Inhaled corticosteroids and pneumonia in chronic obstructive pulmonary disease

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Inhaled corticosteroids are widely used in chronic obstructive pulmonary disease (COPD) and, in combination with long-acting β_2 agonists, reduce exacerbations and improve lung function and quality of life. However, inhaled corticosteroids have been linked with an increased risk of pneumonia in individuals with COPD, but the magnitude of this risk, the effects of different preparations and doses, and the mechanisms of this effect remain unclear. Therefore, making informed clinical decisions—balancing the beneficial and adverse effects of inhaled corticosteroids in individuals with COPD—is difficult. Understanding of the mechanisms of increased pneumonia risk with inhaled corticosteroids is urgently needed to clarify their role in the management of COPD and to aid the development of new, safer therapies.

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Introduction

Chronic obstructive pulmonary disease (COPD) is predicted to be the third leading cause of death worldwide by 2020.[1] People with COPD have acute exacerbations that are associated with accelerated loss of lung function, impaired quality of life, and enormous health-care costs.[1] Prevention of exacerbations is a major therapeutic aim and, because inhaled corticosteroids reduce exacerbations, their use is widespread in people with COPD. However, evidence has emerged linking inhaled corticosteroids with increased risk of pneumonia in COPD. This effect seems paradoxical because both exacerbations and pneumonia are predominantly caused by respiratory infections and therefore the mechanisms of this increased risk of pneumonia are unclear, as are the clinical implications for the use of inhaled corticosteroids in COPD. Inhaled corticosteroid use is likely to increase as generic formulations and new preparations become available, particularly in low-income and middle-income countries that will have a high burden of COPD. Because COPD and age are independent risk factors for pneumonia,[2] increased use of inhaled corticosteroids in an ageing COPD population might have a substantial effect on the incidence of pneumonia. In this Review, we will critically review the evidence from clinical trials and observational studies linking inhaled corticosteroids and pneumonia in patients with COPD. Additionally, we will examine potential mechanisms from in vitro and animal studies and suggest possible strategies for clinicians to reduce pneumonia risk in COPD patients.

Inhaled corticosteroids and COPD

Inhaled corticosteroids were developed for the treatment of asthma and are extremely effective in reducing inflammation and improving symptoms and lung function.[3] Their clinical effects are partly due to their known mechanisms of action in suppressing eosinophilic and Th2-mediated inflammation.[3] Asthma and COPD are both obstructive airway diseases but differ greatly in their causes and pathophysiology. COPD is characterised by increased numbers of neutrophils, macrophages, and CD8-positive T cells,[4] and the effects of inhaled corticosteroids on airway inflammation in COPD are much less clearcut than they are in asthma. Despite this, inhaled corticosteroids were used in COPD even before there was evidence of clinical benefit, such that 54% of patients recruited to one of the first clinical trials of inhaled corticosteroids in COPD had used inhaled corticosteroids before recruitment.[5] Findings from subsequent clinical trials showed clinical benefit of inhaled corticosteroids in COPD, particularly when used in combination with long-acting β_2 agonists,[6] and nowadays up to 80% of people with COPD use inhaled corticosteroids either alone or in combination with a long-acting β_2 agonist.[7,8]

Key messages

- Inhaled corticosteroids are widely used in chronic obstructive pulmonary disease (COPD) but have been linked with an increased risk of pneumonia in both clinical trials and observational studies
- There is substantial overlap in the clinical presentation of pneumonia and COPD exacerbations, and pneumonia is often poorly defined in both observational studies and clinical trials
- The mechanisms of the increased risk in pneumonia with inhaled corticosteroid use remain undetermined, but might include impaired macrophage function, reduced bacterial adherence in the large airways, and alteration of the pulmonary microbiome
- Other factors that might account for the increased risk of pneumonia in inhaled corticosteroid users include confounding factors in observational studies and differences in dropout rates and antibiotic use between groups in clinical trials
- Strategies to reduce pneumonia risk in patients with COPD include discontinuing inhaled corticosteroids, reducing inhaled corticosteroid dose, and changing type of inhaled corticosteroid; the evidence for these approaches remains poor and might be associated with adverse effects

Studies linking pneumonia to inhaled corticosteroids

Clinical trials

The first indication of an association between inhaled corticosteroid use and pneumonia in COPD came from the TORCH study in 2007.[6] This multicentre, randomised, placebo-controlled trial was designed to compare the effect of fluticasone plus salmeterol (single inhaler) with fluticasone monotherapy, salmeterol monotherapy, or placebo on mortality in a 3-year period in patients with COPD. Findings from the study showed a non-significant reduction in mortality rates in the inhaled corticosteroid plus long-acting β_2-agonist group, together with significant reductions in exacerbations, improvements in lung function, and quality of life. An increased incidence of pneumonia reported as an adverse event was noted in both inhaled corticosteroid groups, with the probability of pneumonia being 12·9% with placebo, 13·3% with long-acting β_2-agonist monotherapy, 18·3% with inhaled corticosteroid monotherapy, and 19·6% in the inhaled corticosteroid plus long-acting β_2-agonist group ($p<0·001$ for both the comparison between the inhaled corticosteroid plus long-acting β_2-agonist combination *vs* placebo and fluticasone only group *vs* placebo). Inhaled corticosteroid treatment was associated with an increased relative risk (RR) of pneumonia of 1·52 (95% CI 1·32–1·76), but no significant increase in pneumonia mortality. Findings from a subsequent analysis[9] correcting for increased dropout rates in the placebo group supported increased pneumonia risk with inhaled corticosteroids, with rates of 84 and 88 per 1000 treatment-years in the inhaled corticosteroid and inhaled corticosteroid plus long-acting β_2-agonist groups, respectively, compared with 52 per 1000 treatment-years in the non-inhaled corticosteroid groups.

