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The Risk and Outcomes of Pneumonia in Patients on Inhaled Corticosteroids

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Abstract

Corticosteroids are frequently prescribed anti-inflammatory medications. Inhaled corticosteroids (ICS) are indicated for Chronic Obstructive Pulmonary Disease (COPD) and asthma. ICSs are associated with a decrease in exacerbations and improved quality of life in COPD, however multiple studies have linked the chronic use of ICSs with an increased risk of developing pneumonia, though the effect on mortality is unclear. We review the association of ICS with the risk of pneumonia and the implications on clinical outcomes.

Keywords

pneumonia; inhaled corticosteroids; chronic obstructive pulmonary disease

1. Introduction

Pneumonia is the leading cause of death related to infectious disease in developed countries and the eighth leading cause of death overall in the United States (US). In the US, pneumonia occurs in more than 5 million adults and accounts for more than 1 million admissions a year [1, 2]. It is presumed that, in the US, pneumonia and influenza age-adjusted mortality is increasing [3].

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Corticosteroids are anti-inflammatory medications commonly prescribed in respiratory medicine. Inhaled corticosteroids (ICS) are currently used for most patients with Chronic Obstructive Pulmonary Disease (COPD) and asthma [4,5]. The combination of ICS and Long Acting Beta Agonists (LABA) is considered a treatment of choice for patients with COPD with forced expiratory volume in the first second (FEV1) lower than 50% of predicted and two or more exacerbations per year [5,6]. Inhaled corticosteroids exert an anti-inflammatory and immunosuppressive effect that may affect the pathogenesis of pneumonia [7].

Several studies suggest that in COPD patients receiving chronic ICSs there is a higher risk of developing pneumonia [8-10]. However, the associated impact of ICSs on mortality and poor clinical outcomes among COPD patients who develop pneumonia is a matter of great controversy [11,12].

The purpose of this review is to assess the evidence related to the association of inhaled corticosteroids with the risk of community-acquired pneumonia (CAP) and other related clinical outcomes.

1.1 Methods

We reviewed published available manuscripts in PubMed by using the following search terms: “inhaled corticosteroids” and “pneumonia”. We limited the literature search to manuscripts published in the English language. The date of the most recent search was September 1, 2014.

2. Corticosteroids

Corticosteroids are involved in a wide range of physiological processes, including the regulation of inflammation, immune and stress responses, carbohydrate metabolism, protein catabolism, and serum electrolyte levels [13]. Corticosteroids can be administered through multiple routes, but for the purpose of this review we will focus on the corticosteroids that are administered through the inhalational route. **Table 1** shows the most relevant ICS available on the market.

2.1 Mechanism of action

Corticosteroids inhibit the expression and action of many cytokines involved in the inflammatory response associated with pneumonia. At the cellular level, corticosteroids bind to a heterocomplex receptor located in the cytoplasm present in all human cells. This receptor is known as the glucocorticoid receptor (alpha-GR) [14], which is activated by corticosteroids, resulting in a drug–receptor complex that moves into the nucleus of the cell and binds this complex to the DNA. This will directly or indirectly regulate the transcription of target genes [15]. However, the anti-inflammatory and immunosuppressive effects of corticosteroids are due to three molecular mechanisms [7]. First, the ligand-activated alpha-GR binds as a homodimer to specific DNA sequences located in the promoter regions of target genes inducing transcription (transactivation). Second, an indirect negative regulation of gene expression (transrepression) is achieved by GR-protein interaction. The ligand activated receptor binds as a monomer to key pro-inflammatory transcription factors such as

activator protein (AP)-1 and nuclear factor (NF)-κB. The resulting complex inhibits the initiation of transcription of relevant genes that play a central role in inflammation [7]. Corticosteroids inhibit the synthesis of several cytokines (e.g. tumor necrosis factor alfa [(TNF-alfa] and interleukins [IL] 4, 5, 6 and 13), adhesion molecules (e.g. ICAM-1, VCAM-1) and chemokines (e.g. eotaxin, IL-8) [15]. The third mechanism is corticosteroid signalling through membrane-associated receptors and second messengers (so-called non genomic pathways). The best-described non-genomic mechanism involves the activation of endothelial nitric oxide synthetase (eNOS), which is responsible for a rapid vasodilatory effect [16]. Other mechanism of action includes histone acetylation and deacetylation [17].

