Risk of Infectious Diseases in Patients with COPD

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Abstract: In this paper, we review data on the risk of infectious diseases in chronic obstructive pulmonary disease (COPD), including the efficacy of antibiotics for prevention and treatment of acute COPD exacerbations, with a focus on more recent studies.

Studies indicate that immunological mechanisms in COPD are impaired, leading to increased susceptibility to infection. Exacerbations are often infectious in origin (viral and/or bacterial) although pathogens may also be present in the lungs of person with stable COPD. The detailed mechanisms of exacerbations remain under investigation.

Despite great variations in design and operational definitions of outcome, studies consistently find that patients with COPD are at an increased risk of respiratory infections. Patients with COPD do not appear to be at an increased risk of infections outside the respiratory system, but only a small number of studies have addressed this.

The role of antibiotics in the management of acute exacerbations of COPD is disputed. However, findings from recent studies suggest that antibiotics are effective, although primarily in patients admitted to the hospital, thus representing patients with more severe exacerbations. Still, the question of antibiotic efficacy for different clinically well-defined subgroups of COPD exacerbation as well as the choice of the most appropriate antibiotic for these subgroups is uncertain. Antibiotics may also be efficacious in exacerbation prevention. Recent studies on the efficacy of macrolides for the prevention of COPD exacerbations demonstrated promising results. Nevertheless, questions on the risk-benefit ratio of macrolides, efficacy in subgroups of COPD patients, and long-term effects remain unanswered.

Keywords: Antibiotics, bacteria, COPD, exacerbation, infection, macrolides, pneumonia.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world, resulting in a substantial and increasing economic and social burden [1,2]. COPD is currently estimated to be the fourth leading cause of death worldwide [2]. Patients with COPD are susceptible to a range of medical complications, including infections [1]. In this paper, we review data on the risk of infectious diseases in COPD, including the efficacy of antibiotics for prevention and treatment of acute COPD exacerbations, with a focus on more recent studies.

COPD - DEFINITION AND PATHOPHYSIOLOGY

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a common, preventable, and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1]. COPD is confirmed by spirometry testing and is characterized by a post-bronchodilator FEV1/FVC ratio below 0.70 [1,2]. COPD is mainly caused by a combination of genetic factors (with best documentation existing for a hereditary deficiency of Alpha-1 antitrypsin) and decades of exposure to noxious particles such as tobacco smoke or polluted air [1]. However, other factors (e.g. early childhood lung infections, asthma) may also play an important role in disease development [1]. In COPD, pathophysiologic changes of the lungs occur in the central airways, peripheral airways, parenchyma, and vasculature. Exposure to noxious particles causes a state of chronic inflammation resulting in airflow limitation due to a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). In COPD increased inflammatory cells, including neutrophils, macrophages, and T-lymphocytes (specifically CD8+) are present in the lungs as well as a systemic increase in inflammatory mediators. Generalized manifestations of COPD include systemic inflammation and skeletal muscle wasting [1,2]. Studies indicate that immunological mechanisms in COPD are impaired (e.g. defective alveolar macrophages) due to smoke exposure, leading to increased susceptibility to infection [3,4]. Moreover, persistent bacterial colonization (chronic bronchial infection) may also contribute to disease progression through inflammatory mechanisms [5,6]. In summary, COPD development and progression appear to be the result of a complex ensemble of genetic susceptibility, exposure to noxious particles, microorganism exposure, inflammatory mechanisms, and yet unknown factors.

THE ROLE OF MICROORGANISMS IN COPD PROGRESSION AND EXACERBATION

GOLD defines exacerbation as an event, in the natural course of COPD, characterized by further amplification of the state of chronic inflammation in the airways and acute

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onset of aggravation of baseline symptoms beyond normal day-to-day variations and leads to a change in medication [1]. Detailed mechanisms of exacerbations are incompletely understood [1]. However triggers are often (up to 78%) infectious agents; viral and/or bacterial [7,9], but in up to 25% of exacerbations a clear precipitant is not apparent [1].