Findings from other clinical trials published after the TORCH study supported an increased risk of pneumonia with inhaled corticosteroids. The Investigating New Standards for Prophylaxis In Reduction of Exacerbations (INSPIRE) study compared fluticasone plus salmeterol with the long-acting muscarinic antagonist tiotropium, and reported that the probability of pneumonia within 2 years was 9·4% in the inhaled corticosteroids plus long-acting β_2-agonist group and 4·9% in the tiotropium group.[10] A trial of 994 patients with COPD comparing inhaled corticosteroid fluticasone plus long-acting β_2-agonist salmeterol with long-acting β_2 agonist alone during 44 weeks reported 23 pneumonia adverse events in the inhaled corticosteroid or long-acting β_2-agonist group compared with seven in the long-acting β_2-agonist group.[11] Results from two studies[12,13] of lower dose fluticasone plus salmeterol (500 µg fluticasone daily as opposed to 1000 µg daily in the aforementioned studies) showed rates of pneumonia of 7% in the fluticasone plus salmeterol groups in both studies compared with 2%[12] and 4%[13] in the long-acting β_2-agonist groups. Therefore, higher rates of pneumonia with inhaled corticosteroid use seemed to be consistent across these trials, but the incidence in the TORCH study was about double that reported in the other studies. This finding might be related to study length because TORCH had the longest duration (3 years), and pneumonia risk increases with length of exposure to inhaled corticosteroids,[9] but whether other factors, such as different patient populations, also contributed is unclear. Recognised risk factors for pneumonia in COPD (age, lower forced expiratory volume in 1 s [FEV_1], previous exacerbations) were not over-represented in the TORCH study, but two other risk factors—worse dyspnoea score and lower body-mass index (BMI)—were not reported in all studies. The mean BMI in the TORCH study (25·4 kg/m²) was lower than in the two studies of lower dose fluticasone plus salmeterol (Anzueto and colleagues,[12] mean BMI 27·6 kg/m²; Ferguson and colleagues,[13] mean BMI 27·3 kg/m²). The higher pneumonia incidence in the TORCH study is relevant because it has heavily determined the results of meta-analyses in which it has been included.[14] Findings from three COPD studies[15–17] of the inhaled corticosteroid plus long-acting β_2-agonist combination budesonide plus formoterol did not show an increased risk of pneumonia; however, investigators of one study[18] reported pneumonia in 6·4% of patients using high-dose budesonide plus formoterol compared with 2·7% in those using formoterol alone. A Cochrane review[14] with data from 43 COPD studies reported an increased risk of pneumonia hospital admissions with both fluticasone and budesonide (alone or in combination with a long-acting β_2 agonist).

Observational studies

The association between inhaled corticosteroids and pneumonia has also been examined in population-based cohort studies of COPD. Results from five studies have shown an increased risk of pneumonia with inhaled corticosteroids, with an estimated RR of between 11% and 70%,[19–23] and results from a much smaller (127 patients) case-control study reported a RR 3·26 (95% CI 1·07–9·98),[24] whereas three observational studies showed no increased risk (table 1).[29–31] Observational studies have the advantage of including large numbers of patients over long periods and being designed specifically to address the link between inhaled corticosteriods and pneumonia, but have several weaknesses that will be discussed later.

Mortality

Pneumonia is associated with a 30-day mortality of 10–12% in patients with COPD, and COPD is an independent risk factor for pneumonia mortality.[32] Therefore, an increase in pneumonia associated with inhaled corticosteroids would be expected to result in

	ICS type (dose)	Pneumonia (RR or incidence)	Pneumonia definition	Mortality in ICS users	Patient numbers	Study length	Confounding factors adjusted for	Dose effect
Randomised controlled trials								
Calverley PM[6]	FP (1000 µg) and SFC (1000 µg)	1·52 (95% CI 1·32–1·76; p<0·001)	Adverse event report	No effect	6112	3 years	..	NA
Calverly PM[10]	SFC (1000 µg)	1·94 (95% CI 1·19–3·17; p=0·008)	Adverse event report	NA	1323	2 years	..	NA
Kardos P[11]	SFC (1000 µg)	4·6% (1·43% LABA)	Adverse event report	NA	994	44 weeks	..	NA
Anzueto A[12]	SFC (500 µg)	7% (2% LABA)	Adverse event report	NA	782	1 year	..	NA
Ferguson GT[13]	SFC (500 µg)	7% (4% LABA)	Adverse event report	NA	797	1 year	..	NA
Tashkin DP[15]	FBD (320 µg and 160 µg)	No increase	Adverse event report	NA	1704	6 months	..	NA
Rennard SI[16]	FBD (320 µg and 160 µg)	No increase	Adverse event report	NA	1964	1 year	..	NA
Welte T[17]	FBD (320 µg)	No increase (<1% both groups)	Adverse event report	NA	660	12 weeks	..	NA
Sharafkhaneh A[18]	FBD (320 µg and 160 µg)	6·4% (320 µg), 4·7% (160 µg), and 2·7% (LABA)	Adverse event report	NA	1219	1 year	..	NS
Dransfield M[25]	VFF (50 µg, 100 µg, and 200 µg)	7·3% (3·4% LABA)	Adverse event report	No effect	3255	1 year	..	NS
Meta-analyses								
Drummond[26]	All	1·34 (95% CI 1·03–1·75)	Adverse event reports	No effect	10776	≥6 months	Yes	Yes
Singh S[27]	All	1·60 (95% CI 1·33–1·92; p<0·001)	Adverse event reports	No effect	16996	24–156 weeks	..	NA
Singh S[28]	All	1·57 (95% CI 1·41–1·75; p<0·0001)	Adverse event reports	No effect	23096	..	..	NA
Kew KM[14]	Fluticasone; Budesonide	1·68 (95% CI 1·49–1·90); 1·12 (0·83–1·51)	Adverse event reports	No effect; No effect	15377; 7011	22 months; 10 months	..	No
Observational studies								
Suissa S[19]	All; Fluticasone; Budesonide	1·69 (95% CI 1·63–1·75); 2·01 (95% CI 1·93–2·10); 1·17 (95% CI 1·09–1·26)	Pneumonia hospital admission, pneumonia death	Pneumonia, yes; all cause, no	163514	5·4 years	Age, sex, COPD severity, comorbidity	Yes
Ernst P[20]	All	1·70 (95% CI 1·63–1·77)	Pneumonia hospital admission	Pneumonia, yes; all cause, no	175906	5 years	COPD severity, comorbidity	Yes
Thornton Sn J[21]	All	1·11 (95% CI 1·05–1·18)	Pneumonia hospital admission	NA	83455	..	Demographics, comorbidity, COPD severity, pneumococcal vaccine	Yes
Joo MJ[22]	All	1·38 (95% CI 1·31–1·45)	Pneumonia hospital admission	Reduced	145586	..	Age, comorbidity, medication, COPD severity	No
Yawn BP[23]	All	1·51 (95% CI 1·42–1·61)	OP, ED, IP records	NA	135445	4·75 years	Age, sex, region, diagnosis year, medications, comorbidity, hospital admissions, Emergency room visits	Yes
Almirall J[24]	All	3·26 (95% CI 1·07–9·98)	Hospital admission	NA	127	1 year	COPD severity, comorbidity, vaccination, other treatments	NA
Mullerova H[29]	All	ICS use not associated with pneumonia in COPD	Physician-recorded diagnosis of pneumonia	NA	40414	10 years	..	NA
Mapel D[30]	All	1·29 (95% CI 0·96–1·73; p=0·09)	Pneumonia diagnosis in OP, ER, or IP	NA	5245		Age, sex, asthma diagnosis, comorbidity, COPD severity	NA
Festic E[31]	All	1·40 (95% CI 0·95–2·09; p=0·093)	Pneumonia hospitalisation (single centre)	NA	589	2 years	Age, sex, race, admission source, BMI, alcohol and tobacco use, comorbidity, medications	NA