The mechanisms that could explain why ICSs may cause pneumonia are a matter of scientific interest. We hypothesized several possible explanations based on our review of the literature. The immunosuppressive effect caused by high local lung concentrations found with the use of ICSs may potentially increase the risk of pneumonia [47,48]. Barnes et al [49] showed that in bronchial biopsies from patients receiving ICS/LABA (fluticasone propionate and salmeterol) the number of inflammatory cells was reduced and the expression of pro-inflammatory mediators was decreased. This suggests a possible decrease in local cellular defense mechanisms. This observation was confirmed in a multicenter randomized placebo-controlled trial, which also found a reduction of lung-specific inflammatory biomarkers [50]. The use of an ICS alone or in combination with LABA was associated with lower lung C-reactive protein (CRP), IL-6, and Surfactant protein D (SP-D) levels, but not systemic inflammatory biomarkers, except SP-D, when compared to placebo. Barbier et al. [51] demonstrated that fluticasone reduces bacterial airway epithelial invasion in a murine model of lung infection. And finally, as mentioned before it is possible that lipophilic ICS, such as fluticasone, may exert a stronger immunosuppressive effect, increasing mucosal and epithelial exposure facilitating pneumonic events.

3. Inhaled Corticosteroids

Inhaled corticosteroids (ICS) are commonly prescribed medications for the management of patients with COPD and asthma [4,5,22]. In COPD, they are recommended for patients with severe obstruction (GOLD III or IV) and/or frequent exacerbations [5]. ICSs are recommended for patients with asthma and persistent symptoms [4,23].

The pharmacokinetics of the available inhaled corticosteroids has been described extensively [24,25]. Briefly, the use of ICSs, as opposed to systemic corticosteroids, improves the therapeutic index by decreasing systemic bioavailability, increasing systemic clearance, and prolonging residence time within the lung volume of distribution [26]. All available ICSs may produce systemic effects when administered in the high-dose range as defined by the guidelines [4,5].

Multiple studies have recognized an increased risk of pneumonia associated with the chronic use of inhaled corticosteroids [8-10]. Pneumonia is associated with increased morbidity and mortality. In COPD, it is also associated with worsening quality of life and a decline in lung function [27]. Given their broad use, this has become a significant safety concern.

3.1 Inhaled corticosteroids and pneumonia

We reviewed the relevant literature assessing the association of ICSs and the risk of developing pneumonia among patients with COPD (**Table 2**). The Towards a Revolution in Chronic Obstructive Pulmonary Disease Health (TORCH) study [8], was the landmark randomized controlled trial (RCT) that suggested an associated increased risk of developing pneumonia among COPD patients treated with ICSs. The TORCH study compared the efficacy of salmeterol, fluticasone propionate, or a combination regimen (salmeterol/fluticasone 50/500 μg twice daily) against placebo in COPD patients over a 3-year period. COPD patients who received an ICS, as monotherapy or in combination therapy, had a higher rate of physician-reported pneumonia (19.6% and 18.3%, respectively) when compared to placebo (12.3%, $p<0.001$). However, this study was limited by the lack of radiographic confirmation of the diagnosis of pneumonia. A post hoc analysis of the TORCH study reported by Crim et al. [28] confirmed these results, identifying advanced age, low body mass index, low FEV1, and the presence of an exacerbation in the previous year as risk factors for the development of pneumonia in COPD patients taking ICSs. After the publication of the TORCH trial, interest in assessing this association emerged around the world.

Kardos et al [9], assessed the impact of combination therapy with salmeterol/fluticasone propionate 50/500 μg, twice daily, compared with LABA alone on the rates of moderate and severe acute exacerbations of COPD (AECOPD). The authors concluded that combination LABA/ICS therapy reduces the rate of moderate and severe AECOPD by 35% in patients with severe COPD ($p<0.001$). However, the authors also found that pneumonia events were more likely to occur between COPD patients managed with LABA/ICS when compared to the LABA-only group (4.5 vs. 1.4%; $p=0.005$). In addition, Wedzicha et al. [10], evaluated the effect of combination salmeterol/fluticasone propionate 50/500 μg twice daily vs. tiotropium on reducing exacerbations among patients with COPD. The authors conclude that pneumonia events were more common among COPD patients receiving the ICS-containing regimen (8 vs. 4%; $p=0.008$). A follow-up review of the same data suggested that pneumonia events were less common than AECOPD, and may be present in patients who have persistent exacerbation symptoms. These results may imply that early identification and treatment of exacerbations may decrease the risk of developing pneumonia [29].

