www.brn.cat

PERMANYER

BRN Rev. 2018;4:108-21

BRN Reviews

REVIEW ARTICLE

Pneumonia in Patients with Chronic Obstructive Pulmonary Disease

Marcos I. Restrepo, MD, MSc[1,2], Oriol Sibila, MD, PhD[3], Antonio Anzueto, MD[1,4]

[1]South Texas Veterans Health Care System; [2]Veterans Evidence Based Research Dissemination and Implementation Center (VERDICT) (MR), San Antonio, Texas, USA; [3]Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

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)**

Corresponding author: Antonio Anzueto, anzueto@uthscsa.edu

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

Correspondence to:
Antonio Anzueto, MD
111 E, 7400 Merton Minter Blvd
San Antonio, Texas 78229
E-mail: anzueto@uthscsa.edu

Received in original form: 6-12-2017
Accepted in final form: 26-01-2018
DOI: 10.23866/BRNRev:2017-0004

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

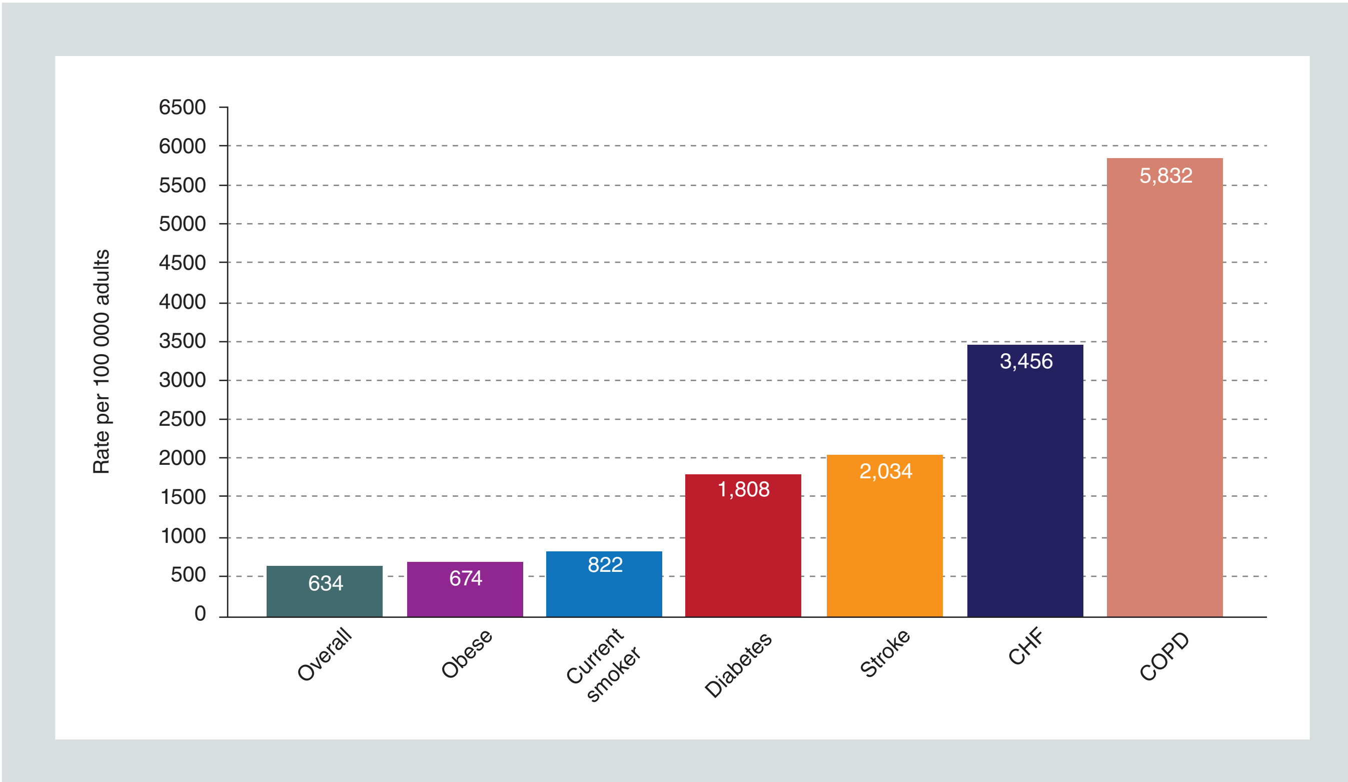

Figure 1. The impact of comorbid conditions on the incidence of patients hospitalized with community-acquired pneumonia *(reproduced with permission from Ramirez JA et al.[17])*.
CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease.

