markers such as C-reactive protein (CRP) and procalcitonin have been studied to select patients who may need antibiotics. Previous randomized controlled trials (RCTs) in both outpatient and inpatient settings have shown that CRP-guided lower antibiotic usage compared to usual care or assessment of clinical symptoms with no increase in adverse outcomes (95,96). Previous systematic reviews on procalcitonin have had conflicting results and were limited by the methodologic quality of existing studies. While procalcitonin-guided strategies may decrease overall antibiotic exposure, the effect on clinical outcomes is unclear and may result in higher mortality for patients in the ICU (97,98).

2.7.7.3 Current guidelines

Current guidelines from GOLD suggest antibiotics for patients with all three cardinal symptoms of increased dyspnea, sputum volume, and sputum purulence, or two of the three if increased sputum purulence is one of the two symptoms (1). Joint guidelines from the European Respiratory Society and American Thoracic Society suggest that while antibiotics reduce treatment failure and increase time to next exacerbation, in ambulatory patients the overall rate of treatment failure is low, even in placebo groups, so additional research is needed to identify which patients require antibiotic therapy (99).

2.7.7.4 Current evidence

Multiple previous RCTs have compared antibiotics with placebo for patients with AECOPD in both inpatient and outpatient settings with conflicting results (100–105). Previous systematic reviews have found that antibiotics are likely beneficial for patients who require admission to the ICU. However, for patients managed in the outpatient setting, the benefit of antibiotics remains inconclusive (106–108).

The choice of antibiotic in AECOPD has been examined in previous systematic reviews. In a systematic review from 2007, "second-line" antibiotics (amoxicillin-clavulanic acid, macrolides, second and third generation cephalosporins, and quinolones) were found to have higher treatment success than "first-line" antibiotics (amoxicillin, ampicillin, pivampicillin, trimethoprim-sulfamethoxazole, and doxycycline) (109). In subsequent systematic reviews, there were no differences in treatment success between macrolides, quinolones, amoxicillin-clavulanic acid, and trimethoprim-sulfamethoxazole (110,111). In terms of antibiotic duration, there were no differences in treatment success when comparing five days of antibiotic therapy with seven or more days, with shorter durations of antibiotics associated with fewer adverse events (112,113).

2.7.7.5 Adverse effects of antibiotics

Unnecessary use of antibiotics should be avoided as antibiotics are known to be associated with promoting resistant organisms, costs, polypharmacy, drug-drug interactions, and adverse effects (106). Antibiotic resistance and alterations in the respiratory microbiome can be attributed to not only long-term prophylactic antibiotic therapy in COPD but also to short courses of antibiotics for acute exacerbations (114).

The use of antibiotics for AECOPD can result in many adverse effects including diarrhea, *Clostridium difficile* infection, allergic reactions, QT interval prolongation, and tendon injury (115). In a previous systematic review, adverse events were reported by 10.6% of patients treated with antibiotics compared to 7.4% in patients treated with placebo, with diarrhea being the most common adverse event (107). Diarrhea associated with antibiotic can occur in 2 to 25% of patients, depending on the antibiotic used (115). When comparing antibiotic classes, there were no differences in adverse effects between macrolides and quinolones, while amoxicillin-clavulanic acid was associated with more gastrointestinal effects than quinolones (111).

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CHAPTER THREE: ANTIBIOTICS FOR ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE MANAGED IN THE OUTPATIENT SETTING: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Introduction

The role of antibiotics in the management of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remains controversial, particularly in the outpatient setting. We aimed to examine the effect of antibiotics on treatment failure for outpatients with AECOPD.

Methods

We searched PUBMED, EMBASE, CINAHL, Web of Science, and the Cochrane Library from inception to March 16, 2022 for randomized controlled trials that compared antibiotics with placebo for outpatients with AECOPD and reported the primary outcome of treatment failure. Two reviewers independently screened citations, extracted data, and assessed quality. For the primary analysis, we performed frequentist random effects meta-analysis to estimate the pooled treatment effect of antibiotics. As a secondary post hoc analysis, we also performed Bayesian meta-analysis using weakly informative priors. We also performed sensitivity analysis including only studies with low risk of bias.

Results

Our search identified 2,141 unique citations. After screening by title, abstract, and full-text, we included 6 studies, totalling 1,130 patients. Frequentist random effects meta-analysis revealed a pooled risk ratio of 0.71 (95% CI 0.50 to 1.01). Bayesian meta-analysis revealed a pooled risk ratio of 0.72 (95% CrI 0.50 to 1.00) with a 97.6% posterior probability of lower treatment failure associated with antibiotics. Results were similar in the sensitivity analysis limited to only studies with low risk of bias.

Conclusion

When considering the results of our study in the context of existing literature, antibiotics likely confer a modest benefit for outpatients with AECOPD for the outcome of treatment failure and should continue to be prescribed by clinicians based on current practice guidelines.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by progressive decline in lung function and acute exacerbations.[1] Acute exacerbations of COPD (AECOPD) are defined as worsening respiratory symptoms requiring additional therapy.[2] Precipitants of AECOPD include bacterial and viral infections, environmental irritant exposures, and disease progression.[3] Conventional management of AECOPD includes short-acting bronchodilators, inhaled anticholinergics, systemic corticosteroids, and antibiotics.[4] Given that only a subset of exacerbations are caused by bacterial infections and thought to respond to antibiotic therapy, the role of antibiotics in the management of AECOPD remains controversial.[5]

Current guidelines recommend antibiotics for patients with all three cardinal symptoms of increased dyspnea, sputum volume, and sputum purulence, or two of the three if increased sputum purulence is one of the two symptoms.[2] These recommendations, however, arise from subgroup analyses of a single trial, and descriptions of symptoms are subjective and usually not measurable by clinicians.[6,7] A recent systematic review and meta-analysis concluded that while current evidence favors the use of antibiotics for patients with AECOPD admitted to the Intensive Care Unit (ICU), the benefit of antibiotics remains inconclusive for outpatients with exacerbations of mild to moderate severity.[7]

Given that over 80% of patients with AECOPD are managed as outpatients, it is imperative to examine if antibiotics provide any benefit in this population.[2] Antibiotic overuse may result in harmful medication side effects, polypharmacy, increased costs, and promote resistant organisms.[7] The primary purpose of this review was to examine the effect of antibiotics compared to placebo on the outcome of treatment failure for patients with AECOPD managed in the outpatient setting.

METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8]

Registration of the review

The protocol for this systematic review was registered to the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021245969).

Eligibility criteria

We included randomized controlled trials that compare an antibiotic to placebo for adult patients with AECOPD managed in the outpatient setting and reported the outcome of treatment failure within 30 days of treatment initiation. The definition of treatment failure included but was not limited to no improvement or worsening of clinical symptoms, initiation of additional antibiotics or medications, hospitalization, or death. We included studies that had full text available with no language restriction.

We excluded studies that were not randomized, lacked a placebo group, did not report treatment failure within 30 days of treatment initiation, or included inpatients. We also excluded studies that examined antibiotics for the prevention of exacerbations.

Data sources and search strategy

We searched PUBMED, EMBASE, CINAHL, Web of Science, and the Cochrane Library from inception to March 16, 2022 using a comprehensive search strategy developed with a health sciences librarian and independently peer-reviewed by a second health sciences librarian

(Appendix).[9] For grey literature, we searched clinicaltrials.gov, WHO Clinical Trials Registry, Google Scholar, and conference proceedings from the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society from the past 3 years (2019, 2020, 2021).

Data collection

We managed study data by directly importing titles into Covidence (Veritas Health Innovation, Melbourne, Australia) and then removing duplicates. In the first phase, two reviewers (BZ and AT) independently screened titles and abstracts of all studies identified by our search. In the second phase, two reviewers (BZ and AT) independently applied eligibility criteria to the selected full text studies from the first phase and reported reasons for exclusion. Disagreements were resolved by consensus.

Two reviewers (BZ and AT) then independently extracted the following information from the included studies: author, year, journal, study setting, sample size, patient characteristics, definition of treatment failure, antibiotic regimen, and number of patients with treatment failure in treatment and placebo groups.

Quality (risk of bias) assessment

We assessed study quality using the Cochrane Risk-of-Bias Tool Version 2 (RoB2). The RoB2 assesses bias in five domains that may affect the results of randomized trials: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Two independent reviewers (BZ and AT) assessed each included study. Disagreements were resolved by consensus.

Data synthesis

For the dichotomous outcome of treatment failure, we reported risk ratios. For our primary analysis, we performed random effects meta-analysis using the Paule-Mandel estimator as we anticipated that the number of included studies would be small with at least moderate between-study heterogeneity. We also used Knapp-Hartung adjustments to calculate the 95% confidence interval around the pooled effect to reduce the chance of false positives.[10] We assessed heterogeneity using the I^2 statistic and visual inspection of the forest plots.

Due to the small number of included studies, we also performed a secondary post hoc Bayesian meta-analysis. Based on clinical experience and previous literature, we did not believe that antibiotics would result in a substantial benefit or harm. Therefore, we used weakly informative priors N(0,1) on the log scale of the pooled risk ratios. This prior assumes that the log of the pooled risk ratios has a normal distribution with a mean of 0 and standard deviation of 1. For the heterogeneity parameter, we used the Half-Cauchy prior with a scaling parameter of 0.5 (a flat prior). We then reported the pooled effect size with corresponding 95% credible intervals as well as the posterior probabilities that treatment with antibiotics is associated with lower treatment failure.

We also performed a pre-specified sensitivity analysis that only included studies with low risk of bias as determined by RoB2 using both frequentist random effects meta-analysis as well as Bayesian meta-analysis.

We used R Version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses. We performed meta-analysis and created forest plots using the "meta" package and created risk of bias plots using the "robvis" package. We performed Bayesian meta-analysis using the "brms" package.[11]

Assessment of publication bias

We assessed publication bias visually using a funnel plot. Egger's weighted regression was used to test for publication bias, where $p < 0.1$ was considered statistically significant.

RESULTS

Our search strategy yielded 2,234 citations. We removed 93 duplicates (59 automatically, 34 manually). After abstract and title screening, we identified 13 articles for full-text review. Six studies, totalling 1,130 patients, were included in the final analysis (Figure 1).[6,12–16]

Study characteristics

The characteristics of the included randomized controlled trials are described in Table 1. Two studies were conducted in the Netherlands, while the other study locations were Egypt, Denmark, Spain, and Canada. All studies were conducted in outpatient clinics. Sample sizes varied between 35 in the smallest study and 310 in the largest study. There was substantial variation in the type and duration of antibiotics used as well as the definition of treatment failure.

Quality (risk of bias) assessment

Quality assessments using the Cochrane Risk-of-Bias Tool Version 2 are summarized in Figure 2. Three studies had low risk of bias overall.[12,13,16] Two studies had some concerns.[6,15] One study was determined to have a high risk of bias due to selection of the reported result.[14]

Primary random effects meta-analysis

The primary analysis was conducted on six randomized controlled trials consisting of 565 patients in the control group and 565 patients in the intervention group (Figure 3). Using random effects meta-analysis, we found a pooled risk ratio of 0.71 (95% CI 0.50 to 1.01). There was moderate heterogeneity by visual analysis of the forest plot and the I^2 was 42%.