It has been suggested that there are two possible ways in which microorganisms contribute to progression of COPD through inflammatory mechanisms [8]: the first is the acute cycle, where bacterial or viral pathogens cause worsening of baseline symptoms due to increased inflammation, as seen in exacerbations of COPD. The second possible mechanism is a cycle characterized by chronic inflammation due to persistent colonization of the lower airways. According to GOLD, bacteria are found in the lower airways of at least 50% of patients with COPD exacerbation, but may also be present in the lower airways of patients with stable COPD [1,10,11]. Bacterial colonization of the airways in stable COPD is associated with greater levels of inflammation measured in sputum as well as increased frequency of exacerbation [6,12]. Although pathogens may be present in both stable COPD and exacerbations, the bacterial load may be larger during exacerbations and microbial strains appear to be different from those present in stable COPD [12-14]. An exacerbation is likely triggered by the intrusion of new strains of bacteria, and the extent of respiratory symptoms depends on the extent of inflammatory increase [8]. Pathogens found in stable COPD and exacerbations vary depending on disease severity [14]. Moreover, heterogeneity in COPD reflected in variations in dominant pathophysiology (e.g. emphysema, chronic bronchitis) could mean differences in susceptibility to bacteria strains and thus exacerbations [15]. Other factors, such as medications, local vaccination recommendations, season of the year, and geography may also play roles.

In community-acquired pneumonia (CAP), *Streptococcus pneumonia* is the most prevalent bacteria [16]. In exacerbations of mild COPD, the most common strain appears to be *Streptococcus pneumonia,* whereas *Haemophilus influenzae* and *Moraxella catarrhalis* are frequently detected in exacerbations of moderate to severe COPD [14]. Other bacteria detected in patients with COPD exacerbations include *Pseudomonas aeruginosa*, *Enterobacteriaceae* [17-19], *Chlamydia pneumoniae,* and *Mycoplasma pneumonia* [20,21].

All of the above mentioned bacteria may also be found in the lower airways of patients with stable COPD, but *Haemophilus influenzae* and, to a lesser extent, *Streptococcus pneumoniae*, *Moraxella catarrhalis,* and possibly *Pseudomonas aeruginosa* are thought to play a role through inflammatory mechanisms [22]. Finally, viruses may contribute to disease progression. Respiratory viruses are found in more than 50% of COPD exacerbations [23]. The most common viruses detected are the *Rhinoviruses*, but *Respiratory Syncytial Virus* and *Influenza* have been associated with acute exacerbations [24-26].

COPD AND RISK OF RESPIRATORY TRACT INFECTIONS

For several reasons it is challenging to answer the apparently simple questions of the risks of respiratory infection in patients with COPD. Investigations addressing this topic vary greatly in study design. Examined COPD populations are very heterogeneous due to variations in COPD severity, inclusion and exclusion criteria, medication usage, smoking status, comorbidities, and other factors [27-31]. Secondly, infectious study outcomes (endpoint) may be defined in varying ways [27-31]. Some studies have "exacerbation" as the study endpoint, whereas others have "pneumonia". Further, the endpoint may be defined as "hospitalized exacerbation", thus not including less severe episodes that did not lead to hospital admission. Thirdly, the operational definition of "exacerbation" varies greatly, as there is a lack of consensus on a precise operational (and clinically useful) definition. The definition of exacerbation presented by GOLD is entirely based on an unspecified worsening in the degree of baseline symptoms of COPD leading to a change in medication. In other words, this definition covers various clinical manifestations with the single commonality of worsening respiratory symptoms. As a consequence of this extremely broad definition, the clinical manifestations considered exacerbation of COPD range from minor conditions treated in a home setting to severe respiratory illnesses requiring intensive care admission. Moreover, when the definition does not address etiology, exacerbation may be caused by airway pollutants or aggressive bacteria strains. Since the definition is inclusive but not specific, studies with exacerbation as the outcome may include a broad range of manifestations, including those of pneumonia, or may include only cases of exacerbation without concomitant pneumonia. A number of studies falling under the overall category of 'risk of respiratory infections in COPD' are described below.