as a risk factor[28]. This prediction rule was based on 20 variables that included five comorbid illnesses (cardiovascular, history of malignancy, cerebrovascular, renal and liver diseases)[28]. In addition, Fine et al.[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.[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.[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[31]. In addition, COPD was not associated with longer 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[32]. 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[33]. 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[34]. Chronic bronchitis in COPD is seen more frequent in persistent smokers and has been associated with increased disease progression, and more frequent exacerbations[34]. 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[35]. 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[36]. In moderate COPD, increases of MUC5AC and MUC5B have been detected compared to non-smokers and smokers without airway obstruction[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 *Pseudomonas aeruginosa* and disease severity[38]. Recently, Sibila et al.[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.[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.[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 *Haemophilus influenzae* adhesion molecule. The authors suggested that this could be one important mechanism that could significantly increase the risk of *Streptococcus pneumoniae* respiratory infection in COPD. Pack-years of smoking were strongly related to epithelial PAFr protein levels in COPD patients[42]. Furthermore, the authors also found that *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. Translational 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[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).

TABLE 1. Factors that may predispose pneumonia in COPD patients

– Chronic bronchitis
– Persistent mucus production
– Presence of bacterial colonization
– Microbioma imbalances
– Increased airway inflammation
– Mpaired host immunity
– Structural damage

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[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 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[46]. 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[32,47]. 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[48]. 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.[49] 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[50]. 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[20,51]. Other risk factors for Pseudomonas and other potentially drug-resistant pathogen such as previous isolation, ICU) admission, immunosupression and prior antimicrobial therapy (< 90 days) have been described in COPD patients[52]. 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[53]. 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[54,55]. In COPD, ICS have demonstrated to reduce the overall frequency of exacerbations and improve quality of life[55-57]. Paradoxically, several large trials have demonstrated that the use of ICS was associated with an increased incidence of pneumonia in COPD patients[58-66] (Table 2). Festic E. and Scanlon P.[67] 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)

Table 2. Studies evaluating the effects of inhaled corticosteroids in COPD patients and the risk of pneumonia

Author/year	Study design	No of COPD patients	Type of corticosteroid	Risk of pneumonia
Kardos et al./ 2006[58]	Randomised controlled trial	n = 994	Fluticasone propionate	Increased
Calverley et al. /2007[57]	Randomised controlled trial	n = 6,112	Fluticasone propionate	Increased
Wedzicha et al./2008[59]	Randomised controlled trial	n = 1,323	Fluticasone propionate	Increased
Ernst et al./2007[60]	Case-control study	n = 175,906	Beclomethasone, budesonide, triamcinolone, fluticasone and flunisolide	Increased
Welte et al./2009[61]	Randomised controlled trial	n = 660	Budesonide	No
Müllerova et al./2012[62]	Cohort study	n = 40,414	Not specified	Increased
Dransfield et al./2013[63]	2 parallel-group randomised controlled trials	n = 3,255	Fluticasone furoate	Increased
Suissa et al./2013[64]	Cohort study	n = 163,514	Beclomethasone, budesonide, fluticasone, triamcinolone and flunisolide	Increased
DiSantostefano et al./2014[65]	Cohort study	n = 11,555	Not specified	Increased

COPD: chronic obstructive pulmonary disease.

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)[58]. 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[59-61,63-66]. This report[67] also reported the risk of pneumonia in COPD patients using ICS from observational studies[68-71]. 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[58-67]. Several observational studies reported either similar or lesser mortality among ICS users, despite increased risk of pneumonia[68-70]. A study of Veterans Affairs (VA) hospitals assessed the association of ICS exposure with mortality for hospitalized subjects with pneumonia that had COPD[68,69]. 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[70] 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[68,69,71].

