

Inhaled corticosteroid dose is associated with *Pseudomonas aeruginosa* infection in severe COPD

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ABSTRACT

Introduction Patients with chronic obstructive pulmonary disease (COPD) with frequent exacerbations (ExCOPD) are commonly treated with inhaled corticosteroids (ICS) and are at risk of infections caused by potential pathogenic bacteria (PPB) including *Pseudomonas aeruginosa* (PsA). **Objectives** To investigate the association between the use of ICS and PsA infection among ExCOPD.

Methods Case-control study with longitudinal follow-up that recruited ExCOPD after a hospitalisation due to exacerbation between 2012 and 2020. Patients with isolation of PsA (COPD-PsA) in sputum either during admission or follow-up were compared with those with other or no PPB. Clinical, functional characteristics, DDD, use of ICS and survival were evaluated. Cox regression analysis was performed to evaluate the risk factors associated to PsA infection and mortality.

Results 358 patients (78% male, mean age 73±9 years) were enrolled and followed up for a median of 4 years (IQR=3–8). 173 patients (48.3%) had at least a positive culture for PsA. COPD-PsA had more frequent exacerbations, more severe airflow limitation and higher mortality (69.4% vs 46.5%, p<0.001). There were no differences in the use of ICS between groups but the dose of ICS was significantly higher among COPD-PsA (median of 500 µg fluticasone propionate equivalents (IQR=250–1000) vs 400 µg (IQR=200–1000), p=0.007). Blood eosinophil count (BEC) was not different between ICS users and non-users. In multivariate analysis, the dose of ICS was an independent risk factor for PsA infection and mortality but not ICS use.

Conclusions ICS dose, but not its use, could be a risk factor for PsA infection in patients with severe COPD regardless of BEC.

INTRODUCTION

Chronic obstructive pulmonary disease with frequent exacerbations (ExCOPD) is a specific clinical phenotype that is associated with progressive decline in lung function, higher mortality and morbidity.^{1,2} About 50% of acute COPD exacerbations (AECOPD) are caused by potential pathogenic bacteria (PPB) infections either isolated from sputum or bronchial secretions cultures.^{3–5}

Key messages

- Are inhaled corticosteroids (ICS) use a potential risk factor for *Pseudomonas aeruginosa* infection among frequent-exacerbator severe chronic obstructive pulmonary disease (COPD)?
- The use of high-dose ICS in severe patients with COPD with frequent exacerbations is associated to *Pseudomonas aeruginosa* infection and poorer survival, regardless of blood eosinophil count, effect not observed with low to medium doses.
- These findings should help the clinicians modify their daily practice regarding their decision on prescribing ICS for patients with severe COPD, especially regarding the dose of ICS.

Haemophilus influenzae, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are the most commonly isolated PPB.^{3,4} Other Gram-negative bacteria, specifically *Pseudomonas aeruginosa* (PsA) and *Stenotrophomonas maltophilia*, are associated with more severe exacerbations and debilitated patients.^{6,7} PsA isolation during AECOPD hospitalisations is associated with greater degree of airway obstruction, use of systemic corticosteroids, poorer lung function, previous isolation of PsA and previous hospital admission.^{8–10} Further, PsA has been linked to increased airway inflammation in patients with COPD¹¹ and mortality.¹²

Inhaled corticosteroids (ICS) are indicated in the treatment of ExCOPD, especially if blood eosinophil count (BEC) are higher than 300 cells/µL^{13,14}; however, ICS therapy is associated with various adverse effects especially the risk of pneumonia¹⁵ which raises the debate about the prescription of ICS in patients with infectious exacerbations. Further, long-term use of ICS is associated with increased bacterial load in airway as well as modification of microbiome composition.¹⁶ The relationship between ICS use and



the risk of PsA infection and its clinical consequences in patients with COPD are not well established and could modify the indication of this treatment in patients with ExCOPD caused by PsA.

Accordingly, our study aimed to: (1) investigate the association between the use of ICS and PsA infection among ExCOPD; (2) identify the risk factors associated with PsA infection among ExCOPD population and (3) study the risk factors associated with mortality among ExCOPD.

