Published in final edited form as:

Clin Pulm Med. 2013 January 1; 20(1): . doi:10.1097/CPM.0b013e31827a2a60.

THE PARADOXICAL EFFECT ON PNEUMONIA OF CHRONIC INHALED CORTICOSTEROIDS

Oriol Sibila, MD^{1,2}, Antonio Anzueto, MD^{1,3}, and Marcos I. Restrepo, MD, MSc.^{1,3,4}

¹University of Texas Health Science Center at San Antonio, San Antonio, TX

²Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

³South Texas Veterans Health Care System

⁴Veterans Evidence Based Research Dissemination and Implementation Center (VERDICT).

Abstract

Community-acquired pneumonia (CAP) is the leading infectious cause of death in developed countries. Several studies have shown that the risk of pneumonia is increased in patients with Chronic Obstructive Pulmonary Disease (COPD) who are receiving chronic inhaled corticosteroids (ICS). The impact of ICS on pneumonia prognosis is controversial. Recent studies have shown that COPD patients with prior ICS use have less mortality after developing CAP as compared with patients with COPD without prior ICS use. This review discusses the association of ICS and the risk of CAP and its association with clinical outcomes in patients with COPD and pneumonia.

INTRODUCTION

Community-Acquired Pneumonia (CAP) is the leading infectious cause of death in developed countries. It affects more than 5 million adults and accounts for more than 1 million admissions each year in the United States (1, 2). Pneumonia and influenza are the eighth leading causes of death in the United States, and age-adjusted mortality attributable to these illnesses is increasing (3).

It has been shown that the risk of developing pneumonia is increased in patients with Chronic Obstructive Pulmonary Disease (COPD), but is even higher for those who are receiving chronic inhaled corticosteroids (ICS) (4-6). The impact of ICS on pneumonia mortality is controversial, and recent studies have shown that COPD patients with prior ICS use have better clinical outcomes after developing CAP as compared with COPD patients without prior ICS use (7, 8).

The main purpose of this report is to review the evidence behind the association of ICS and the risk of CAP, and whether ICS use is associated with worse clinical outcomes in CAP patients. For this purpose we performed a review of published articles in the English language with the following search terms: inhaled corticosteroids and pneumonia.

Corresponding author: Marcos I. Restrepo, MD, MSc; VERDICT (11C6) – South Texas Veterans Health Care System ALMD - 7400 Merton Minter Boulevard - San Antonio Texas, 78229; Phone: (210)-617-5300 ext. 15413 - Fax: (210) 567-4423; restrepom@uthscsa.edu.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids (ICS) are anti-inflammatory agents widely used in patients with obstructive airways diseases. Based on their established efficacy and adequate safety profile these medications are recommended in the treatment of the most prevalent chronic respiratory diseases such as asthma and COPD (9, 10).

ICS agents currently available are: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate (mometasone), triamcinolone acetonide (triamcinolone) and ciclesonide. Table 1 shows all current ICS and their therapeutic doses.

Mechanism of action

ICS are known to exert their effects by binding to a glucocorticoid receptor located in the cytoplasm of target cells. Once activated, the drug–receptor complex moves into the nucleus of the cell and binds to the DNA and directly or indirectly regulates the transcription of target genes. Through the mechanisms of transactivation, corticosteroids may inhibit the transcription of proinflammatory cytokines and chemokines and upregulate production of anti-inflammatory proteins. The drug–receptor complex may also interact with DNA-binding transcription factors to repress proinflammatory protein production (11). The potency of a given corticosteroid is governed by the affinity of the drug to bind to the glucocorticoid receptor. Receptor affinity is usually measured relative to dexamethasone. Of the currently available compounds, mometasone has the highest relative receptor affinity, followed by fluticasone and the active metabolites of beclomethasone (17-BDP monopropionate) and ciclesonide (des-CIC) (12, 13, 14).