Ernst et al [27], in a large observational study in Canada of over 175,000 patients, found that elderly COPD patients with an active ICS prescription had a two-fold-increased risk of hospitalization with a primary diagnosis of pneumonia ($p<0.001$). The rate of hospitalization of elderly COPD patients who developed pneumonia was 1.9 per 100 per year, and it was higher among those receiving higher doses of ICS (fluticasone propionate 1000 μg per day). Müllerova et al. [30] examined the risk of CAP in a cohort of 40,411 COPD patients. The authors showed that patients with COPD who were treated with an ICS were more likely to develop CAP. This increased risk was independently associated with prior COPD exacerbations requiring hospitalization (OR 2.7, 95%CI 2.3-3.2), severe COPD requiring home oxygen or nebulized therapy (OR 1.4, 95%CI 1.1-1.6), and specific comorbidities such as dementia (OR 2.6, 95%CI 1.9-3.0) and congestive heart failure (OR 1.4, 95%CI 1.2 – 1.6). Suissa et al. [31] found that, in a nested cohort of over 160,000 patients, ICS use by

patients with COPD was associated with a 69% increase in the rate of serious pneumonia (e.g. those requiring hospitalization or resulting in death), with a two-fold increase of this risk in patients on high-dose fluticasone.

In contrast, Welte and colleagues [32] assessed the efficacy of tiotropium against a combination of ICS/LABA (budesonide/formoterol) plus tiotropium in a randomized controlled trial. Patients on combination therapy of ICS/LABA/tiotropium had a rapid and sustained improvement in lung function, health status, morning symptoms, and physical activities, as well as reduced rates of exacerbations when compared to patients on tiotropium alone. Only three cases of pneumonia were reported within each treatment group (<1%).

Few studies have evaluated the impact of different fixed combinations of ICS and long acting β2 agonists on the risk of pneumonia in COPD patients. The recent PATHOS study [33], a retrospective cohort study comparing two different ICS/LABA combinations (salmeterolfluticasone vs. budesonide-formoterol) found a significantly higher rate of pneumonia, pneumonia-related hospital admissions, and pneumonia-related mortality in patients using the fluticasone-containing regimen. No dose-response relationship was found in the study. This correlates with previous findings that suggest an increased number of adverse events with fluticasone (vs. placebo, salmeterol alone [8,28], or tiotropium [10,29]). The authors proposed greater immunosuppressant potency and increased permanence in the mucosa and epithelium due to the highly lipophilic molecule of fluticasone as an explanation for their findings.

In a cluster analysis of two pooled one-year randomized exacerbation trials [34] of over 3,000 patients to identify patient groups at greatest risk of pneumonia, fluticasone furoate/vilanterol was found to increase the risk of pneumonia (OR 1.89, 95% 1.25-2.84) and serious pneumonia (OR 2.92, 95%CI 1.40-6.01). Other nested cohort studies have evaluated the incidence of pneumonia in certain subpopulations. Eurich and collaborators [35] found that among a high-risk cohort of elderly patients who survived an episode of pneumonia, there was a 90% relative increase in the risk of a recurrent pneumonia event (5% absolute increase, number needed to harm 20) among patients currently using ICSs compared to non-users.

Several meta-analyses have evaluated the association of ICS use in patients with COPD and the risk of developing pneumonia. Drummond et al. identified 11 RCTs of stable COPD patients treated with ICSs. The authors conclude that administration of ICSs is associated with a 34% increased risk of developing pneumonia [36]. Singh et al [37] confirmed, in 18 trials including 16,996 patients, that ICSs were associated with an increased risk of pneumonia when compared to controls (RR 1.60; 95% CI 1.33-1.92 [p<0.001]). Similar results were reached by the meta-analysis performed by Rodrigo and collaborators [38]. Singh and colleagues [39] reported, in a trial-level meta-analysis enhancing their own prior meta-analysis, that ICSs (fluticasone and mometasone) were associated with an increased risk of pneumonia. Finally, Sin et al [40] published a meta-analysis of individual patient data restricted to clinical trials using budesonide as the ICS and found no evidence of an increased risk of developing pneumonia.