METHODS

Study design and ethics

Case-control study that recruited patients with confirmed diagnosis of COPD based on Global Initiative for Chronic Obstructive Lung Diseases (GOLD) criteria with a history of frequent exacerbations after a hospitalisation due to AECOPD.¹³ The study was conducted in a tertiary teaching hospital between 2012 and 2020. All patients were regularly followed up after discharged in ordinary outpatient respiratory clinics or through an integrated care programme for ExCOPD running in the same hospital¹⁰ for a maximum of 8 years. All the patients signed a written informed consent.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Population

All patients who had a diagnosis of COPD according to GOLD criteria¹³ after a hospitalisation for AECOPD with a history of 2 or more exacerbations per year, able to produce a sputum sample either during admission or follow-up, and living in the area of influence of the hospital were included in the study. Patients with COPD with growing of PsA in at least one sputum culture taken either during admission or follow-up (either being as single isolated microorganism or mixed with other PPB) were considered cases (COPD-PsA group). Patients with cultures resulting in other PPB different to PsA or growing of usual respiratory flora were considered controls (COPD-non-PsA group). Further, patients during the follow-up who had invalid sputum sample or unable to produce sputum with no previous sputum sample positive for PsA were considered as COPD-non-PsA. Patients with COPD with non-respiratory comorbidity including deteriorative cognitive function or psychiatric illness that affected their mental capacity and substantially affected the prognosis of the disease were excluded from the study.

Procedures

All patients underwent clinical evaluation, pulmonary function testing, chest X-ray and chest CT to rule out

bronchiectasis when suspected (>98% underwent CT scan during hospitalisation or on follow-up). Detailed drug history—namely long-acting β_2 agonist, long-acting antimuscarinic bronchodilators, and inhaled ICS including the type of ICS and its dose modification over the study duration—was taken. All the doses of ICS were calculated as fluticasone propionate equivalents where 100–250 μg daily dose was considered as low dose, 400–500 μg as medium dose and ≥ 1000 μg as high dose.¹⁷ All acute exacerbations as defined by GOLD guidelines¹³ and requiring hospital contact (as outpatients or requiring an emergency visit or new hospitalisation) were recorded. AECOPD was treated according GOLD guidelines.¹³ The patients were followed up after discharge from the hospital initially after 2 weeks and later every 3 to 6 months as scheduled visits.

Sputum culture

A sputum sample was taken for microbiological evaluation during hospitalisation for AECOPD for every patient admitted, on follow-up if the patient had either previous positive culture for PPB or at presentation with symptoms of AECOPD. Respiratory samples were collected in sterile containers within 24 hours of admission during hospitalisation and on follow-up while presenting to the hospital outpatient respiratory clinics. Samples were transferred within 2 hours to the microbiological laboratory for Gram staining and bacterial culture. Sputum samples were tested for viability of culture according to Murray-Washington criteria.¹⁸ In case of non-viable sample, another sputum sample was recollected. Patients who were unable to give valid sputum sample during hospitalisation, bronchoscopy was performed and bronchial aspirate was collected. A sputum bacterial load $\geq 10^6$ or bronchial aspirate bronchial load $\geq 10^4$ colony forming units/mL was considered as significant. The identified microorganisms were classified as PsA and other PPB including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* and other Gram negative-bacilli. Other micro-organisms such as *Streptococcus viridans*, *Staphylococcus epidermidis* or *Candida* spp were considered non-PPB.

Variables and outcomes

ExCOPD and mortality were recorded for every patient during follow-up. The higher value of blood eosinophils was recorded. New episodes of PsA infection, PPB infection or pneumonia during hospitalisation and follow-up were also recorded. Further, the use of ICS and its dose were also recorded during follow-up of patients for further analysis.

Statistical analysis

Quantitative data were presented as mean \pm SD or median and IQR according to its normal distribution, while

qualitative data were presented as number and percentage (%). Unpaired Student's t-test, Mann-Whitney U test and χ^2 tests were used as appropriate. Spearman correlation coefficient was used to study the collinearity between BEC, ICS and PsA infection. Bivariate and multivariate Cox regression analysis were used to evaluate the hazard factors associated with PsA infection as well as mortality. Cox regression analysis was considered based on the fact of the change of ICS use and dose—as a covariate—over the follow-up duration of the study. A multivariate model was built on the basis of the prescreening univariable significance and the clinical relevance of covariates in the initial comparisons according to the presence or absence of PsA infection. The covariates were introduced in the model manually where multiple multivariate models were evaluated. The multivariate model with the best overall goodness-of-fit was chosen. HR and 95% CI were shown. In all Cox regression models, fluticasone propionate equivalents ICS doses were considered for both groups of patients. Kaplan-Meier survival analysis was plotted in order to identify the survival probability among ICS users during follow-up. A two-tailed $p \leq 0.05$ was considered statistically significant. SPSS package (V.22.0, IBM) was used for all analyses.

