

Corticosteroids and Pneumonia in Chronic Obstructive Pulmonary Disease: A Dual Effect?

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ABSTRACT

Corticosteroids are anti-inflammatory medications frequently prescribed in chronic obstructive pulmonary disease. Inhaled corticosteroids are indicated in these patients with forced expiratory volume in one second lower than 50% of predicted and/or frequent exacerbations. In addition, systemic corticosteroids are used to treat chronic obstructive pulmonary disease exacerbations. However, the immunosuppressive effect caused by corticosteroids may have side effects and increase the incidence of infections. Multiple studies have linked the chronic outpatient use of inhaled corticosteroids and the risk of developing pneumonia. Furthermore, chronic uses of systemic corticosteroids have been related to a higher incidence of pneumonia due to highly resistant bacteria. Nevertheless, several studies found a beneficial effect of inhaled corticosteroids, lowering mortality in chronic obstructive pulmonary disease patients who have already developed pneumonia. And the use of systemic corticosteroids as adjunctive therapy in community acquired pneumonia may be beneficial. We review the association of inhaled corticosteroids and systemic corticosteroids with the risk of pneumonia and the implications on clinical outcomes in patients with chronic obstructive pulmonary disease. (BRN Rev. 2015;1:105-15)

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease that is responsible for substantial and growing morbidity, mortality, and healthcare expenses worldwide. It is projected that COPD will become the third leading cause of death worldwide in 2020¹.

Corticosteroids are anti-inflammatory medications commonly prescribed in COPD. Inhaled corticosteroids (ICS) reduce the frequency of exacerbations and improve quality of life^{2,3}. They are currently recommended in COPD patients with severe obstruction (forced expiratory volume in 1 second, FEV₁, < 50%) and/or frequent exacerbations¹. In addition, systemic corticosteroids (SCS) are used during the treatment of moderate-to-severe acute exacerbations of COPD¹.

Potential side effects from corticosteroid treatment are an important issue to take into account in COPD patients. The use of corticosteroids has been related to immunosuppression and increased risk of superinfection⁴⁻⁶. Several studies suggest that in COPD patients receiving chronic ICS, there is a higher risk of acquiring pneumonia⁷⁻⁹. This potential association is important because patients with COPD who develop pneumonia may experience worse clinical outcomes¹⁰⁻¹². Furthermore, SCS use is associated with opportunistic or highly resistant bacteria pneumonia due to their immunosuppressive properties¹³⁻¹⁸. However, the associated impact of ICS among COPD patients who develop 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^{19,20}. And recent studies have suggested that SCS may be used as an adjunctive therapy for community acquired pneumonia (CAP), improving clinical outcomes, although few COPD patients were included^{21,22}.

The purpose of this review is to assess the evidence related to the association of corticosteroids (both inhaled and systemic) and the risk of CAP, and the implications in clinical outcomes in COPD patients.

CORTICOSTEROIDS

Corticosteroids are involved in a wide range of physiological processes, including regulation of inflammation, immune response, carbohydrate metabolism, protein catabolism, and blood electrolyte levels^{23,24}. Corticosteroids can be administered through multiple routes, but for the purpose of this review we will focus on the corticosteroids administered through systemic and inhalational routes. Table 1 shows the most relevant ICS and SCS available in the market.

Mechanism of action

Corticosteroids inhibit the expression and action of many inflammatory mediators. To exert their effects, corticosteroids need to bind to a specific cytoplasmic glucocorticoid receptor found in respiratory epithelial cells and other cell lines. The activation of the glucocorticoid receptor by the administration of the corticosteroids moves the drug-receptor complex into the nucleus of the cell and binds to the DNA²³.