Nannini and collaborators [41,42], in two separate meta-analyses, one comparing LABA/ICS vs. placebo and another comparing LABA/ICS vs. LABA alone, found that the corticosteroid-containing regimen was associated with an increased risk of pneumonia (OR 1.62, 95%CI 1.36-1.94, and OR 1.55, 95%CI 1.20-2.01, respectively). In these studies, the LABA/ICS combination resulted in a lower rate of exacerbations and improved quality of life, symptoms, and lung function.

Most recently, a Cochrane review [43] published in 2014 assessed the risk of pneumonia in over 30,000 patients with COPD (41 studies) taking ICS; they compared fluticasone and budesonide, as they are the most commonly prescribed ICS. They found an increase in non-fatal serious adverse pneumonia events (i.e. requiring hospital admission) (OR 1.78, 95CI 1.5-2.12) with fluticasone and found no difference between monotherapy or combination therapy with LABA/ICS. Budesonide was also found to have an increased incidence of pneumonia events, however the effect was less precise (OR 1.86, 95%CI 1.0-2.62) and evidence was based on shorter trials. As no trials have directly compared the two drugs, an indirect analysis was performed, which revealed a higher risk of any pneumonia event (i.e. including less serious cases) in patients taking fluticasone when compared with budesonide (OR 1.86, 95% 1.04-3.34). This was the only significant difference between the two drugs.

Until recently, there had been few prospective trials assessing the increased risk of pneumonia with ICS. A secondary analysis of the Lung Injury Prediction Score (LIPS) cohort [44], a multicenter prospective cohort of over 5,000 patients at risk for ARDS, found that, after adjusting for multiple confounders, prehospital ICS use was not independently associated with an increased risk for pneumonia requiring hospitalization. There were no statistically significant differences between COPD, asthma, and non-COPD/asthma subgroups. A prospective randomized study of COPD patients comparing the use of high- vs. medium-dose ICSs (in combination with LABA) [45] found that high-dose ICSs had more treatment benefits (as demonstrated by an improvement in FEV1 and COPD Assessment Test scores, and a reduced rate of exacerbations), without a significant increase in the incidence of pneumonia. Ferrer and colleagues [46] found that ICS treatment in patients with CAP is associated with a reduced systemic inflammatory response, as evidenced by lower TNF-alpha levels, without any impact on long-term mortality. These findings persisted in the COPD subpopulation.

Though there is a consistent trend suggesting a higher risk of pneumonia among COPD patients managed with ICS, most trials were not designed to assess this risk. In addition, the majority of these studies is limited by the lack of a uniform radiographic definition of pneumonia and did not adjust for important covariates. There is some overlap between the clinical presentations of pneumonia and acute exacerbations of COPD, which may have led to an overestimation of this association. Also, in many trials the diagnosis of COPD or asthma was not consistently based on spirometric data. Given the overall low risk of pneumonia in these studies (ranging from 3-16%) and the fact that most studies were not designed with pneumonia as a pre-specified end-point, their ability to detect this association may have been limited.

In a recent study, Sibila et al. [52] suggested that prior ICS use is associated with higher pneumonia severity at admission and an increased incidence of antimicrobial drug-resistant pathogens in patients hospitalized with CAP. In this study, most of the ICS users had a preexisting diagnosis of COPD (66%). In a subgroup analysis of COPD patients, the association of the outpatient use of ICSs with drug resistant pathogens persisted (12,1% vs. 3.4%, OR 3.9, 95%CI 1.1-13.2, p=0.03). However, non-COPD patients receiving ICSs did not have an increased rate of infection of drug resistant pathogens. These findings may suggest a disease-specific susceptibility linked to COPD that requires further exploration. Liapikou et al. [53] also reported that COPD patients treated with chronic ICSs had a higher rate of pneumonia due to *P. aeruginosa* when compared to COPD patients with pneumonia but without chronic ICS treatment. These data suggest that COPD patients do indeed have a higher rate of pneumonia due to potential drug resistant pathogens.