ICS=inhaled corticosteroids. COPD=chronic obstructive pulmonary disorder. RR=relative risk. FP=fluticasone propionate. SFC=salmeterol plus fluticasone. LABA=long-acting β agonist. FBD=formoterol plus budesonide. VFF=vilanterol plus fluticasone furoate. NA=not applicable. NS=not specified. OP =outpatients. ER=emergency room. IP=inpatients. BMI=body-mass index.

Table 1: **Summary of studies examining the risk of pneumonia with use of ICS in COPD**

increased mortality. Paradoxically, inhaled corticosteroid use is associated with reduced mortality in COPD, and no increases in pneumonia-related deaths or hospital admissions were reported in clinical trials.[9,10] Observational studies also mainly support a protective effect of inhaled corticosteroids, with results from three studies[22,33,34] showing a significant reduction in pneumonia mortality with inhaled corticosteroid use, one study[20] reporting

increased mortality (RR 1·53, 95% CI 1·30–1·80) at 30 days (but no effect on in-hospital mortality or overall mortality) and two studies[35,36] reporting no effect on mortality. Results from meta-analyses[14,27,37] have also shown no significant increase in pneumonia-related mortality in inhaled corticosteroid users. Results from a study[25] of a new inhaled corticosteroid plus long-acting β_2-agonist combination (fluticasone furoate plus vilanterol) showed increased pneumonia deaths in the inhaled corticosteroid plus long-acting β_2-agonist groups compared with long-acting β_2-agonist monotherapy (eight *vs* one). However, in the two studies done (one which covered 167 sites in 15 countries and the other which covered 183 sites in 15 countries), the numbers were small, and six of the deaths occurred in only two centres in the Philippines and Peru, so might be accounted for by local factors. Therefore, despite inhaled corticosteroid use being associated with an increased risk of pneumonia in COPD, it does not seem to result in increased mortality.

Limitations of studies linking inhaled corticosteroids with pneumonia

Despite many studies linking inhaled corticosteroid use to pneumonia, several unexplained and paradoxical findings such as the opposite effects of inhaled corticosteroids on pneumonia and exacerbations and the reduction in mortality with inhaled corticosteroid use remain. We will explore some of the limitations of the available evidence and how these might account for the reported association between inhaled corticosteroids and pneumonia.

Limitations of observational studies

Study design

Observational studies have the advantages over clinical trials of including large numbers of real life patients, including patients with comorbidities that are often excluded from drug trials. These patients are at a higher risk of pneumonia, and therefore if inhaled corticosteroid use is associated with pneumonia, this association might be underestimated in clinical trials. However, the absence of randomisation in observational studies leads to the possibility of confounding by indication.

Diagnosis of pneumonia

Pneumonia is diagnosed on clinical grounds and on physical signs, or by the presence of consolidation on a chest radiograph, but can be difficult to diagnose even in patients without underlying pulmonary disease. The clinical features of pneumonia show substantial overlap with COPD exacerbations, and therefore accurate diagnosis might be even more problematic in patients with COPD. The association between COPD exacerbations and pneumonia is complex because some studies[38–40] include pneumonia as a cause of exacerbations, reporting it in 10–33% of COPD exacerbations, whereas other researchers view them as separate clinical and pathological entities.[41]

The methods used to define pneumonia in observational studies include primary care records, outpatient visits, emergency department attendances, hospital admissions, and deaths. Diagnosis of pneumonia on clinical grounds alone has poor sensitivity and specificity.[42,43] Patients admitted to hospital are usually diagnosed on the basis of infiltrates or consolidation on chest radiography, and these indicators are often construed to be the gold standard for the diagnosis of pneumonia. Most observational studies base pneumonia diagnosis on hospital coding[21,22,35,44] but this is often inaccurate,[45] as is interpretation of chest radiographs.[46] In an observational study[31] in which radiographic confirmation of pneumonia was required, inhaled corticosteroid use was not associated with increased risk, although this study was small and might have been underpowered. Therefore, the accuracy of pneumonia diagnosis in observational studies remains a concern.

Confounding factors

Observational studies are affected by the possibility of confounding by indication—ie, people with COPD using inhaled corticosteroids have more severe COPD and therefore are at a higher risk of pneumonia independent of inhaled corticosteroid use. Studies have confirmed that people with COPD using inhaled corticosteroids had more admissions to hospital; greater use of respiratory medications, oral corticosteroids, and antibiotics; and more comorbidities compared with those with COPD not using these drugs.[19,21,23,29] Confounding factors are adjusted for in studies, but not all potentially important factors such as smoking, immunisation history, functional status, and comorbidities were taken into account in all studies. Additionally, other hidden confounders might be relevant to pneumonia risk but are not adjusted for. In most studies, COPD severity was not defined by lung function, but on the basis of surrogate markers, including use of other inhaled medications, exacerbation treatments, and hospital admissions.[19,22,23] These definitions have not been validated against standard measures of COPD severity such as FEV_1 or the BODE index, and therefore their accuracy in establishing COPD severity is not known. The inclusion of patients with asthma might also affect the results, because most studies did not support diagnosis of COPD with spirometry but relied on a physician's diagnosis[19,44] or on the prescription of respiratory medications in patients with no diagnosis of asthma.[19–22] Comorbidities such as diabetes, cardiovascular disease, cerebrovascular disease, and neurological disease are associated with an increased risk of pneumonia[21,23,24,47] and are common in patients with COPD.[48] In observational studies, comorbidities were measured by use of relevant treatments, and in some studies, there was an excess of non-respiratory medication use in patients with COPD

using inhaled corticosteroids, suggesting that even with matching there was a higher prevalence of comorbidities and higher pneumonia risk in inhaled corticosteroid users than in those who did not use inhaled corticosteroids.[19,20]