A large cohort study published in 2008 by Benfield *et al*. (12,389 persons classified according to the GOLD criteria) with 25 years of follow-up investigated the risk of infection in COPD [27]. COPD diagnosis was based on spirometry and the study outcome was identified through a national registry of discharge diagnosis (World Health Organization International Classification of Diseases). The risk of hospitalization for lower respiratory tract infection increased with all stages of COPD as compared to persons without COPD; multivariate adjusted and statistically significant RRs were 1.24 (95% CI: 1.01-1.53), 2.00 (95% CI: 1.71-2.32), and 3.28 (95% CI: 2.60-4.13) for mild, moderate, and severe COPD, respectively. The same trend was found for hospitalization due to upper respiratory tract infections: multivariate adjusted and statistically significant RRs were 0.95, 1.98, and 5.26, respectively [27]. Another large cohort study (20,375 participants) investigated if COPD severity was a predictor of hospitalization for pneumonia [29]. Study participants had spirometry performed at baseline, but only pre-bronchodilator values were available. COPD was classified according to a modified GOLD classification: GOLD 3 and 4 were defined as FEV1 <50% predicted and GOLD 2 was defined as a FEV1 ≥50% predicted. Compared to persons without COPD, GOLD stages 3-4 and 2, respectively, were associated with an increased risk of hospitalization for pneumonia corresponding to multi-adjusted HRs of 5.65 (95% CI: 3.29-9.67) and 2.25 (95% CI: 1.35-3.75). Again, in this study the diagnosis of pneumonia was based entirely on data from hospital discharge registries [29], thus potentially adding some misclassification.

In summary, these studies found an increased risk of hospitalization for lower respiratory tract infections/ pneumonia for persons with COPD as compared to persons without COPD as well as an increased risk of hospitalization for upper respiratory tract infections. In both situations, risk increases with COPD severity. Concerning COPD exacerbations, numerous other studies (placebo-limb from randomized trials) demonstrated a similar "dose-response" relationship of increasing frequency of exacerbations with increasing COPD severity, for example the TORCH study [32], the Uplift study [33], the ECLIPSE study [31], etc. Seemungal *et al*. studied 84 outpatients with moderate to severe COPD for one year [30]. Exclusion criteria were asthma, bronchiectasis, bronchial carcinoma, or inability to complete daily diary cards (self-reported peak expiratory flow rate, increase in respiratory symptoms and presence of fever). An exacerbation was diagnosed if the following symptoms were present for at least two consecutive days: at least two of three major symptoms (increased dyspnea, sputum purulence, and increased sputum volume), or one major symptom with any minor symptoms (increase in nasal discharge, wheeze, sore throat, cough, or fever). They observed an exacerbation rate of 1.5 episodes per patient-year with some patients experiencing repeated exacerbations during the one-year follow-up (mean 2.7 episodes per person, range 1-8). Only 16% of all exacerbations required hospitalization. A recent large cohort study (2,138 patients with COPD) by Hurst *et al*. [31] investigated the risk of exacerbation for different stages of COPD. Outcome was defined in accordance with GOLD‟s definition of COPD exacerbation and based on the assessment of the patients primary clinician or study personnel and included both in- and outpatient contacts. Exacerbation rates in the first year of follow-up were 0.85, 1.34, and 2.00 per person-year for patients with moderate, severe, and very severe COPD, respectively. They found that 22% of patients with moderate COPD, 33% with severe COPD, and 47% with very severe COPD had two or more exacerbations in the first year of follow-up. Langsetmo *et al*. also studied COPD exacerbation rate; this study aimed to determine the incidence of unreported episodes [28]. In an outpatient setting, among 421 patients with spirometrically diagnosed COPD, patients were to register an exacerbation in a diary when worsening of one of the following symptoms was present for at least two days: dyspnea, sputum amount, or sputum color. Reported episodes were those leading to any health care contact. Patients were excluded if they received regular long-term oxygen therapy, were scheduled for COPD rehabilitation, had any unstable or life-threatening comorbidity, used beta-blockers, or if they were being treated with a combination of inhaled corticosteroids and long-acting beta-agonist at study enrolment. Notably, all included patients were to receive Symbicort® (budesonide/formoterol) turbuhaler. The study found an exacerbation rate of 2.7 per person-year, but the rate of reported episodes was only 0.8 per person-year. A recent trial by Albert *et al*. investigating the effects of azithromycin for the prevention of COPD exacerbations (n=1,142) demonstrated an exacerbation rate of 1.83 per person-year for the placebo limb [34]. Exacerbation was defined according to the recent GOLD guidelines. However, patients were selected according to specific inclusion and exclusion criteria (details described below) corresponding to a study population of more advanced COPD patients.