3.2 Pneumonia related mortality in COPD patients receiving ICS

The evidence confirming a higher risk of developing pneumonia does not necessarily translate into poor clinical outcomes (**Table 3**). The landmark TORCH study [8] did not show a difference in mortality among those patients treated with ICS [8,28]. The INSPIRE study [10] showed that ICS in combination with LABA and tiotropium had a lower mortality rate. However, these studies were not powered to show mortality differences among groups. The meta-analyses by Drummond et al. [36] and Singh et al. [37] did not find mortality differences among ICS and non-ICS users. Likewise, in a trial level meta-analysis, Singh et al [39] reported that the increased risk of pneumonia was not associated with an increased risk of pneumonia-related mortality. Two observational studies in COPD patients hospitalized with pneumonia found that chronic ICS use was associated with lower all-cause mortality. Malo de Molina and collaborators [11], reported that in 6,353 patients hospitalized with pneumonia with a concomitant COPD diagnosis, patients on chronic ICSs had a lower 30- and 90-day mortality. Subsequently, Chen et al [12], using a larger cohort of 15,768 COPD patients hospitalized with pneumonia, found that ICS users had a lower short-term mortality and use of mechanical ventilation. Singanayagam [55], showed in a prospective study of 490 spirometry-confirmed COPD patients presenting with a primary diagnosis of CAP that there was no statistically significant difference in 30-day mortality when comparing ICS-users and non-users. Finally, Sellares et al. recently reported that patients receiving ICS have less parapneumonic pleural effusions, but no differences in mortality [54].

In contrast, Ernst et al. [27] reported that, in a cohort of 23,942 COPD patients with pneumonia, ICS users had an increased 30-day mortality compared to non-users, particularly those receiving higher doses of ICS. However, the rate of all-cause mortality was similar in ICS-users and non-users that required hospitalization for pneumonia. These findings were confirmed in the PATHOS study [33], which found an increased rate of pneumonia-related deaths among patients taking fluticasone-salmeterol in comparison with those taking budesonide-formoterol (97 deaths (3.5%) and 52 deaths (1.9%), respectively).

Therefore, the final verdict remains to be seen about the protective effects of ICS once patients develop pneumonia. As their mechanism of action is anti-inflammatory, the

rationale for the use of ICS in patients with COPD should be based on their direct effect on inflammatory outcomes [56-58], in addition to their indirect effect on clinical and functional outcomes. Identifying COPD patients who are most likely to benefit from ICS treatment or at a higher risk for side effects associated with these drugs could facilitate personalized pharmacotherapeutic strategies [59].

3.3 The risk of pneumonia with inhaled corticosteroids in asthma

The association between ICS use and pneumonia has been extensively described in patients with COPD, however few studies have addressed these issues among diseases other than COPD, as is the case with asthma [60]. Asthma is known to be an independent risk factor for invasive pneumococcal disease [61], however the association with pneumonia is less clear.

O'Byrne et al [60] reported in a meta-analysis of clinical randomized trials of asthmatics using ICSs (budesonide and fluticasone propionate) that patients did not have an increased risk of pneumonia, even at higher doses or among the different ICSs. Conversely, McKeever et al [62] found, in a case-control study, that patients receiving ICSs were at an increased risk for pneumonia and lower respiratory tract infections (LRTIs). This association seems to be greater among patients receiving higher doses of ICS. In addition, the risk was higher for patients treated with beclomethasone, budesonide, and fluticasone. Interestingly, the risk only persisted for patients on fluticasone when the analysis was restricted to patients under the age of 40 without bronchiectasis.

3.4 Inhaled corticosteroids and other lung infections

Other lung infections, such as tuberculosis may be associated with the use of ICS in patients with chronic lung diseases [63,64]. Brassard et al demonstrated in a large cohort of 427,648 patients with airways diseases (mostly COPD) that exposure to ICS was associated with increased risk of tuberculosis. Interestingly, patients taking both inhaled and systemic corticosteroids were not at higher risk of tuberculosis. In addition, Lee et al. have recently shown that ICS use increases the risk of TB, as compared to matched controls, in a large database in South Korea (OR 1.20, 95%CI 1.08-1.34) [64].

In a meta-analysis [65] on ICSs and the risk of tuberculosis and influenza in patients with COPD, the use of ICSs was associated with a two-fold increase of tuberculosis, but not influenza infection. Fluticasone was also found to confer a greater risk of TB when compared to lower potency ICSs, such as mometasone or budesonide. A similar meta-analysis including 5 studies (33,328 subjects) found an association between ICS use and the risk of mycobacterial infection in all patients with chronic respiratory diseases [66]. This finding persisted among the subgroups of *Mycobacterium tuberculosis* infection, COPD patients, patients on high-dose corticosteroids (≥500 ug fluticasone), and patients with prior pulmonary tuberculosis.

4. Conclusions

Inhaled corticosteroids are widely used in respiratory medicine. Their immunosuppressive and anti-inflammatory effects may affect the pathogenesis of pneumonia and clinical

outcomes. Conversely, their anti-inflammatory effect may have a role as adjunctive therapy in severe pneumonia.