Secondary Bayesian meta-analysis

Using a Bayesian method with weakly informative priors, we found a pooled risk ratio of 0.72 (95% CrI 0.50 to 1.00). The estimate of the heterogeneity parameter (τ) was 0.28 (95% CrI 0.02 to 0.73). Figure 4 shows the cumulative probability plot of the pooled treatment effect using the empirical cumulative distribution function. There was a 97.6% posterior probability that antibiotics were associated with lower treatment failure (RR < 1.00). There was a 75.7% and 42.9 % posterior probability of moderate (RR < 0.80) and large (RR < 0.70) benefit in favor of antibiotics, respectively.

Sensitivity analysis of only studies with low risk of bias

Three studies with some concerns or high risk of bias as determined by RoB2 were excluded for the sensitivity analysis.[6,14,15] When analysing only the studies with low risk of bias, random effects meta-analysis resulted in a pooled risk ratio of 0.63 (95% CI 0.35 to 1.14) (Figure 5). Bayesian meta-analysis using weakly informative priors resulted in a pooled risk ratio of 0.64 (95% CrI 0.36 to 1.15).

Assessment of publication bias

There was no evidence of asymmetry on visual inspection of the funnel plot (Figure 6) or small-study effects by Egger's test ($p = 0.244$).

DISCUSSION

Interpretation

In this systematic review and meta-analysis, we examined RCTs comparing antibiotics to placebo for patients with AECOPD managed in the outpatient setting and assessed the outcome of treatment failure. We found that the definitions of treatment failure and antibiotic regimens used varied greatly between studies. The results from the primary frequentist analysis were imprecise and compatible with a large (up to 50%) reduction in the risk of treatment failure or a small (up to 1%) increase in risk. These results are consistent with our secondary Bayesian analysis, which demonstrated a posterior probability of 97.6% of treatment benefit with antibiotics. We also did not detect any important differences in the pooled risk ratios in the sensitivity analysis limited to only studies with low risk of bias. Overall, there were a small number of studies available for analysis, which resulted in wide confidence intervals in the estimation of the treatment effect and indicates substantial uncertainty.

Previous literature

Previous systematic reviews examining antibiotics for AECOPD have demonstrated similar results. A recent systematic review that examined all pharmacologic interventions for AECOPD found an overall benefit for antibiotics, though differentiation was not made between inpatients and outpatients.[17] Two previous Cochrane systematic reviews have both demonstrated

a modest benefit for antibiotics on treatment failure in outpatients with AECOPD.[7,18] Both reviews found point estimates of the treatment effect similar to those in our study. The confidence intervals around the pooled effects in these reviews were narrower than in our review but this is likely attributable to differences in the statistical methodology of the meta-analysis. We utilized the Paule-Mandel estimator instead of the traditional DerSimonian-Laird estimator used in previous reviews to minimize the risk of bias, especially since the number of included studies was small.[19,20] We also applied Knapp-Hartung adjustments to reduce the risk of a false positive result due to the small number of included studies, which may have resulted in wider confidence intervals.[21,22] Despite minor methodologic differences in previous reviews, the findings together likely indicate a small signal for benefit in favor of antibiotics in the outpatient treatment of AECOPD.

Limitations

We acknowledge important limitations of this study. Despite the best efforts of our health science librarians, we were unable to obtain the full text for two possibly relevant citations (Supplementary Table 1). Both of these studies, however, are from over 30 years ago so their clinical relevance has likely diminished over that time. These citations were also not included in other recent systematic reviews on this topic.[7,17,18]

Another limitation is that we only examined the outcome of treatment failure in our review. We did not evaluate outcomes such as hospitalization, ICU admission, or death and only one study included these outcomes in their composite definition of treatment failure.[12] These outcomes, however, are rare for patients with AECOPD who are managed as outpatients.[23]

Consequently, these outcomes are difficult to study and due to lack of power in RCTs and are often not reported.[7]

Perhaps the most significant limitation of this study was that there were only a small number of RCTs available for analysis and these RCTs had considerable heterogeneity with respect to the definitions of treatment failure, antibiotic regimens used, and cotreatment with corticosteroids. Unfortunately, this is an inherent limitation of the available RCTs on this clinical question. Due to the small number of included studies, the confidence intervals in our random effects meta-analysis were wide, indicating uncertainty but a likely benefit for antibiotics. We were able to supplement the results of the frequentist analysis with a Bayesian meta-analysis, which reinforces the conclusion of a likely benefit for antibiotics.

The definition of treatment failure is critical for studying AECOPD and yet there is no consensus definition.[24] Based on the European Respiratory Society core outcome set, a recent methodologic systematic review proposes that clinical cure should be defined as sufficient improvement in signs and symptoms such that no additional systemic treatments are required.[25] Our understanding and management of AECOPD has also evolved over time and these changes are reflected in differences in antibiotic selection and cotreatment with corticosteroids in different studies.[5] Nevertheless, the definitions of treatment failure and antibiotic regimens used were similar enough clinically that we believed pooling of data in a meta-analysis would still yield meaningful results. Due to the above limitations, however, it is difficult to make any definitive conclusions until further data from more randomized trials becomes available.

Clinical implications

Acute exacerbations of COPD are heterogeneous and there is likely a subset of patients who stand to benefit more from antibiotics than others. This concept is reflected in our current understanding of the pathophysiology of AECOPD as well as practice guidelines.[2,26,27] Clinical features such as sputum volume and purulence, fever, and consolidation on chest radiography are useful in identifying patients who should receive antibiotics. In addition, laboratory biomarkers such as CRP and procalcitonin also have potential to provide meaningful clinical data.[28,29] Ultimately, the decision to prescribe antibiotics should incorporate the best available evidence, provider clinical judgement, and patient preference.

Research implications

For patients with AECOPD managed in the outpatient setting, the benefit of antibiotics is not conclusive. Heterogeneity and small sample sizes in previous studies create considerable uncertainty. Further studies are needed to obtain a consensus definition of treatment failure in the management of AECOPD. While antibiotic regimens may depend on local resistance patterns, future studies may consider adopting guideline recommendations for antimicrobial use in community acquired pneumonia.[30] A robust, multicenter RCT would be needed to provide reliable evidence on the degree to which antibiotics confer benefit. Additionally, future studies should also examine specific subgroups of patients based on laboratory biomarkers and exacerbation phenotype, as well as measure adverse events related to antibiotic use.

Conclusion

Our systematic review and meta-analysis contributes to a growing body of evidence about the impact of antibiotic treatment in the outpatient management of patients with AECOPD. When considering the results of our study in the context of existing literature, antibiotics likely confer a modest benefit for outpatients with AECOPD and should continue to be prescribed by clinicians based on current practice guidelines. Further research is needed to better delineate the magnitude of benefit provided by antibiotics as well as differences among patient subgroups.

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TABLES AND FIGURES

Figure 1: PRISMA flow diagram.

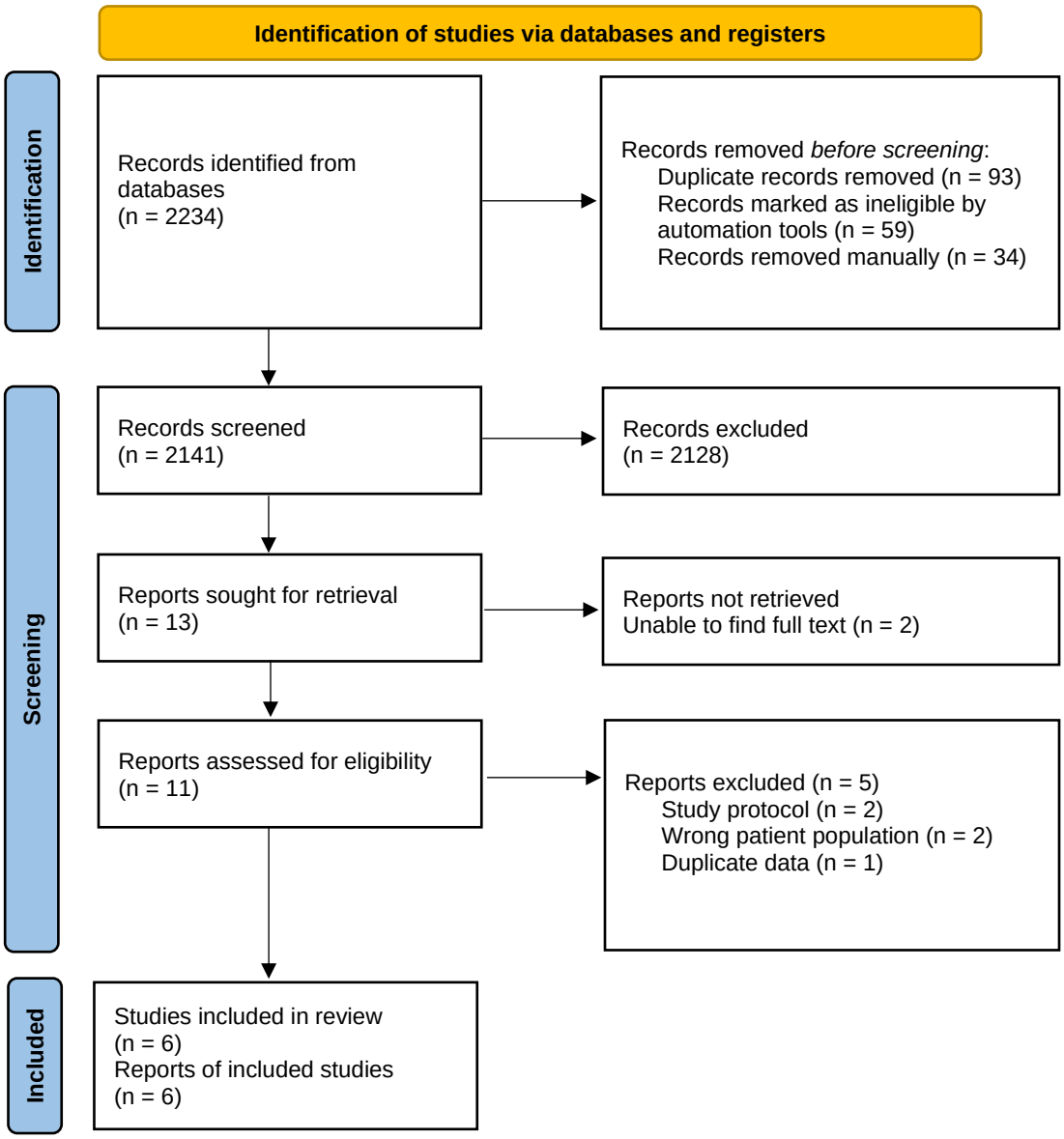


Table 1: Study characteristics.