In summary, based on these studies the average annual COPD exacerbation rate varies from 0.8 to 2.7 per person-year depending on (among other factors) study population characteristics and the operational definition of exacerbation. The majority of exacerbations (approximately 85%) do not lead to hospitalization. Furthermore, milder episodes of worsening of baseline symptoms may be underreported in terms of no contact with health care facilities. Many COPD patients experience repeated exacerbations - particular those with more severe COPD - and the incidence of exacerbations increases with increasing COPD severity. For studies of COPD exacerbation it is rarely apparent if cases of pneumonia are counted as exacerbations and thus included in the outcome. In other words, knowledge on the incidence of exacerbations for different grades and subgroups of COPD remains incomplete [1,27,31].

The Infectious Diseases Society of America (IDSA) and American Thoracic Society Consensus Guidelines recommend that the diagnosis of CAP should be based on the presence of clinical features suggestive of pneumonia (e.g. cough, fever, purulent sputum) supported by the finding of a pneumonia infiltrate demonstrated by radiograph or other imaging techniques, such as computed tomography [35]. As illustrated, the definitions of 'pneumonia' in comparison to 'exacerbation' present overlapping elements that make a clear differentiation based on these definitions difficult. Furthermore, in the clinical context, exacerbation and pneumonia share common clinical findings (e.g. cough, sputum, dyspnea). C reactive protein (CRP) may be relevant in distinguishing bacterial exacerbation and pneumonia from viral exacerbations or exacerbations of non-infectious cause [36]; CRP likely already plays an important role when physicians decide whether to initiate antibiotics for exacerbations. Procalcitonin may be a predictor of bacterial infection in patients with COPD [37], however this test is expensive, and thus not widely used [1]. Furthermore, a recent study published by Bafadhel *et al*. in 2011 demonstrated biologic clusters (and clinical phenotypes) for COPD exacerbations, and suggested that sputum IL-1beta level could be used as a marker of bacterial exacerbation [38].

In summary, definitions that easily translate into operationally reliable and useful tools in a clinical context or study design are needed. Precise definitions and criteria are of particular importance in a clinical context, since differentiating exacerbations with and without concomitant respiratory bacterial infection (e.g. pneumonia) is essential in deciding who will or will not benefit from antibiotics. Moreover, objective clinical parameters with high sensitivity and specificity as predictors of bacterial infection in exacerbation of COPD would be of significant importance.