The anti-inflammatory and immunosuppressive effects of corticosteroids are due to three

TABLE 1. Inhaled and systemic corticosteroids available

Inhaled corticosteroids	Inhaled corticosteroids/Long-acting beta-agonists	Systemic corticosteroids
Beclomethasone dipropionate	Beclomethasone/Formoterol	Cortisone
Budesonide	Budesonide/Formoterol	Dexamethasone
Flunisolide	Fluticasone propionate/Salmeterol	Hydrocortisone
Fluticasone propionate	Fluticasone/Formoterol	Methylprednisolone
Fluticasone furoate	Fluticasone furoate/Vilanterol	Prednisolone
Mometasone furoate	Mometasone/Formoterol	Prednisone
Triamcinolone acetonide		Triamcinolone
Ciclesonide		

molecular mechanisms (Fig. 1). First, the ligand-activated alpha-glucocorticoid receptor binds as a homodimer to specific DNA sequences located in the promoter regions of target genes to induce transcription of anti-inflammatory molecules such as interleukin (IL)-10, IL-1 receptor, or lipocortin 1 (transactivation). Second, an indirect negative regulation of gene expression is achieved by glucocorticoid receptor-protein interaction (transrepression). The ligand-activated receptor binds as a monomer to key proinflammatory transcription factors, such as activator protein-1 and nuclear factor-kB. The resulting complex inhibits the initiation of transcription of relevant genes that play a central role in inflammation²³. The synthesis of several cytokines (e.g. tumour necrosis alpha, and IL-4, -5, -6, and -13), adhesion molecules (e.g. ICAM -1, VCAM-1) and chemokines (e.g. eotaxin, IL-8) are inhibited^{25,26}. 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, which is responsible for a rapid vasorelaxation effect²⁷.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids are commonly prescribed medications for the management of COPD and asthma patients^{28,29}. They are recommended by current guidelines in symptomatic COPD patients with a post-bronchodilator FEV₁ of < 60% predicted and/or repeated exacerbations¹. A recent study by Pascoe et al.³⁰ demonstrated that ICS are more effective in reducing COPD exacerbations in COPD patients with increased serum eosinophils (> 25%). However, due to the wide use of ICS, there is a recent safety concern related to the risk of developing pneumonia³¹. In addition, some studies have reported increased mortality in hospitalized patients with pneumonia who have underlying COPD compared with those without COPD¹⁰⁻¹².

Inhaled corticosteroids and pneumonia

Several randomized controlled trials (RCT) and observational studies have addressed the association of chronic ICS use and the risk of developing pneumonia among COPD patients