Study	Country	Setting	Total sample size	Intervention	Definition of treatment failure
van Velzen et al., 2017	Netherlands	Outpatient clinic	301	Doxycycline 100mg PO once daily for 7 days (200mg on first day)	No resolution of patient reported respiratory symptoms, prescription of open label antibiotics, prescription of new course of oral corticosteroids, admission to hospital for AECOPD, or death at day 21
Brusse-Keizer et al., 2014	Netherlands	Outpatient pulmonary clinic	35	Amoxicillin/clavulanic acid 500/125mg PO TID for 7 days	No resolution of AECOPD within 28 days
Hassan et al., 2015	Egypt	Outpatient clinic	100	Ciprofloxacin 500mg BID for 10 days or amoxicillin 500mg q8H for 10 days	No resolution or deterioration of patient reported symptoms at day 21
Jorgensen et al., 1992	Denmark	Outpatient clinic	268	Amoxicillin 750mg PO BID for 7 days	Unchanged or deteriorated patient condition on physician assessment at day 8
Llor et al., 2012	Spain	Primary care centers	310	Amoxicillin/clavulanic acid 500/125mg PO TID for 8 days	No clinical improvement based on physician assessment at day 9-11
Anthonisen et al., 1987	Canada	Outpatient clinic	116	Trimethoprim-sulfamethoxazole 160/800mg PO BID for 10 days or amoxicillin 250mg PO QID for 10 days or doxycycline 100mg PO once daily for 10 days (200mg on first day)	No resolution or worsening patient reported symptoms at day 21

PO, per os; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; TID, three times a day; BID, two times a day; q8H, every 8 hours; QID, four times a day

Figure 2: Risk of bias assessment using the Cochrane Risk-of-Bias Tool Version 2.

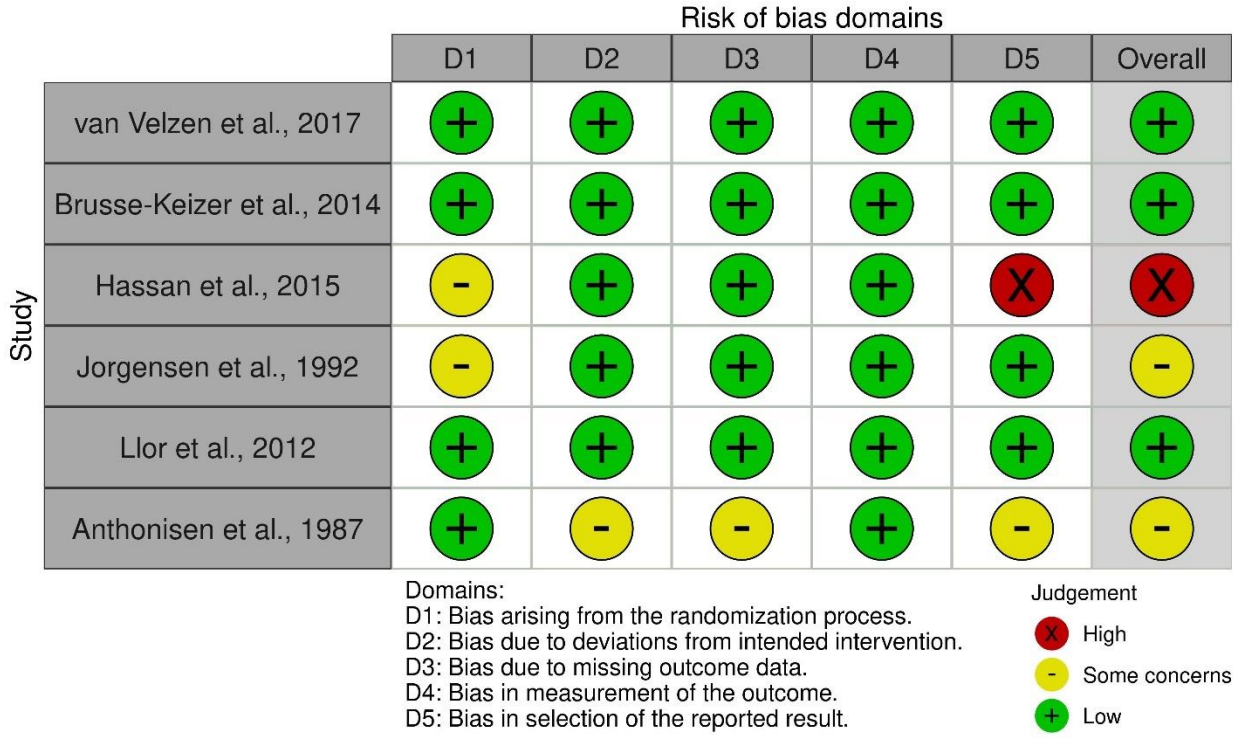


Figure 3: Primary analysis of antibiotics compared to placebo on the outcome of treatment failure using random effects meta-analysis.

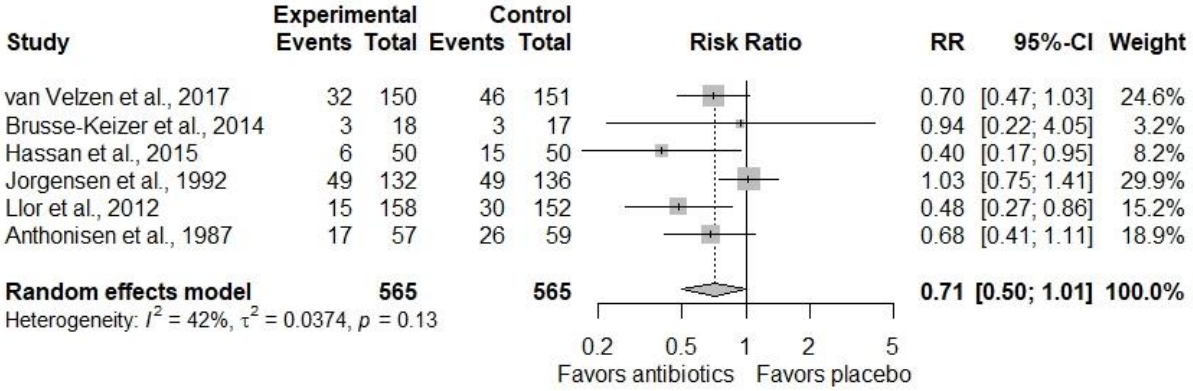


Figure 4: Cumulative probability of the pooled effect size of treatment with antibiotics using a Bayesian approach with weakly informative priors

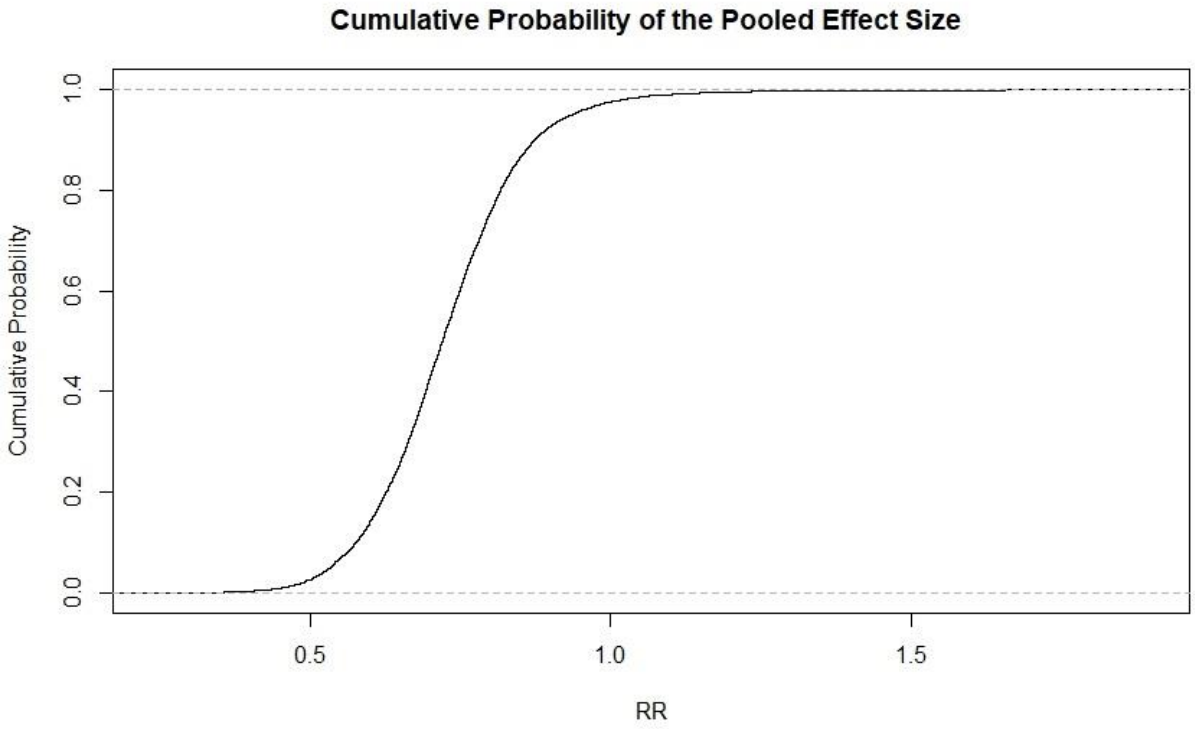


Figure 5: Sensitivity analysis using random effects meta-analysis limiting to low risk of bias studies

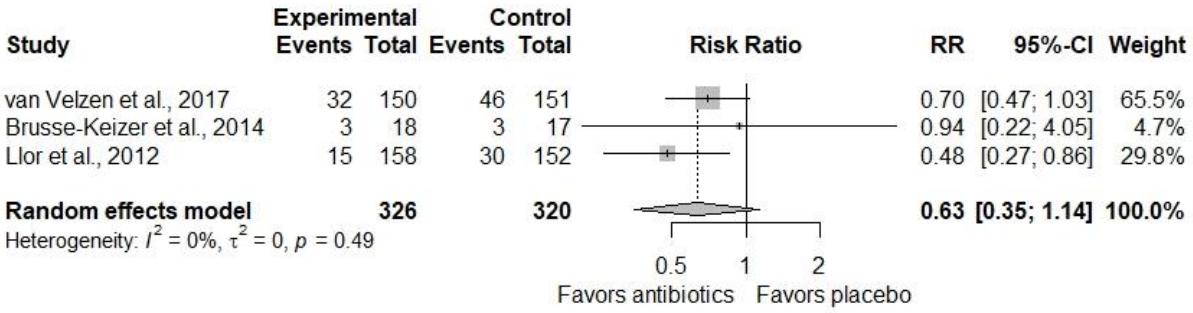
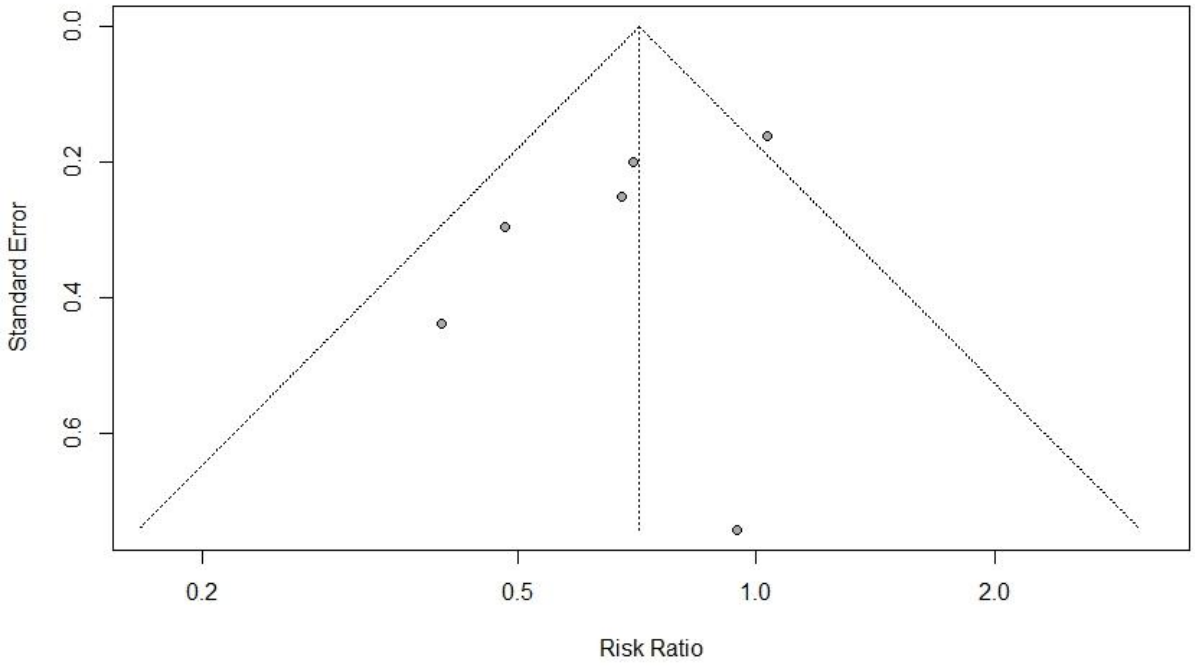