Indications

The main indications for the use of ICS are in COPD and asthma (9). In COPD patients, ICS are only approved to be used in combination with long active beta agonists. Non-well established indications are in other lung pathologies with bronchial hyperreactivity.

In COPD, ICS effects on airway inflammation are still controversial, but they have been demonstrated to reduce the overall frequency of exacerbations and improve quality of life (15, 16). Thus, ICS are important anti-inflammatory therapy in COPD and are approved in different doses. For example, in the U.S. the dose of fluticasone is 250 µg twice a day, while in Europe it is >500 µg twice a day. They are recommended in symptomatic patients with a forced expiratory volume in the first second of expiration of less than 50% predicted (stage III, severe COPD; stage IV, very severe COPD) and frequent exacerbations (10).

In asthma, ICS are effective at suppressing airway inflammation and are the preferred controller medication. In addition, ICS improve asthma control more effectively than any other single long-term controller medication. ICS are the only asthma medication that have been shown to reduce mortality and the risk of hospitalization (17). Therapeutic benefit is obtained at low doses such as fluticasone 200 µg/day or the equivalent (18) while adverse effects increase with higher doses (19). These medications are recommended in persistent asthma and are indicated in all symptomatic patients (9, 20).

Side Effects

Potential ICS related side effects are shown in Table 2. ICS are delivered using Metered-Dose Inhaler (MDI) or Dry Powder Inhaler (DPI) device. Initially, a large proportion of the ICS is swallowed. Oral bioavailability depends on absorption characteristics from the gastrointestinal tract, lipophilicity of the compound and the extent of first-pass metabolism. These absorptions range from 1% (fluticasone) to 26% (active metabolite of

beclomethasone) for currently available compounds. Local adverse events described include oropharyngeal candidiasis, hoarseness and dysphonia, pharyngeal irritation and cough (21).

Pulmonary bioavailability depends on the amount of ICS deposited in the lungs. It differs for different delivery devices and ranges from 11% for mometasone delivered via a DPI to 52% for the active metabolite of ciclesonide. Once it reaches the circulation, most of the absorbed drug binds to plasma proteins (22, 23). Only the unbound fraction is pharmacologically active. All current ICS are cleared by the liver. Despite the general acceptance of ICS over the past several decades, substantial concerns about their undesirable effects have occurred. The systemic effects of ICS are caused by their absorption into the systemic circulation. ICS, usually high doses, have been shown to increase the risk of skin-bruising, hyperglycemia in diabetics, and the risk of adrenocortical suppression (at unlabeled unapproved high doses) (21, 22). The risk of glaucoma, cataract formation, and osteoporotic fractures have, as of yet, been inconclusive in COPD patients on ICS agents (24, 25, 26). Finally, recent studies have suggested an increased risk of pneumonia associated with moderate to high doses of ICS in COPD patients (4-6).

INHALED CORTICOSTEROIDS AND PNEUMONIA

Different studies have evaluated the relationship between ICS use and risk of pneumonia (table 3). Several recent studies have demonstrated that the use of ICS was associated with an increased risk of CAP in COPD patients (4-6). However, this increased risk has been not described in other diseases such asthma (27).

COPD is a common disease and the fourth leading cause of morbidity and mortality in the United States (28, 29). The disease represents a substantial public health burden, affecting 10 to 15 million persons in the United States (30). ICS therapy is central to the long-term management of COPD. Elevated levels of systemic and pulmonary inflammation in stable COPD patients have led to the use of ICS therapy for these patients. The results of the majority of ICS trials in COPD have conflicting results regarding their effects on airway inflammation, but the use of ICS has been shown to reduce the incidence of exacerbations and improve health status in these patients. Therefore, current international guidelines recommend ICS therapy in addition to bronchodilators for severe COPD patients and those with frequent exacerbations (10).

