ERJ Express. Published on March 23, 2011 as doi: 10.1183/09031936.00077010

Impact of Inhaled corticosteroid use on outcome in COPD patients admitted with pneumonia

Aran Singanayagam[1], James D Chalmers[1], Ahsan R Akram[1], Adam T Hill[1]

1. Department of Respiratory Medicine

Royal Infirmary of Edinburgh

51 Little France Crescent
Old Dalkeith Road
Edinburgh
EH16 4SA

Corresponding author:

Aran Singanayagam

aransinga@gmail.com

fax: 0131 2421870

Keywords: chronic obstructive pulmonary disease; community-acquired pneumonia; inhaled corticosteroids; outcome

Word count = 2395

Short title: **inhaled corticosteroids and pneumonia in COPD**

Abstract

Background: The aim of this study was to investigate if inhaled corticosteroid(ICS) use impacts on outcome in patients with chronic obstructive pulmonary disease(COPD) admitted with community-acquired pneumonia(CAP).

Methods: A prospective observational study of patients with spirometry-confirmed COPD presenting with a primary diagnosis of CAP in Lothian,UK. Outcome measures were compared between ICS users and non-users.

Results: Of 490 patients included in the study, 76.7% were classified as ICS users. ICS users had higher GOLD stage compared with non-users (mean(SD) 3.2(0.8) vs 2.6(0.9); p<0.0001). There were no significant differences in pneumonia severity (mean(SD) pneumonia severity index(PSI) 4.2(0.8) vs 4.3(0.8), p = 0.3; mean(SD) CURB65 score 2.1(1.3) vs 2.3(1.3), p=0.07) or markers of systemic inflammation (median CRP 148(58-268) vs 183(85-302) mg/L; p=0.08) between ICS users and non-users.

On multivariable analysis, after adjustment for COPD severity and PSI, ICS use was not independently associated with 30-day mortality (OR 1.71 [95% CI 0.75-3.90], p=0.2), 6-month mortality (OR 1.62 [95% CI 0.82-3.16], p=0.2), requirement for mechanical ventilation and/or inotropic support (OR 0.73 [95% CI 0.33-1.62], p=0.4) or development of complicated pneumonia (OR 0.71 [95% CI 0.25-1.99], p=0.5).

Conclusion: Prior ICS use has no impact on outcome in patients with COPD admitted with CAP.

Introduction

Several large trials have reported increased community acquired pneumonia (CAP) risk associated with use of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) [1-3]. There is some evidence that patients with COPD who develop pneumonia may experience worse clinical outcomes [4-6], although this association is debated [7-9]. Despite the increased pneumonia frequency observed with use of ICS in COPD, there has been no associated rise in mortality reported by any of the recent trials [1-3]. This has led to speculation that ICS use may increase CAP risk but protect against severe pneumonia or pneumonia-related complications [10-11].

The aim of our study was to assess the impact of ICS pre-treatment on admission markers of severity and outcome in COPD patients presenting with community-acquired pneumonia.

Methods

The Edinburgh Pneumonia Study was a prospective observational study of adult patients presenting with a diagnosis of CAP between January 2005 and December 2009 to NHS Lothian, UK [12]. This manuscript reports a sub-analysis of this study investigating the effect of ICS use on severity and outcome in patients with spirometry-confirmed COPD. The study was approved by the Lothian Research Ethics Committee.

All patients included in the study had a diagnosis of COPD confirmed by spirometry according to published criteria [13] and presented with a new infiltrate on chest radiograph along with 3 or more of the following symptoms or signs: cough, sputum production, breathlessness, pleuritic chest pain or signs consistent with pneumonia on auscultation.

Exclusion criteria were: hospital-acquired pneumonia (development of symptoms >48 hours following admission or discharge from an acute care facility <2 weeks prior to admission); active thoracic malignancy; a primary diagnosis of asthma;

immunosuppression (defined as long term (>28 day) use of oral prednisolone at any dose or other immunosuppressive drugs (methotrexate, azathioprine, cyclosporin and anti-tumour necrosis factor alpha agents) or patients with solid organ transplantation; pulmonary embolism and patients in whom active treatment was not considered appropriate (palliative care).