Figure 6: Funnel plot for assessment of publication bias.



SUPPLEMENTARY MATERIAL

Appendix 1: Search strategy.

Embase Classic+Embase <1947 to 2022 March 16>
Ovid MEDLINE(R) ALL <1946 to March 16, 2022>
EBM Reviews - Cochrane Central Register of Controlled Trials <January 2022>

Medline

1 exp Pulmonary Disease, Chronic Obstructive/ 223867
2 copd.tw,kf. 172129
3 chronic obstructive pulmonary disease*.tw,kf. 152134
4 (chronic obstructive lung* or chronic obstructive airway*).tw,kf. 15416
5 chronic bronchitis.tw,kf. 28420
6 PULMONARY EMPHYSEMA.tw,kf. 11921
7 or/1-6 328933
8 (exacerbat* or severe).tw,kf. 3128123
9 7 and 8 86930
10 AECOPD.tw,kf. 5152
11 9 or 10 87093
12 exp Anti-Bacterial Agents/ 5032212
13 (anti biotic* or antibiotic* or anti-bacterial agent* or antibacterial agent*).tw,kf. 988604
14 (penicillin* or amoxycillin or Amoxicillin 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 fluoroquinoln* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or floxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem).tw,kf. 688859
15 12 or 13 or 14 5428657
16 11 and 15 14746
17 randomized controlled trial.pt. 1107420
18 controlled clinical trial.pt. 187696
19 random*.tw. 4183167
20 placebo.ab. 872676
21 clinical trials as topic.sh. 232822
22 trial.ti. 993065
23 or/17-22 5153642
24 exp animals/ not humans/ 17863932
25 23 not 24 4245350
26 16 and 25 3070
27 26 use medall 867
28 limit 27 to dt=20210330-20220317 26

Embase

29 chronic obstructive lung disease/ 207114
30 (copd or chronic obstructive pulmonary disease*).tw. 218117
31 chronic airflow obstruction*.tw. 1377
32 chronic obstructive lung disease*.tw. 12622
33 chronic bronchitis.tw. 27882
34 PULMONARY EMPHYSEMA.tw. 10104
35 (chronic obstructive lung* or chronic obstructive airway*).tw. 14986
36 or/29-35 315137
37 disease exacerbation/ 342578
38 (exacerbat* or severe).tw. 3120651
39 37 or 38 3379021
40 36 and 39 91136
41 aecopd.tw. 5107
42 40 or 41 91293
43 exp *antibiotic agent/ 664871
44 *antiinfective agent/ 95181
45 (anti biotic* or antibiotic* or anti-bacterial agent* or antibacterial agent*).tw. 957945
46 (penicillin* or amoxycillin or Amoxicillin 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 fluoroquinoln* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or floxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem).tw. 674245
47 43 or 44 or 45 or 46 1818686
48 42 and 47 9636
49 random*.tw. or placebo*.mp. or double-blind*.mp. 4771671
50 trial*.ti. 1217125
51 49 or 50 5077699
52 48 and 51 3118
53 52 use emczd 1363
54 limit 53 to dc=20210330-20220317 60

Cochrane

55 exp Pulmonary Disease, Chronic Obstructive/ 223867
56 copd.tw,kw. 171221
57 chronic obstructive pulmonary disease*.tw,kw. 151931
58 chronic bronchitis.tw,kw. 28457
59 PULMONARY EMPHYSEMA.tw,kw. 11574
60 (chronic obstructive lung* or chronic obstructive airway*).tw,kw. 21770
61 or/55-60 329225
62 (exacerbat* or severe).tw,kw. 3123832
63 61 and 62 86763
64 AECOPD.tw,kw. 5136
65 63 or 64 86930
66 exp Anti-Bacterial Agents/ 5032212

67 (anti biotic* or antibiotic* or anti-bacterial agent* or antibacterial agent*).tw,kw. 988628
68 (penicillin* or amoxycillin or Amoxicillin 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 fluoroquinoln* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or floxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem).tw,kw. 686415
69 66 or 67 or 68 5429625
70 65 and 69 14736
71 70 use cctr 1421
72 limit 71 to yr="2021 -Current" 40
73 28 or 54 or 72 126

Web of Science – March 17, 2022

Search
#3 AND #4 AND #5
9:55 AM | Timespan: 2021-03-30 to 2022-03-17 (Index Date)
Web of Science Core Collection
26

Search
TS=(random*) OR TS=(placebo) OR TS=(double blind*) OR TI=trial*
9:48 AM | Timespan: 2021-03-30 to 2022-03-17 (Index Date)
Web of Science Core Collection
181,220

Search
TS=(penicillin* or amoxycillin or Amoxicillin or ampicillin or cefalosporin* or cefaclor or cefalexin 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 fluoroquinoln* or ciprofloxacin or gatifloxacin or gemifloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or floxacins or chloramphenicol or clindamycin or trimethoprim or sulfamethoxazole or cotrimoxazole or carbapenem* or meropenem or imipenem) OR TS=(anti biotic* or antibiotic* or anti-bacterial agent* or antibacterial agent*)
9:45 AM
Web of Science Core Collection
640,880

Search
#2 AND #1
9:44 AM
Web of Science Core Collection
14,462

Search
TS= ("ACUTE EXACERBATIONS")
OR TI=(severe or
exacerbat*)
9:43 AM
Web of Science Core Collection
240,675

Search
TS=(copd) OR TS=(chronic obstructive pulmonary disease*) OR
TS=(chronic bronchitis) OR TS=(PULMONARY EMPHYSEMA)
OR TS=(chronic obstructive lung disease*)
OR TS=("OBSTRUCTIVE PULMONARY-DISEASE")
9:43 AM
Web of Science Core Collection
122,884

CinahlComplete – March 17, 2022

#	Query	Limiters/Expanders	Results
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	21,597
S2	TI copd OR TI chronic obstructive pulmonary disease OR TI chronic bronchitis OR TI PULMONARY EMPHYSEMA	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	17,395
S3	AB copd OR AB chronic obstructive pulmonary disease OR AB chronic bronchitis OR AB PULMONARY EMPHYSEMA	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	19,821
S4	S1 OR S2 OR S3	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	31,338
S5	(MH "Antibiotics+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	86,156
S6	TI ((anti biotic* or antibiotic* or anti-bacterial agent* or antibacterial agent*).) OR AB ((anti biotic* or antibiotic* or anti-bacterial agent* or antibacterial agent*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	56,706
S7	AB penicillin* or amoxycillin or Amoxicillin 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	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	22,322

	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 fluoroquinoln* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or floxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem		
S8	S5 OR S6 OR S7	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	119,178
S9	S4 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,258
S10	(MH "Disease Exacerbation")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,336
S11	TI exacerbat* OR AB exacerbat* OR TI severe OR AB severe	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	246,225
S12	S10 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	247,650
S13	S9 AND S12	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	828
S14	(MH "Clinical Trials+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	335,489
S15	TI random* OR AB random* OR TI placebo OR AB placebo OR TI trial*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	469,859
S16	S14 OR S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	598,233
S17	S13 AND S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	269
S18	EM 20210330-20220317	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	386,810
S19	S17 AND S18	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	7

Supplementary Table 1: Excluded full-text citations.

Citation	Reason for exclusion
Placebo Versus Antibiotics in Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)	Wrong patient population – included hospitalized patients
The effects of the use of antibiotics during acute exacerbations in COPD on the severity and duration of exacerbations: the ABC-trial. - ABC-trial 2005	Study protocol
The effects of the use of antibiotics during acute exacerbations in chronic obstructive pulmonary disease (COPD) on the severity and duration of exacerbations: the ABC-trial	Study protocol
Hansen et al. A randomized double-blind trial between amoxycillin and placebo in the treatment of acute exacerbations of chronic bronchitis. European respiratory journal - supplement 1990;3(Suppl 10):89S.	Unable to find full text
Allegra et al. The role of antibiotics in the treatment of chronic bronchitis exacerbation: Follow-up of a multicenter study. Giornale Italiano della Malattie del Torace 1991;45(3):138-148.	Unable to find full text
Sachs et al. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. Thorax 1995;50(7):758-763.	Wrong patient population – included patients with asthma
Brusse-Keizer et al. Antibiotics in Patients with a Mild to Moderate Home-Treated COPD Exacerbation: The ABC-Trial. American Journal of Respiratory and Critical Care Medicine 2009;179.	Duplicate data

CHAPTER FOUR: ASSOCIATION BETWEEN ANTIBIOTICS AND REHOSPITALIZATION IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE DISCHARGED FROM THE EMERGENCY DEPARTMENT

ABSTRACT

Background

Patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are frequently discharged from the emergency department (ED) and treated with antibiotics. The role of antibiotics in the outpatient management of AECOPD is controversial and has never been studied in the ED setting.

Methods

We conducted a secondary analysis of prospectively collected data from the validation study of the Ottawa COPD Risk Scale. We included adult patients with AECOPD who were discharged from six tertiary care EDs in Canada over a two-year period and assessed rates of rehospitalization within 14 days of ED discharge. To examine the association between antibiotic treatment and rehospitalization, we performed multivariable logistic regression and propensity score matched analyses.

Results

A total of 774 patients were included in the analysis. The mean age was 69.4 years, 388 patients (50.1%) were female, and 451 patients (58.3%) were discharged with antibiotics. Twenty-nine (6.4%) and 36 (11.1%) patients returned to hospital with admission in the antibiotic and no antibiotic groups, respectively (unadjusted OR 0.55; 95% CI 0.33 to 0.92); adjustment for prespecified baseline characteristics using logistic regression yielded OR 0.65; 95% CI 0.38 to 1.08. In the propensity score matched analysis comprising of 197 matched pairs, 15 (7.6%) and

19 patients (9.6%) in the antibiotic and no antibiotic groups returned with admission, respectively (OR 0.69; 95% CI 0.29 to 1.62).