Limitations of randomised clinical trials

Misdiagnosis of pneumonia

Randomised clinical trials are not affected by confounding, but many factors could still influence the reported association between inhaled corticosteroid use and pneumonia. In clinical trials,[6,10] the incidence of pneumonia was derived from adverse event reports, not all of which were confirmed with chest radiography. In the TORCH study, pneumonia was reported in 15·9%, chest radiography was done in 72% of reported pneumonia cases, and parenchymal infiltrates were present in 81% (58% of all reported pneumonias);[6] in the INSPIRE study, pneumonia was reported in 5·6%, 57·5% of pneumonias were confirmed on chest radiography;[10] and in the fluticasone plus vilanterol trial,[25] a chest radiograph was available for 85·9% of pneumonia adverse events and consolidation was present in 64% (55% of reported pneumonias). Therefore, even in clinical trials only about half of reported pneumonias were confirmed by radiography. In the study by Ferguson and colleagues,[13] the protocol stated that pneumonia was confirmed with radiography, but no details were provided as to what percentage had definitive evidence of pneumonia. Further evidence of diagnostic inaccuracy emerged from INSPIRE[10] in which 18% of reported pneumonia adverse events were not treated with antibiotics and 39% were treated with antibiotics and oral corticosteroids, a treatment regime used for COPD exacerbations. These data cast further doubts on the validity of the diagnosis in more than 50% of patients labelled as having pneumonia.[10]

Both the TORCH study and the INSPIRE study were multicentre trials done in 44 and 20 countries, respectively, and diagnostic criteria for pneumonia are likely to differ between countries. Although misdiagnosis of pneumonia is unlikely to occur to a great extent in patients using inhaled corticosteroids, it might lead to an overestimation of the true risk of pneumonia with inhaled corticosteroid use. In the fluticasone plus vilanterol trials, reported pneumonia rates were 3·4% in patients receiving long-acting β_2 agonists alone and 7·3% in patients receiving inhaled corticosteroid plus long-acting β_2 agonist.[25] However, using radiographically confirmed pneumonia only, the rates were substantially lower: 1·8% in patients receiving long-acting β_2 agonist alone and 4·0% in patients receiving inhaled corticosteroid plus long-acting β_2 agonist.

Therefore, use of radiologically diagnosed pneumonias only confirms an association with inhaled corticosteroid use, but the magnitude of that risk might not be as high as suggested by use of a clinical diagnosis of pneumonia. Diagnostic inaccuracy might also account for the paradox of inhaled corticosteroid use not being associated with increased mortality despite increased incidence of pneumonia. Two possible explanations that have been suggested for this are that inhaled corticosteroids reduce other causes of mortality outweighing an increase in pneumonia mortality, or inhaled corticosteroids reduce systemic inflammation and thereby reduce pneumonia severity and mortality. No effect of inhaled corticosteroids on markers of systemic inflammation in COPD has been identified,[27] and the effects of systemic corticosteroids on mortality in pneumonia are unclear.[49,50] However inhaled corticosteroid use was associated with a lower incidence of parapneumonic effusions, suggesting that inhaled corticosteroids can affect the clinical course of pneumonia.[51] An alternative hypothesis for no increase in mortality associated with inhaled corticosteroid use in COPD is that a significant proportion of events labelled as pneumonia are actually miscellaneous lower respiratory infectious syndromes, such as mild COPD exacerbations with a low mortality.

Effects of inhaled corticosteroids on antibiotic use

Inhaled corticosteroids reduce exacerbations, which will result in reduced use of antibiotics in inhaled corticosteroid-treated patients. Antibiotics have an effect beyond the index exacerbation because they also increase the time to the next exacerbation.[52] Singanayagam and colleagues[53] proposed that inhaled corticosteroids reduce use of antibiotics because of a reduction in exacerbations, and this reduction in antibiotic use might affect the bacterial flora in a manner that leads to increased risk of pneumonia, thus accounting for the opposite effects of inhaled corticosteroids on exacerbations and pneumonia. In support of this hypothesis is a study reporting that inhaled corticosteroid use is associated with higher sputum bacterial loads in patients with COPD.[54]

Differential dropout rates

Clinical trials in COPD are characterised by high dropout rates that vary between the different study groups. In the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study,[5] 53% of patients in the placebo group withdrew compared with 43% in the treatment group, and in the TORCH study,[55] 44·2% of patients in the placebo group and 34·1% in the fluticasone plus salmeterol group withdrew. The differential withdrawal between the two TORCH treatment groups occurred mainly in the first 48 weeks of the study, with 25% withdrawing from the placebo arm and 15% from the fluticasone plus salmeterol group. This effect is more pronounced in patients with severe COPD with withdrawal rates of 59% (placebo) and 42% (inhaled corticosteroid plus long-acting β_2 agonist) in patients with a FEV_1 of less than 30% in the TORCH study,[56] and 57% and 38% in the ISOLDE study in patients with a FEV_1 of less than 50%.[5] In two studies[57,58] of budesonide plus formoterol, withdrawal rates were 44% and 41% in

the placebo group and 28% and 29% in the inhaled corticosteroid plus long-acting β_2 agonist. Therefore, lower dropout rates in inhaled corticosteroid-treated patients are likely to result in retention of patients at higher risk of pneumonia. Moreover, in the ISOLDE study, patients in the placebo group who withdrew had a lower initial FEV_1 than those who completed follow-up, but this effect was not seen in fluticasone-treated patients, suggesting that the patients retained in the placebo group were healthier and at lower risk of pneumonia.[59]

Mechanisms of increased pneumonia risk with inhaled corticosteroid use in COPD

Host immunity in COPD exacerbations

Corticosteroids have immunosuppressive effects and increased susceptibility to infections is recognised as an adverse effect of long-term use of oral corticosteroids. The aetiology of COPD exacerbations and pneumonia are remarkably similar, with bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* and viruses such as rhinoviruses commonly detected in both conditions.[60,61] Therefore, the completely opposite effect of inhaled corticosteroids on two syndromes with similar aetiology seems paradoxical. The key difference between pneumonia and COPD exacerbations is the anatomical site, with exacerbations caused by infection mainly within the larger airways,[62] whereas pneumonia includes the lung parenchyma and small airways.[63] The distribution of immune cells differs within the lung and between these airway compartments. Induced sputum shows the cellular composition of the large airways and 60–80% of inflammatory cells in sputum in people with COPD are neutrophils, whereas only 15–25% are macrophages.[64] Conversely, bronchoalveolar lavage samples derive from smaller airways and the alveolar spaces, and greater than 90% of cells are macrophages and only 2% are neutrophils.[65] Therefore, if inhaled corticosteroids have different effects on neutrophils and macrophages, their effects on host immunity could vary in different airway compartments and this might result in diverse effects on exacerbations and pneumonia.