Study Protocol

For all patients admitted with community acquired pneumonia, a pro-forma was completed on admission that includes baseline observations (pulse, blood pressure, respiratory rate, temperature) and standard blood tests (full blood count, urea and electrolytes, liver function tests, and C-reactive protein). All variables were taken within 4 hours of hospital admission. On admission, patients were risk assessed using the CURB65 score and the Pneumonia severity index (PSI) (see appendix 1) [14-15]. All patients received standard antibiotic therapy in accordance with British Thoracic Society guidelines [16].

Assessment of COPD and Inhaled corticosteroid use

COPD was defined according to GOLD criteria [13]. All patients included in the study had a confirmed diagnosis of COPD made by spirometry in primary or secondary care within 6 months of admission to hospital with CAP, while clinically stable. The use of inhaled corticosteroids (either in single inhaler or combination ICS/long acting Beta2 agonist (LABA) preparation) was recorded on admission. Patients were classified as ICS users if they self-reported prescription of any of these medications on repeat prescription from their General Practitioner at the time of admission. The prescriptions for all patients were confirmed by contacting the patient's General Practitioner within 1 working day of admission. All patients classified as ICS users

had been taking ICS for at least one month, prior to admission with CAP. Compliance with medication was not recorded.

Patients using ICS were then further sub-divided according to type of ICS used: budesonide (alone or in combination with formoterol), fluticasone (alone or in combination with salmeterol), beclomethasone or ciclesonide.

Outcomes

The outcomes of interest were 30-day mortality, 6-month mortality, need for mechanical ventilation and/or inotropic support and development of complicated pneumonia (complicated parapneumonic effusion, empyema or pulmonary abscess). The indications for mechanical ventilation and inotropic support were left to the discretion of the attending physician. We also assessed time to clinical stability (defined using the modified Halms criteria as the first 24 hour period in which the following criteria were met: temperature <37.2°C; heart rate <100/minute; respiratory rate <24/minute; systolic blood pressure >90mmHg; oxygen saturations >90% on room air; able to maintain oral intake; baseline mental status)[17] and the length of hospital stay.

Statistical analysis

All data were analysed using SPSS version 13 for windows (SPSS inc., Chicago, IL). Descriptive statistics of demographic and clinical variables are presented as median (IQR) unless otherwise stated. The Chi-squared test was used to compare categorical data between groups. The Mann-Whitney *U* test was used for comparison of 2 groups of continuous data. Kaplan–Meier analysis was used for comparison of survival between ICS users and non ICS users. The statistical significance was evaluated using the log-rank test.

We used multivariable logistic regression to compare the outcomes of interest in patients with ICS pre-treatment compared to non ICS users. To the baseline model we included COPD severity (GOLD criteria) and the pneumonia severity index. We also used multivariable logistic regression to compare 30 day mortality in ICS users with non-ICS users in the subgroups of ICU admitted patients and those in PSI class V. To both these models, we included COPD severity (GOLD criteria). A 2 tailed p value <0.05 was considered statistically significant for all tests.

Power calculation

With a sample size of 376 (inhaled corticosteroid group) and 114 (no inhaled corticosteroid group), this study is powered for an effect size of 9% using two sided, two sample test with 5% level of significance and 80% power.

Results

The study enrolled a total of 1883 cases of community acquired pneumonia. Spirometry results were available for 718 patients, of which 490 confirmed a suspected diagnosis of chronic obstructive pulmonary disease. 376 patients were classified as inhaled corticosteroid users and 114 were not prescribed ICS. A flowchart of patient enrolment into the study is illustrated in figure 1. There were no patients treated with inhaled therapy in whom spirometry results were not available.