Conclusion

For patients with AECOPD discharged from the ED, we did not find an association between outpatient treatment with antibiotics and lower rates of rehospitalization after accounting for differences in baseline patient characteristics. However, the small sample size and low observed rate of the primary outcome created substantial risk of Type II error. Until further evidence is available, clinicians should continue prescribing antibiotics for patients with AECOPD based on clinical judgement and current practice guidelines.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by respiratory symptoms due to airflow obstruction caused by airway and alveolar abnormalities.[1] During the natural course of COPD, patients experience acute exacerbations and progressive decline in lung function.[2] Acute exacerbations of COPD (AECOPD) are key indicators of disease progression and can negatively impact quality of life, health care costs, lung function, and survival.[3–7] Conventional management of AECOPD includes the use of short-acting bronchodilators, inhaled anticholinergics, systemic corticosteroids, and antibiotics.[7] The benefit of antibiotics in the treatment of AECOPD, however, has been and remains controversial, especially for patients in the outpatient setting.[7–10] Clinical trials in the outpatient setting demonstrate conflicting results and a recent systematic review and meta-analysis concluded that the current evidence remains inconclusive for outpatients with mild to moderate severity exacerbations.[9,11–16]

Patients with AECOPD are frequently assessed and managed in the emergency department (ED).[2,17] While guidelines classify any patient presenting to the ED with COPD as having a "severe" exacerbation, many of these patients are discharged directly from the ED and managed as outpatients.[1,18] Although antibiotics are commonly prescribed for patients with AECOPD, there is currently no consensus as to who benefits most from treatment.[2,9,19] Criteria proposed by Anthonisen *et al.* in 1987 are reflected in current international guidelines, which recommend antibiotics for patients with all three cardinal symptoms of increased dyspnea, sputum volume, and sputum purulence, or two of the three if increased sputum purulence is one of the two symptoms.[1,20] However, these recommendations arise from subgroup analyses of a single trial and descriptions of symptoms provided by patients may be subjective and unreliable.[9]

Considering how frequently AECOPD is encountered in the ED setting and the potential harms of antibiotic overuse, it is imperative to determine the role of antibiotics in outpatient management. The objective of this study was to determine whether treatment with antibiotics is associated with lower rates of rehospitalization in patients with AECOPD who are discharged from the ED.

METHODS

Study design

We conducted a secondary analysis of prospectively collected data from the Ottawa COPD Risk Scale (OCRS; Supplementary Table 1) validation study.[21]

Study setting

The validation of the OCRS was a prospective cohort study conducted in the EDs of six tertiary care hospitals in Canada from May 2011 to December 2013. These six EDs had a combined annual census of approximately 400,000 patient visits.

Study population

We included adults 50 years of age or older who presented to the ED with AECOPD and were discharged. The diagnosis of COPD was either previously established or made in the ED based on a one-year history of chronic dyspnea or cough with sputum production. Exacerbation of COPD was defined as an increase in at least two of the following three criteria: breathlessness, sputum volume, and sputum purulence.

We excluded patients who required admission, had confusion, dementia, ischemic chest pain requiring treatment, acute ischemic changes on electrocardiography, death expected within weeks from chronic illness, residence in a long-term care or chronic care facility, on long-term

hemodialysis, or enrolled in the study in the previous two months. We also excluded patients who had missing data on discharge with antibiotics.

Outcome measures

The primary outcome of interest was return to the ED for respiratory complaints resulting in admission to hospital within 14 days of the initial visit. Secondary outcomes were return to the ED within 14 days without admission to hospital, return with admission to the intensive care unit, and all-cause mortality within 30 days of the initial visit.

Statistical analysis

As this study was a secondary analysis, the sample size was determined by the original patient cohort from the OCRS validation study.

We used descriptive statistics to summarize patient characteristics in the antibiotic and no antibiotic cohorts and compared characteristics using standardized differences. We then used two approaches to examine the association between antibiotics and rehospitalization. In the first analysis, we used bivariable and multivariable logistic regression to estimate the unadjusted and adjusted odds ratios (ORs) with 95% confidence interval (CI) for each predictor. The multivariable model was constructed using prespecified variables selected based on their clinical relevance and informed by the analysis of case mix differences between the cohorts. Goodness-of-fit was assessed using Hosmer-Lemeshow test and C-statistic. Because the number of events was relatively low, restricting the available degrees of freedom for the multivariable model, we conducted a second analysis using propensity score matching.

For the propensity score matched analysis, patients treated with antibiotics were matched 1:1 without replacement with patients not treated with antibiotics based on propensity score. The propensity score was calculated using all patient baseline characteristics described in Table 1.

Matched pairs were formed using greedy nearest neighbor matching with a caliper distance of 0.2 of the pooled standard deviation of the logit of the propensity score. We then used McNemar's Test to compare outcomes between matched pairs. Results were reported descriptively for secondary outcomes with low cell frequencies.

We considered discharge with oral corticosteroids to be a co-treatment rather than a confounder as this variable was not a known patient characteristic during the ED visit. Therefore, this variable was not included in the model to derive the propensity score. To determine whether there was any effect modification due to oral corticosteroids, we repeated the multivariable logistic regression analysis and included the main effect for treatment with oral corticosteroids as well as its interaction with antibiotic treatment into the model. In the propensity score cohort, we presented outcomes descriptively after stratifying by treatment with corticosteroids.

Patients who were on antibiotics prior to ED presentation but did not receive a new antibiotic prescription on their ED visit were classified into the "no antibiotics" group. However, these patients may have continued to take their previous antibiotic after discharge, possibly resulting in misclassification. In addition, patients in the "no antibiotics" group who received antibiotics in the ED could result in further contamination. Therefore, we performed a sensitivity analysis where we re-classified "no antibiotic" patients who were on previous antibiotics or received antibiotics in the ED into the antibiotics cohort.

We considered absolute values of standardized differences greater than 0.2 to be clinically important. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 1,415 patients were enrolled during the study period, of which 779 patients were discharged from the ED. After excluding five patients for whom discharge antibiotic prescription data were missing, 774 patients were included in the final analysis (Figure 1).

Patient characteristics for antibiotic and no antibiotic groups are depicted in Table 1. There were no important differences between age, sex, or vital signs on arrival between the two groups. More patients arrived by ambulance, had a history of heart failure, were already on antibiotics and oral corticosteroids in the no antibiotic group compared to the antibiotic group. Table 2 shows outcomes for patients discharged with and without antibiotics. Twenty-nine patients (6.4%) in the antibiotic cohort returned with admission compared to 36 patients (11.1%) in the no antibiotic cohort (unadjusted OR 0.55; 95% CI 0.33 to 0.92). There were no important differences in secondary outcomes.

Logistic regression analysis

For the multivariable logistic regression model, history of heart failure, age, arrival by ambulance, home oxygen use, current smoking status, and COPD Risk Score were considered clinically important characteristics to account for in measuring the association between antibiotics and rehospitalization. Unadjusted and adjusted ORs with 95% CIs for antibiotic treatment and clinically important predictors are shown in Table 3. The adjusted OR measuring the association between outpatient treatment with antibiotics and rehospitalization was 0.65; 95% CI 0.38 to 1.08. Home oxygen use (adjusted OR 2.06; 95% CI 1.13 to 3.74) and higher COPD Risk Score (adjusted OR 1.32; 95% CI 1.12 to 1.56) was associated with higher odds of rehospitalization in both unadjusted and adjusted analyses. Hosmer-Lemeshow Goodness-of-Fit test did not reveal lack of fit ($p = 0.81$) and the c-statistic was 0.704 for the model.

Propensity score matched analysis

In the propensity score matched analysis, a total of 197 matched pairs were formed. Consequently, 51% of the entire cohort contributed to the analysis. Characteristics of the propensity score matched cohorts are shown in Table 4. Table 5 shows the outcomes in the propensity score matched cohorts. Fifteen patients (7.6%) in the antibiotics cohort returned with admission compared to 19 patients (9.6%) in the no antibiotics cohort (OR 0.69; 95% CI 0.29 to 1.62). Forty-two patients (21.3%) in the antibiotic cohort and 38 patients (19.3%) in the no antibiotic cohort had any return visit to the ED within 14 days (OR 1.12; 95% CI 0.66 to 1.89). There were no important differences in the other secondary outcomes in the propensity score matched cohorts.

Analysis of effect modification by oral corticosteroids

There were 380 patients (84.3%) and 144 patients (44.6%) in the antibiotic and no antibiotic cohorts who were also discharged with oral corticosteroids, respectively. Supplementary Table 2 shows the logistic regression model examining the interaction term between antibiotics and oral corticosteroids and Supplementary Table 3 shows propensity score matched cohorts with patient outcomes stratified by oral corticosteroids. The interaction term in the logistic regression model was not statistically significant ($p = 0.32$) and there were no important differences in outcomes in the stratified analysis.

Analysis of patients on prior antibiotics or receiving ED antibiotics

There were 69 patients (21.4%) and 73 patients (22.6%) in the no antibiotics group who were already on antibiotics prior to their ED presentation or received antibiotics in the ED, respectively. Unadjusted and adjusted ORs with 95% CIs for this sensitivity analysis are shown

in Supplementary Table 4. The adjusted OR measuring the association between outpatient treatment with antibiotics and rehospitalization in this analysis was 0.87; 95% CI 0.49 to 1.55.

DISCUSSION

Interpretation

In this secondary analysis of patients with AECOPD discharged from the ED, we examined the association between treatment with antibiotics and rehospitalization within 14 days. In the unadjusted analysis, treatment with antibiotics was significantly associated with lower rehospitalization. In the multivariable logistic regression and propensity score matched analyses, the association was not statistically significant but had wide confidence intervals, indicating substantial uncertainty.

Previous literature

Previous randomized controlled trials (RCTs) examining patients with AECOPD recruited from outpatient clinics have demonstrated conflicting results. In a recent RCT conducted in multiple outpatient clinics in the Netherlands, treatment with doxycycline did not prolong time to next exacerbation compared to placebo. In the same study, 21% of patients treated with doxycycline had treatment non-response at 21 days compared to 31% of patients treated with placebo. However, this difference was not statistically significant.[15] This non-significant trend towards benefit for antibiotics is similar to our study. In another RCT from one outpatient pulmonary clinic, there was no difference in the rate of resolution or relapse within 28 days whether patients were treated with amoxicillin/clavulanic acid or placebo.[16]

In contrast, an RCT conducted in multiple primary care centres in Spain found that treatment with amoxicillin/clavulanic acid was associated with significantly higher treatment

success and prolonged time to next exacerbation compared to placebo.[12] A recent systematic review demonstrated that antibiotics were significantly associated with increased exacerbation resolution and decreased treatment failure, independent of study setting or exacerbation severity.[7]

Strengths and limitations

Our study has important limitations. This study was a secondary analysis of an observational study and the sample size was not established for our study question. In the original OCRS validation study, consecutive eligible patients presenting to the ED were enrolled over a two-year period. There were 1185 and 119 eligible patients who missed enrollment due to unavailability of research staff and patient refusal, respectively. However, we do not believe that this would introduce significant bias in the results of our analysis as these reasons are unrelated to the current study.

