Pneumonia in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a frequent comorbid condition associated with increased morbidity and mortality. Pneumonia is the most common infectious disease condition. The purpose of this review is to evaluate the impact of pneumonia in patients with COPD. We will evaluate the epidemiology and factors associated with pneumonia. We are discussing the clinical characteristics of COPD that may favour the development of infections conditions such as pneumonia. Over the last 10 years, there is an increased evidence that COPD patients treated with inhaled corticosteroids are at increased risk to develop pneumonia. We will review the available information as well as the possible mechanisms for these events. We will also discuss the impact of influenza and pneumococcal vaccination in the prevention of pneumonia in COPD patients. (BRN Rev. 2018;4:108-21)

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Key words: COPD. Inhaled corticosteroids. Pneumonia. Pneumonia vaccine.
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the leading cause of death for both males and females in the United States (US) and is projected to rise in ranking by 2020\(^1\). According to data from the National Center for Health Statistics of the Centers for Disease Control and Prevention, COPD became the third leading cause of death by 2008\(^2\). Furthermore, according to the World Health Organization in 2014, lower respiratory tract infections and COPD represented the third and fourth leading causes of death worldwide\(^3\). In addition, community-acquired pneumonia (CAP) is cause of morbidity and mortality around the world\(^4\). Pneumonia is the seventh leading cause of death overall and first leading cause of infectious death in the US\(^5\) and Europe\(^6\). Pneumonia was associated with more than 1.1 million inpatient hospitalizations and 50,000 deaths in 2010\(^7,8\); the vast majority of deaths due to pneumonia occur in patients over 65 years of age. This condition is responsible for a high financial burden with over $10 billion spent caring for patients with pneumonia\(^7,8\). Therefore, it is important to understand the association between COPD and pneumonia, as well as their impact in patient’s management.

EPIDEMIOLOGY

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing\(^9-13\). Clinical studies of pneumonia including outpatient, inpatient and intensive care unit (ICU) cohorts have shown that COPD is a frequently reported comorbid condition\(^14-18\) (Fig. 1). Compared to patients without COPD, pneumonia patients with COPD are likely to have more severe pneumonia, increased number of hospital admissions, and worse outcome\(^19-21\). In the first year after a COPD diagnosis, individuals are at 16 times the risk for pneumonia compared to those without COPD\(^22\). In a recent study, the incidence rate of community acquired pneumonia was 22.4 events per 1,000-person years in the 10 years following the diagnosis of COPD, and more than 50% higher in those categorized as having severe COPD\(^23\). Furthermore, the economic impact of pneumonia is greater for those with COPD, illustrated by a doubling of direct medical costs following an inpatient hospitalization for pneumonia compared to those without COPD in a study of older individuals. More recent studies evaluated the risk of pneumonia in COPD patients that also have other co-morbid conditions such as cardiovascular disease (CVD). COPD patients with CVD had increased risk of pneumonia\(^24\). Lin et al.\(^24\) reported that COPD patients with CVD who received inhaled corticosteroids (ICS)-containing therapy had significantly increased risk of developing pneumonia compared to those who did not receive ICS-containing therapy or those who only had comorbid CVD. The increased incidence of pneumonia in COPD patients using ICs is discussed later.