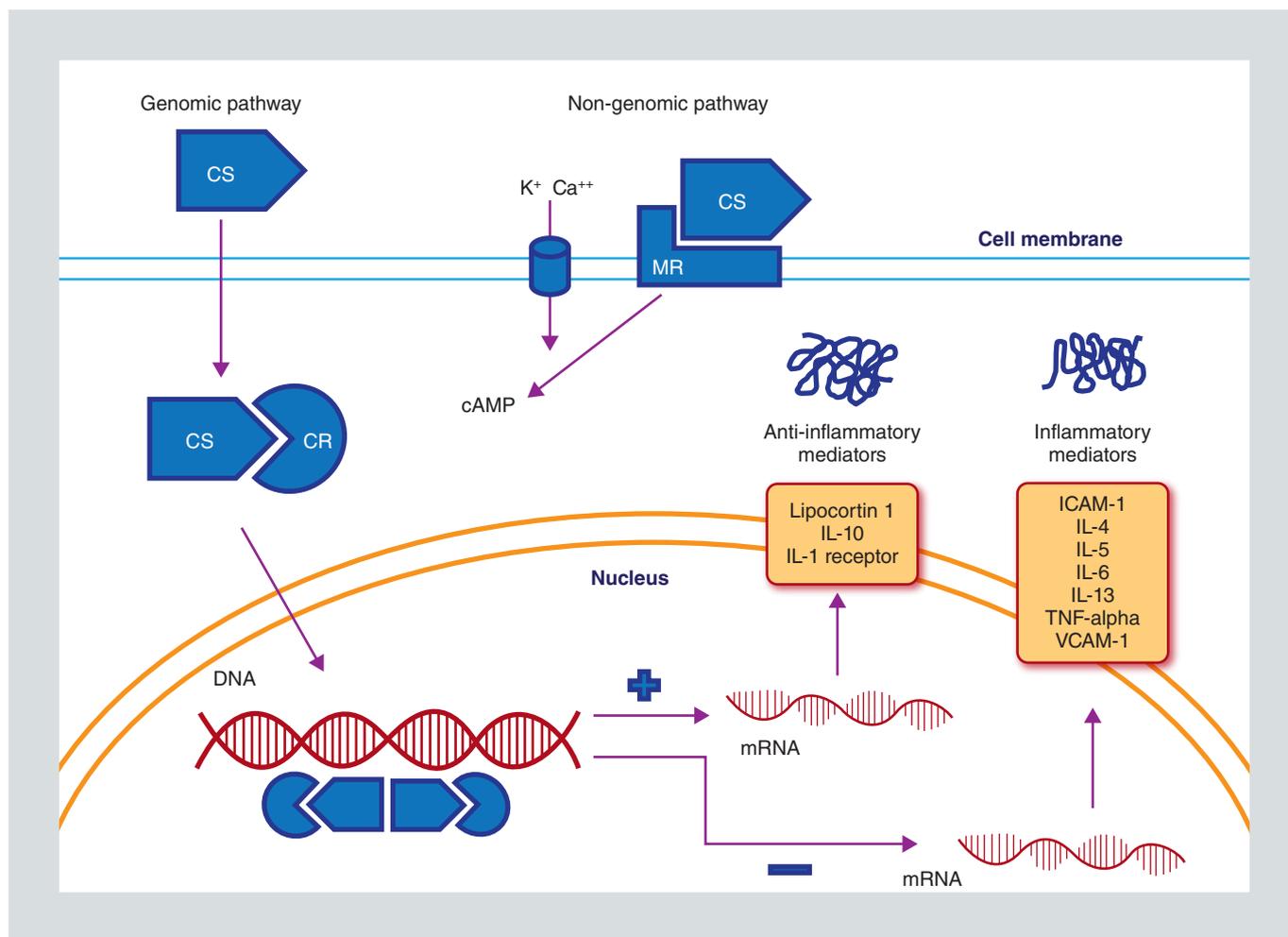


FIGURE 1. Cellular mechanism of action of corticosteroids in the inhibition of inflammation.

Three anti-inflammatory mechanisms are originated by corticosteroids: (i) transactivation: increasing anti-inflammatory mediators, (ii) transrepression: decreasing inflammatory mediators, and (iii) increasing anti-inflammatory messengers through membrane-associated receptors.

CR: corticosteroid receptor; CS: corticosteroids; ICAM: intercellular adhesion molecule; IL: interleukin; MR: membrane receptor; TNF: tumour necrosis factor; VCAM: vascular cell adhesion molecule.

in the last ten years (Table 2). The TORCH (Towards a Revolution in Chronic Obstructive Pulmonary Disease Health) study⁷ was the landmark randomized controlled trial (RCT) that suggested a risk of developing pneumonia among COPD patients who received ICS. In this three-year follow-up study, COPD patients who received 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%;

$p < 0.001$)⁷. However, this study was limited by the lack of radiological confirmation of the pneumonia diagnosis. A *post hoc* analysis of the TORCH study confirmed these previous results, and found that older age, low FEV₁, and the presence of an exacerbation in the previous year were risk factors to develop pneumonia in COPD patients taking ICS³².