Effect of inhaled corticosteroids on macrophage and neutrophil function

Neutrophils and macrophages are essential for effective immune responses as they possess multiple effector mechanisms for the killing and removal of pathogens. Despite increased numbers of macrophages and neutrophils in the airways in COPD, respiratory infections are common, suggesting that cellular immune function is impaired. Macrophage activation is triggered by recognition of pathogens by pathogen recognition receptors, such as the toll-like receptors (TLR), resulting in production of microbicidal enzymes and cytokines and chemokines that attract neutrophils and promote phagocytosis of pathogens. Macrophage phagocytosis of bacteria, such as *H influenzae* and *S pneumoniae* is defective in patients with COPD,[66,67] but the effects of COPD on cytokine production are less clear.[68,69] Impaired production of interleukin 8 and tumour necrosis factor (TNF) α by macrophages in response to bacterial infection might be related to exacerbation frequency in COPD.[70]

Corticosteroids seem to have no effect on macrophage phagocytosis,[66,71] but do inhibit production of pro-inflammatory cytokines in response to both bacterial and viral stimuli in animal models, monocyte-derived macrophages, and alveolar macrophages.[71–76] The results of studies with different inhaled corticosteroids have been somewhat contradictory. Fluticasone was more potent than budesonide in suppressing cytokine production in macrophages in vitro,[75] but in a rat model, budesonide reduced monocyte numbers and TNF α in response to lipopolysaccharide challenge, whereas fluticasone did not.[76] Conversely, other studies have reported that fluticasone enhanced gene expression of innate immune responses in macrophages,[77] and budesonide increased expression of chemokines and cytokines in a mouse model of COPD.[77]

Few studies have investigated the effects of corticosteroids on macrophage function specifically in patients with COPD. Dexamethasone inhibited lipopolysaccharide-induced cytokines in COPD macrophages in most[68,69,73] but not all studies.[78] Budesonide and beclometasone suppressed lipopolysaccharide-induced production of cytokines in macrophages from people with COPD;[79,80] however, the response was variable with some patients showing no, or poor, responses.[79] Haque and colleagues[81] showed that high-dose fluticasone increased nuclear translocation of the glucocorticoid receptor in macrophages from people with COPD; this effect was enhanced by the addition of a long-acting β_2 agonist, and low-dose fluticasone increased translocation only in combination with a long-acting β_2 agonist. No data was provided regarding the effects on cytokine production. In one study, a macrophage phenotype in people with COPD has been described[82] that did not express any of the established macrophage phenotypic markers, and budesonide did not suppress lipopolysaccharide-induced production of pro-inflammatory cytokines in this subset.

Therefore, the effects of inhaled corticosteroids on macrophage function are complex and are affected by factors such as the sources of cells, animal versus human models, different corticosteroids, and different macrophage stimuli. From the studies so far, no consistent results have emerged implicating effects of inhaled corticosteroids on macrophage function as a mechanism underlying increased risk of pneumonia, and further work is needed.

Neutrophils are recruited to sites of infection where they kill microorganisms by the generation of reactive oxygen species and proteases such as neutrophil elastase. Studies[83,84] have reported both reduced and preserved neutrophil phagocytosis of *Escherichia coli* in COPD.

Corticosteroids seem to have no effect on many important neutrophil antimicrobial functions, including phagocytosis and oxidative burst,[84,85] production of proteases,[85] neutrophil adhesion,[86] and formation of neutrophil extracellular traps.[87] This finding might be because of the fact that the glucocorticoid receptor is expressed at very low levels in airway neutrophils compared with macrophages and lymphocytes.[88] Moreover, inhaled corticosteroids prolong neutrophil survival and this effect is enhanced by concomitant treatment with long-acting β_2 agonists.[89,90] Therefore, although there is some evidence for an effect of corticosteroids on macrophage function, neutrophil function does not seem to be compromised by inhaled corticosteroids.

Inhaled corticosteroids and models of respiratory infection

The available data regarding the effects of inhaled corticosteroids on respiratory infections in vivo are somewhat contradictory, with both beneficial and harmful effects reported. Fluticasone impaired clearance of *Klebsiella pneumoniae* in mice, resulting in increased mortality,[71] and in a mouse model of allergic airway disease, budesonide impaired host defence to *Pseudomonas aeruginosa*.[91] However, in other animal models and in cell lines, fluticasone reduced cellular adherence of *S pneumoniae*, *H influenzae*, and *P aeruginosa*.[92,93] Conversely in children with asthma, inhaled corticosteroid use was associated with increased pharyngeal carriage of *S pneumoniae*.[94] Reduced bacterial adhesion has been upheld as a beneficial effect and one mechanism whereby inhaled corticosteroids reduce exacerbations;[93] however, it could also be postulated that this promotes deeper transmission of microorganisms and conversion of an airway based infection to pneumonia. In a cell-free culture, inhaled corticosteroids inhibited the growth of *Staphylococcus aureus* biofilms, suggesting that inhaled corticosteroids might have direct antibacterial effects independent of effects on host immune responses.[95]

Although the role of respiratory infection in COPD is well documented, there is a paucity of data regarding the effects of inhaled corticosteroids on infection in COPD. Chronic bacterial infection is common in COPD and contributes to worse clinical outcomes.[96] Two studies[96,97] using sputum cultures found no association between inhaled corticosteroid use and bacterial infection, but in a study[54] using quantitative PCR, higher doses of inhaled corticosteroids were associated with greater bacterial loads.

New molecular techniques have identified a wide range of bacteria that cannot be identified with standard culture and these are likely to revolutionise our understanding of the role of micro-organisms in the pathogenesis of diseases such as COPD. Results from studies have shown that the lower respiratory tract is colonised by a microbiome even in healthy individuals. One study[98] reported that COPD is not associated with an alteration of the respiratory microbiome, whereas others[99,100] have reported changes in relative abundance of specific microbial phyla and in microbial diversity, and inhaled corticosteroid use alters the microbiome in patients with COPD.[101] These findings might be relevant to the effects of inhaled corticosteroid on exacerbations and pneumonia, and future studies are likely to yield further insights into the effects of inhaled corticosteroids on the respiratory microbiome.[102]