Despite COPD being one of the most frequent comorbid conditions and a risk factor for developing pneumonia, it has not been recognized as an increased risk factor for mortality in pneumonia patients\(^25-27\). Furthermore, the well-validated prediction rule developed as part of the pneumonia Patient Outcomes Research Team (PORT) cohort study, that evaluated 30-day mortality in patients with pneumonia, excluded chronic pulmonary disease.
as a risk factor\textsuperscript{28}. This prediction rule was based on 20 variables that included five comorbid illnesses (cardiovascular, history of malignancy, cerebrovascular, renal and liver diseases)\textsuperscript{28}. In addition, Fine et al.\textsuperscript{30} published a meta-analysis related to prognosis and outcomes in CAP patients, and found that patients with pulmonary diseases, including COPD, asthma and interstitial lung disease, did not show higher mortality. However, in previous research (PORT studies and the meta-analysis), the diagnosis of COPD was combined with asthma and interstitial lung diseases, which might be inaccurate given that these conditions exhibit different natural histories and may bias the overall impact of COPD on pneumonia morbidity and mortality. Restrepo et al.\textsuperscript{20} reported that COPD patients hospitalized with pneumonia, compared to patients without COPD, show significantly higher 30- and 90-day mortality and later Rello et al.\textsuperscript{21} showed also increased mortality in pneumonia patients with COPD that required mechanical ventilation. In addition, hospitalized pneumonia patients with COPD exhibited significantly higher rates of ICU admission and a longer length of hospital stay compared with those without COPD. However, a systematic review and meta-analysis of 11 studies (cohort [n=9] and case-control [n = 2]) showed that COPD was not associated with increased mortality in cohort studies and reduced mortality in case-control studies of hospitalized patients with pneumonia\textsuperscript{31}. In addition, COPD was not associated with longer

**Figure 1.** The impact of comorbid conditions on the incidence of patients hospitalized with community-acquired pneumonia (reproduced with permission from Ramirez JA et al.\textsuperscript{17}).

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease.
hospital stay and more need for mechanical ventilation. Therefore, despite a higher risk to develop pneumonia the current evidence suggests that COPD may not be associated with increased morbidity and mortality in patients hospitalized with pneumonia. However, some of these studies had important limitations such as an imprecise COPD and pneumonia diagnosis. Furthermore, distinguishing among pneumonic and non-pneumonic exacerbations in COPD patients is still a matter of controversy in the big epidemiological studies. For all those reasons, prospective population-based cohort studies are needed to further clarify this issue.

**PATHOGENESIS**

The mucosal surface of the COPD patient’s lung is constantly exposed to microbial pathogens that have the potential to cause pneumonia in susceptible hosts. The risk of developed pneumonia could be related to host-related factors, or microbiome changes that allow increased presence of pathogenic organisms. Microbiome imbalances can contribute to disease as they disrupt normal micro-environmental stimuli for the human host. An effective early immune response in the lower respiratory tract is crucial for a successful balance of the microbiome. Cells of the innate immune system possess germline-encoded pattern-recognition receptors that can sense conserved microbial molecules referred to as pathogen associated molecular patterns and set off a cascade of immune responses. Among pattern-recognition receptors, nucleotide oligomerization domain (NOD)-like receptors (NLRs) are unique cytosolic receptors, which constantly patrol for changes in pathogens in cytoplasm. There is intense research to describe inflammasome assembly, activation, and their role in acute pneumonia. Furthermore, understanding the interactions between different inflammasomes during the innate immune response is essential for identifying how immune sensors are stimulated by ligands and, ultimately, for development of therapies to attenuate excessive tissue damage.

COPD patients may be more susceptible to develop pneumonia based on their clinical characteristics such as having chronic bronchitis with persistent mucus production, and the presence of potential pathogenic bacteria in the airways, the presence of bacteria in the airway in stable COPD patients and increased numbers during exacerbations have been associated with increased inflammation and the host immune response. Chronic bronchitis in COPD is seen more frequent in persistent smokers and has been associated with increased disease progression, and more frequent exacerbations. This is likely due to the fact that chronic bronchitis is associated with airway infection. Mucus production is an important feature in COPD patients with chronic bronchitis. Mucus that is formed in the airways is a protective barrier composed of water, salt and proteins. The major macromolecular components of the mucus are proteins called mucins. Experimental studies have demonstrated that mucin secretion is required for defence against bacterial infections, linking mucin deficiency with chronic airway infections. Airway mucins (MUC) have been shown to be an important airway mucus transport, leading to sputum production, increased airway inflammation, infection, worsening airflow obstruction and markers of disease progression. In moderate COPD, increases of MUC5AC and MUC5B have been detected compared to non-smokers.
and smokers without airway obstruction\textsuperscript{37}, although these findings have not been related to airway infection. In non-cystic fibrosis (CF) bronchiectasis, elevated MUC2 levels were related to the presence of \textit{Pseudomonas aeruginosa} and disease severity\textsuperscript{38}. Recently, Sibila et al.\textsuperscript{39} reported that airway MUC2 levels are decreased in severe COPD patients colonized by positive pathogen microorganism. These studies suggest that mucins changes may be one of the mechanisms underlying airway bacterial changes in COPD patients and may be associated with presence of pathogenic bacteria, but its role in the development of pneumonia has not been described.