ANTIBIOTICS FOR COPD EXACERBATIONS

In addition to initiating and/or regulating the use of bronchodilators, corticosteroids, respiratory support, and treatment for complicating comorbid conditions [1], physicians also must determine whether a patient with exacerbation will benefit from antibiotics. GOLD recommends the use of antibiotics in COPD exacerbations

when the patient presents with purulent sputum and dyspnea and/or increased sputum volume [1]. The American Thoracic Society (ATS) and European Respiratory Society (ERS) also provide recommendations concerning the use of antibiotics in COPD exacerbations: "antibiotics may be initiated in patients with altered sputum characteristics (purulence and/or volume)" [2]. In other words, there is a lack of precise recommendations that easily translate into useful and reliable tools in the clinical context. Patients requiring admission to intensive care or special care units are an exception: in this case both GOLD and ATS/ERS explicitly recommend the use of antibiotics under any circumstances [1,2]. GOLD recommendations are primarily based on two systematic reviews. The first, a systematic Cochrane review, identified 11 placebo-controlled, randomized trials (917 patients) investigating the effect of antibiotics on acute exacerbations of COPD [39]. This review demonstrated a statistically significant reduction in the risk of short-term mortality by 77%, a decrease in the risk of treatment failure by 53%, and a reduced risk of sputum purulence by 44% in favor of antibiotics. Only 2 of the 11 studies included took place in community settings. Analysis restricted to these two studies did not show a significant difference between placebo and antibiotics. In summary, the review showed that antibiotics are beneficial for exacerbations associated with increased cough and sputum purulence and in particular for patients admitted to the hospital. This suggests benefit from antibiotics is primarily seen among patients with more severe symptoms. The authors of the review stated that the results should be interpreted with caution due to extensive differences in patient selection, type of antibiotic, the small number of trials included, and the lack of control for other interventions influencing outcome (e.g. systemic corticosteroids and ventilatory support). Notably, from the Cochrane review described above it is seen that 4 of the 11 studies excluded patients with pneumonia, but for the remaining studies it is not apparent whether patients with pneumonia were included or excluded; these inter-study variations may very well contribute to variation in the degree of observed antibiotic effect. Despite inter-study variations in the measured size of the effect of antibiotics, 9 of the 11 studies more or less support that antibiotics are effective. This common trend in favor of antibiotics could be due to bias in study selection. Although the authors of the review stated that they had made every effort to include all relevant studies, publication bias due to lack of publication of studies demonstrating no effect of antibiotics cannot be excluded. The second systematic review by Quon *et al*. also evaluated the efficacy of antibiotics in acute exacerbations [40]. This study is similarly based on 11 placebo-controlled trials, of which 10 are also included in the Cochrane review described above. Not surprisingly, this second review draws the same main conclusions as the first: despite inter-study variations in size of the effect measure, the overall tendency was towards benefit (as compared to placebo) from antibiotics, in particular for those with more severe exacerbations. The review by Quon *et al*. concludes that antibiotics are effective in terms of reducing treatment failures (requiring additional antibiotics or when symptoms are unchanged or deteriorated), however this reduction was only statistically significant for those admitted to the hospital (RR 0.34; 95% CI 0.20-0.56), but not outpatients (RR 0.88; 95% CI 0.56-1.39). Moreover, pooled data (181 persons) from the 3 of the 11 trials that investigated mortality demonstrated a 78% reduction in in-hospital mortality associated with the use of antibiotics (RR 0.22; 95 % CI 0.08-0.62) [40]. Notably, the largest of these three studies on mortality included only patients receiving mechanical ventilation [41]. A recently published randomized, placebo-controlled trial by Daniels *et al*. investigated the effects of doxycycline in addition to corticosteroids for 265 patients with COPD exacerbation [42]. Doxycycline showed superiority over placebo in terms of clinical success on day 10 by intention-to-treat analysis (odds ratio, 1.9; 95% CI 1.1-3.2), but not on day 30. Patients were assessed on days 1, 10, and 30 based on blood samples, serologic testing, expectorated sputum samples, and symptoms in terms of dyspnea, cough, fatigue, and sputum purulence; however, a precise definition of the term „clinical success" is not explicitly presented in the article. Notably, patients with fever and/or signs of pneumonia confirmed by radiograph were excluded from the study, which is not necessarily the case for other studies investigating the efficacy of antibiotics for COPD exacerbations (as described for the two review articles above). In other words, patients expected to benefit the most from antibiotics were not included in the study by Daniels *et al*.