In the INSPIRE study, most cases of pneumonia in people with COPD using inhaled corticosteroids occurred after episodes of increased respiratory symptoms, and these have been interpreted as representing unresolved exacerbations.[10] Most of these episodes were treated with antibiotics but still progressed to pneumonia and, therefore, an alternative hypothesis is that they were in fact viral infections. In support of this hypothesis was the observation that pneumonia in inhaled corticosteroid users was associated with cold symptoms,[10] but in a retrospective analysis, their cause is impossible to measure. Bacterial pneumonia can occur after an initial virus infection,[103] and our group has reported that after experimental rhinovirus infections, bacterial infections occurred in 60% of patients with COPD;[104] moreover, rhinovirus infection induced changes in the microbiome favouring the growth of *H influenzae*.[105] *H influenzae* is one of the common causative agents of pneumonia and, therefore, these data suggest that virus infection can lead to secondary bacterial infections and potentially pneumonia. The patients with COPD in this study[104] were inhaled corticosteroid-naive and, therefore, the effects of inhaled corticosteroids on virus infection and secondary bacterial infection in patients with COPD are unknown. Virus infections can impair host immunity to bacterial infection through multiple mechanisms[104,106] and in an animal model, mice infected with influenza and treated with dexamethasone had higher bacterial loads after subsequent infection with *Listeria monocytogenes*.[107] Whether similar mechanisms occur in human beings or with other viruses and bacterial species is not known. Because both bacterial and virus infections are common in COPD, studies of the effects of inhaled corticosteroids on virus—bacteria interactions in human beings are urgently needed.

Therefore, studies so far have not provided a convincing mechanistic explanation for increased pneumonia and reduced exacerbations with inhaled corticosteroid use. Macrophage phagocytosis is defective in COPD and inhaled corticosteroids might further inhibit macrophage immune responses to infection. The combination of impaired macrophage function and an altered respiratory microbiome might provide conditions in the lung that favour the development of pneumonia. If an additional insult occurs, such as a respiratory virus infection, this insult might further alter the immune, inflammatory, or microbiological milieu resulting in pneumonia (figure). However, these hypotheses remain speculative and in-vivo studies in patients with COPD are needed to investigate them further.

Use of inhaled corticosteroids in clinical practice

Guidance for clinicians

Both pneumonia and exacerbations are common in patients with COPD and have significant morbidity and mortality. The paradoxical effects of inhaled corticosteroids on exacerbations and pneumonia present clinicians with dilemmas regarding their use, but current guidelines have not kept pace with the rapid developments in this field in recent years and offer no practical guidance. We will describe potential therapeutic options available to clinicians and examine the evidence that can help to guide treatment decisions (table 2).

Continue inhaled corticosteroids

COPD is an independent risk factor for pneumonia, and, in the TORCH study, 9% of patients in the placebo group had pneumonia recorded as an adverse event.[6] Therefore, it is not possible to definitively establish a causative association between inhaled corticosteroid use and pneumonia in individual patients with COPD. The identification of specific risk factors for pneumonia could provide a more accurate risk–benefit assessment of inhaled corticosteroids in individuals with COPD. The risk factors for pneumonia in COPD (independent of inhaled corticosteroid use) include older age (more than 65 years), lower % predicted FEV_1 (especially less than 30% predicted), previous COPD exacerbations, worse Medical Research Council dyspnoea score, and lower BMI. The only independent risk factor for pneumonia identified in the TORCH study in patients using inhaled corticosteroid was a low BMI.[9] In the INSPIRE study, high C-reactive protein and increased dyspnoea were associated with pneumonia but lung function, age, and BMI were not.[10] Unfortunately, many of these factors also identify patients at high risk of exacerbations and, therefore, who stand to obtain most benefit from inhaled corticosteroid. In the study of fluticasone plus vilanterol, the total number of exacerbations plus the number of pneumonias in the 100 mcg fluticasone combination group (554 and 58, respectively, total 612; n in the combination group=806) was less than the number of similar events in the long-acting β_2-agonist-only group (741 and 28, respectively, total 769; n=818).[25] Therefore the reduction in exacerbations is greater than the increase in pneumonias and the overall effect of inhaled corticosteroids is generally thought to be protective, although this continues to be debated.[117] Identifying markers of clinical responses to inhaled corticosteroids, such as sputum eosinophils might allow targeting of inhaled corticosteroids to patients with COPD who will derive clinical benefit, and thereby reduce the overall incidence of adverse effects such as pneumonia.

Discontinue inhaled corticosteroids

The occurrence of pneumonia in a patient with COPD might prompt clinicians (or patients) to consider discontinuation of inhaled corticosteroids. Suissa and colleagues reported that discontinuation of inhaled corticosteroids is associated with a reduced risk of pneumonia that returns to baseline levels after 6 months,[19] although other studies reported an increased risk even with past use (albeit lower than current use).[20,22] However,

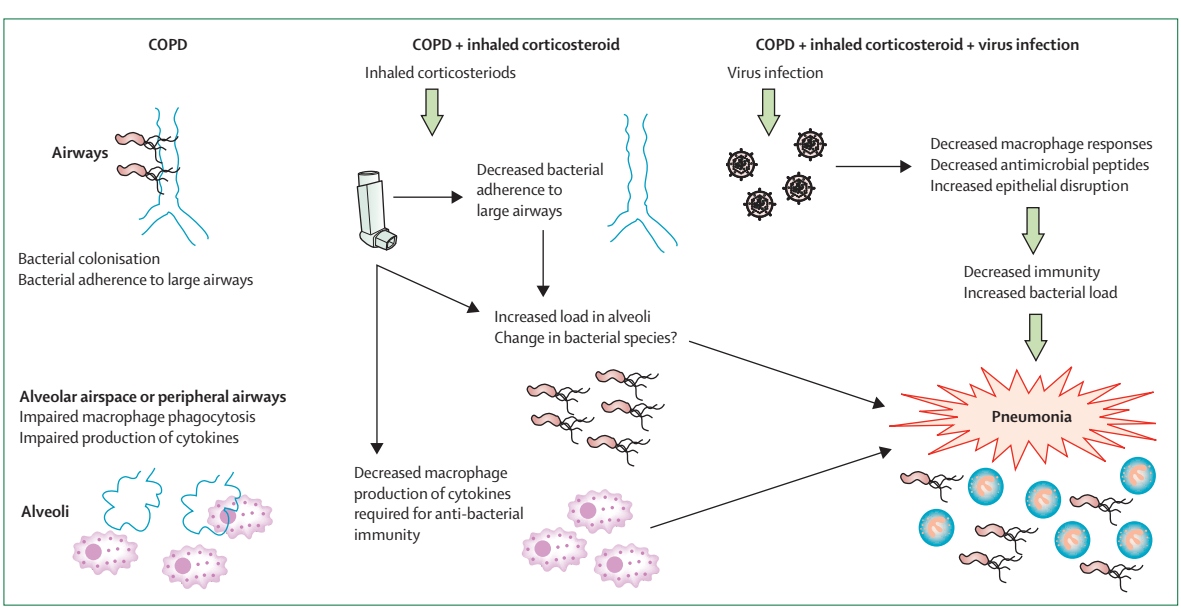

Figure: **Possible mechanisms of increased pneumonia risk with inhaled corticosteroids in COPD**
COPD is associated with increased bacterial colonisation in the large airways and impaired macrophage phagocytosis and production of cytokines. Inhaled corticosteroids reduce bacterial adherence and, therefore, might favour displacement of bacteria to the distal airways and might also increase bacterial loads and change the respiratory microbiome. Inhaled corticosteroids might also further impair macrophage function. An additional trigger such as a virus infection might produce further acute impairment of host immune functions, resulting in increased bacterial growth and the clinical syndrome of pneumonia.