Braeken et al.\textsuperscript{40} reported the associations between COPD and pneumonia in a large population-based study. The authors discussed potential smoking-induced mechanisms leading to increased risk of pneumonia in COPD, such as host physiological and structural changes, increased bacterial virulence and impaired host immunity. Shukla et al.\textsuperscript{41,42} found increased respiratory tract epithelial expression of specific bacterial adhesion factors in COPD, platelet-activating factor receptor (PAFr) which is the major pneumococcal and \textit{Haemophilus influenzae} adhesion molecule. The authors suggested that this could be one important mechanism that could significantly increase the risk of \textit{Streptococcus pneumoniae} respiratory infection in COPD. Pack-years of smoking were strongly related to epithelial PAFr protein levels in COPD patients\textsuperscript{42}. Furthermore, the authors also found that \textit{Streptococcus pneumoniae} expresses phosphorylcholine in its cell wall that specifically binds to PAFr, leading to initial attachment and subsequent translocation of bacteria into deeper tissue. Translation research in this area of bacterial–epithelial interactions can provide novel insights into pathogenesis of pneumonia in COPD patients, its natural history, as well as new therapeutic targets. Blocking the initial stages of bacterial adhesion and colonization in already activated epithelium in COPD patients could emerge as a promising target for the development of alternate, non-antibiotic pharmacotherapies for the management of the disease and its infective complication\textsuperscript{43}. Therefore, there are multiple factors in COPD patients that may predispose them to have an increased risk factor for development of pneumonia (Table 1).

### PATHOGENS

Understanding of the role of bacteria in patients with stable COPD, and how potentially pathogenic microorganisms isolated in these patients under stable conditions can contribute to pneumonia is not well known. Some studies suggested that these bacteria contribute to chronic airway inflammation leading to COPD progression and increased risk to develop pneumonia\textsuperscript{44,45}. More important, the description of the lung microbiome on healthy individuals using molecular culture-independent techniques have identified that normal airway has multiple bacteria species and these are different in patients with underlying lung

<table>
<thead>
<tr>
<th>Table 1. Factors that may predispose pneumonia in COPD patients</th>
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<tbody>
<tr>
<td>- Chronic bronchitis</td>
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<tr>
<td>- Persistent mucus production</td>
</tr>
<tr>
<td>- Presence of bacterial colonization</td>
</tr>
<tr>
<td>- Microbiota imbalances</td>
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<tr>
<td>- Increased airway inflammation</td>
</tr>
<tr>
<td>- Impaired host immunity</td>
</tr>
<tr>
<td>- Structural damage</td>
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conditions like COPD. Analysis of the highly-conserved 16S rRNA gene has been used to assign phylogeny and allowed a picture of the complete microbial community in the respiratory tract including upper airway, sinus, and bronchial tree. The number of studies examining the lower airways microbiome have significant increased over the past few years and they describe the differences in bacteria philia in patients with chronic disease including COPD and asthma, and in healthy individuals. A study reported a significantly different bacterial community in patients with very severe COPD compared with nonsmokers, and among smokers compared to patients with cystic fibrosis. Clinical studies are needed to understand the role of bacteria microbiomes in COPD patients and the risk of pneumonia. Furthermore, we need to understand the impact of antibiotics, given for either acute exacerbations, or chronic long-term administration, on these bacterial communities and pneumonia.