Inhaled corticosteroids have been associated with an increased risk of pneumonia, which appears to be class-related and may be more pronounced with particular formulations and higher-doses. This association has been better described in patients with COPD than in asthma; the reason for this is unclear, but it appears that COPD patients may be more prone to experiencing side effects from inhaled corticosteroids. Despite this increased risk of pneumonia, whether or not inhaled corticosteroids lead to increased pneumonia-related and all-cause mortality is unclear. Inhaled corticosteroids also appear to increase the risk of atypical infections, particularly *Mycobacterium tuberculosis*, however this effect may be more pronounced in endemic areas. Inhaled corticosteroids, particularly in combination with long-acting beta-agonists, have been shown to reduce exacerbations, improve quality of life and lung function in patients with COPD, so the risks and benefits must be carefully evaluated for each individual patient.

Further prospective studies with rigorous criteria for the definition of pneumonia are needed to clarify the impact of chronic ICS use on the development of pneumonia, particularly in COPD patients. Research studies focusing on the mechanisms associated with the increased risk and the pharmacoepidemiological phenotypes that may assist clinicians to assess the risks and benefits associated with the use of ICS may advance the science in this highly and clinically relevant area. Finally, research that evaluates the outcomes after stopping, continuing, changing the dose or the type of ICS will inform clinicians about how to deal with the collateral damage associated with the use of ICS.

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Table 1

Types of inhaled corticosteroids

Inhaled corticosteroids	Combination Inhaled Corticosteroids/Long-Acting Beta-Agonists
Beclomethasone dipropionate	Fluticasone/Salmeterol
Budesonide	Budesonide/Formoterol
Flunisolide	Mometasone/Formoterol
Fluticasone propionate	Fluticasone/Vilanterol
Mometasone furoate	
Triamcinolone acetonide	
Ciclesonide	

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Table 2

Studies evaluating the risk of pneumonia in COPD patients treated with inhaled corticosteroids.

ASSOCIATION OF ICS USE AND RISK OF PNEUMONIA IN COPD PATIENTS		
INCREASED RISK OF PNEUMONIA		
AUTHOR/YEAR	**STUDY DESIGN**	**COMMENTS**
Kardos, et al. [9] – 2006	Randomized Controlled Trial	4% of patients in the salmeterol/fluticasone group and 1% of patients in the salmeterol group were reported to have suspected pneumonia, however there was no radiographic confirmation.
Calverley, et al. [8] – 2007	Randomized Controlled Trial	Probability of pneumonia increased with LABA/ICS compared to placebo, though pneumonia-related mortality was similar among all groups. No prospective definition for pneumonia on study protocol (e.g. no radiographic confirmation), as this was an unexpected event.
Wedzicha, et al. [10] – 2007	Randomized Controlled Trial	Increased rates of pneumonia with LABA/ICS, as opposed to tiotropium, though the LABA/ICS group had a lower rate of death. Diagnosis of pneumonia was clinical (e.g. radiographic confirmation was not required).
Ernst, et al. [27] – 2007	Observational	ICS use is associated with an excess risk of pneumonia hospitalization and pneumonia hospitalization leading to death. Definition of pneumonia based on diagnostic codes.
Nannini, et al. [42] – 2007	Meta-analysis	Combined LABA/ICS therapy led to fewer exacerbations and a reduction in all-cause mortality, though an increased risk of pneumonia was noted (OR 1.62) with a three-year NNTH of 17 (mostly based on the results of the TORCH trial).
Drummond, et al [36] – 2008	Meta-analysis	In patients with COPD, ICS use was associated with an increased risk of pneumonia, especially in the following subgroups: higher ICS dose, shorter duration of ICS use, lower baseline FEV1, and combined LABA/ICS.
Singh, et al. [37] – 2009	Meta-analysis	ICS use was associated with increased rates of pneumonia and serious pneumonia events when comparing to placebo vs. ICS-alone or LABA alone vs. combination LABA/ICS.
Rodrigo, et al. [38] – 2009	Meta-analysis	Combination LABA/ICS was associated with an increased risk of pneumonia (RR 1.65), although it did significantly reduce the number of moderate exacerbations and improved St. George Respiratory Questionnaire scores.
Singh, et al. [39] – 2010	Meta-analysis	ICS use was associated with an increase in mortality, particularly in the elderly and patients with more severe disease and lower FEV1.
Mullerova, et al. [30] – 2012	Observational	Definition of pneumonia based on diagnostic codes.
Nannini, et al. [41] – 2012	Meta-analysis	Pneumonia was more frequent with LABA/ICS combination (4%) than LABA alone (3%), but no significant differences in rates of hospitalization or mortality.
Jansson, et al. [33] – 2013	Observational	Higher rates of pneumonia and pneumonia-related mortality were seen in patients on fluticasone/salmeterol when compared to those on budesonide/formoterol. Diagnosis of pneumonia based on diagnostic codes.
Suissa, et al. [31] – 2013	Observational	ICSs were associated with increased rates of serious pneumonia events, particularly with fluticasone when compared with budesonide.
DiSantostefano, et al [34] – 2014	Cluster analysis of RCTs	ICS use was associated with an increased risk of pneumonia and serious pneumonia events independent of cluster.
Kew, et al. [43] – 2014	Meta-analysis	ICS use, alone or in combination with LABA, was associated with an increased risk of pneumonia events, without significant differences in mortality. Fluticasone was associated with higher rates of pneumonia, though not serious pneumonia events, when compared with budesonide.
Ferrer, et al. [46] – 2014	Prospective Cohort Study	Use of ICSs prior to admission for community-acquired pneumonia was associated with a reduced inflammatory response, but with no difference in long-term mortality.