The mechanism of the association of ICS therapy with pneumonia remains unclear. ICS achieve local high concentrations in the lungs and may increase the risk of pneumonia due to their immunosuppressive effects (31, 32). Barnes et al (33) demonstrated that the combination of fluticasone and salmeterol significantly reduces the inflammatory cells in bronchial biopsies and decrease the expression of proinflammatory mediators. This hypothesis is supported by a multicenter trial that suggested that ICS use reduces local but not systemic biomarkers of inflammation in patients with COPD (34). Inhaled fluticasone at doses of 1000 µg per day exerts effects on serum cortisol levels that are equivalent to 10 mg of oral prednisone. Patients with advanced COPD who are at the highest risk of colonization with potentially pathogenic bacteria may be uniquely susceptible to these local immunosuppressive effects. In addition, Gutierrez et al. (35) demonstrated that the microenvironment of the lungs modulates the macrophage activation in exacerbated COPD with and without CAP.

In asthma, in contrast, the use of ICS does not appear to increase the risk of pneumonia. O'Byrne et al, in a recent meta-analysis of randomized clinical trials of budesonide compared to placebo or fluticasone in patients with asthma did not demonstrate an increased risk of pneumonia when ICS was compared to non-ICS treatment. In addition, there was no

evidence of increased risk of pneumonia with higher doses of budesonide, or any difference when budesonide was compared to fluticasone (27).

INHALED CORTICOESTEROIDS AND RISK OF PNEUMONIA IN COPD PATIENTS

The TORCH (Towards a Revolution in Chronic Obstructive Pulmonary Disease Health) study (4), was the first large randomized controlled trial (RCT) suggesting an excess in pneumonia events in COPD patients who received ICS. This study compared the efficacy of fluticasone propionate, salmeterol or their combination (salmeterol/fluticasone 50/500 µg twice daily) versus placebo in COPD patients over a 3 year period. Patients receiving ICS (fluticasone propionate, whether as monotherapy or in combination with LABA had higher rate of physician reported pneumonia (19.6% and 18.3%, respectively) when compared with the placebo group, 12.3% ($p<0.001$) (4). The main limitation of this finding was the lack of radiological pneumonia confirmation. Further review of these data, did not establish a relationship between pneumonia and increased risk for COPD exacerbations, hospitalizations or mortality (36).

The association between ICS and pneumonia in COPD patients has been reported in two other large RCT's (Table 4). Kardos et al (5), assessed the impact of combination therapy of salmeterol/fluticasone propionate 50/500 µg twice daily compared with LABA alone on moderate and severe AECOPD in patients with severe COPD. The study authors concluded that LABA+ICS therapy reduced the rate of moderate and severe AECOPD in these patients by 35% ($p<0.001$). However, more pneumonia events were reported in the ICS+LABA group compared to the LABA alone group (4.5 vs. 1.4%; $p=0.005$). In addition, Wedzicha et al (6), evaluated the effect on reducing COPD exacerbations of the combination of salmeterol/fluticasone propionate 50/500 µg twice daily against tiotropium in COPD patients. They also found an increased rate of pneumonia events in the fluticasone containing regimen (8 vs. 4%; $p=0.008$). In a subsequent review of these data, the investigators concluded that pneumonia is less frequent than exacerbations, and seemed to be present in patients that had persistent exacerbation symptoms, suggesting that early identification and treatment of exacerbations may decrease the risk for pneumonia (37).