Liapikou et al. reported in a study of severe pneumonia patients with COPD that microbiological diagnosis occurred in 46% of the patients, and blood cultures were diagnostic in 12% of the cases. The most frequent microorganism identified in COPD patients with pneumonia was Streptococcus pneumoniae. Other investigators also reported that in elderly patients with COPD and pneumonia, Streptococcus pneumoniae was the most frequent organisms isolated. Patients with COPD also had more infections attributable to Pseudomonas aeruginosa, but fewer attributable to Legionella pneumophila compared to non-COPD patients, respectively. Other studies suggest that hospitalized pneumonia patients with COPD have more infections attributable to Pseudomonas aeruginosa, particularly those patients with bronchiectasis. Other risk factors for Pseudomonas and other potentially drug-resistant pathogen such as previous isolation, ICU admission, immunosuppression and prior antimicrobial therapy (<90 days) have been described in COPD patients. These data support the Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) recommendation that appropriate diagnostic procedures and anti-pseudomonas coverage should be considered in pneumonia patients with severe COPD, whether bronchiectasis is present, particularly in those treated with corticosteroids. Therefore, it is important to recognize COPD in patients with pneumonia so that they may receive appropriate antimicrobial therapy.

**INHALED CORTICOSTEROIDS AND PNEUMONIA**

Inhaled corticosteroids (ICS) are anti-inflammatory agents widely used in respiratory medicine. Their established efficacy and safety profile have placed this class of medications at the current treatment recommendations in chronic respiratory diseases such as asthma and COPD. In COPD, ICS have demonstrated to reduce the overall frequency of exacerbations and improve quality of life. Paradoxically, several large trials have demonstrated that the use of ICS was associated with an increased incidence of pneumonia in COPD patients (Table 2). Festic E. and Scanlon P. reported systematic literature review identified randomised controlled trials (RCTs) that had pneumonia measured as a safety or adverse effect; these trials reported an increased risk of pneumonia. The most studied medication was fluticasone, followed by budesonide and mometasone. The Towards a Revolution in COPD Health (TORCH)
The trial was the largest RCT; it included more than 6,000 patients and was the first trial to show significantly increased risk of pneumonia (hazard ratio [HR], 1.64; 95% confidence interval [CI]: 1.33–2.02)\(^5\). The risk of developing pneumonia increased with duration of therapy, dose, age and disease severity. Several other trials demonstrated increased risk of pneumonia among ICS users\(^5\)–\(^6\),\(^6\)–\(^6\). This report\(^6\) also reported the risk of pneumonia in COPD patients using ICS from observational studies\(^6\)–\(^7\). All observational studies showed increased risk of pneumonia. Several of the RCTs of ICS in COPD have reported unadjusted risk of pneumonia-related mortality; none found a difference between ICS and non-ICS arms\(^5\)–\(^6\),\(^6\)–\(^6\). Several observational studies reported either similar or lesser mortality among ICS users, despite increased risk of pneumonia\(^6\)–\(^7\). A study of Veterans Affairs (VA) hospitals assessed the association of ICS exposure with mortality for hospitalized subjects with pneumonia that had COPD\(^6\),\(^6\). The use of ICS showed a protective effect with an unadjusted relative risk of 0.50 (95% CI: 0.41–0.60) for 30-day mortality. Joo et al\(^7\) analysed a dataset from the VA and Centers for Medicare and Medicaid Services and also showed a decreased risk of 30-day mortality followed admission for pneumonia. Some of these studies also reported an improvement in other pertinent outcomes among patients using ICS, such as decreased risk of parapneumonic effusion and less frequent need for mechanical ventilation and use of vasopressors\(^6\),\(^6\),\(^7\).