RESULTS

Patient characteristics

The current study enrolled 358 patients with COPD after discharge for an AECOPD and followed-up for a median of 4 years (IQR=3–8). 173 patients (48.3%) had at least one sputum with growing of PsA. **Table 1** shows the baseline and clinical characteristics of the studied COPD population classified according to presence (COPD-PsA) or absence of PsA infection (COPD-non-PsA).

Male constituted the majority of COPD-PsA and COPD-non-PsA groups (86.7% and 69.7%, respectively, $p < 0.001$; **table 1**). There was no statistically significant difference regarding age, smoking history, associated comorbidities, modified medical research council (mMRC) dyspnoea scale, history of AECOPD or pneumonia ($p > 0.05$, **table 1**); however, more frequent exacerbations and lower forced expiratory volume in 1 s (FEV_1) predicted were detected among COPD-PsA group ($p < 0.001$ and 0.036 respectively, **table 1**). The majority of COPD-PsA group were GOLD III and IV (46.8% and 28.1% respectively, $p = 0.008$; **table 1**). Bronchiectasis was more frequently associated with PsA infection (26% vs 11.4%, $p = 0.001$; **table 1**). COPD-PsA group had more frequently detected PPB compared with COPD-non-PsA group (4.49 ± 4.66 vs 0.66 ± 1.02 , respectively, $p < 0.001$; **table 1**). Inhaled antibiotics, either colistin or tobramycin, were more frequently prescribed among COPD-PsA group ($p < 0.01$, data not shown). Systemic corticosteroids courses administrated during AECOPD were significantly more frequent among those with PsA infection rather than non-PsA group (7.68 ± 7.14 vs 5.39 ± 5.50 , $p = 0.001$, **table 1**). Further,

mortality was higher among COPD-PsA throughout the 8 years of follow-up (69.4% vs 46.5%, $p < 0.001$; **table 1**).

Inhaled corticosteroids

The use of ICS was not different between patients in the COPD-PsA group when compared with COPD-non-PsA (87.9% vs 82.7%, $p = 0.170$, **table 1**). The daily dose of ICS was significantly higher among COPD-PsA group when compared with COPD-non-PsA infection (median of 500 (IQR=250–1000) vs 400 (IQR=200–1000) μg / day fluticasone propionate equivalents respectively, $p = 0.007$, **table 1**). Fluticasone propionate was the most frequently used ICS, followed by budesonide ($p = 0.003$, **table 1**). On follow-up, there was a statistically significant reduction of the daily ICS dose used in both groups when compared with the doses at the time of enrolment to the study (median of 400 (IQR=100–1000) vs 500 (IQR=200–1000) μg /day fluticasone propionate equivalents, $p < 0.0001$, online supplemental figure S1).

We found no statistically significant difference between COPD-PsA and COPD-non-PsA groups regarding the incidence of pneumonia ($p = 0.118$, **table 1**). Further, there was no association between the use of ICS and pneumonia ($p = 0.858$, data not shown). Moreover, BEC was not different between ICS users and non-users (270.8 ± 318.4 vs 252.5 ± 263.5 , $p = 0.692$).

Correlations

PsA infection positively correlated with BEC ($r = 0.381$, $p \leq 0.001$, (online supplemental table S2) as well as ICS dose ($r = 0.107$, $p = 0.042$, (online supplemental table S2); but there was no correlation between PsA infection and ICS use ($r = -0.008$, $p = 0.884$ online supplemental table S2). Further, there was neither correlation between BEC and ICS dose nor BEC and ICS use ($p > 0.05$, (online supplemental table S2).

Regression and survival analysis

In the bivariate cox regression analysis, neither ICS use nor the type of ICS nor the use of systemic corticosteroids during AECOPD (> 3 courses throughout follow-up duration) were independent risk factors associated to PsA infection among patients with COPD ($p > 0.05$; online supplemental table S1); however, the dose of ICS was a statistically significant independent risk factor for PsA infection (OR 1.15, 95% CI 1.04 to 1.28, $p = 0.009$; online supplemental table S1). Similarly, ICS use was not a risk factor for development of pneumonia (HR 1.28, 95% CI 0.83 to 1.98, $p = 0.270$); while the dose of ICS was a significant weak risk factor for development of pneumonia (HR 1.12, 95% CI 1.0 to 1.25, $p = 0.043$).