Kardos et al.⁸, assessed the impact of combination therapy of ICS plus long-acting beta

TABLE 2. Randomized controlled trials and observational studies evaluating the risk of pneumonia in chronic obstructive pulmonary disease patients treated with inhaled corticosteroids

Author/Year	Study design	Number of patients	Type of corticosteroid	Duration of treatment	Main effect	Risk of pneumonia
Kardos et al. ⁸ 2007	Randomized controlled trial	994 COPD patients	Fluticasone propionate	44 weeks	Decreased exacerbations	Increased risk
Calverley et al. ⁷ 2007	Randomized controlled trial	6,112 COPD patients	Fluticasone propionate	3 years	Decreased exacerbations	Increased risk
Wedzicha et al. ⁹ 2008	Randomized controlled trial	1,323 COPD patients	Fluticasone propionate	2 years	Decreased mortality	Increased risk
Ernst et al. ³⁴ 2007	Case-control study	175,906 COPD patients	Fluticasone propionate	13 years	Increased risk of hospitalization for pneumonia	Increased risk
Crim et al. ³² 2009	Randomized controlled trial	6,184 COPD patients	Fluticasone propionate	3 years	Prior COPD exacerbation increase risk of pneumonia	Increased risk
Welte et al. ³⁶ 2009	Randomized controlled trial	660 COPD patients	Budesonide	12 weeks	Reduced severe exacerbations	No increased risk
Mullerova et al. ³⁵ 2012	Cohort study	40,414 COPD patients	Not specified	10 years	Prior severe COPD exacerbation increased risk of pneumonia	Increased risk
Dransfield et al. ³⁷ 2013	Two parallel-group randomized controlled trials	3,255 COPD patients	Fluticasone furoate	2 years	Decreased rate of moderate and severe exacerbations	Increased risk
Suissa et al. ³⁸ 2013	Cohort study	163,514 COPD patients	Fluticasone propionate	15 years	Increased risk of serious pneumonia	Increased risk
DiSantostefano et al. ³⁹ 2014	Cohort study	11,555 COPD patients	Beclomethasone dipropionate	8 years	Increased risk of hospitalization for pneumonia	Increased risk

COPD: chronic obstructive pulmonary disease.

agonist (LABA) compared with LABA alone on the rate of moderate and severe acute exacerbations of COPD (AECOPD). The authors conclude that ICS/LABA therapy reduces the rate of moderate and severe AECOPD by 35% in patients with severe COPD ($p < 0.001$). Once again, the concern was that pneumonic events were more likely to occur among COPD patients managed with ICS/LABA when compared to the LABA-only group (4.5 vs. 1.4%; $p = 0.005$). In addition, Wedzicha et al.⁹ evaluated the effect on reducing COPD exacerbations among COPD patients managed by the combination of ICS/LABA against long-acting muscarinic agonists (LAMA). The authors found that pneumonia events were more common among COPD

patients receiving the ICS (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 pneumonia³³.

Ernst et al.³⁴, in a large observational study in Canada of over 175,000 patients, found that elderly COPD patients with an active ICS prescription had a twofold 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. Mullerova et al.³⁵ examined the risk of CAP in a cohort of 40,411 COPD patients. The authors showed that COPD-treated patients with ICS were more likely to develop CAP (incidence rate, 22.4%). This increased risk was independently associated with prior exacerbations of COPD 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).

In contrast, Welte et al.³⁶ assessed in a RCT the efficacy of LAMA against a combination of ICS/LABA plus LAMA. The combination therapy of ICS/LABA/tiotropium had a rapid and sustained improvement of lung function, health status, morning symptoms, and physical activities, and reduced AECOPD rates compared to tiotropium alone. Only three cases of pneumonia were reported within each treatment group (< 1%)³⁶. It is important to point out that this was a six-month study and also patients were treated with budesonide; all these factors may have contributed to the low rate of CAP.