Ernst et al (38), in a large observational study in Canada of over 175,000 patients, found that elderly patients with COPD with a current prescription for an ICS were 70% more likely to be hospitalized with a primary diagnosis of pneumonia (relative risk (RR) 1.70, 95% confidence interval (CI) 1.63-1.77, $p<0.001$). The number of elderly COPD patients that were hospitalized with pneumonia was 23,942, which corresponds to a rate of 1.9 per 100 per year. In addition, these data suggested that there was a two-fold-increased risk of hospitalization in the entire sample and the risk was greatest with higher doses of ICS (fluticasone propionate of 1000 µg per day). Mullora et al (39) showed an increased risk of CAP among COPD patients in a recent observational study examining a cohort of 40411 COPD patients. In this study, the increased risk of CAP in COPD patients was independently associated with prior exacerbations requiring hospitalization (OR 2.7, 95 IC 2.3-3.2), severe COPD requiring home oxygen or nebulized therapy (OR 1.4, 95 IC 1.1-1.6) and specific comorbidities such as dementia (OR 2.6, 95 IC 1.9, 3.0) and congestive heart failure (OR 1.4, 95 IC 1.2 – 1.6).

In contrast, an RCT by Welte et al (40) assessed the efficacy of budesonide/formoterol added to tiotropium in patients eligible for ICS/LABA combination therapy. The authors concluded that budesonide/formoterol added to tiotropium versus tiotropium alone provided rapid and sustained improvements in lung function, health status, morning symptoms and

activities, and reduced AECOPD. There were only three cases of pneumonia within each treatment group (<1%), which is consistent with previous smaller RCT studies (41, 42).

Finally, several meta-analyses have also evaluated the relationship between ICS and pneumonia in COPD patients. Drummond et al. evaluated 11 RCT of ICS therapies in patients with stable COPD, and concluded that ICS therapy was associated with a 34% increased risk of pneumonia (43). Singh et al (44) assessed the results of 18 trials that included 16,996 patients, and showed that the use of ICS was associated with a significantly increased risk of any pneumonia event when compared to controls (RR 1.60; 95 CI 1.33-1.92 ($p<0.001$)). Rodrigo et al (45) evaluated the association of ICS and important adverse events including pneumonia and reached the same conclusions. In addition, Singh et al (46), in a more recent trial-level meta-analysis, which was a revised and updated version of a previous meta-analysis (44), showed that inhaled fluticasone and mometasone exposure remain significantly associated with an increase in the risk of pneumonia. In addition, they reported a numerical increase in the risk of pneumonia with budesonide exposure, but not statistically significantly different (RR 1.1, 95 CI 0.9-1.5). In contrast, a meta-analysis of individual patient data restricted to clinical trials of budesonide treatment for 12 months in patients with COPD, did not find an excess of pneumonia events (47).

In all of these studies, the main limitation was the use of a non-consistently objective definition of pneumonia without radiological confirmation in most of the cases. Therefore, the data suggest that there is an increased risk of developing pneumonia events while exposed to ICS. However, due to the lack of radiological confirmation, the assessment of severity of illness of pneumonia at diagnosis, the rate of influenza and/or pneumonia vaccination and other potential unmeasured confounders, it remains a matter of controversy.

PNEUMONIA-RELATED MORTALITY IN COPD PATIENTS TAKING ICS

The evidence from RCTs and meta-analyses suggest that the increased risk of pneumonia associated with ICS may not translate to poor outcomes in those subjects who developed pneumonia. In the TORCH study (4), there were no statistically significant differences among groups in the overall mortality rate. Similarly, in the INSPIRE study (6), the authors demonstrated a lower death rate in the ICS+LABA group (salmeterol/fluticasone propionate 50/500 µg twice daily in combination) compared to tiotropium. The meta-analyses by Drummond et al. (43) and Singh et al. (44) found no differences in overall mortality among ICS and non-ICS users. More specifically, Singh et al reported a trial level meta-analysis on pneumonia (adverse events and serious adverse events) and pneumonia-related mortality, and showed that the increased risk of pneumonia was not accompanied by an increased risk of pneumonia-related mortality (46).