Moreover, the daily dose of ICS, not its use, was a significant risk factor associated to PsA infection in multivariate Cox regression analysis (HR 1.26, 95% CI 1.01 to 1.57, $p = 0.040$, **table 2**) after correction for age, mMRC dyspnoea scale, the degree of airway obstruction based



Table 1 Baseline characteristics of the COPD population classified according to PsA infection during the study duration (2012–2020)

Character	COPD-PsA (n=173, 48.3%)	COPD-non-PsA (n=185, 51.7%)	Sig. (P value)
Age	73.63±8.43	73.29±9.71	0.729
Gender			<0.001*
Male	150 (86.7)	129 (69.7)	
Female	23 (13.3)	56 (30.3)	
Smoking status			
Active smoker	40 (23.1)	48 (26.2)	0.794
Ex-smoker	132 (76.3)	136 (73.2)	
Non-smoker	1 (0.6)	1 (0.5)	
Smoking index	64.14±30.42	59.94±30.49	0.207
Comorbidities	171 (99.4)	181 (97.8)	0.204
Associated bronchiectasis†	45 (26)	21 (11.4)	0.001*
No of exacerbations	6.62±5.91	4.08±3.61	<0.001*
Associated pneumonia	82 (47.4)	76 (41.1)	0.118
mMRC dyspnoea scale	2.53±0.84	2.44±0.77	0.289
No of cultures with PBB‡	4.49±4.66	0.66±1.02	<0.001*
Baseline pulmonary function testing			
FEV ₁ % predicted	41.34±17.7	45.2±16.53	0.036*
DLCO % predicted	41.46±17.21	43.9±19.16	0.301
RV	198.64±61.92	196.93±61.56	0.841
GOLD classification			0.008*
I	10 (5.8)	6 (3.3)	
II	33 (19.3)	62 (34.4)	
III	80 (46.8)	77 (42.8)	
IV	48 (28.1)	35 (19.4)	
Medications			
ICS	152 (87.9)	153 (82.7)	0.17
Type of ICS			0.003*
Fluticasone propionate	108 (62.4)	78 (42.2)	
Fluticasone furoate	6 (3.5)	14 (7.6)	
Beclomethasone	10 (5.8)	22 (11.9)	
Budesonide	28 (16.2)	39 (21.1)	
Dose of ICS§	500 (250–1000)	400 (200–1000)	0.007*
LAMA	158 (91.3)	174 (94.1)	0.306
LABA	168 (97.1)	177 (95.7)	0.558
Theophylline	28 (16.2)	34 (18.4)	0.584
Roflumilast	8 (4.6)	5 (2.7)	0.331
Courses of systemic corticosteroids	7.68±7.14	5.39±5.50	0.001*
Mortality	120 (69.4)	86 (46.5)	<0.001*

*Significant $p \leq 0.05$.

†Bronchiectasis diagnosed based on CT taken either during hospitalisation or on follow-up of the patients.

‡Positive sputum or bronchial aspirate culture for potential pathological bacteria.

§Fluticasone propionate equivalents (daily dose).

COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified medical research council; PsA, *Pseudomonas aeruginosa*; RV, residual volume.

Table 2 Multivariate Cox regression analysis of predictors of acquiring PSA infection

	B	SE	Df	Sig.	HR	95% CI for HR	
						Lower	Upper
Age	0.025	0.081	1	0.758	1.03	0.88	1.20
Basal mMRC dyspnoea scale	0.340	0.112	1	0.002*	1.41	1.13	1.75
FEV ₁ % predicted	-0.182	0.088	1	0.038*	0.83	0.70	0.99
Systemic corticosteroids use†	-0.254	0.187	1	0.175	0.78	0.54	1.12
ICS use	-0.499	0.433	1	0.249	0.61	0.26	1.42
ICS dose‡	0.232	0.113	1	0.040*	1.26	1.01	1.57

*Significant $p \leq 0.05$.

†Systemic corticosteroids use >3 courses during the follow-up duration (2012–2020).

‡Fluticasone propionate equivalents (daily dose).

FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; mMRC, modified medical research council; PsA, *Pseudomonas aeruginosa*.

on GOLD classification and the use of systemic corticosteroids during AECOPD with cumulative hazard of 90% of acquiring PsA infection in case of high ICS dose (figure 1) on follow-up.

Patients with COPD using higher daily ICS dose, but not the use of ICS, were also at 1.33 hazard of mortality in multivariate cox regression analysis (95% CI 1.07 to 1.65, $p=0.01$, table 3) after being adjusted for age, mMRC dyspnoea scale and FEV₁% predicted as a measure of airway obstruction severity. The use of ICS had a protective trend against mortality; however, it does not reach a statistical significance (HR=0.55, $p=0.172$, table 3). Both PsA infection and higher mMRC dyspnoea scale were additional hazard factors of mortality ($p < 0.05$). Further, BEC ≥ 300 cells/uL was a protective factor against mortality (HR 0.71, 95% CI 0.52 to 0.99, $p=0.04$). Kaplan-Meier survival analysis showed that the high dose of ICS was associated with significant worse survival of 25% vs 50% compared with low-to-medium ICS dose users ($p=0.001$, figure 2).