Sub-classes of ICS

Among ICS users, 67.9% were prescribed fluticasone/salmeterol combination, 21.1% were prescribed budesonide/formoterol combination and 11% were taking a single ICS inhaler without long acting beta-agonist. Of the 41 single agent ICS users, 18 were prescribed fluticasone, 17 were prescribed beclometasone, 5 were prescribed budesonide and 1 patient was prescribed ciclesonide. The doses of ICS prescribed were as follows:- fluticasone users: mean dose 948mcg/day (Standard deviation (SD) 424.8); budesonide users: mean dose 909.5mcg/day (SD 374.4); beclomethasone users: mean dose 741.2 mcg/day (SD 209.3).

Baseline characteristics

Baseline characteristics of the ICS and non ICS groups are shown in table 1. ICS users were more likely to have cardiac failure and also be classified with GOLD stage 4 disease, while non ICS users were more likely to be classified with GOLD stage 1 and 2 disease. Otherwise, there was no significant differences between the two groups in terms of age, comorbidities, clinical parameters, markers of systemic inflammation and radiographic findings. Rates of administration of systemic steroids on admission were similar between the two groups (table 1).

Table 1: Baseline characteristics of ICS users and non ICS users			
Clinical Characteristics	Inhaled corticosteroid users (n = 376)	Non-ICS users (n =114)	p-value
Age (mean (SD))	71.5 (9.92)	72.7 (11.02)	0.3
Gender (% males)	48.9%)	50%	0.9
Cardiac failure	31.9%	25.4%	0.005
Liver disease	4.3%	2.6%	0.6
Cerebrovascular disease	13.0%	16.7%	0.4
Chronic renal failure	7.2%	8.8%	0.5
Gold stage 1	0.3%	7.0%	<0.0001
Gold stage 2	22.6%	45.6%	<0.0001
Gold stage 3	29.5%	28.9%	1.00
Gold stage 4	47.6%	18.4%	<0.0001
New onset confusion	13.3%	20.2%	0.07
Respiratory rate (breaths/min)	24 (20-30)	24 (16-32)	0.2
Systolic blood pressure (mm Hg)	120 (104-140)	119 (95-138)	0.1
Diastolic blood pressure (mm Hg)	69 (60-78)	68 (57-76)	0.3
Temperature (^{o}C)	37.4 (37.1-38.2)	37.3 (37.1-38.0)	0.08
Pulse rate (beats/min)	100 (90-120)	100 (88-114)	0.3
Haematocrit	39.7% (36%-43.4%)	38.9% (34.5%-41.8%)	0.07
White cell count (x10^{9}/L)	14.4 (10.9-18.7)	13.5 (10.1-18.0)	0.2
Platelet count (x$10^{9/}$L)	246 (194-324)	252 (191-361)	0.8
Urea (mmol/L)	7.2 (5.2-10.7)	8 (5.8-11.5)	0.08
Sodium (mmol/L)	137 (134-139)	137 (134-139)	0.7
Potassium (mmol/L)	4.1 (3.8-4.4)	4.1 (3.7-4.5)	0.8
Albumin(g/L)	37 (33-40)	36 (32-39)	0.09
C-reactive protein (mg/L)	148 (58-268)	183 (85-302)	0.08
Multilobar chest x-ray shadowing	14.6%	14.9%	1.0
Pleural effusion	9.8%	9.6%	1.0
Systemic corticosteroid administration on admission	50.5%	48.2%	0.75
Data presented as % of group or median (IQR) unless otherwise stated			

Stratification of ICS and non ICS users according to CURB65 and PSI

Table 2 shows ICS and non ICS users, stratified according to pneumonia severity index (PSI) class and CURB65 class. There was no significant difference between ICS users and non ICS users, when stratified according to either scoring system.

Table 2: ICS users and Non-ICS users stratified according to PSI and CURB65 class.