Two observational studies using large administrative databases in COPD patients hospitalized with pneumonia, showed a decreased risk of mortality among the ICS users group. Malo de Molina et al. (7), in a cohort of 6,353 patients admitted with pneumonia and prior COPD, demonstrated that outpatient therapy with ICS was associated with a significantly lower 30- and 90-day mortality. Subsequently, Chen et al (8), in a different cohort of 15,768 COPD patients hospitalized with pneumonia who received ICS, found an independent association with a decreased risk of short-term mortality and use of mechanical ventilation after hospitalization for pneumonia. By contrast, Ernst et al. (38) reported in a cohort of 23,942 patients with COPD and pneumonia an increase in 30-day mortality associated with pneumonia, secondary to ICS use (adjusted rate ratio (RR) 1.53; 95%CI 1.30-1.80). The increased risk of CAP was associated with higher doses of ICS. In this study, all-cause mortality was similar for patients hospitalized for pneumonia, whether or not they had received ICS in the recent past. Finally, a prospective study conducted in 490

spirometry-confirmed COPD patients with a primary diagnosis of CAP did not find differences in 30-day mortality among ICS and non-ICS users (48).

CONCLUSIONS

The use of ICS in COPD patients is common practice with benefits of reducing the rate of COPD exacerbations, and improving symptoms and quality of life. However, it is concerning that the data are highly suggestive of an increased risk of the development of pneumonia, although the risk of acquiring pneumonia may not translate to higher mortality among ICS users who require hospitalization for pneumonia.

Further studies with rigorously defined pneumonia and exacerbation outcomes, of sufficient duration and sample size are required to further clarify these issues. Clinicians should remain particularly vigilant for the development of pneumonia in COPD patients on inhaled corticosteroids. Instructions and recommendations should be given to patients, as the signs and symptoms of pneumonia may mimic COPD exacerbations.

Acknowledgments

Support Dr. Sibila is supported by Instituto de Salud Carlos III (BAE11/00102) and Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Dr. Restrepo time is partially protected by Award Number K23HL096054 from the National Heart, Lung, and Blood Institute.

The funding agencies had no role in the preparation, review, or approval of the manuscript. The views expressed in this article are those of the author and do not necessarily represent the views of the Department of Veterans Affairs, nor the University of Texas Health Science Center at San Antonio.

REFERENCES

1. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. *JAMA*. 2005; 294:1255–1259. [PubMed: 16160134]
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global burden of disease study. *Lancet*. 1997; 349:1498–1504. [PubMed: 9167458]
3. Heron M, Hoyert DL, Murphy SL, et al. Deaths: final data for 2006. *Natl Vital Stat Rep*. 2009; 57:1–134. [PubMed: 19788058]
4. 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(8):775–789. [PubMed: 17314337]
5. 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(2):144–149. [PubMed: 17053207]
6. 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(1):19–26. [PubMed: 17916806]
7. Malo de MR, Mortensen EM, Restrepo MI, et al. Inhaled corticosteroid use is associated with lower mortality for subjects with COPD and hospitalized with pneumonia. *Eur Respir J*. 2010; 36:751–757. [PubMed: 20413535]
8. 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; 184:312–316. [PubMed: 21512168]
9. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). 2011. Available from: <http://www.ginasthma.org/>

10. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2011. Available from: <http://www.goldcopd.org/>
11. Barnes PJ. Corticosteroid effects on cell signaling. *Eur Respir J*. 2006; 27:413–26. [PubMed: 16452600]
12. Crim C, Pierre LN, Daley-Yates PT. A review of the pharmacology and pharmacokinetics of inhaled adults with asthma. *Cochrane Database Syst Rev*. 2000; 2:CD001117. [PubMed: 10796600]
13. Rohatagi S, Arya V, Zech K, Nave R, Hochhaus G, Jensen BK, et al. Population pharmacokinetics and pharmacodynamics of ciclesonide. *J Clin Pharmacol*. 2003; 43:365–78. [PubMed: 12723457]
14. Sharpe M, Jarvis B. Inhaled mometasone furoate: a review of its use in adults and adolescents with persistent asthma. *Drugs*. 2001; 61:1325–50. [PubMed: 11511026]
15. 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; 361:449–456. [PubMed: 12583942]
16. 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.
17. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol*. 2001; 107:937–944. [PubMed: 11398069]
18. Masoli M, Weatherall M, Holt S, Beasley R. Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax*. 2004; 59:16–20. [PubMed: 14694240]
19. Lipworth BJ. Systemic adverse effects of inhaled corticosteroids therapy: a systematic review and meta-analysis. *Arch Intern Med*. 1999; 159:941–955. [PubMed: 10326936]
20. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, Fitzgerald M, Gibson P, Ohta K, O'Byrne PM, Pedersen S, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008; 31:143–178. [PubMed: 18166595]
21. Glaab T, Taube C. Effects of inhaled corticosteroids in stable chronic obstructive pulmonary disease. *Pulmonary Pharmacology and therapeutics*. 2011; 24:15–22. [PubMed: 20816832]
22. Shepherd J, Rogers G, Anderson R, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. *Health Technol Assess*. May; 2008 12(19):iii–iv. 1–360.
23. Brutsche MH, Brutsche IC, Munawar M, et al. Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet*. 2000; 356:556–61. [PubMed: 10950233]
24. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA*. 1997; 277:722–7. [PubMed: 9042844]
25. Weatherall M, Clay J, James K, Perrin K, Shirtcliffe P, Beasley R. Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. *Respirology*. 2009; 14:983–90. [PubMed: 19740259]
26. Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med*. 2004; 169:83–8. [PubMed: 14551165]
27. O'Byrne PM, Pedersen S, Carlsson LG, et al. Risks of pneumonia in asthmatic patients taking inhaled corticosteroids. *Am J Respir Crit Care Med*. 2011; 183:589–595. [PubMed: 20889908]
28. National Heart Lung and Blood Institute. Morbidity and mortality: 2002 chart book on cardiovascular, lung, and blood diseases. US Department of Health and Human Services, National Institutes of Health; Bethesda: 2002.
29. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance: United States, 1971–2000. *MMWR Surveill Summ*. 2002; 51:1–16.
30. Wilt TJ, Niewoehner D, Kim C, et al. Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD). *Evid Rep Technol Assess (Summ)*. 2005; 121:1–7. [PubMed: 16238364]

31. Whitford H, Orsida B, Kotsimbos T, et al. Bronchoalveolar lavage cellular profiles in lung transplantation: the effect of inhaled corticosteroids. *Ann Transplant*. 2000; 5:31–37. [PubMed: 11147027]
32. Hogg JC, Chu FS, Tan WC, et al. Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *Am J Respir Crit Care Med*. 2007; 176:454–459. [PubMed: 17556723]
33. Barnes NC, Qiu YS, Pavord ID, et al. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006; 173(3): 736–43. [PubMed: 16424444]
34. Sin DD, Man SF, Marciniuk DD, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008; 171:1207–1214. [PubMed: 18310480]
35. Gutierrez P, Closa D, Piñer R, et al. Macrophage activation in exacerbated COPD with and without community-acquired pneumonia. *Eur Respir J*. 2010; 36:285–291. [PubMed: 20032016]
36. Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J*. 2009; 34:641–7. [PubMed: 19443528]
37. Calverley PM, Stockley RA, Seemungal TA, et al. Reported Pneumonia in Patients With COPD: Findings From the INSPIRE Study. *Chest*. 2011; 139:505–512. [PubMed: 20576732]
38. 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(2):162–166. [PubMed: 17400730]
39. Mullerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: A population database analysis. *Respiratory Medicine*. 2012 doi: 10.1016/j.rmed.2012.04.008.
40. Welte T, Miravittles 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. [PubMed: 19644045]
41. Calverley PM, Boonsawat W, Cseke, et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Resp J*. 2003; 22:912–919.
42. 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; 69:549–565. [PubMed: 19368417]
43. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008; 300:2407–2416. [PubMed: 19033591]
44. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009; 169:219–229. [PubMed: 19204211]
45. Rodrigo GJ, Castro-Rodriguez JA, Plaza V. Safety and efficacy of combined long-acting beta-agonists monotherapy for stable COPD: a systematic review. *Chest*. 2009; 136:1029–1038. [PubMed: 19633090]
46. Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in COPD: A critical review and update. *Curr Opin Pulm Med*. 2010; 16(2):118–122. [PubMed: 19926996]
47. Sin DD, Tashkin D, Zhang X, Radner F, Sjobring U, Thoren A, Calverley PM, Rennard S. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet*. 2009; 374:712–719. [PubMed: 19716963]
48. Singanayagam A, Chalmers JD, Akram AR, Hill AT. Impact of inhaled corticosteroid use on outcome in COPD patients admitted with pneumonia. *Eur Respir J*. 2011; 38:36–41. [PubMed: 21429980]