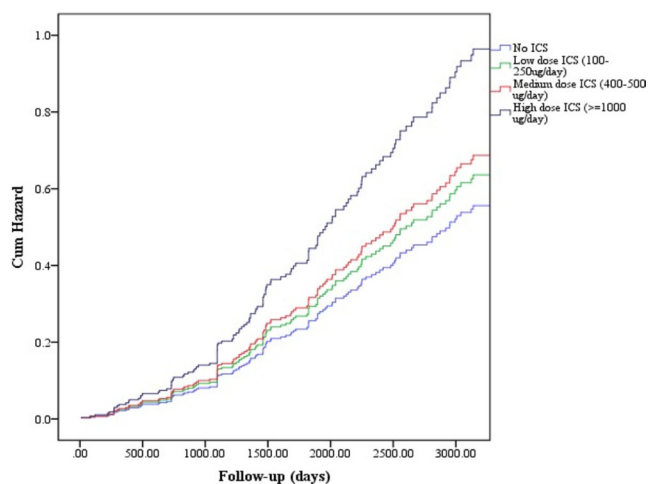


Figure 1 Hazard function analysis of dose of ICS and its relation to acquiring PsA infection. ICS, inhaled corticosteroids; PsA, *Pseudomonas aeruginosa*.

DISCUSSION

Severe ExCOPD are frequently infected by PsA at some point in the natural course of their disease. ExCOPD are commonly treated with ICS and we have shown that the presence of PsA in sputum is a marker of severity and mortality. In an attempt to demonstrate an association between PsA and ICS use, we show here that higher dose of ICS was an independent risk factor for PsA infection but not the use of them. Moreover, patients with continued use of high daily dose of ICS had worse survival compared with low-to-medium ICS dose. Meanwhile, the use of ICS was not associated with poorer survival, and in fact, it seemed to be a protective factor against mortality in multivariate analysis.

Previous studies

Almagro *et al* found that 16% of their AECOPD admissions were caused by PsA infection and that PsA infection was significantly related to posthospitalisation mortality up to 3 years.¹⁹ Similarly, Eklöf *et al* found that PsA was a strong independent risk factor for all causes of death during AECOPD admissions and a cause of subsequent hospitalisation on 2 years of follow-up of their patients with COPD.¹² Further, Jacobs *et al* found that those outpatient COPD with PsA isolation had lower FEV₁% predicted and were at higher risk of mortality compared with negative PsA group.²⁰ Ni *et al* in their meta-analysis found that the coexistence of COPD and bronchiectasis was associated with higher rate of PsA infection.²¹ Martínez-García *et al* found that severe exacerbations and severe airway obstruction were risk factors for first PsA isolation among COPD cohort; while persistent PsA infection was related to the presence of bronchiectasis and severe persistent exacerbation as well as associated with increased mortality.²² Our results agree with these studies as our COPD population with PsA had more severe airway obstruction, more frequent exacerbations, higher mortality and higher frequency of associated bronchiectasis. We found also that PsA infection was a risk factor

Table 3 Multivariate Cox regression analysis of predictors of mortality among COPD population

	B	SE	Df	Sig.	HR	95% CI for HR	
						Lower	Upper
Age	0.088	0.077	1	0.253	1.09	0.94	1.27
Basal mMRC dyspnoea scale	0.348	0.102	1	0.001*	1.42	1.16	1.73
FEV ₁ % predicted	-0.097	0.081	1	0.231	0.91	0.78	1.06
<i>Pseudomonas aeruginosa</i> infection	0.464	0.165	1	0.005*	1.59	1.15	2.20
Blood eosinophils ≥ 300 cells/uL	-0.340	0.166	1	0.040*	0.71	0.52	0.99
ICS use	-0.593	0.435	1	0.172	0.55	0.24	1.30
ICS dose†	0.283	0.110	1	0.010*	1.33	1.07	1.65

*Significant $p \leq 0.05$.

†Fluticasone propionate equivalents (daily dose).