Severity score	ICS users (n=376)	Non-ICS users (n=114)	p-value
PSI			
- 1	0%	0%	n/a
- 2	3.7%	2.6%	0.77
- 3	14.9%	14.9%	1.0
- 4	39.6%	34.2%	0.32
- 5	41.8%	48.2%	0.24
CURB65			
- 0	13.3%	10.5%	0.52
- 1	22.9%	21.1%	0.80
- 2	29.8%	26.3%	0.56
- 3	20.5%	22.8%	0.60
- 4	10.9%	15.8%	0.19
- 5	2.6%	3.5%	0.75

ICS use and outcome

Table 3 shows markers of severity and outcome in ICS users and non-users. ICS users had higher mean GOLD stage, indicating more severe COPD. There were no significant differences in 30 day mortality, 6 month mortality, need for mechanical ventilation and/or inotropic support, development of complicated pneumonia, length of hospital stay and time to clinical stability, when comparing ICS users with non-ICS users.

Table 3: Markers of severity and outcome in ICS users and Non-ICS Users			
	ICS Users	Non-ICS Users	P value
GOLD stage (mean (SD))	3.2 (0.8)	2.6 (0.9)	<0.0001
CURB65 (mean (SD))	2.1 (1.3)	2.3 (1.3)	0.07
PSI class (mean(SD))	4.2 (0.8)	4.3 (0.8)	0.3
30 day mortality	12.0%	8.9%	0.5
6 month mortality	18.4%	14.9%	0.5
Need for MV/IS	6.9%	10.7%	0.2
Complicated pneumonia	4.0%	5.4%	0.8
Time to clinical stability (days)	3 (2-6)	3 (1-5)	0.4
Length of hospital stay (days)	6 (3-11)	6 (4-12)	0.6
Data presented as % of group or median (IQR), unless otherwise stated			

Survival Analysis

Figure 2 shows Kaplan Meier analysis for 30 day mortality in ICS users and non-ICS users. There was no significant difference in survival, when comparing ICS users with non-ICS users (Log rank test chi square 0.83; df=1, p=0.4).

Multivariable analysis

On multivariable analysis, after adjustment for severity of COPD (GOLD criteria) and PSI score, ICS use was not independently associated with 30-day mortality (OR 1.71 [95% CI 0.75-3.90], p=0.2), 6-month mortality (OR 1.62 [95% CI 0.82-3.16], p=0.2), requirement for MV/IS (OR 0.73 [95% CI 0.33-1.62] ,p=0.4) or development of complicated pneumonia OR 0.71 [95% CI 0.25-1.99] , p=0.5)

Outcome in ICU admitted patients and those with severe pneumonia (PSI class V)

There were 39 patients admitted to ICU. Mortality in this group was 38.5%. Of those admitted to the ICU, 26 (66.7%) were ICS users and 13 (33.3%) were non-ICS users. On multivariable analysis, ICS use was not associated with 30-day mortality in the sub-group admitted to ICU (OR 0.37 [95 % CI 0.07-1.95], p-0.3).

There were 212 patients in PSI class V. Mortality in this group was 20.8%. Of those in PSI class V, 157 (74.1%) were ICS users and 55 (25.9%) were non-ICS users. On multivariable analysis, ICS use was not associated with 30-day mortality for patients in PSI class V (OR 1.92 [95% CI 0.76-4.86], p=0.2).

Discussion

Our study has found that prior ICS use has no impact on severity and outcomes in patients with COPD who are hospitalised with CAP. We assessed a range of clinical outcomes including 30-day mortality, 6-month mortality, need for mechanical ventilation and/or inotropic support, development of complicated pneumonia, time to clinical stability and length of hospital stay. Regardless of which outcome measure was used, we found no significant differences between ICS users and non-ICS users, after adjustment for COPD severity (GOLD criteria) and pneumonia severity (PSI criteria).