Some studies have related ICS use with potentially drug resistant pathogens. Sibila et al\(^7\) showed in COPD patients hospitalized with pneumonia that prior outpatient use of ICS was associated with a higher severity of illness at admission and antimicrobial drug-resistant pathogens. This study found that ICS was not associated with higher mortality and/or length of hospitalization. Liapikou et al\(^4\) reported that COPD patients treated with chronic ICS used a summary table to evaluate the effects of inhaled corticosteroids in COPD patients and the risk of pneumonia. The table is as follows:

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Study design</th>
<th>No of COPD patients</th>
<th>Type of corticosteroid</th>
<th>Risk of pneumonia</th>
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</thead>
<tbody>
<tr>
<td>Kardos et al./2006(^5)</td>
<td>Randomised controlled trial 994</td>
<td>Fluticasone propionate</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Calverley et al./2007(^5)</td>
<td>Randomised controlled trial 6,112</td>
<td>Fluticasone propionate</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Wedzicha et al./2008(^9)</td>
<td>Randomised controlled trial 1,323</td>
<td>Fluticasone propionate</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Ernst et al./2007(^9)</td>
<td>Case-control study 175,906</td>
<td>Beclomethasone, budesonide, triamcinolone, fluticasone and flunisolide</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Welte et al./2005(^5)</td>
<td>Randomised controlled trial 6,600</td>
<td>Budesonide</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Müllerova et al./2012(^2)</td>
<td>Cohort study 40,141</td>
<td>Not specified</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Dransfield et al./2013(^3)</td>
<td>2 parallel-group randomised controlled trials 3,255</td>
<td>Fluticasone furoate</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Suissa et al./2013(^4)</td>
<td>Cohort study 163,514</td>
<td>Beclomethasone, budesonide, fluticasone, triamcinolone and flunisolide</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>DiSantostefano et al./2014(^5)</td>
<td>Cohort study 11,555</td>
<td>Not specified</td>
<td>Increased</td>
<td></td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease.
had a higher rate of pneumonia due to *Pseudomonas aeruginosa* but less *Legionella* spp infection. However, antimicrobial resistance was not assessed in COPD patients treated with ICS. Thus, Sibila et al. raised the concern of a possible association with the use of ICS and antimicrobial drug resistant pathogens. In summary, these studies suggest that ICS may alter habitual flora and antimicrobial susceptibility particularly in COPD patients with chronic airway infections.

There are indications of ICS-interclass differences in pneumonia risk with some evidence of a weaker association of pneumonia with budesonide than with fluticasone propionate therapy. In RCTs, treatment with fluticasone propionate alone or in combination with salmeterol was associated with increased prevalence of pneumonia compared with long-acting bronchodilator monotherapy (salmeterol or tiotropium) or placebo\(^58-62\). This risk appeared to increase with decreased lung function and duration of therapy\(^75\). A systematic review of six randomized, placebo-controlled trials tested the new formulation of fluticasone furoate alone or in combination with a new long-active beta-agonist, vilanterol for at least 28 weeks of duration showed a significant increased risk of pneumonia in ICS compared with vilanterol\(^76\). In an epidemiological study in COPD population from Canada, Suissa et al.\(^77\) reported a 101% higher risk of pneumonia in COPD patients treated with fluticasone propionate and a 17% increased risk in budesonide-treated patients when compared with controls not treated with ICSs. Most randomised controlled studies of budesonide alone or in combination with long-acting beta agonists (LABA) (formoterol) reported no or lower increased risk of pneumonia\(^78-80\). Sharafkhaneh et al.\(^81\) found an association between budesonide treatment and increased risk of pneumonia. In the Cochrane review by Kew and Seniukovich\(^82\), an indirect comparison found no significant difference between fluticasone propionate and budesonide monotherapy in the risk of serious adverse events (pneumonia-related or all-cause) or mortality, but a higher risk of any pneumonia event (including less serious cases treated in the community) mainly for fluticasone compared to budesonide. In the report by Halpin et al.\(^83\), an indirect comparison between budesonide and fluticasone propionate found that adverse pneumonia events and serious pneumonia adverse events were lower for budesonide. However, a retrospective analysis of the large, 4-year, prospective, randomized Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial evaluated differences in incidence of adverse respiratory events among patients entering the study on no ICS, on fluticasone propionate, or on any other ICSs, respectively\(^84\).