More recently, Dransfield et al.³⁷, in a two-replicate, double-blind, RCT performed in more than 3,000 COPD patients, reported a higher incidence of serious pneumonia in patients with ICS/LABA (3%) vs. patients on LABA alone (1%). Suissa et al.³⁸, in a cohort of 163,000 COPD patients, demonstrated an incidence rate of 2.4/100/year of serious pneumonia during the five years of follow-up. Current use of ICS was associated with a 69% increase in the rate of serious pneumonia (RR: 1.69; 95% CI: 1.63-1.75). And, in a cohort of 11,555 COPD patients, DiSantostefano et al.³⁹

showed that ICS use was associated with a 20-50% increased risk of pneumonia. This excess risk of pneumonia was reduced with exposure time (≥ 1 month or ≥ 6 months of new use³⁹).

The mechanisms that could explain why ICS may cause pneumonia is a matter of scientific research interest. We hypothesized several possible explanations according to the literature findings. The immunosuppressive effect caused by high local lung concentrations found with the use of ICS may potentially increase the risk of pneumonia^{40,41}. Barnes et al.⁴² showed that the number of inflammatory cells and the expression of proinflammatory mediators was decreased in bronchial biopsies from COPD patients receiving ICS/LABA. Barbier et al.⁴³ demonstrated that fluticasone reduces bacterial airway epithelial invasion in a mouse model of lung infection. Gutierrez et al.⁴⁴ showed that the microenvironment of the lungs modulates the macrophage activation in exacerbated COPD with and without CAP. In addition, Sibila et al.⁴⁵ demonstrated that prior ICS use is associated with an increased incidence of antimicrobial drug-resistant pathogens in patients hospitalized with CAP. In this study, most of the ICS users had a pre-existing COPD diagnosis (66%). In a subgroup analysis of COPD patients, the outpatient use of ICS persisted was associated with the presence of drug-resistant pathogens (12.1 vs. 3.4%; OR: 3.9; 95% CI: 1.1-13.2; $p = 0.03$). However, non-COPD patients receiving ICS were not associated with drug-resistant pathogens⁴⁵. These findings may suggest a disease-specific susceptibility linked to COPD that requires further exploration. Liapikou et al.⁴⁶ also reported that COPD patients treated with chronic ICS had a higher rate of pneumonia due to *Pseudomonas aeruginosa* when compared to COPD

patients with pneumonia without chronic ICS treatment. Finally, Ferrer et al.⁴⁷ demonstrated that previous use of ICS in patients hospitalized with CAP was associated with a reduced systemic inflammatory response, without any impact on long-term outcomes.

Pneumonia-related mortality in chronic obstructive pulmonary disease patients receiving inhaled corticosteroids

The evidence confirming a higher risk of developing pneumonia does not necessarily translate into poor clinical outcomes. The landmark TORCH study⁷ did not show a difference in mortality among those patients treated with ICS^{7,32}. Meta-analyses performed by Drummons et al.⁴⁸ and Singh et al.⁴⁹ did not find mortality differences among ICS and non-ICS users, although patients on ICS had higher rates of pneumonia. In addition, in a trial level meta-analysis, Singh et al.⁵⁰ reported that the increased risk of pneumonia was not followed by an increased risk of pneumonia-related mortality.

Two observational studies in COPD patients hospitalized with pneumonia showed that chronic ICS use was associated with lower all-cause mortality. Malo de Molina et al.²⁰ reported that 6,353 hospitalized patients with pneumonia with a concomitant COPD diagnosis had a lower 30- and 90-day mortality when ICS were used. Subsequently, Chen et al.¹⁹, 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. In contrast, Ernst et al.³⁴ reported, in a cohort of 23,942 COPD

patients with pneumonia, that 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 for ICS and non-ICS users that required hospitalization for pneumonia. Singanayagam et al.⁵¹ showed, in a prospective study of 490 spirometry-confirmed COPD patients, that 30-day mortality was not statistically significantly different when comparing ICS and non-ICS users. Finally, Sellares et al.⁵² reported that patients receiving ICS have less parapneumonic pleural effusions, but no differences in mortality were found.

SYSTEMIC CORTICOSTEROIDS

The most common indication for SCS in COPD is acute exacerbations¹. Compared to ICS, less controversy exists regarding the link between the chronic use of SCS and the increased risk of pneumonia. However, the use of SCS as adjunctive treatment in COPD patients with pneumonia may be beneficial due to its acute anti-inflammatory effect.