	Advantages	Disadvantages
Continue ICS	Reduce exacerbations, improve lung function, and health status[5,6,11,12,13,15-18]	Increased pneumonia risk[6,10,12,13,14,18-24]
Discontinue ICS	Reduced risk of pneumonia[19,20,22]	Adverse effects reported with ICS withdrawal[108-113]
Change fluticasone to budesonide	Pneumonia risk might be less with budesonide[15-17,19,46,57,58,114,115]	Pneumonia risk might not be less with budesonide[14,18,28]
Reduce dose of ICS	Pneumonia risk might be reduced[19-21,23,25,26]	No evidence of dose effect in some studies[12,13,30,46,116] Reduced mortality only reported with higher doses[6]

ICS=inhaled corticosteroids. COPD=chronic obstructive pulmonary disease.

Table 2: **Summary of advantages and disadvantages of different therapeutic strategies regarding use of ICS in COPD**

withdrawal of inhaled corticosteroids is associated with an increased frequency of adverse effects. This was first reported in the ISOLDE study[108] in which 38% of patients in whom inhaled corticosteroids were withdrawn before study entry had an exacerbation, compared with 6% of those not on inhaled corticosteroid treatment.This increase in exacerbations with inhaled corticosteroid withdrawal was subsequently supported by other studies[109–111] in addition to other adverse effects, including deterioration in lung function,[109,111–113] increased symptoms,[109,111,113] and impaired quality of life.[110,113] Two studies[109,118] examined the effects of maintaining of patients on a long-acting β_2 agonist after inhaled corticosteroid withdrawal. In a randomised study[109] in patients with mean FEV_1 of less than 50% of predicted, inhaled corticosteroid withdrawal under cover of a long-acting β_2 agonist was associated with deterioration in lung function and dyspnoea, increased mild exacerbations, but no increase in moderate to severe exacerbations. The second study was not randomised and only included patients with FEV_1 more than 50% of predicted and reported no adverse effects of inhaled corticosteroids withdrawal under cover of a long-acting β_2 agonist.[118] A study[119] investigated the inhaled corticosteroid withdrawal in COPD patients receiving dual bronchodilator therapy (long-acting β_2 agonist and long-acting muscarinic antagonist). Corticosteroid withdrawal was not associated with an increased risk of exacerbations but did result in greater falls in lung function. Therefore, this study offers reassurance that withdrawal of inhaled corticosteroids is safe if patients are maintained on maximum bronchodilator therapy. Therefore, discontinuation of inhaled corticosteroids in patients with COPD will reduce pneumonia risk, but must be balanced against an increase in other adverse effects.

Change to a different inhaled corticosteroid

The initial reports of increased risk of pneumonia with inhaled corticosteroids were from studies using the inhaled corticosteroid plus long-acting β_2-agonist combination fluticasone plus salmeterol, whereas studies of the inhaled corticosteroid plus long-acting β_2-agonist combination budesonide or formoterol did not report this,[15–17,57,58] and a meta-analysis of studies of budesonide in COPD agreed with this finding.[114] However, many methodological issues regarding this analysis have been raised,[28] mainly that patient data were only collected up to 1 year. The TORCH study was of 3 years duration and the incidence of pneumonia increased with duration of treatment, so studies with shorter follow-up might fail to detect an increase in pneumonia.[9] Additionally, the meta-analysis[114] included a trial[120] that did not meet the pre-specified eligibility criteria of a ten-pack-year smoking history and the rate of pneumonia was actually lower with budesonide than with placebo. A subsequent study[18] not included in this meta-analysis did report an increased risk of pneumonia associated with use of budesonide plus formoterol. The Cochrane review[14] that did an indirect analysis of fluticasone and budesonide identified no difference in pneumonia hospital admissions but a higher risk of any pneumonia event with fluticasone (OR 1·86, 95% CI 1·04–3·34). A comparison of pneumonia rates in people with COPD in Sweden using budesonide plus formoterol and fluticasone plus salmeterol reported higher rates of pneumonia and pneumonia mortality in the fluticasone plus salmeterol group,[44] and an analysis of new users of inhaled corticosteroids identified an increased incidence of serious pneumonia with fluticasone (RR 2·01, 95% CI 1·93–2·10) compared with budesonide (1·17, 1·09–1·26) during a mean of 5·4 years.[19] Halpin and colleagues[115] used data from trials of the two inhaled corticosteroids plus long-acting β_2-agonist preparations to perform an indirect comparison between them and reported that pneumonia-related adverse events were significantly lower in the budesonide plus formoterol group. However, this study had several limitations, particularly that most of the effect of fluticasone plus salmeterol was due to the contribution of the TORCH study to the analysis. A potential confounder in all these studies could be the preferential use of budesonide in patients with asthma or mild COPD who are at lower risk of pneumonia,[46] and greater use of fluticasone in patients with more severe COPD.[19]

There are differences between fluticasone and budesonide in their pharmacokinetic and pharmacodynamic properties that might account for differences in pneumonia risk between the two. Fluticasone is more lipophilic, has greater receptor affinity, and remains in the mucosa and epithelial lining fluid of the lung longer than budesonide, so it might have a greater and more prolonged

local immunosuppressive effect.[121] In vitro, fluticasone also has a greater suppressant effect on cytokine production by alveolar macrophages.[75] However, in an animal model the anti-inflammatory activity of budesonide was more prolonged compared with fluticasone because of retention of budesonide secondary to reversible fatty acid esterification within airway tissue.[76] These esters are gradually hydrolysed, leading to release of budesonide over a prolonged period.