Our multivariable logistic regression analysis included all available patients but had insufficient degrees of freedom to allow adjustment for all relevant patient characteristics. Our propensity score matched analysis created comparable groups but the matching process precluded the analysis of the entire cohort. Both analyses attempted to create prognostic balance but residual confounding by indication remains a possibility. Neither analysis demonstrated an association between antibiotics and lower rehospitalization but the number of events and sample size available for both analyses were small, resulting in substantial risk of Type II error. A much larger randomized trial would be required to determine whether clinical benefit truly exists. For example, using an event rate of 10% for the primary outcome, at least 4010 patients would be required in a trial with 1:1 allocation to detect a 25% relative reduction in the primary outcome

with 80% power. This sample size is substantially larger than the available sample size of our study as well as previous trials designed to address similar questions.[9]

We did not have data about the cardinal symptoms of sputum volume and purulence and were unable to assess whether antibiotics would benefit these specific subgroups of patients. In addition, we had no data about laboratory biomarkers such as C-reactive protein (CRP) or procalcitonin, which may be useful for management decisions.[22,23]

Notwithstanding these limitations, our study utilized prospectively collected data from multiple tertiary care EDs in Canada We analyzed relevant and patient-oriented outcomes using robust statistical methods. Finally, we examined the impact of antibiotics on patients with AECOPD in the ED setting, which has not been previously evaluated in any other study.

Clinical implications

Acute exacerbations of COPD are heterogeneous and there is likely a subset of patients who benefit from antibiotics that may not be easily identifiable based on current evidence. Patients with increased sputum volume and purulence, fever, or consolidation on chest radiography would benefit from antibiotics. The decision to prescribe antibiotics, however, becomes more difficult when these signs are absent. Clinicians should synthesize all available clinical data as well as patient-specific factors. For example, our study also demonstrated that home oxygen use and higher COPD Risk Score were associated with increased rehospitalization. Finally, shared decision making with patients based on risk and patient preference may also be a valid approach.

Research implications

Given the clinical equipoise demonstrated in this study, further RCTs in the ED setting are needed to examine the role of antibiotics in the management of AECOPD. Additional studies

could also examine whether the impact of antibiotics is different for specific subgroups of patients based on laboratory biomarkers or Anthonisen criteria as well as measure adverse events related to antibiotic use.

Conclusion

Our observational study was unable to demonstrate an association between antibiotics and rehospitalization for patients with AECOPD discharged from the ED. However, the low rate of the primary outcome and small sample size created substantial risk of Type II error. In the context of prior knowledge and the limitations of the current study, antibiotics likely confer benefit in AECOPD but this benefit may be modest and differ among patient subgroups. Until further evidence is available and there is greater clarity about COPD subgroups, clinicians should continue prescribing antibiotics for patients with AECOPD based on clinical judgement and current practice guidelines.

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TABLES AND FIGURES

Figure 1: Patient flow

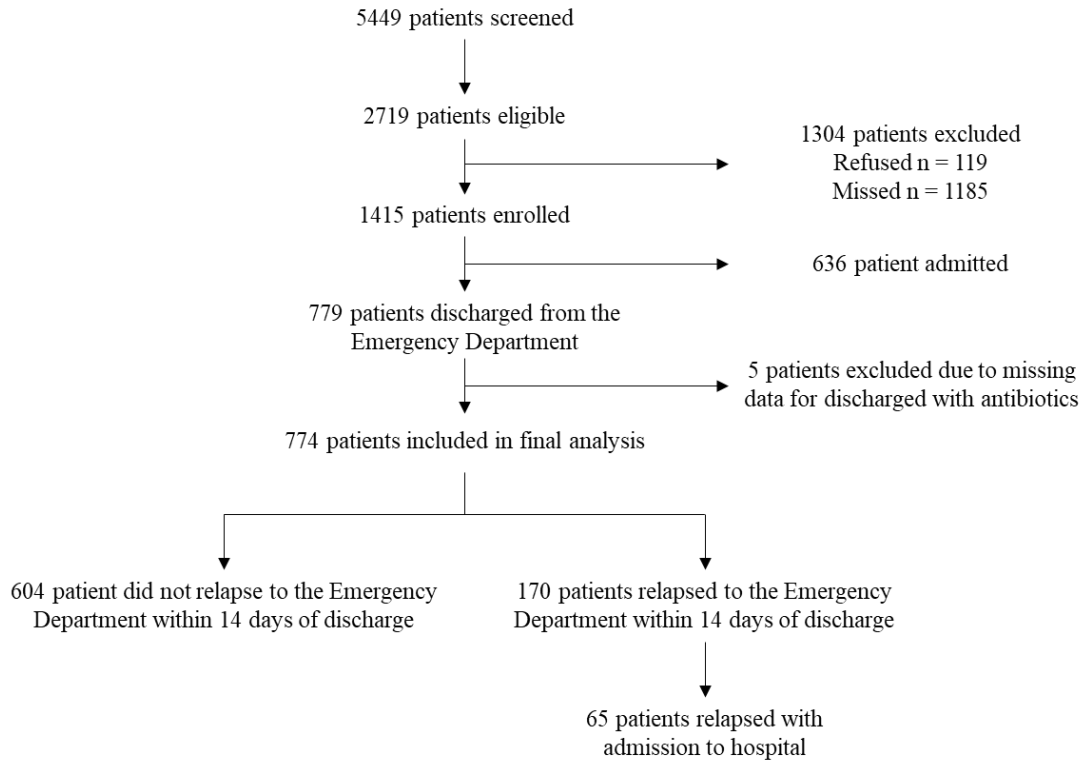

Table 1: Patient characteristics

			Antibiotics on discharge	No antibiotics on discharge	Standardized difference
			n = 451	**n = 323**	
Age, mean years (SD)			69.2 (10.7)	69.6 (10.7)	-0.03
Female			217 (48.1)	171 (52.9)	-0.10
Arrival status					
	CTAS				
		1	0 (0.0)	4 (1.2)	0.23
		2	168 (37.3)	129 (40.1)	
		3	269 (59.7)	174 (54.0)	
		4	13 (2.9)	14 (4.4)	
		5	1 (0.2)	1 (0.3)	
	Arrival by ambulance		180 (39.9)	166 (51.4)	-0.23
	Tachycardia (HR ≥ 100)		133 (29.7)	101 (31.6)	0.04
	Tachypnea (RR ≥ 20)		318 (71.3)	236 (74.0)	0.06
	Hypotension (SBP < 90)		4 (0.9)	3 (0.9)	0.00
	Hypoxia (SpO_2 < 88)		19 (4.2)	11 (3.4)	0.04
	Fever (T ≥ 38)		7 (1.6)	5 (1.6)	0.00
	Duration of respiratory distress, mean hours (SD)		71.3 (57.0)	58.0 (52.7)	0.24
Past medical history					
	COPD		437 (96.9)	313 (96.9)	0.00
	Heart failure		49 (10.9)	57 (17.7)	-0.20
	Intubation for respiratory distress		12 (2.7)	14 (4.3)	-0.09
	MI or angina		82 (18.2)	67 (20.7)	-0.07
	CABG or PCI		41 (9.1)	36 (11.1)	-0.07
	Pacemaker		14 (3.1)	12 (3.7)	-0.03
	Atrial fibrillation		36 (8.0)	28 (8.7)	-0.03
	Peripheral vascular disease		8 (1.8)	10 (3.1)	-0.09
	Cancer		10 (2.2)	12 (3.7)	-0.09
	Hypertension		215 (47.7)	153 (47.4)	0.01
	Stroke or TIA		54 (12.0)	25 (7.7)	0.14
	Diabetes		82 (18.2)	56 (17.3)	0.02
	Valvular heart disease		13 (2.9)	14 (4.3)	-0.08
	Dementia		13 (2.9)	9 (2.8)	0.01
	Chronic renal failure		20 (4.4)	20 (6.2)	-0.08
Current home oxygen use			71 (15.7)	57 (17.7)	-0.05
Person who smokes, current or former			295 (65.4)	220 (68.1)	-0.06

Current respiratory medications				
	Antibiotic	45 (10.0)	69 (21.4)	-0.32
	Oral steroid	44 (9.8)	54 (16.8)	-0.21
	Inhaled beta-agonist	395 (88.0)	296 (91.9)	-0.13
	Inhaled anticholinergic	308 (68.6)	223 (69.3)	-0.01
	Inhaled steroid	295 (65.7)	223 (69.3)	-0.08
Treatment received in the ED				
	Inhaled beta-agonist	359 (79.6)	267 (82.7)	-0.08
	Antibiotic (IV or PO)	288 (63.9)	73 (22.6)	0.92
	Systemic steroid (IV or PO)	313 (69.4)	193 (59.8)	0.20
	Noninvasive ventilation	3 (0.7)	2 (0.6)	0.01
Chest radiography				
	Normal	355 (80.5)	230 (75.4)	0.12
	Pneumonia	33 (7.5)	13 (4.3)	0.14
	Pleural effusion	33 (7.5)	28 (9.2)	-0.06
	Cardiomegaly	24 (5.4)	37 (12.1)	-0.24
	Pulmonary congestion	14 (3.2)	19 (6.2)	-0.15
Secondary diagnosis				
	Heart failure	3 (0.7)	11 (3.4)	-0.19
COPD Risk Score, mean (SD)		0.8 (1.3)	1.1 (1.4)	-0.17

SD, standard deviation; CTAS, Canadian Triage Acuity Scale; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation; T, temperature; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; ED, emergency department; IV, intravenous; PO, per os

Table 2: Patient outcomes

			Antibiotics on discharge	No antibiotics on discharge	All patients
			n = 451	n = 323	n = 774
Return with admission to hospital within 14 days			29 (6.4)	36 (11.1)	65 (8.4)
	Return with admission to ICU		1 (0.2)	3 (0.9)	4 (0.5)
Any return to ED within 14 days			100 (22.2)	70 (21.7)	170 (22.0)
	Reason for return visit				
		Worsening dyspnea	71 (15.7)	52 (16.1)	123 (15.9)
		Chest pain	12 (2.7)	8 (2.5)	20 (2.6)
		Fever	4 (0.9)	6 (1.9)	10 (1.3)
		Sepsis	2 (0.4)	2 (0.6)	4 (0.5)
		Unable to ambulate	4 (0.9)	3 (0.9)	7 (0.9)
Death within 30 days			0 (0.0)	4 (1.2)	4 (0.5)

ICU, intensive care unit; ED, emergency department

Table 3: Unadjusted and adjusted odds ratios from multivariable logistic regression analysis to identify factors associated with return to hospital with admission within 14 days of ED discharge