Some studies have related ICS use with potentially drug resistant pathogens. Sibila et al.[74] 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.[49] reported that COPD patients treated with chronic ICS 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[85]. 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[86]. 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[87] (Fig. 2). Thus, in the different ICSs 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 (FEV_1)% predicted[87]. Furthermore, it was shown that ICS use may alter the airway microbiota composition[88-92]. 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.[91] 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[93]. Some studies have demonstrated that COPD patients receiving ICS that developed pneumonia had lower mortality[68,69]. 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[94-96]. 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[97-99]. In COPD patients, influenza vaccination can also reduce serious illness (such as lower respiratory tract infections requiring hospitalization[100] and death[101-103]). Nichols et al.[101] demonstrated that influenza vaccination

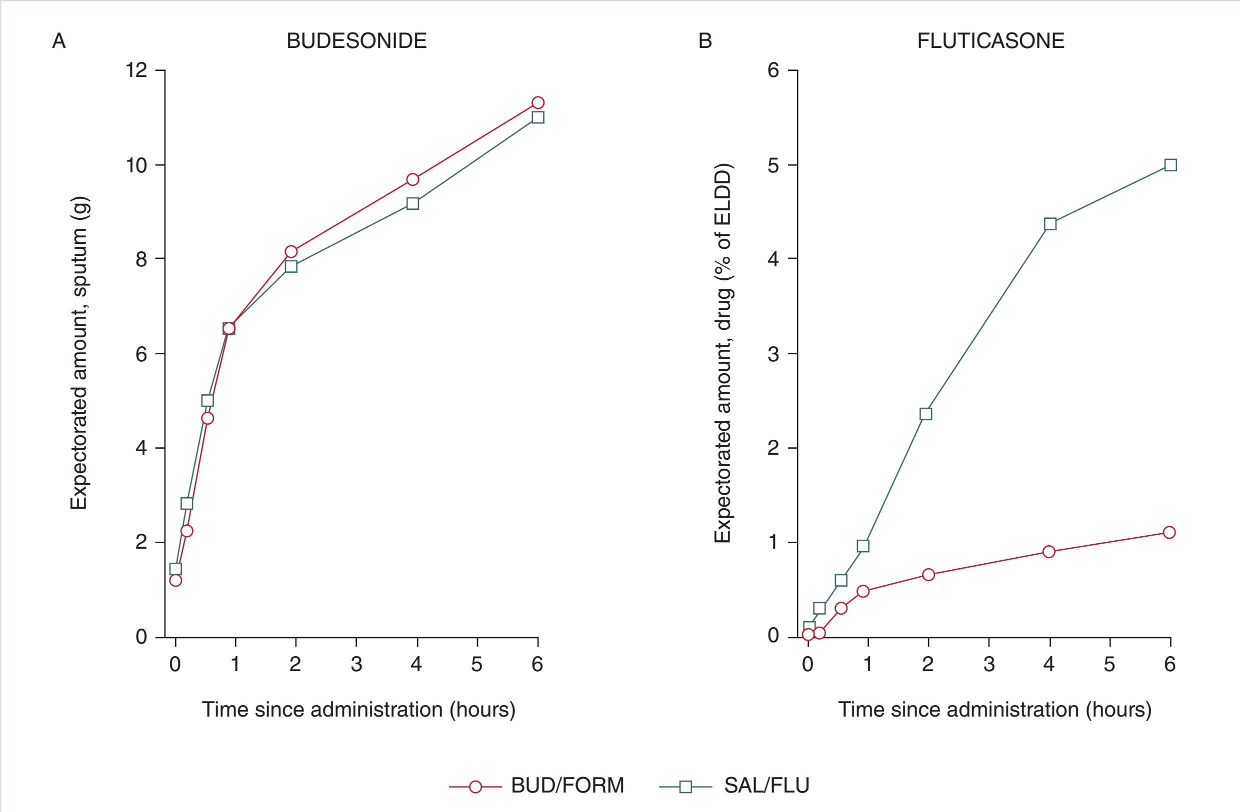

FIGURE 2. Cumulative mean amounts of expectorated sputum (**A**) and budesonide and fluticasone propionate (**B**) over 6-hour collection after inhalation of a dose of salmeterol/fluticasone propionate (50/500 µg via Diskus®; GlaxoSmithKline, Brentford, UK) or budesonide/formoterol (400/12 µg via Turbuhaler®; 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.[88])*.
BUD/FORM: budesonide/formoterol; ELDD: estimated lung-deposited dose; SAL/FLU: salmeterol/fluticasone propionate.