Table 1

Types and therapeutic doses of current inhaled corticosteroids (modified from GINA 2011 (9)).

Drug	Low daily dose (µg)	Medium daily dose (µg)	High daily dose (µg)
Beclomethasone dipropionate	200-500	500-1000	1000-2000
Budesonide	200-400	400-800	800-1600
Ciclesonide	80-160	160-320	320-1280
Flunisolide *	500-1000	1000-2000	2000
Fluticasone propionate	100-250	250-500	500-1000
Mometasone furoate	200	400	800
Triamcinolone *	400-1000	1000-2000	2000

* These medications are not available in all countries.

Table 2

Adverse effects of inhaled corticosteroids (adapted from Glaab et al (21)).

Local adverse effects:	Oropharyngeal candidiasis
	Hoarseness and dysphonia
	Pharyngeal irritation/cough
Systemic adverse effects:	Skin-bruising
	Bone demineralization, risk of fracture
	Risk of cataracts
	Risk of glaucoma
	Adrenocortical suppression
	Hyperglycemia in diabetics
	Elevated risk of pneumonia

Table 3

Studies evaluating the effects of inhaled corticosteroids and risk of pneumonia

Study	Disease	Type of study	Risk of pneumonia
Calverley et al (4)	COPD	RCT	Increased risk
Kardos et al (5)	COPD	RCT	Increased risk
Wedzicha et al (6)	COPD	RCT	Increased risk
Welte et al (40)	COPD	RCT	No risk
Ernst et al (38)	COPD	Observational	Increased risk
Mullerova et al (39)	COPD	Observational	Increased risk
Drummond et al (43)	COPD	Meta-analyses	Increased risk
Singh et al (44)	COPD	Meta-analyses	Increased risk
Rodrigo et al (45)	COPD	Meta-analyses	Increased risk
Singh et al (46)	COPD	Meta-analyses	Increased risk
Sin et al (47)	COPD	Meta-analyses	No risk
O'Byrne et al (27)	Asthma	Meta-analyses	No risk

Table 4

Randomized controlled trials evaluating effects of inhaled corticosteroids on risk of pneumonia.

Source	Location	Drug (number of patients)	Odds Ratio (95% CI)
Calverley et al, 2007 (4)	44 centers in 42 countries	SFC (n=1546); placebo (n=1544) SFC (n=1546); S (n=1542) F (n=1555); placebo (n=1544)	1.48 (1.25-1.76) 1.47 (1.25-1.73)
Kardos et al, 2007 (5)	95 centers in German	SFC (n=507); S (n=487)	3.16 (1.37-7.29)
Wedzicha et al, 2008 (6)	179 centers in 20 countries	SFC (n=658); T (n=665)	2.11 (1.31-3.38)
Welte et al, 2009 (40)	102 centers in 9 countries	T + BF (n=331); T+placebo(n=329)	Incidence <1% in each group (p=NS)

SFC= salmeterol/fluticasone; S= salmeterol; F= fluticasone; T= tiotropium; BF= Budesonide/Formoterol.