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Discharged with antibiotics	0.55 (0.33-0.92)	0.65 (0.38-1.08)
History of heart failure	1.52 (0.79-2.93)	1.31 (0.66-2.62)
Age	0.99 (0.97-1.02)	0.99 (0.97-1.02)
Arrival by ambulance	1.95 (1.16-3.26)	1.49 (0.87-2.53)
On home oxygen	2.30 (1.30-4.06)	2.06 (1.13-3.74)
Person who currently smokes	1.71 (0.94-3.09)	1.71 (0.93-3.15)
COPD Risk Score	1.39 (1.18-1.63)	1.32 (1.12-1.56)

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease
*Adjusted for all other variables in the model

Table 4: Propensity score matched characteristics of patients discharged with and without antibiotics

			Antibiotics on discharge	No antibiotics on discharge	Standardized difference
			n = 197	**n = 197**	
Age, mean years (SD)			69.4 (10.7)	70.1 (10.8)	-0.06
Female			105 (53.3)	99 (50.3)	0.06
Arrival status					
	CTAS				0.18
		1	0 (0.0)	3 (1.5)	
		2	72 (36.6)	79 (40.1)	
		3	118 (59.9)	104 (52.8)	
		4	7 (3.6)	10 (5.1)	
		5	0 (0.0)	1 (0.5)	
	Arrival by EMS		77 (39.1)	84 (42.6)	-0.07
	Tachycardia (HR ≥ 100)		67 (34.0)	63 (32.0)	0.04
	Tachypnea (RR ≥ 20)		138 (70.1)	146 (74.1)	-0.09
	Hypotension (SBP < 90)		0 (0.0)	1 (0.5)	-0.10
	Hypoxia (SpO_2 < 88)		8 (4.1)	7 (3.6)	0.03
	Fever (T ≥ 38)		6 (3.1)	2 (1.0)	0.15
	Duration of respiratory distress, mean hours (SD)		65.6 (54.5)	62.0 (53.7)	0.07
Past medical history					
	COPD		189 (95.9)	188 (95.4)	0.02
	Heart failure		25 (12.7)	28 (14.2)	-0.04
	Intubation for respiratory distress		6 (3.1)	5 (2.5)	0.03
	MI or angina		35 (17.8)	38 (19.3)	-0.04
	CABG or PCI		24 (12.2)	24 (12.2)	0.00
	Pacemaker		6 (3.1)	8 (4.1)	-0.05
	Atrial fibrillation		22 (11.2)	15 (7.6)	0.12
	Peripheral vascular disease		3 (1.5)	6 (3.1)	-0.10
	Cancer		7 (3.6)	6 (3.1)	0.03
	Hypertension		97 (49.2)	83 (42.1)	0.14
	Stroke or TIA		18 (9.1)	20 (10.2)	-0.03
	Diabetes		33 (16.8)	31 (15.7)	0.03
	Valvular heart disease		7 (3.6)	7 (3.6)	0.00
	Dementia		6 (3.1)	7 (3.6)	-0.03
	Chronic renal failure		9 (4.6)	10 (5.1)	-0.02
Current home oxygen use			32 (16.2)	29 (14.7)	0.04

Person who smokes, current or former		129 (65.5)	126 (64.0)	0.03
Current respiratory medications				
	Antibiotic	28 (14.2)	32 (16.2)	-0.06
	Oral steroid	28 (14.2)	26 (13.2)	0.03
	Inhaled beta-agonist	175 (88.8)	178 (90.4)	-0.05
	Inhaled anticholinergic	134 (68.0)	133 (67.5)	0.01
	Inhaled steroid	132 (67.0)	139 (70.6)	-0.08
Treatment received in the ED				
	Inhaled beta-agonist	151 (76.7)	165 (83.8)	-0.18
	Antibiotic (IV or PO)	73 (37.1)	65 (33.0)	0.09
	Systemic steroid (IV or PO)	118 (59.9)	121 (61.4)	-0.03
	Noninvasive ventilation	3 (1.5)	1 (0.5)	0.10
Chest radiography				
	Normal	151 (76.7)	158 (80.2)	-0.09
	Pneumonia	14 (7.1)	10 (5.1)	0.08
	Pleural effusion	16 (8.1)	15 (7.6)	0.02
	Cardiomegaly	17 (8.6)	15 (7.6)	0.04
	Pulmonary congestion	9 (4.6)	10 (5.1)	-0.02
Secondary diagnosis				
	Heart failure	3 (1.5)	3 (1.5)	0.00
COPD Risk Score, mean (SD)		1.0 (1.4)	0.9 (1.3)	0.08

SD, standard deviation; CTAS, Canadian Triage Acuity Scale; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation; T, temperature; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; ED, emergency department; IV, intravenous; PO, per os

Table 5: Propensity score matched outcomes of patients discharged with and without antibiotics

	Antibiotics on discharge	No antibiotics on discharge	OR (95% CI)
	n = 197	**n = 197**	
Return with admission to hospital within 14 days	15 (7.6)	19 (9.6)	0.69 (0.29-1.62)
Return with admission to ICU	0 (0.0)	1 (0.5)	
Any return to ED within 14 days	42 (21.3)	38 (19.3)	1.12 (0.66-1.89)
Reason for return visit			
Worsening dyspnea	28 (14.2)	28 (14.2)	
Chest pain	6 (3.0)	7 (3.6)	
Fever	2 (1.0)	2 (1.0)	
Sepsis	1 (0.5)	1 (0.5)	
Unable to ambulate	2 (1.0)	2 (1.0)	
Death within 30 days	0 (0.0)	2 (1.0)	

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; ED, emergency department
*Adjusted for all other variables in the model

CHAPTER FIVE: DISCUSSION

5.1 Interpretation of the Results

5.1.1 Results of systematic review and meta-analysis

In Chapter Three, a systematic review and meta-analysis was conducted to examine randomized controlled trials (RCTs) comparing antibiotics to placebo for patients with AECOPD managed in the outpatient setting. A frequentist random effects meta-analysis resulted in a wide confidence interval of the estimation of the pooled treatment effect, compatible with a large (up to 50%) reduction in the risk of treatment failure or a small (up to 1%) increase in risk. A secondary post hoc Bayesian meta-analysis using weakly informative priors revealed a posterior probability of 97.6% of treatment benefit with antibiotics.

The small number of studies eligible for inclusion limited the frequentist random effects meta-analysis and led to an imprecise estimate of the pooled treatment effect. In this situation with a small sample size, Bayesian methods are thought to be more effective for meta-analyses (1). The subsequent Bayesian analysis provided a result that is easier to interpret and more clinically informative. Not only did the Bayesian meta-analysis determine a very high probability of treatment benefit with antibiotics, the empiric cumulative distribution function was also able to provide estimations of the posterior probabilities of moderate (RR < 0.80) and large (RR < 0.70) treatment benefit.

5.1.2 Results of logistic regression and propensity score matched analyses

In Chapter Four, a secondary analysis of prospectively collected data was performed to examine the association between treatment with antibiotics and rehospitalization within 14 days for patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD)

discharged from the emergency department. There was an association between treatment with antibiotics and lower rehospitalization in the unadjusted bivariate logistic regression analysis. However, this association was no longer statistically significant after adjustment for prespecified clinically relevant covariates in the multivariable logistic regression analysis. Propensity score matched analysis also did not demonstrate a statistically significant association between antibiotics and lower rehospitalization.

Based on visual inspection of the frequency tables and confidence intervals, there seemed to be a trend towards benefit for treatment with antibiotics. The confidence intervals of the point estimates from both logistic regression and propensity score matched analyses were wide, which indicates substantial uncertainty. Given the low numbers of events for the primary outcome as well as the small sample sizes for both analyses, there was a substantial risk of Type II error.

To estimate the risk of Type II error, power calculations can be performed. Based on the results of the study, 10% can be used as an approximate estimation of the incidence of the primary outcome. A reasonable clinically important difference would be a 25% relative risk reduction in the primary outcome (2.5% absolute risk difference). Using an alpha value of 0.05 and a sample size of 323 (the smaller of the two groups in the logistic regression analysis) would then result in a power of approximately 0.20 and an 80% chance of Type II error. In the propensity score matched analysis, the sample size of 197 equates to a power of approximately 0.14 and an 86% chance of Type II error.

There were no important differences in the secondary outcomes of the propensity score matched analysis. Similar numbers of patients returned to the emergency department overall (with or without admission) and the distribution of reasons for the return visit as well as all-cause mortality within 30 days were also similar between antibiotic and no antibiotic groups. As these

secondary outcomes also had low event rates, the results are purely speculative, and it is difficult to make any definitive conclusions.

Another finding in the logistic regression analysis was that home oxygen and higher COPD risk score were associated with increased rehospitalization. These findings were consistent in both unadjusted and adjusted analyses. These factors represent patients who are more comorbid and with more severe disease so it is not surprising that they would be associated with an increased risk of rehospitalization for patients discharged with AECOPD. Furthermore, home oxygen therapy has been previously shown to be associated with worse outcomes for emergency department patients with AECOPD and higher COPD risk score has been validated to predict higher risk of short-term serious outcomes (2,3). This interesting finding is hypothesis generating and represents a potential area that can be incorporated into future research.

5.1.2 Overall interpretation of the results

The results of the two studies presented in this thesis, when considered together and in the context of previous literature, indicate a likely benefit for treatment with antibiotics in the management of AECOPD in the outpatient setting. While the true magnitude of the treatment effect is difficult to determine based on the current analysis, the overall benefit of antibiotics in the outpatient population is likely modest.

5.2 Previous Literature

There have been no previous studies examining the impact of antibiotic treatment on patients with AECOPD in the emergency department setting. Multiple previous RCTs have compared antibiotics and placebo for patients from outpatient clinics and hospitalized patients

with AECOPD. While emergency department patients who are admitted to the hospital are comparable to inpatients, it is difficult to find a population that is comparable to emergency department patients who are discharged.

In addition to differences in patient populations, there are also considerable variations in the treatment regimens used, the definitions of treatment success, as well as the rates of treatment success or failure in previous studies. It is unclear whether some of the sample size calculations in previous studies were based on accurate estimations of treatment success or failure rates. That is, it is possible that some of the previous studies may have been underpowered to detect the likely modest treatment effect of antibiotics.

5.2.1 Previous inpatient RCTs

A recent RCT conducted in one hospital in China enrolled 194 hospitalized patients with AECOPD who had procalcitonin levels less than 0.1ng/mL and compared treatment with antibiotics versus placebo. The primary outcome was treatment success at 10 days and was seen in 93.7% of patients in the antibiotics group and 95.8% of patients in the placebo group. Patients with fever, pneumonia, or who were immunocompromised were excluded. The most common antibiotic used was piperacillin-sulbactam and the duration was not standardized. Furthermore, this study was also not blinded and no information was provided about other AECOPD treatments (4).

Another RCT conducted in two hospitals in the Netherlands assigned 265 episodes of AECOPD requiring hospitalization to either doxycycline or placebo for seven days. Patients with fever or radiographic evidence of pneumonia were excluded. All enrolled patients received concomitant treatment with bronchodilators and corticosteroids. The primary outcome, clinical

cure at 30 days, was observed in 51% in the doxycycline group and 41% in the placebo group, though this difference was not statistically significant. One of the secondary outcomes, clinical cure at 10 days, was seen in 67% in the doxycycline group and 51% in the placebo group and this difference was statistically significant (5). The sample size in this study was determined based on a previous RCT on outpatients with AECOPD where clinical success was seen in 52% and 67% of patients treated with placebo and antibiotics, respectively (6). Interestingly, a secondary analysis of the data showed that doxycycline had a bigger treatment effect in patients with procalcitonin levels below 0.1ng/mL compared to those with procalcitonin above 0.1ng/mL (7).