Rothberg *et al*. performed a retrospective cohort study investigating the effect of antibiotics on COPD exacerbations [43]. Patients receiving antibiotics within the first two days of hospitalization were compared to those receiving antibiotics later or not at all. The study was based on administrative data. Of 84,621 patients, 79% received antibiotics for at least two consecutive days. Patients receiving antibiotics had lower multivariate adjusted rates of inpatient mortality of 1.04% (95% CI: 1.03%-1.05%) *vs* 1.59% (95% CI: 1.57%-1.61%), readmissions for exacerbation of 7.91% (95% CI: 7.89%-7.94%) *vs* 8.79% (95% CI: 8.74%-8.83%), and mechanical ventilation of 1.07% (95% CI: 1.06%-1.08%) *vs* 1.80% (95% CI: 1.78%-1.82%). Although confounding-by-indication could hypothetically be present as a consequence of the study design, as the authors point out, if more severely ill patients were more likely to receive antibiotics this would bias the result away from any observed benefit from antibiotics. In summary, most studies demonstrate a result in favor of the use of antibiotics for COPD exacerbation; this is despite significant heterogeneity in study design, variations in type of antibiotic used, and definition of exacerbation and COPD, respectively. For this reason, the question is perhaps not *if* antibiotics are relevant in exacerbations, but rather *in which particular clinically well-defined subgroups* it is effective? And additionally, *what type of antibiotic* produces the most benefit in these subgroups? In this assessment, possible risks and adverse events associated with different types of antibiotics (for example, possible cardiotoxic effect of macrolides [44]) should also be taken into account. Future randomized trials could be initiated to investigate this topic in further detail by focusing on different well-defined subgroups of COPD patients and different antibiotic types. Observational studies comparing subgroups within a study population of patients receiving antibiotics could provide information on which subgroups benefit the most from antibiotic therapy.

Concerning which type of antibiotic to choose when treating patients with COPD exacerbations, the majority of previous studies, either by design or result, have failed to prove superiority of one antibiotic over another [45,46]. However, in 2005 Sethi presented a risk stratification approach based on review of the literature [45]. This approach suggests categorizing those with moderate-severe exacerbation as either „simple" or „complicated". The latter is characterized by severe COPD, bronchiectasis, hospitalizations, or receipt of multiple courses of antibiotics. For „simple" exacerbations, the antibiotic suggested by Sethi is an advanced macrolide, ketolide, cephalosporin, or doxycycline; for complicated cases, fluoroquinolone, amoxicillin/clavulanate, or (if at risk of *Pseudomonas*) ciprofloxacin are suggested. Furthermore, as recommended in the current GOLD guidelines, the choice of antibiotic should be based on the local bacterial resistance pattern [1].

ANTIBIOTICS FOR PREVENTION OF COPD EXACERBATIONS

To reduce symptoms, limit disease progression, and decrease the rate of exacerbations, GOLD recommendations include smoking cessation, rehabilitation, vaccinations, and pharmacotherapy, including bronchodilators and inhaled corticosteroids [1]. However, prevention of exacerbations/ respiratory infections remains challenging. Inhaled corticosteroids are recommended by GOLD to reduce exacerbations, but this same agent seems to increase the risk of pneumonia [1,47]. Furthermore, both influenza and pneumococcal vaccinations are recommended by GOLD [1], but a recent article published in *Expert Review Vaccines* [48] questions the evidence for efficacy of any of the polyvalent pneumococcal vaccinations (PPVs) since studies focusing on COPD patients are very sparse and often statistically underpowered. The authors do point out that, to date, of all pneumococcal vaccinations the PPV23 appears to be the most effective type. Evidence that PPV23 decreases the risk of non-invasive pneumococcal disease or all-cause pneumonia is also controversial. In other words, there is a lack of strong evidence for some of the recommended approaches with the aim of reducing exacerbations/respiratory infections. Additional methods to effectively reduce exacerbations/respiratory infections and thus disease progression and early death are desirable.