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[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[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[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[105]. The Community-Acquired

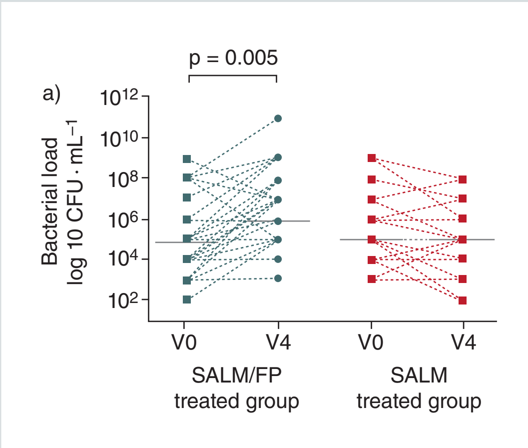

FIGURE 3. Airway bacterial load and microbiome analysis. Total bacterial load is shown as colony-forming units (CFU) per mL and was assessed at baseline (V0) and after 12 months of therapy (V4) in sputum samples from patients in both the salmeterol/fluticasone (SALM/FP) and SALM alone groups *(reproduced with permission from Contoli M et al.[92])*. CFU: colony-forming units; SALM/FP: salmeterol/fluticasone.

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.

REFERENCES

1. Heron M. Deaths: leading causes for 2010. National vital statistics reports. Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2013;62:1–97.
2. Chronic obstructive pulmonary disease. In: *Services UDoHaH*, (ed.). Washington, DC: USDHHS; Data fact sheet; 2003.
3. World Health Organization. The top 10 causes of death. The 10 leading causes of death in the world, 2000 and 2012;[accessed November 10, 2017]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en.
4. Cilloniz C, Torres A. Comunico-Acquired Pneumonia 2000-2015: What is New? BRN Rev. 2016;2:253-73.
5. Jain S, Self WH, Wunderink RG et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med. 2015;373: 415-27.
6. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012; 67:71-9.
7. CDC/NHS. Number and rate of discharges from short-stay hospitals and of days of care, with average length of stay and standard error, by selected first-listed diagnostic categories: United States, 2010. CDC/NCHS National Hospital Discharge Survey. 2010. Available from: http://www.cdc.gov/nchs/data/nhds/2average/2010ave2_firstlist.pdf. Accessed November 10, 2017.
8. Murphy SL, Xu J, Kochanek KD. Deaths: Final Data for 2010. Natl Vital Stat Rep. 2013;61:1-117.
9. Ruiz M, Ewig S, Marcos MA et al. Etiology of communityacquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med. 1999;160:397–405.
10. Farr BM, Bartlett CL, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group. Respir Med 2000;94:954–63.
11. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. Ann Intern Med. 1991;115:428–36.
12. Fine MJ, Smith MA, Carson CA et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA. 1996; 275:134–41.
13. Torres A, Serra-Batlles J, Ferrer A et al. Severe community-acquired pneumonia. Epidemiology and prognostic factors. Am Rev Respir Dis. 1991;144:312–8.
14. Almirall J, Bolibar I, Balanzo X, Gonzalez CA. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. Eur Respir J. 1999;13:349–55.
15. Garcia-Ordonez MA, Garcia-Jimenez JM, Paez F et al. Clinical aspects and prognostic factors in elderly patients hospitalized for community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 2001;20:14–9.
16. Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community acquired pneumonia: a validation study. Thorax. 2000;55:219–23.
17. Lim WS, van der Eerden MM, Laing R et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377–82
18. Ramirez JA, Wiemken TL, Peyrani P et al. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. Clin Infect Dis. 2017;65:1806–12.
19. Chen Y, Stewart P, Dales R, Johansen H, Bryan S, Taylor G. In a retrospective study of chronic obstructive pulmonary disease inpatients, respiratory comorbidities were significantly associated with prognosis. J Clin Epidemiol. 2005;58:1199–1205.
20. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J.2006;28:346–51.
21. Rello J, Rodriguez A, Torres, A et al. Implications of COPD in patients admitted to the intensive care unit by community acquired pneumonia. Eur Respir J. 2006;27:1210–6
22. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest. 2005;128:2099–2107.
23. Mullerova H, Chigbo C, Hagan GW et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012;106:1124–33
24. Sheng-Hao Lin, Diahn-Warng Perng, Ching-Pei Chen et al. Increased risk of community-acquired pneumonia in COPD patients with comorbid cardiovascular disease Int J Chron Obstruct Pulmon Dis. 2016:11:3051–8.
25. Feldman C, Viljoen E, Morar R, Richards G, Sawyer L, Goolam Mahomed A. Prognostic factors in severe community-acquired pneumonia in patients without comorbid illness. Respirology. 2001;6:323–30.
26. Community-acquired pneumonia in adults in British hospitals in 1982–1983: a survey of aetiology, mortality, prognostic factors and outcome. The British Thoracic Society and Public Health Laboratory Service. Q J Med. 1987;62:195–220.
27. Fine MJ, Orloff JJ, Arisumi D et al. Prognosis of patients hospitalized with community-acquired pneumonia. Am J Med. 1990;88:1N–8N.
28. Fine MJ, Auble TE, Yealy DM et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243–50.
29. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-acquired pneumonia. Ann Intern Med. 2003;138:109–18.
30. Fine MJ, Smith MA, Carson CA et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA. 1996;275:134–41.
31. Jiang HL,Chen X, Liu W et al. Is COPD associated with increased mortality and morbidity in hospitalized pneumonia? A systematic review and meta-analysis Respirology. 2015;20:1046-54.
32. Mammen MJ, Sethi S. Microbiome in Chronic Lung Diseases. BRN Rev. 2017;3:102-20
33. Schroder K, Tschopp J. The inflammasomes. Cell. 2010;140:821-32.
34. Seemugal TAR, Donaldson GC, Paul EA et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respi Crit Care Med. 1998; 157:1418-22.
35. Rose MC, Voynow JA. Respiratory tract mucin genes and mucin glycoproteins in health and disease. Physiol Rev. 2006;86:245-78.
36. Kesimer M, Frod AA, Cepe A et al Airway mucin concentration as a marker of chronic bronchitis, N Eng J Med. 2017;377:911-22.
37. Kirkham S, Kolsum U, Rousseau K, Singh D, Vestbo J, Thornton DJ. MUC5B is the major mucin in the gel phase of sputum in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;178:1033-9.
38. Sibila O, Suarez-Cuartin G, Rodrigo-Troyano A et al: Secreted mucins and airway bacterial colonization in non-CF bronchiectasis. Respirology. 2015;20:1082-8.
39. Sibila O, Garcia-Bellmunt L, Giner J et al. Airway mucin 2 is decreased in patients with severe chronic obstructive pulmonary disease with bacterial colonization. Ann Am Thorac Soc. 2016;13:636–42.
40. Braeken DC, Rohde GG, Franssen FM et al. Risk of community-acquired pneumonia in chronic obstructive pulmonary disease stratified by smoking status: a population-based cohort study in the United Kingdom. Int J Chron Obstruct Pulmon Dis. 2017;12:2425–32.
41. Shukla SD, Muller HK, Latham R, Sohal SS, Walters EH. Platelet-activating factor receptor (PAFr) is upregulated in small airways and alveoli of smokers and COPD patients. Respirology. 2016;21:504–10.
42. Shukla SD, Sohal SS, Mahmood MQ, Reid D, Muller HK, Walters EH. Airway epithelial platelet-activating factor receptor expression is markedly