Another RCT of 90 hospitalized patients with AECOPD in Spain did not show any differences in spirometry or clinical evaluation at hospital discharge when comparing treatment with cotrimoxazole, amoxicillin-clavulanic acid, or placebo (8).

5.2.2 Previous outpatient RCTs

Studies conducted in outpatient settings have demonstrated similar mixed results. A recent RCT conducted in multiple outpatient clinics in the Netherlands assigned 305 patients with AECOPD to either treatment with doxycycline or placebo. The primary outcome was time to next exacerbation, which was similar between the two groups. One of the secondary outcomes was treatment non-response at 21 days and this was seen in 21% of patients treated with doxycycline and 31% of patients treated with placebo. The difference in this secondary outcome was not statistically significant (9).

Another RCT conducted in multiple primary care centres in Spain assigned 318 outpatients with AECOPD to either amoxicillin-clavulanic acid or placebo. The primary

outcome was clinical cure at days 9 to 11, which was seen in 74.1% of the amoxicillin-clavulanic acid group and in 59.9% of the placebo group. This difference was statistically significant. Among their secondary outcomes they also found that the antibiotic group had significantly higher rates of clinical cure at day 20 and prolonged time to next exacerbation compared to placebo (10).

Another RCT from general practice clinics in Denmark assigned 268 outpatients with acute exacerbations of chronic bronchitis to either amoxicillin or placebo for seven days. The primary outcome was treatment success at day eight, which was seen in 63% of the amoxicillin group and 64% of the placebo group (11).

5.2.3 Previous systematic reviews

A recent systematic review that examined all pharmacologic interventions for AECOPD and concluded that antibiotics reduce treatment failure. Multiple outcomes were assessed and no differentiation was made between inpatients and outpatients. Antibiotics were found to be associated with the outcome of increased exacerbation resolution (OR 2.03; 95% CI 1.47 to 2.80) in a meta-analysis of three RCTs. Antibiotics were also found to be associated with the outcome of decreased treatment failure (OR 0.54; 95% CI 0.34 to 0.86) in a meta-analysis of two RCTs. There were no statistically significant differences in other outcomes including mortality, quality of life, need for intubation, or repeat exacerbations (12).

Two previous Cochrane systematic reviews have also examined the effect of antibiotics on the primary outcome of treatment failure for AECOPD and differentiation was made between inpatients and outpatients. In 2012, Vollenweider and colleagues included five outpatient RCTs that used currently available medications in a meta-analysis and did not find a statistically

significant association between antibiotics and lower rates of treatment failure within four weeks (RR 0.80; 95% CI 0.63 to 1.01). For inpatients, three RCTs were included and there was a statistically significant association between antibiotics and lower treatment failure (RR 0.77; 95% CI 0.55 to 0.92) (13).

In 2018, the same review was updated by Vollenweider and colleagues and seven outpatient RCTs were included in a meta-analysis, which showed a statistically significant association between antibiotics and lower rates of treatment failure within four weeks (RR 0.72; 95% CI 0.56 to 0.94). For inpatients, four RCTs were included and interestingly the association between antibiotics and treatment failure was no longer statistically significant (RR 0.65; 95% CI 0.38 to 1.12) (14).

For both the 2012 and 2018 Cochrane systematic reviews, an outpatient RCT was included in the meta-analyses that included patients with asthma (15). This RCT was excluded from the meta-analysis in Chapter Three of this thesis. The small sample size and low event rate of the RCT in question, however, likely would not have made a significant impact on the overall results. While the existing systematic reviews on this topic all seem to have similar results, they all suffer from the small number of studies available for analysis resulting in volatile results and wide confidence intervals of the estimations of the treatment effect.

5.3 Strengths

5.3.1 Strengths of the systematic review and meta-analysis

The systematic review was performed using a comprehensive search strategy developed and peer-reviewed by health science librarians. Two separate statistical approaches were utilized in conducting the meta-analysis and both revealed similar results. This systematic review and

meta-analysis examining the impact of antibiotics for AECOPD was first to use Bayesian methods, which rendered a result that is more easily interpreted and clinically useful than previous frequentist analyses.

5.3.2 Strengths of the secondary analysis

The secondary analysis of prospectively collected data from multiple Canadian tertiary care hospitals was the first study to examine the impact of antibiotics on patients with AECOPD in the emergency department setting. The outcomes assessed were relevant and patient oriented. The patient cohort was well-defined with few missing data. The statistical methods, namely both logistic regression and propensity score matching, were robust and demonstrated similar results.

5.4 Limitations

5.4.1 Limitations of the systematic review and meta-analysis

The first limitation of the systematic review was that there were only a small number of RCTs available for analysis. The sample sizes of the available RCTs were also generally small. The small number of RCTs and small sample sizes limited the meta-analysis and resulted in an imprecise estimate of the pooled treatment effect.

The second limitation was that there was considerable heterogeneity in the definitions of treatment failure, antibiotic treatments used, and cotreatment with corticosteroids. Unfortunately, this seems to be an inherent shortcoming of having multiple separate studies done on this question across different settings, with different patient populations, and during different time periods. In a clinical context, however, the definitions of treatment failure and antibiotic

regimens used in previous studies were likely still similar enough to allow pooling of data in a meta-analysis.

The third limitation was that there were two citations for which the full text was not obtainable. Both of these citations, however, were from over 30 years ago, limiting the applicability of their data, and they were also not included in other systematic reviews on this topic (12–14).

The fourth limitation was that outcomes such as hospitalization, admission to ICU, or death were not assessed. Few studies of patients with AECOPD treated in the outpatient setting report these outcomes, likely because they are rare occurrences. Nonetheless, they are important, patient-oriented outcomes that may be relevant to include in future studies.

5.4.2 Limitations of the secondary analysis

Perhaps the most significant limitation was that the sample size and event rate for the primary outcome were both relatively small. As this study was a secondary analysis, the sample size was determined by the original patient cohort from the parent study. As a result, the degrees of freedom in the multivariable logistic regression analysis were limited and the inclusion of all relevant patient characteristics was not possible. The propensity score matched analysis was able to generate two comparable cohorts with similar prognostic baseline characteristics. However, the matching process precluded the analysis of the entire cohort and further limited the sample size available for analysis. Neither analysis demonstrated a significant association between antibiotic treatment and lower rehospitalization but the risk of Type II error was high in both analyses.

Another important limitation was that data about exacerbation phenotype, including the cardinal symptoms of sputum volume and purulence, were not available. Data about laboratory biomarkers such as C-reactive protein, eosinophil count, procalcitonin were also not available. As a result, it was not possible to analyze the benefit of antibiotics for specific patient subgroups, such as the exacerbation types defined by Anthonisen or patients with exacerbations of infectious compared to non-infectious etiologies (6,16).

A third potential limitation was that the original Ottawa COPD Risk Score validation study (from which the secondary analysis data was obtained) had a proportion of eligible patients who missed enrollment (3). The validation study enrolled consecutive eligible patients from the emergency department however 1,304 out of 2,719 total eligible patients missed enrollment. Most of these patients were missed due to unavailability of research staff and a smaller proportion due to patient refusal. While there is no data on the patients who missed enrollment, the reasons for their exclusion should not introduce significant bias to the research question.

5.4.3 Definition of treatment failure

A limitation that is common to both projects in this thesis is that the definition of treatment failure in the treatment of AECOPD is not well established. There is substantial variation in the definitions of treatment failure or success used in previous studies, each with their own advantages and disadvantages (17).

Patient reports of symptom improvement or resolution may be subjective and patients can sometimes have prolonged symptoms up to 35 days after an exacerbation. Composite outcomes of treatment failure, like many other composite outcomes, have the downside of containing outcomes of varying clinical importance. Due to the dynamic nature of exacerbations, the

optimal timepoint for assessing these outcomes is also unclear and could affect the results of clinical trials (18).

A recent methodologic review proposes that clinical cure should be an outcome assessed in all COPD trials. The European Respiratory Society core outcome set panel recommends that clinical cure should be defined as sufficient improvement in signs and symptoms such that no additional systemic treatments are required (18). It has also been proposed that evaluation of treatment success in AECOPD may be most clinically relevant in the first 14 days immediately following initiation of therapy (17).

5.5 Clinical Implications

Acute exacerbations of COPD are heterogeneous and there are likely subsets of patients who benefit more from antibiotics than others. These groups of patients are not easily identifiable based on current evidence.

Patients with fever, immunocompromise, and signs of pneumonia on chest radiography were usually excluded from previous trials as treatment with empiric antibiotics is considered standard of care for these patients. Patients with increased sputum volume and purulence should also likely receive antibiotics based on previous RCT data and current international guidelines (6,19). Laboratory biomarkers such as C-reactive protein and procalcitonin can also provide meaningful datapoints in helping clinicians decide when to initiate antibiotics, though these tests are not universally available and standard cut-off points are not well established (20,21).

Ultimately, the decision to prescribe antibiotics should integrate all clinical data, the best available evidence, provider clinical judgement, as well as patient preference.

5.6 Research Implications

A substantially large multicentre RCT would be needed to properly address the clinical question of whether antibiotics confer benefit for AECOPD managed in the outpatient setting. Previous negative trials on this topic have demonstrated trends towards benefit and were likely underpowered. The main issue is that, based on currently available evidence, the benefit of antibiotics is likely modest and the sample size calculation of a future trial needs to incorporate a realistic, correspondingly small, clinically meaningful difference in the treatment effect. The definition of treatment success or failure needs to be standardized and objective and incorporate a timepoint that reflects the usual short courses of treatment that patients with AECOPD typically receive.

Future research should also focus on the impact of biomarkers and exacerbation phenotype, as certain subgroups may reveal a larger treatment benefit for antibiotics while other subgroups may reveal no benefit at all. These prognostic variables would be critical data to collect and analyze in any future studies.

The risk and clinical impact of adverse effects caused by antibiotics in patients with AECOPD is also unclear. It may be difficult to collect this data, however, due to patients with AECOPD usually receiving multiple medications such as corticosteroids and bronchodilators at the same time. In addition to traditional outcomes used to assess medication side effects, it may also be worthwhile for future studies to evaluate pragmatic outcomes such as quality of life and overall symptom burden.

5.7 Conclusion

This thesis examined the impact of antibiotics in the outpatient management of AECOPD through a systematic review and meta-analysis of all available RCTs as well as a secondary analysis of prospectively collected data from emergency department patients. When considering the results of these two studies in the context of previous literature, treatment with antibiotics likely provides a modest benefit in the outpatient management of AECOPD. This conclusion, however, is not definitive given methodologic limitations and limitations in the data of existing trials. It is also unclear what magnitude of benefit antibiotics provide as well as for which patient subgroups antibiotics would benefit most. Further research on these topics is needed to help guide clinicians in providing targeted management of patients with AECOPD and minimize the use of unnecessary antibiotics.

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