The data discussed suggested that there are differences in the risk of ICS formulations and pneumonia, the question is why? First, we can evaluate the pharmacokinetics and drug absorption of different ICS formulations. The use of ICS ensures that high concentration of active drug is delivered locally to the airways and lungs with a relatively low systemic burden. After inhalation, ICS are deposited as small particles on the surface of airway mucosa, and they gradually dissolve in mucosal lining fluid before they are absorbed into airway/lung tissue, target cells to exert local immunosuppression and reduction of inflammation\(^85\). The local pharmacokinetic profile of ICSs, i.e. the rate and extent
of airway/pulmonary absorption, is strongly dependent on the intrinsic physicochemical properties of corticosteroids, particularly lipophilicity, aqueous solubility, and airway epithelial permeability. The important determinant of dissolution rate of ICS particles in the airway epithelial lining fluid is aqueous solubility, which greatly differs between various ICSs. Fluticasone propionate: its long duration of action in the airways is determined by prolonged presence of slowly dissolving particles of fluticasone propionate in airway luminal fluid and the long presence of the medication within airway/lung tissue due to high lipophilicity. On the other hand, budesonide is rapidly absorbed from the airway lumen, and in patients with COPD, a larger fraction of fluticasone was expectorated in the sputum compared with budesonide (Fig. 2). Thus, in the different ICS molecules, their pharmacokinetics determine the duration that the compound is in the airway epithelium, and these factors may impact the lung microbiota and the risk of pneumonia.

In stable COPD patients, higher airway bacterial load was shown to be significantly correlated to higher ICS dosage, and this relationship remained significant in a multivariate analysis including age, smoking status, and forced expiratory volume in one second (FEV1) % predicted. Furthermore, it was shown that ICS use may alter the airway microbiota composition. Importantly, according to the “keystone pathogen” hypothesis, even small alterations in the abundance of a few bacterial species can have great effects on microbial community and subsequently modify disease status. The prolonged presence of slowly dissolving particles of fluticasone propionate in the airway epithelial lining fluid compared with budesonide may cause a protracted local immunosuppression. Contoli et al. demonstrated that long-term use of fluticasone affects bacterial load in stable COPD patients (Fig. 3). Thus, local immunosuppression by ICS may enhance susceptibility to respiratory infections and change the microbiome in the airways and lungs to allow more potential pathogenic bacteria. These changes may lead to increased risk to develop pneumonia. However, the associated impact of ICS among patients who developed pneumonia on mortality and poor clinical outcomes is a matter of significant controversy. Some studies have demonstrated that COPD patients receiving ICS that developed pneumonia had lower mortality. Further studies are needed to better understand this potentially dual effect on pneumonia due to the ICS use in patients with COPD.

PREVENTION – VACCINATION

Annual influenza vaccination is recommended for all adults, mainly in patients with underlying conditions such as COPD. Influenza vaccine has been shown to decrease pneumonia diagnoses, as well as related hospitalizations and cardiac events. Current options specifically for patients 65 years of age and older include the Fluzone high-dose vaccine, which was shown to be 24% more effective in preventing flu with a standard-dose vaccine. In COPD patients, influenza vaccination can also reduce serious illness (such as lower respiratory tract infections requiring hospitalization and death). Nichols et al. demonstrated that influenza vaccination...
resulted in a significant decreased in hospitalizations due to respiratory conditions. Only few studies have evaluated the impact of influenza vaccination on COPD exacerbations and showed significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo\textsuperscript{102}. A population-based study suggested that COPD patients, particularly the elderly, had decreased risk of ischaemic heart disease when they were vaccinated with influenza vaccine over subsequent years\textsuperscript{103}. Thus, yearly influenza vaccination clearly provides a significant protection to COPD patients and decreases the risk of hospitalization due to respiratory conditions. Pneumococcal vaccines have demonstrated efficacy in preventing vaccine-strain pneumococcal pneumonia, bacteraemia, and invasive disease, but do not prevent all types of CAP\textsuperscript{104}. The addition of pneumococcal conjugated vaccine (PCV13) to the paediatric immunization schedule in 2010 has resulted in an indirect reduction of pneumococcal infections in adults\textsuperscript{105}. The Community-Acquired