upregulated in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2014;9:853–861.
43. Kc R, Shukla SD, Walters EH, O'Toole RF. Temporal upregulation of host surface receptors provides a window of opportunity for bacterial adhesion and disease. Microbiology. 2017;163:421–30.
44. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease.N Engl J Med. 2008;359:2355-65.
45. Wilkinson TMA, Patel IS, Wilks M, Donaldson GC, Wedzicha JA. Airway bacterial load and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;167:1090-5.
46. Clarridge JE 3rd. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. Clin Microbiol Rev. 2004;17: 840–62.
47. Sze MA, Dimitriu PA, Hayashi S et al. The lung tissue microbiome in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012; 185:1073-80.
48. Erb-Downward JR, Thompson DL, Han MK et al. Analysis of the lung microbiome in the "healthy" smoker and in COPD. PLoS ONE. 2011;6:e16384.
49. Liapikou A, Polverino E, Ewig S et al. Severity and outcomes of hospitalized community-acquired pneumonia in COPD patients. Eur Respir J. 2012; 39:855-61.
50. El-Solh A, Sikka P, Ramadan F, Davies J. Etiology of Severe Pneumonia in the Very Elderly. Am J Respir Crit Care Med. 2001;163:645–51.
51. Arancibia F, Bauer TT, Ewig S et al. Community-acquired pneumonia due to Gram-negative bacteria and Pseudomonas aeruginosa: incidence, risk, and prognosis. Arch Intern Med. 2002;162:1849–58.
52. Sibila O, Rodrigo-Troyano A, Shindo Y et al. Multidrug-resistant pathogens in patients with pneumonia coming from the community. Curr Opin Pulm Med. 2016;22:219-26.
53. Niederman MS, Mandell LA, Anzueto A et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med. 2001;163:1730–54.
54. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2017. Available from: http://www.ginasthma.org/.
55. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, *Global In*itiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://www.goldcopd.org/
56. Calverley P, Pauwel R, Vestbo J et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. Lancet. 2003;361:449-56.
57. Nannini LJ, Cates CJ, Lasserson TJ et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007;4:CD 003794.
58. Calverley PMA, Anderson JA, Celli B; TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775-89.
59. Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175:144-9.
60. Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RA; INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177:19-26.
61. Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med. 2007;176:162-6.
62. Welte T, Miravitlles M, Hernandez P et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180:741-50.
63. Mullerova H, Chigbo C, Hagan GWet al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012;106:1124-33.
64. Dransfield MT, Bourbeau J, Jones PW et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med. 2013;1:210-23.
65. Suissa S, Patenaude V, Lapi F, Ernst P: Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013, 68:1029-36.
66. DiSantostefano RL, Sampson T, Le HV, Hinds D, Davis KJ, Bakerly ND. Risk of pneumonia with inhaled corticosteroid versus long-acting bronchodilator regimens in chronic obstructive pulmonary disease: a new-user cohort study. PLoS One. 2014; 9:e97149.
67. Festic E, Scanlon P. Incident Pneumonia and Mortality in Patients with Chronic Obstructive Pulmonary Disease A Double Effect of Inhaled Corticosteroids? Am J Respir Crit Care Med. 2015;191:141-48.
68. Chen D, Restrepo MI, Fine MJ et al. Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. Am J Respir Crit Care Med. 2011;184:312–6.
69. Malo de Molina R, Mortensen EM, Restrepo MI, Copeland LA, Pugh MJV, Anzueto A. Inhaled corticosteroid use is associated with lower mortality for subjects with COPD and hospitalized with pneumonia. Eur Respir J. 2010;36:751–7.
70. Joo MJ, Au DH, Fitzgibbon ML, Lee TA. Inhaled corticosteroids and risk of pneumonia in newly diagnosed COPD. Respir Med. 2010;104:246–52.
71. Sellares J, López-Giraldo A, Lucena C et al. Influence of previous use of inhaled corticoids on the development of pleural effusion in community-acquired pneumonia. Am J Respir Crit Care Med. 2013;187:1241–8.
72. Stuck AE, Minder CE, Frey FJ. Risk of infectous complications in patients taking glucocorticoids. Rev Infect Dis. 1989; 69:954-63.
73. Conesa D, Rello J, Valles J et al. Invasive aspergillosis: a life-threatening complication of short-term steroid treatment. Ann Pharmacother. 1995;29: 1235-7.
74. Wiest PM, Flanigan T, Salalta RA et al. Serious complications of corticosteroid therapy for COPD. Chest. 1989;95:1180-4.
75. Sibila O, Laserna E, Mortensen EM, Anzueto A, Restrepo MI. Effects of inhaled corticosteroids on pneumonia severity and antimicrobial resistance. Respir Care. 2013; 58:1489-94.
76. Jenkins CR, Jones PW, Calverley PM et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10:59.
77. Rodrigo GJ, Neffen H. A systematic review with meta-analysis of fluticasone furoate/vilanterol combination for the treatment of stable COPD. Pulm Pharmacol Ther. 2017;42:1–6
78. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68:1029–36.
79. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003;22:912–9.
80. Rennard SI, Tashkin DP, McElhattan J et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009;69:549–65.
81. Janson C, Larsson K, Lisspers KH et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting beta 2 agonist: observational matched cohort study (PATHOS). BMJ. 2013;346:3306.
82. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respir Med. 2012;106:257–68.
83. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;CD010115.
84. Halpin DM, Gray J, Edwards SJ, Morais J, Singh D. Budesonide/formoterol vs. salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomised controlled trials. Int J Clin Pract. 2011;65:764–74.