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; mMRC, modified medical research council.

of mortality in multivariate analysis which could be an important factor explaining the higher mortality among our COPD-PsA population. Further, we found that low lung function as expressed by FEV₁% predicted was a risk factor for acquiring PsA infection which is in accordance with Martínez-García *et al.*²²

Interpretation of the results

Frequent antibiotic and oral corticosteroid courses used commonly in the management of AECOPD¹³ could cause a microbiota modification that leads to isolation of PsA.²⁰ ICS is recommended in the management of ExCOPD,¹³ but some controversies are present about the prescription of ICS in stable COPD since ICS use has been linked to increased risk of pneumonia in previous studies.^{15 23}

Interestingly, in the current analysis, we found that neither ICS use nor ICS type nor the use of systemic corticosteroids during AECOPD was a risk factor associated to

PsA infection. Conversely, the use of ICS showed a protective trend against mortality in our studied ExCOPD population. Additionally, ICS use was not associated with increased risk of pneumonia; however, high dose of ICS was a weak risk factor for development of pneumonia (HR=1.12). In line with our results, Garcia-Vidal *et al* found that there is no relation between the use of ICS and PsA infection in their COPD cohort.⁸ However, ICS use was linked to increased risk of pneumonia in previous studies^{15 23} especially the use of fluticasone propionate compared with budesonide.^{24 25} Martínez-García *et al* found that ICS increased the risk of pneumonia among patients with COPD with low BEC (<100/uL) and it was associated with chronic bronchial infection.²⁶ We found that there was no association between the use of ICS and BEC in our severe COPD population; however, BEC ≥ 300 cells/uL was protective against mortality. Yang and Yang found that increased blood eosinophils is associated with decreased mortality in severe AECOPD.²⁷

In addition, we found that high dose ICS is a strong independent risk factor for acquiring PsA infection even after adjustment to use of systemic corticosteroids as well as for mortality. This could be explained on the basis that ICS use, especially in high doses, is associated with change of local airway defence mechanisms including T-cells, alveolar macrophages and various signalling cytokines.^{16 28–30} Garca *et al* found that airway bacterial load in stable COPD is related to higher dose of ICS use.³⁰ Similarly, Contoli *et al* found that 1 year of high-dose fluticasone propionate use among stable COPD was associated with significant increase of sputum total bacterial load specially referred to *Streptococcus pneumoniae* and *Haemophilus influenzae*.¹⁶ Further, Håkansson *et al* found in bronchiectasis patients that PsA isolation was more frequent among those using ICS and that higher ICS dose was associated with mortality.³¹

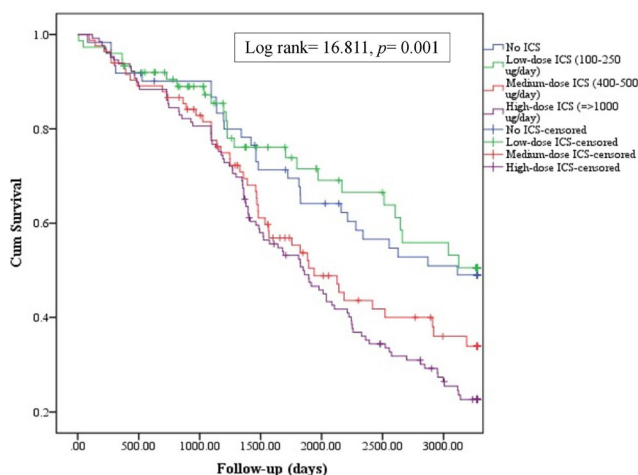


Figure 2 Kaplan-Meier survival analysis according to the dose of ICS among the patients with COPD throughout the study (2012–2020) (log rank=16.811, $p=0.001$). COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

Clinical implications

Our data could reinforce the concept that, by itself, the use of ICS in ExCOPD are of benefit regardless the infectious aetiology based on the improvement of their survival.

In addition, our data discourage the use of high doses of ICS in ExCOPD, since it was directly linked to increased risk of PsA infection and mortality. Current guidelines recommend the use of the lowest effective ICS dose^{32 33} and to consider the benefit–risk balance before initiating an ICS prescription. Previous reviews showed a relatively flat dose-response curve for ICS-clinical response and a steep dose-response for ICS-side effects.^{34 35} Both the Informing the Pathway of COPD Treatment (IMPACT) study³⁶ and TRIBUTE study³⁷ used low-medium doses of ICS and found that there was a significant reduction of moderate-to-severe AECOPD with no increased risk of pneumonia after 52 weeks of therapy. Interestingly, in line with our data, a recent study by Eklöf *et al* found that ICS was a risk factor for acquiring PsA infection as a dose-dependent risk compared with those not using ICS in severe COPD Danish cohort.³⁸