| Figure 2. Cumulative mean amounts of expectorated sputum (A) and budesonide and fluticasone propionate (B) over 6-hour collection after inhalation of a dose of salmeterol/fluticasone propionate (50/500 μg via Diskus\textsuperscript{®}; GlaxoSmithKline, Brentford, UK) or budesonide/formoterol (400/12 μg via Turbuhaler\textsuperscript{®}; AstraZeneca, Gothenburg, Sweden). Mean value plots of the amount of (A) expectorated sputum (arithmetic means) and (B) budesonide and fluticasone propionate in the expectorated sputum (percentage of ELDD, geometric means), cumulative over the 6-hour collection period (reproduced with permission from Dalby C et al.\textsuperscript{88}). BUD/FORM: budesonide/formoterol; ELDD: estimated lung-deposited dose; SAL/FLU: salmeterol/fluticasone propionate. |
Pneumonia Immunization Trial in Adults, (CAPITA), a large, double-blind, randomized study, confirmed the efficacy of PCV13 in preventing vaccine-type pneumonia and invasive pneumococcal disease in adults ≥ 65 years of age\(^{106}\). In this study, PCV13 demonstrated significant efficacy in the per-protocol population protecting against first episodes of confirmed vaccine-type pneumonia and confirmed nonbacteraemic and noninvasive vaccine-type pneumonia; in addition, immunogenicity studies of older adults in the US and Europe demonstrated that conjugated vaccine generated an immune response comparable to that of polysaccharide vaccine\(^{106}\). Pneumococcal polysaccharide vaccine (PPV) is recommended for COPD patients of 65 years and older, and in younger patients with significant comorbid conditions such as cardiac disease\(^{107}\). Specific data on the effects of PPV in COPD patients are limited. PPV has been shown to reduce the incidence of CAP in COPD patients younger than age 65 with an FEV\(_1\) < 40% predicted or with comorbidities (especially cardiac comorbidities)\(^{108}\). A systematic review of injectable vaccines in COPD patients identified twelve randomised studies for inclusion; the authors concluded that injectable polyvalent pneumococcal vaccination provided significant protection against pneumonia, although no evidence indicated that vaccination reduced the risk of confirmed pneumococcal pneumonia, which was a relatively rare event. Vaccination reduced the likelihood of a COPD exacerbation, and moderate-quality evidence suggests the benefits of pneumococcal vaccination in patients with COPD. Evidence was insufficient for comparison of different pneumococcal vaccine types\(^{109}\). Therefore, it is recommended that patients with COPD receive influenza and both pneumococcal vaccinations to prevent poor related outcomes.

**CONCLUSION**

COPD is the most frequent comorbid condition that is present in patients with pneumonia. These patients are older and have other co-morbidities like cardiovascular disease that will further impact patients’ outcomes. Human microbiome that is different in COPD patients compared with normal individuals may be impacted by medical interventions such as the use of ICS. COPD and its pharmacotherapy should be considered as a risk factor for pneumonia. Furthermore, strategies to improve implementation of influenza and/or pneumococcal vaccination is critical in COPD patients at risk to develop pneumonia.
CONFLICT OF INTEREST

Dr. Antonio Anzueto has nothing to disclose. Dr. Marcos I. Restrepo has nothing to disclose. Dr. Oriol Sibila has nothing to disclose.

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