Impact of chronic outpatient systemic corticosteroid use in developing pneumonia

The use of chronic SCS in the outpatient setting is recognized as an immunosuppressive medication associated with a risk factor of developing pneumonia. Different studies have identified an increased incidence of potentially highly resistant bacteria^{15,53} and opportunistic infections of the lung, such as *Aspergillus* spp¹³, *Pneumocystis jirovecii*¹⁷ and *Nocardia* spp⁵⁴, in patients taking chronic SCS. Different studies

in chronic inflammatory diseases, such as rheumatoid arthritis, demonstrated that patients who were using chronic SCS have an elevated risk of pneumonia, with increased mortality⁵⁵.

Few studies have evaluated the impact of prior SCS in patients who subsequently developed pneumonia. Malave et al.⁵⁶ studied the impact of prior systemic corticosteroid use in clinical outcomes in a cohort of 787 CAP hospitalized patients. In this study, prior corticosteroid use was not associated with poor outcomes such as increased 30-day mortality higher severity of illness at the time of presentation or in the presence of resistant or opportunistic pathogens. However, there was no information regarding the indication, dose, duration, and withdrawal of corticosteroids in these CAP patients. Patients with corticosteroid use had a higher rate of COPD (35 vs. 21%; $p < 0.001$). Polverino et al.⁵⁷ published the reasons for acute SCS use in a large cohort of 3,257 patients admitted for CAP. In this study, 260 patients (8%) received corticosteroids at admission. The main reasons for administering acute corticosteroids were the presence of chronic respiratory conditions such as COPD and severe clinical presentation. However, systemic corticosteroid use did not influence mortality or clinical stability as was expected according to the initial severity of illness score. By contrast, corticosteroids were significantly associated with a longer length of stay.

Systemic corticosteroids as adjuvant therapy in pneumonia

The use of corticosteroids as adjunctive therapy in CAP remains controversial⁵⁸. Garcia-Vidal et al.¹⁶ performed a retrospective study with

308 patients with severe CAP showing that mortality decreased in patients who received simultaneous administration of SCS with antibiotic treatment (OR: 0.28; 95% CI: 0.113-0.732). In this study, male age and the presence of COPD were associated with SCS treatment use. Recently, another retrospective study performed in 6,925 patients with severe CAP in Japan demonstrated that the use of low-dose corticosteroids might be associated with reduced 28-day mortality in patients with septic shock. Again, COPD was associated with the use of SCS (27 vs. 11%; $p < 0.001$)⁵⁹.

Several RCT have evaluated the effect of acute administration of corticosteroids in patients with CAP in the last ten years, including COPD patients (Table 3). Confalonieri et al.¹⁴ assessed the efficacy and safety of continuous infusion of hydrocortisone in 46 patients with CAP requiring intensive care unit (ICU) admission. These authors demonstrated a mortality reduction in the group treated with SCS, a better modulation of systemic inflammatory response, and significant improvement in clinical endpoints such as chest X-ray, multiple organ dysfunction syndrome severity scale, $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio, and ICU and hospital stay. However, the small sample size and the small number of COPD patients admitted ($n = 3$) limited our ability to generalize these results in COPD. Furthermore, the SCS group had zero mortality, something difficult to believe in this patient population. Snijders et al.⁶⁰ studied the impact of prednisolone compared to placebo among 213 hospitalized patients with CAP. Of them, 32 had COPD (15%). The authors found no differences regarding the rate of 30-day mortality, time to clinical stability, or length of hospital stay. In

TABLE 3. Double blind randomized controlled trials evaluating the effects of corticosteroids as adjuvant therapy in community-acquired pneumonia in the last 10 years including chronic obstructive pulmonary disease patients