Considering the role of microorganisms in both stable COPD and exacerbations, there has been a revival of focus on antibiotic approaches for exacerbation prevention. In particular there has been an interest in macrolides due to their anti-inflammatory properties, their ability to alter biofilm formation, and their possible synergistic effects with other antibiotics [34, 49-53]. A recently published article in the New England Journal of Medicine reported promising results [34]: a randomized, placebo-controlled trial investigated the effects of azithromycin for the prevention of exacerbations among 1,142 COPD patients at increased risk of exacerbations. Azithromycin was given for one year at a daily dose of 250 mg in addition to usual treatment. The proportion with one-year follow-up was 89% and 90% for those receiving azithromycin and placebo, respectively. The median time to first exacerbation was 266 days (95% CI: 227-313) and 174 days (95% CI: 143-215) for the azithromycin and placebo groups, respectively, thus showing a statistical significant difference in favor of azithromycin. The rate of exacerbations was 1.48 per person-year for those receiving azithromycin and 1.83 per person-year for the placebo group (p=0.01). In addition, quality of life measured by the St. George"s Respiratory Questionnaire improved more in the azithromycin group as compared to the placebo group, but the mean change did not exceed the minimal clinically important difference of at least four units. Azithromycin was also, however, associated with a small but statistically significant increase in hearing decrement (25% *vs* 20%) and an increase in the incidence of macrolide-resistance (81% *vs* 41%). Study population inclusion criteria were COPD patients characterized by either the use of continuous supplemental oxygen, systemic corticosteroids within the previous year, or hospitalization or emergency room contact within the previous year. Thus, the results of the study are only valid for this particular subgroup of COPD patients having features of more advanced COPD. Moreover, exclusion criteria before enrollment were asthma, hearing impairment, resting tachycardia, or apparent risk of QTc prolongation and exacerbation within one month prior to enrollment. Furthermore, 80% of study participants received inhaled corticosteroids and therefore it is unknown how patients not receiving this agent would respond to azithromycin. Several other studies investigated the effects of macrolides on exacerbation rate, but results are somewhat conflicting [49-52]. A possible explanation is heterogeneity in study design. Seemungal *et al*. performed a randomized, placebo-controlled trial studying the effect of long-term erythromycin on exacerbation rate; they found a rate ratio of 0.65 (95% CI; 0.49-0.86) in favor of azithromycin. Study participants had moderate-severe COPD. Exacerbations were defined as increased baseline symptoms persisting for at least two days. Two other studies have similarly investigated the effect of macrolides, but found no differences among the compared groups [50,53].

However, one of the two studies had a retrospective design comparing patients that received versus not received macrolides of any type [50]. This study does not describe the duration of received macrolide treatment or if the control group received other antibiotics; it was only specified that these individuals did *not* receive macrolides. The other study was a randomized trial but was continued for only three months and included only 46 patients [53], and thus may have been underpowered to detect a difference. A recent study by Sethi *et al*. also investigated the effect of moxifloxacin for the prevention of COPD exacerbations [22], but in this study azithromycin was given as intermittent pulsed therapy: 1,157 persons with COPD received six courses of therapy for six weeks every eight weeks. The study lasted 48 weeks with a further 24 weeks of follow up. Moxifloxacin reduced the odds of exacerbation by 20% in the intention-to-treat group (not statistically significant), by 25% in the per-protocol group, and by 45% in per-protocol patients with purulent/mucopurulent sputum at baseline. There were no significant differences between moxifloxacin and placebo in hospital rates, mortality rates, lung function, or changes in quality of life measured by the Saint George Questionnaire.

Additionally, other studies suggest that the subgroup of COPD patients with a bronchitic phenotype may benefit the most from long-term antibiotics [8,54], since this phenotype

is associated with lower airway bacterial colonization [55,56]. Further investigation of the possible benefits of long-term antibiotics in the bronchitic phenotype using techniques to register changes in bacterial colonization is needed [54].