Limitations

The current study has some limitations. First, we did not study the underlying mechanisms of increasing mortality among COPD-PsA population using ICS. However, increased airway inflammation caused by PsA and its high virulence in terms of biofilm formation and resistance of airway-mediated clearance mechanism could be possible mechanisms among ExCOPD patients.^{39–41} Second, an overlap between the airway colonisation and new airway infection could be present as we did not analyse separately those with chronic bronchial infection. However, lower airways bacterial colonisation is associated with frequent AECOPD and could modulate the characteristics of the exacerbation.⁴² Lastly, we used only ordinary microbiological culture rather than quantitative PCR for bacterial detection in the current study. Microbiological detection in the airways using molecular techniques could be more accurate and discriminatory³⁰; however, it is costly and not available in all centres. To our knowledge, this is the first case–control study with longitudinal follow-up that demonstrates that not ICS use, but ICS dose is associated to PsA infection in frequent exacerbator COPD patients.

CONCLUSIONS

ICS dose could be an important risk factor for PsA infection in ExCOPD but not its use. Further, high ICS dose is an independent risk factor for mortality. Moreover, PsA infection is another important risk factor for mortality among those patients. However, further studies are still required to evaluate the relationship between ICS and PsA infection in patients with COPD.

Contributors HS and NT-P: acquisition of data, analysis and interpretation of the data, statistical analysis, drafting the manuscript; JV and LR-C: recruitment of the

patients, acquisition of data, interpretation of the data, drafting the manuscript; AI, CL-C, CJ, PF-R and AO: sputum analysis and microbiological evaluation, data analysis, interpretation of the data, critical revision of the manuscript; BGC: conception and design of the research, analysis and interpretation of the data, supervision of the work, drafting the manuscript, critical revision of the manuscript for important intellectual content.

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Patient consent for publication Not applicable.

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REFERENCES

- Vestbo J, Edwards LD, Scanlon PD, *et al*. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011;365:1184–92.
- Suissa S, Dell'Aniello S, Ernst P. Long-Term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;67:957–63.
- Fagon JY, Chastre J, Trouillet JL, *et al*. Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Use of the protected specimen brush technique in 54 mechanically ventilated patients. *Am Rev Respir Dis* 1990;142:1004–8.
- Monsó E, Ruiz J, Rosell A, *et al*. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995;152:1316–20.
- Moghoofei M, Azimzadeh Jamalkandi S, Moein M, *et al*. Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Infection* 2020;48:19–35.
- Bogaert D, van der Valk P, Ramdin R, *et al*. Host-Pathogen interaction during pneumococcal infection in patients with chronic obstructive pulmonary disease. *Infect Immun* 2004;72:818–23.
- Soler N, Torres A, Ewig S, *et al*. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998;157:1498–505.
- García-Vidal C, Almagro P, Román V, *et al*. Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. *Eur Respir J* 2009;34:1072–8.
- Lode H, Allewelt M, Balk S, *et al*. A prediction model for bacterial etiology in acute exacerbations of COPD. *Infection* 2007;35:143–9.
- Cosío BG, Shafiek H, Verdú J, *et al*. Implementation of an integrated care model for Frequent-Exacerbator COPD patients: a controlled prospective study. *Arch Bronconeumol* 2021. doi:10.1016/j.arbres.2021.01.025. [Epub ahead of print: 13 Feb 2021].
- Hill AT, Campbell EJ, Hill SL, *et al*. Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000;109:288–95.