Author/Year	Number of patients Number of COPD (%)	Disease	Type of corticosteroid, dosage	Duration of treatment	Gradual withdrawal	Main effect	Side effects
Confalonieri et al. ¹⁴ 2005	n = 48 n = 3 (6%) COPD	CAP requiring ICU	Hydrocortisone, 240 mg/day	7 days	No	Decrease mortality	None
Snijders et al. ⁶⁰ 2010	n = 213 n = 32 (15%) COPD	Hospitalized CAP	Prednisolone, 40 mg/day	7 days	No	Increase late failure	None
Meijvis et al. ²¹ 2011	n = 304 n = 34 (11%) COPD	Hospitalized CAP	Dexamethasone, 5 mg/day	4 days	No	Reduce length of stay	Hyperglycaemia
Fernandez-Serrano et al. ⁶¹ 2011	n = 56 n = 6 (10%) COPD	Hospitalized CAP	Methylprednisolone, 620 mg	9 days	Yes	Decrease length of stay	None
Torres et al. ²² 2015	n = 120 n = 19 (15%) COPD.	Hospitalized severe CAP	Methylprednisolone 0.5 mg/kg/12 hours	5 days	No	Decrease treatment failure	None
Blum et al. ⁶² 2015	n = 785 n = 133 (16%) COPD	Hospitalized CAP	Prednisone 50 mg/day	7 days	No	Decrease time to clinical stability	Hyperglycaemia

COPD: chronic obstructive pulmonary disease; CAP: community-acquired pneumonia; ICU: intensive care unit.

addition, patients treated with corticosteroids had a faster decline in serum C-reactive protein levels compared to placebo. By contrast, late clinical failure (> 72 hours from admission) was more common in the corticosteroid group. Meijvis et al.²¹ evaluated the effect of intravenous dexamethasone versus placebo in the first four days after CAP admission in 304 patients, 34 of them (10%) with COPD. The authors found no differences in the main outcomes, including in-hospital mortality, ICU admission, and severe adverse events. However, corticosteroid-treated patients had a shorter length of hospital stay compared to the placebo group. Fernandez-Serrano et al.⁶¹ reported, in 56 hospitalized CAP patients (6% of them with COPD), that a combination of antibiotics with methylprednisolone improved respiratory failure rates and accelerated the timing of clinical resolution.

During 2015, two positive RCT have been published regarding the use of SCS in CAP. Torres et al.²² demonstrated that acute administration of SCS reduced treatment failure in a population of 120 patients with severe CAP that had high inflammatory response (elevated C reactive protein levels). This study included 19 COPD patients (15% of the population). And Blum et al.⁶² showed that prednisone treatment for seven days in CAP admitted patients shortens time to clinical stability without an increase in complications. In this study, among 785 patients included, 133 (16%) had COPD. All these findings may suggest a corticosteroid benefit in patients with pneumonia and concomitant corticosteroid treatment, especially in the most severe population. However, the prevalence of COPD in these studies was very low (6-16%), and these results should be taken with caution in patients with COPD.

CONCLUSIONS

Our current view of the risk of pneumonia and impact of outcomes from ICS and SCS treatment in COPD patients emphasizes the importance of balancing the immunosuppressive and anti-inflammatory effects of corticosteroids. An excessive immunosuppressive effect may be harmful for the host, increasing the risk of developing pneumonia or the risk of highly resistant or opportunistic pathogens due to a chronic use of both ICS and SCS, respectively. However, during the acute phase of pneumonia, corticosteroids may modulate associated inflammatory responses to pneumonia due to their anti-inflammatory and immunomodulatory effects, which may have an impact on important short- and long-term clinical outcomes. In the next years we hope that more studies will assess risks and benefits of corticosteroid treatment and its association with pneumonia in COPD patients. Further studies with an appropriate sample size and radiological confirmatory diagnosis of pneumonia and AECOPD are needed to better understand the dual effect on pneumonia due to corticosteroids use in patients with COPD.

CONFLICT OF INTEREST

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