85. Morjaria JB, Rigby A, Morice AH. Inhaled corticosteroid use and the risk of pneumonia and COPD exacerbations in the UPLIFT study. Lung. 2017; 195:281–8.
86. Edsbacker S, Wollmer P, Selroos O, Borgstrom L, Olsson B, Ingelf J. Do airway clearance mechanisms influence the local and systemic effects of inhaled corticosteroids? Pulm Pharmacol Ther. 2008;21:247–58.
87. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. J Allergy Clin Immunol. 1996;97:169–76.
88. Dalby C, Polanowski T, Larsson T, Borgstrom L, Edsbacker S, Harrison TW. The bioavailability and airway clearance of the steroid component of budesonide/formoterol and salmeterol/fluticasone after inhaled administration in patients with COPD and healthy subjects: a randomized controlled trial. Respir Res. 2009;10:104.
89. Garcha DS, Thurston SJ, Patel AR et al. Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. Thorax. 2012;67:1075–80.
90. Huang YJ, Sethi S, Murphy T, Nariya S, Boushey HA, Lynch SV. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. J Clin Microbiol. 2014;52:2813–23.
91. Pragman AA, Kim HB, Reilly CS, Wendt C, Isaacson RE. The lung microbiome in moderate and severe chronic obstructive pulmonary disease. PLoS One. 2012;7:e47305.
92. Contoli M, Pauletti A, Rossi MR et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. Eur Respir J. 2017; 50:1700451.
93. Talbot HK, Zhu Y, Chen Q et al. Effectiveness of influenza vaccine for preventing laboratory-confirmed hospitalizations in adults, 2011-2012 influenza season. Clin Infect Dis. 2013;56:1774-7.
94. Sibila O, Rodrigo-Troyano A, Suarez-Cuartin G, Anzueto A. Corticosteroids and Pneumonia in Chronic Obstructive Pulmonary Disease: A Dual Effect? BRN Rev. 2015;1:105-15.
95. Udell JA, Zawi R, Bhatt DL et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA. 2013;310:1711-20.
96. Centers for Disease Control and Prevention. Fluzone high-dose seasonal influenza vaccine. Available at http://www.cdc.gov/flu/protect/vaccine/qa_fluzone.htm. Accessed November 30, 2016.
97. DiazGranados CA, Dunning AJ, Kimmel M et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014; 371:635-45.
98. Centers for Disease Control and Prevention. FLUAD™ flu vaccine with adjuvant. Available at http://www.cdc.gov/flu/protect/vaccine/adjuvant.htm. Accessed November 30, 2016.
99. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. Chest 2004;125: 2011-20.
100. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006: CD002733.
101. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med. 1994;331:778-784.
102. Fiore AE, Shay DK, Broder K et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep. 2009;58:1-52.
103. Huang CL, Nguyen PA, Kuo PL, Iqbal U, Hsu YH, Jian WS. Influenza vaccination and reduction in risk of ischemic heart disease among chronic obstructive pulmonary elderly. Comput Methods Programs Biomed. 2013; 111:507-11.
104. Kobayashi M, Bennett NM, Gierke R et al. Intervals between PCV13 and PPSV23 vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2015;64:944-7.
105. Bonten MJM, Huijts SM, Bolkenbaas M et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015; 372:12.
106. Jackson LA, Gurtman A, Rice K et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2013;31:3585–93.
107. Tomczyk S, Bennett NM, Stoecker C et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2014;63:822-5.
108. Alfageme I, Vazquez R, Reyes Net al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006;61:189-95.
109. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;1:Cd001390.