In conclusion, current data suggest a promising role of antibiotics for prevention of exacerbations in COPD patients that are particularly susceptible to exacerbations; this is a highly desirable approach considering the vast consequences of frequent exacerbations on quality of life, disease progression, early death, and health-care related costs. However, many questions of importance remain unanswered. The risk-benefit ratio is unknown. Long term positive versus negative effects of persistent or pulsed antibiotic therapy in terms of increased bacterial resistance and adverse effects (e.g. hearing decrement and cardiac complications) have not been thoroughly investigated. It is also unclear whether some of the positive effects of macrolides on exacerbation rate may be due to their immunomodulatory effects [57]. Finally, questions remain concerning the most appropriate type of macrolide, the dosage with the best benefit-risk ratio, potential interaction with other medications, the efficacy of antibiotics other than macrolides, and which particular subgroups of COPD patients would benefit the most from this therapy.

RISK OF NON-RESPIRATORY INFECTIONS IN COPD

In the light of an increasing understanding of COPD as a disease with systemic manifestations in terms of chronic systemic inflammation [58,59], one could speculate that COPD patients are at increased risk of not only respiratory infections but of infections in general. Knowledge in this field is scarce and data in the literature is limited [27,60]. One cohort study specifically addressed this topic [27]. This study investigated the risk of hospitalization for infectious diseases based on a cohort of COPD patients and persons without COPD. Follow up time was over 25 years. Based on the World Health Organization International Classification of Diseases, the study investigated the following categories of infectious diseases: diarrheal diseases, hepatitis, HIV/ AIDS, influenza, lower respiratory tract infection, meningitis, other viral infection, parasitic infection, pulmonary abscess/pyothorax, sepsis, skin infection, tuberculosis, urinary tract infection, and upper respiratory tract infection. The authors demonstrated that the risk of hospitalization due to infectious diseases increased with severity of COPD; statistically significant RRs after adjustment were 1.06 for mild COPD, 1.39 for moderate COPD, and 2.21 for severe/ very severe COPD as compared to persons without COPD. However, this increased risk with increasing severity of COPD was entirely due to an increased risk of respiratory infections and not other infections [27]. In other words, COPD patients seem to be at increased risk of hospitalization for respiratory tract infections, but not of hospitalization due to non-respiratory infections.

CLOSING REMARKS

The literature on understanding of COPD and infections is continuously growing. Still, many aspects remain controversial and unclear. This is partly due to different and to some extent even incompatible operational definitions used in various studies. The differences in operational definitions may be explained by the lack of consensus regarding precise definitions of the key phenomena that easily translate into reliable and useful measurements and tools in a clinical context or study design. In this perspective, research on COPD is still in the pre-paradigmatic phase [61]. Despite numerous variations in study design and operational definitions of the object under investigation, studies consistently find that patients with COPD are at increased risk of respiratory infections, a risk that increases with severity of COPD.

The role of antibiotics in acute exacerbations of COPD is a cause of much dispute. However, based on the present literature antibiotics appear to be effective, although primarily in persons admitted to the hospital, and thus patients with more severe exacerbations. However, the question of the efficacy of antibiotics in clinically well-defined subgroups is not answered with sufficient detail; nor is the question of which types of antibiotic are most effective in the respective clinical subgroups. Studies designed to answer these questions are desirable and results from such studies would be of great importance in a clinical context. Antibiotics may also be of relevance for the prevention of exacerbations. Recent studies on the efficacy of macrolides for the prevention of COPD exacerbations demonstrate promising results. However questions concerning the risk-benefit ratio of macrolides, their efficacy in subgroups of COPD patients, as well as long-term effect of persistent use remain unanswered. Future studies aimed at answering these questions would be highly valuable for clinical practice.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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ABBREVIATIONS

FVC = Forced vital capacity

FEV1 = Forced expiratory volume in 1 second

HR = Hazard ratio

RR = Relative risk

95% CI = 95% confidence intervals

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