NO INCREASED RISK OF PNEUMONIA		
AUTHOR/YEAR	**STUDY DESIGN**	**COMMENTS**
Welte, et al. [32] – 2009	Randomized Controlled Trial	Patients in the budesonide/formoterol plus tiotropium had less exacerbations and improved lung function, health status, and morning symptoms, when compared to tiotropium alone, however rates of pneumonia were similar among both groups (<1%).
Sin, et al. [40] – 2009	Meta-analysis	Budesonide, with or without formoterol, for 12 months did not increase the risk of pneumonia in COPD patients with stable disease.
Cheng, et al. [45] – 2014	Randomized Controlled Trial	Patients on high-dose fluticasone/salmeterol had more improvements in FEV1, CAT scores, and decreased rate of exacerbations, when compared to medium-dose fluticasone/salmeterol, with no significant difference in the rates of pneumonias between groups.
Festic, et al. [44] – 2014	Cohort study	ICS use was not associated with an increased risk of pneumonia requiring hospitalization.

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Table 3

The use of inhaled corticosteroids and effect on mortality.

ASSOCIATION BETWEEN INHALED CORTICOSTEROIDS AND PATIENT MORTALITY	
INCREASED MORTALITY	
Author/Year	**Comments**
Ernst, et al. [27] – 2007	Increased pneumonia related mortality, however all-cause mortality similar among groups
Jansson, et al. [33] – 2013	Higher mortality rates in the fluticasone/salmeterol group than in the budesonide/formoterol group.

NO EFFECT ON MORTALITY	
Author/Year	**Comments**
Calverley, et al. [8] – 2007	Mortality rates in salmeterol/fluticasone and salmeterol groups were not significantly different to placebo.
Drummond, et al [36] – 2008	No significant differences in 1-year all-cause mortality among patients with COPD.
Singh, et al. [37] – 2009	No significant increase in the risk of death, despite an increased risk of serious pneumonia.
Singanayagam, et al. [55] – 2011	COPD patients treated with ICSs had no significant differences in pneumonia severity, markers of systemic inflammation, requirement for mechanical ventilation, or 30-day and 6-month mortality, when compared to non-ICS users.
Sellares, et al. [54] – 2013	In patients with respiratory disorders who developed pneumonia, prior treatment with ICSs reduced the incidence of parapneumonic effusion, however mortality rates were similar across both groups.

DECREASED MORTALITY	
Author/Year	**Comments**
Wedzicha, et al. [10] – 2007	In a comparison between LABA/ICS vs. LAMA, mortality was lower in the salmeterol/fluticasone group when compared to the tiotropium group.
Malo de Molina, et al. [11] – 2010	Outpatient ICS use was associated with a significantly lower 30-day and 90-day mortality in COPD patients hospitalized with pneumonia.
Chen, et al. [12] – 2011	In patients with COPD hospitalized with pneumonia, prior use of ICSs was associated with a decreased risk of short-term mortality and need for mechanical ventilation.