Therefore, to establish conclusively that pneumonia risk is greater with fluticasone compared with budesonide is difficult from the available studies and only likely to be resolved with a prospective head-to-head trial directly comparing the two drugs. However, if clinicians are concerned about the risk of pneumonia in individual patients using fluticasone, changing to budesonide could be considered.

Dose reduction of inhaled corticosteroids

In the TORCH study and the INSPIRE study, the dose of fluticasone used was 1000 µg daily and this is the licensed dose of fluticasone (in combination with salmeterol) for COPD in Europe, whereas the 500 µg dose is licensed in the USA. Two studies of fluticasone 500 µg daily in combination with salmeterol confirmed an increased risk of pneumonia compared with salmeterol alone (7% *vs* 2%[12] and 7% *vs* 4%[13]). A small non-randomised trial[116] of inhaled corticosteroids reported no increased risk of pneumonia with higher doses, but the total number of events was small. A dose response has been reported in several observational studies,[19–21] and a meta-analysis.[26] Compared with non-users, Yawn and colleagues reported a 38% (RR 1·38, 95% CI 1·27–1·49 increased risk of pneumonia in low-dose inhaled corticosteroid users, a 69% (1·69, 1·52–1·88) increase in medium dose inhaled corticosteroid users, and a 157% (2·57, 1·98–3·33) increased risk in patients using the highest dose of inhaled corticosteroids.[23] Conversely, two observational studies[30,46] reported no association between inhaled corticosteroid dose and pneumonia risk. The Cochrane review[14] found no dose effect for fluticasone but did find such an effect for budesonide. Pneumonia was reported more frequently with the higher dose of fluticasone plus vilanterol and, therefore, only the lower dose is licensed for use in COPD, whereas the high dose is also licensed in asthma.[122]

In the face of conflicting results and inadequate evidence, what practical steps can clinicians take to minimise the risk of pneumonia, while not depriving their patients of the beneficial effects of inhaled corticosteroids? Firstly, inhaled corticosteroid use should be restricted to people with COPD most likely to benefit from their use. Treatment guidelines currently recommend that they are used in patients with a FEV_1 of less than 50% of predicted and at least two exacerbations in the previous year.[1] However, up to 70% of people with COPD who do not meet these criteria are taking inhaled corticosteroids.[7,8] In patients with a FEV_1 of more than 50% of predicted other treatment options such as use of dual bronchodilatation with long-acting β_2 agonist plus long-acting muscarinic antagonist should be explored before commencing of inhaled corticosteroid treatment. Despite the conflicting evidence regarding the effects of inhaled corticosteroid dose, to maintain patients on as low a dose of inhaled corticosteroid as possible seems prudent. Other factors that increase pneumonia risk are often present in people with COPD and if amenable to intervention should be corrected. These include smoking,[47] malnutrition,[123] immunodeficiency,[124] poor uptake of vaccination,[125] other medications,[126] vitamin D deficiency,[127] and aspiration.[128]

Conclusions and future research

An increased risk of pneumonia with inhaled corticosteroid use in COPD was first described in 2007 and has been subsequently reported in both randomised trials and observational studies. Despite the number of studies reporting this association, many unresolved issues remain regarding the association between inhaled corticosteroid use and pneumonia in COPD. These include the strength of the association, whether the risk varies with different inhaled corticosteroids and different doses, the effect on mortality, and the underlying mechanisms. Although we have suggested potential mechanisms whereby inhaled corticosteroid might increase pneumonia risk, these are speculative and remain to be confirmed. In the absence of a plausible biological mechanism to account for the differential effects of inhaled corticosteroid on COPD exacerbations and pneumonia, factors such as differential dropout rates and reduced antibiotic use in inhaled corticosteroid users in clinical trials, and preferential use of inhaled corticosteroids in patients at higher risk of pneumonia in observational studies, could possibly account for the higher pneumonia rates in people with COPD using inhaled corticosteroids. The studies needed to overcome these methodological issues and resolve the unanswered questions will need to be long-term, prospective, use predefined diagnostic criteria for pneumonia that include radiography, and include head-to-head comparisons between different inhaled corticosteroids. Such studies are expensive and time-consuming, and it is unlikely they will ever be undertaken. Studies analysing the effects of inhaled corticosteroids on host immunity and infection in COPD are a potentially more feasible route to establish whether there are true biological mechanisms that could account for the increased risk of pneumonia. In-vitro studies have had conflicting results and are unlikely to show the complexity of the effects of inhaled corticosteroids in patients with COPD so in-vivo studies are needed. Pneumonia in inhaled corticosteroid users might be related to virus infections, but because these precede the pneumonia, investigation of this association would need to follow up large cohorts of patients discordant for inhaled corticosteroid use over a long period to capture all episodes of respiratory infection.

Search strategy and selection criteria

We searched PubMed and Web of Science for studies published between Jan 1, 2000, and March 25, 2014, using the terms ([COPD] or [chronic obstructive pulmonary disease]) and ([inhaled corticosteroids or [corticosteroids]) and [pneumonia] to identify relevant studies. Studies we know to be relevant but that might not have been identified by this search strategy were also screened. We screened the list of articles manually by reading the abstracts and excluded congress abstracts and articles not related to the topic. We read in full all clinical and in-vitro or ex-vivo studies published in English with original data that reported data relevant to the role of corticosteroids in pneumonia in COPD.

With use of experimental rhinovirus infection, we have shown that virus infection alters the microbiome and impairs host immunity in patients with COPD. Therefore, this finding offers a potential model to study the effects of inhaled corticosteroids on the interactions between virus infection, host immunity, and the microbiome in small numbers of patients over a short period. By comparison of the effects of virus infection between patients using inhaled corticosteroids and inhaled corticosteroid-naive patients, experimental rhinovirus infection has the potential to identify mechanisms of increased pneumonia risk with inhaled corticosteroids. Understanding of these mechanisms is crucial to enable identification of patients at high risk of pneumonia, develop strategies for reduction of pneumonia risk, and design new, safer anti-inflammatory therapies in COPD.

Contributors

PM and LF conceived and designed the Review and contributed equally in searching the literature, collecting, analysing, and interpreting the data, and writing the manuscript. MB, AS, SLE, and SLJ contributed to the literature search, writing and editing the manuscript, and editing the figure.

Declaration of interests

SLJ has received grant funding and personal fees from Centocor, Sanofi Pasteur, GlaxoSmithKline, Chiesi, Boehringer Ingelheim, Novartis, Grunenthal, and Synairgen. AS has received speakers' honoraria from GlaxoSmithKline. PM has received travel grants and speakers' honoraria for speaking from GlaxoSmithKline and Novartis. LF, MB, and SLE declare no competing interests.

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