- 12 Eklöf J, Sørensen R, Ingebrigtsen TS, *et al.* Pseudomonas aeruginosa and risk of death and exacerbations in patients with chronic obstructive pulmonary disease: an observational cohort study of 22 053 patients. *Clin Microbiol Infect* 2020;26:227–34.
- 13 Vogelmeier CF, Criner GJ, Martinez FJ, *et al.* Global strategy for the diagnosis, management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Arch Bronconeumol* 2017;53:128–49.
- 14 Miravittles M, Calle M, Molina J, *et al.* Spanish COPD guidelines (GesEPOC) 2021: updated pharmacological treatment of stable COPD. *Arch Bronconeumol* 2021. doi:10.1016/j.arbr.2021.03.014. [Epub ahead of print: 17 Mar 2021].
- 15 Crim C, Calverley PMA, Anderson JA, *et al.* Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: torch study results. *Eur Respir J* 2009;34:641–7.
- 16 Contoli M, Pauletti A, Rossi MR, *et al.* Long-Term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. *Eur Respir J* 2017;50:1700451.
- 17 National Institute for Health and Care Excellence. Inhaled corticosteroid doses for NICE's asthma guideline, [NICE Guideline NG80], 2018. Available: <http://nice.org.uk/guidelines/NG80>
- 18 Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975;50:339–44.
- 19 Almagro P, Salvadó M, Garcia-Vidal C, *et al.* Pseudomonas aeruginosa and mortality after hospital admission for chronic obstructive pulmonary disease. *Respiration* 2012;84:36–43.
- 20 Jacobs DM, Ochs-Balcom HM, Noyes K, *et al.* Impact of Pseudomonas aeruginosa Isolation on Mortality and Outcomes in an Outpatient Chronic Obstructive Pulmonary Disease Cohort. *Open Forum Infect Dis* 2020;7:ofz546.
- 21 Ni Y, Shi G, Yu Y, *et al.* Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2015;10:1465–75.
- 22 Martínez-García Miguel Ángel, Faner R, Oscullo G, *et al.* Risk Factors and Relation with Mortality of a New Acquisition and Persistence of Pseudomonas aeruginosa in COPD Patients. *COPD* 2021;18:333–40.
- 23 Festic E, Bansal V, Gupta E, *et al.* Association of inhaled corticosteroids with incident pneumonia and mortality in COPD patients. *Systematic Review and Meta-Analysis, COPD* 2016;13:312–26.
- 24 Lodise TP, Li J, Gandhi HN, *et al.* Intraclass difference in pneumonia risk with fluticasone and budesonide in COPD: a systematic review of evidence from Direct-Comparison studies. *Int J Chron Obstruct Pulmon Dis* 2020;15:2889–900.
- 25 Yang M, Du Y, Chen H, *et al.* Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *Int Immunopharmacol* 2019;77:105950.
- 26 Martínez-García MA, Faner R, Oscullo G, *et al.* Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease. A network analysis. *Am J Respir Crit Care Med* 2020;201:1078–85.
- 27 Yang J, Yang J. Association between blood eosinophils and mortality in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease: a retrospective cohort study. *Int J Chron Obstruct Pulmon Dis* 2021;16:281–8.
- 28 Suissa S, Patenaude V, Lapi F, *et al.* Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax* 2013;68:1029–36.
- 29 Brassard P, Suissa S, Kezouh A, *et al.* Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *Am J Respir Crit Care Med* 2011;183:675–8.
- 30 Garcha DS, Thurston SJ, Patel ARC, *et al.* Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012;67:1075–80.
- 31 Håkansson KEJ, Fjællegaard K, Browatzki A, *et al.* Inhaled corticosteroid therapy in bronchiectasis is associated with all-cause mortality: a prospective cohort study. *Int J Chron Obstruct Pulmon Dis* 2021;16:2119–27.
- 32 Soler-Cataluña JJ, Piñera P, Trigueros JA, *et al.* Spanish COPD guidelines (GesEPOC) 2021 update diagnosis and treatment AF COPD exacerbation syndrome. *Arch Bronconeumol* 2021. doi:10.1016/j.arbres.2021.05.011. [Epub ahead of print: 26 May 2021].
- 33 de la Rosa Carrillo D, López-Campos JL, Alcázar Navarrete B, *et al.* Consensus document on the diagnosis and treatment of chronic bronchial infection in chronic obstructive pulmonary disease. *Arch Bronconeumol* 2020;56:651–64.
- 34 Lipworth BJ. Airway and systemic effects of inhaled corticosteroids in asthma: dose response relationship. *Pulm Pharmacol* 1996;9:19–27.
- 35 Kankaanranta H, Lahdensuo A, Moilanen E, *et al.* Add-On therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. *Respir Res* 2004;5:17.
- 36 Lipson DA, Barnhart F, Brealey N, *et al.* Once-Daily Single-Inhale triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–80.
- 37 Papi A, Vestbo J, Fabbri L, *et al.* Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (tribute): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018;391:1076–84.
- 38 Eklöf J, Ingebrigtsen TS, Sørensen R, *et al.* Use of inhaled corticosteroids and risk of acquiring Pseudomonas aeruginosa in patients with chronic obstructive pulmonary disease. *Thorax* 2021. doi:10.1136/thoraxjnl-2021-217160. [Epub ahead of print: 26 Aug 2021].
- 39 Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–52.
- 40 Cullen L, McClean S. Bacterial adaptation during chronic respiratory infections. *Pathogens* 2015;4:66–89.
- 41 Riquelme SA, Ahn D, Prince A. Pseudomonas aeruginosa and Klebsiella pneumoniae adaptation to innate immune clearance mechanisms in the lung. *J Innate Immun* 2018;10:442–54.
- 42 Patel IS, Seemungal TAR, Wilks M, *et al.* Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax* 2002;57:759–64.