The hypothesis that ICS use may be associated with improved outcomes of CAP in patients with COPD has been raised by a number of large randomised controlled trials which, despite showing significantly increased pneumonia rates associated with ICS use, have reported no overall increase in mortality [1-3]. A post hoc analysis of the TORCH trial has shown that although rates of pneumonia are higher in ICS receiving groups, there is no difference in serious adverse events (death or hospitalisation) [10]. This has led to the speculation that episodes of pneumonia associated with ICS use may be mild in severity and that ICS may increase risk of pneumonia but protect against pneumonia-related complications [10-11]. The results of our study do not support this hypothesis. ICS are proposed to improve outcome in CAP by causing a reduction in airway inflammation and neutrophil influx, leading to a blunted systemic inflammatory response [18-21]. However, we found no significant difference in levels of markers of systemic inflammation such as c-reactive protein and white cell count between ICS users and non ICS users in our study. In addition, there is no convincing evidence that systemic corticosteroid administration improves outcomes in CAP [22-23]. This adds further weight to our findings as locally-acting inhaled corticosteroids would, therefore, also be expected to have minimal impact on mortality.

Our findings contradict a recent study by Malo de Molina and colleagues.[21] They analysed a large database of patients >64 years with COPD who were hospitalised with CAP and found that ICS use was associated with reduced 30 day and 90 day

mortality. Although the current study utilises a smaller cohort, significant methodological differences may explain the discrepancy in findings between the two studies. Firstly, the study by Malo de Molina et al used ICD-9 discharge codes to classify CAP, while inclusion criteria into our study required radiographic confirmation of CAP. Previous studies suggest that ICD-9 codes will miss approximately 25% of CAP cases admitted to hospital [24]. As there is no specific ICD-9 code for community-acquired pneumonia, retrospective studies rely on less precise definitions such as pneumonia, respiratory failure or sepsis. This raises the possibility that some of the patients included in the study by Malo de Molina *et al* may have been misclassified as CAP and thus included, despite presenting with an acute 'non-pneumonic' exacerbation of COPD. Inhaled corticosteroids may have differential effects on these two disease entities and if a greater proportion of episodes of CAP were misclassified in one group compared to the other, this may have had a confounding effect on mortality. Furthermore, our study includes only patients with spirometry-confirmed COPD, in contrast to Malo de Molina *et al*, who used ICD9 code based definitions of COPD. Patients included in their study could have therefore been misclassified with COPD and actually have had an alternative chronic respiratory disease. In addition, we were able to use spirometric data to adjust for severity of COPD. Without adjustment for severity, it is unclear whether the lower rates of mortality seen in ICS users are due to differences in severity of disease between the 2 groups rather than use of ICS itself per se. Our data show that ICS use is more common in patients with more severe COPD.

Although the study by Malo de Molina *et al* utilised a much larger sample size, power calculations suggest that, based on a sample size of 490 patients, our study is adequate to detect an improvement in survival of >9%. Notably, the study by Malo de Molina *et al* demonstrated a 24% reduction in 30 day mortality associated with ICS use. Our study is, therefore, adequately sized to detect such a large effect but may not detect more subtle changes. Further validation of our findings in larger independent cohorts is needed.

The issue of whether ICS use contributes to increased risk of development of CAP in patients with COPD is controversial [11, 25-28] and requires further characterisation. Our study was not designed to address this question but rather to determine if ICS associated CAP differs from non-ICS associated CAP in terms of severity and outcome. It has been suggested recently that lower strength ICS such as budesonide may have less influence on development of CAP than higher potency preparations such as fluticasone [29]. However, due to lack of detailed information about doses of

ICS and duration and compliance with therapy, we were unable to assess whether lower and higher strength ICS had differential effects on outcome in CAP in our study. Variation in dose and formulation presents difficulties when analysing data on treatments from observational studies and this is a recognised limitation to our study.

In summary, this study found no evidence to support the hypothesis that ICS related CAP has a distinct clinical phenotype, or that prior ICS use improves clinical outcomes in CAP. Our results are in contrast to some of the existing studies and, thus, further independent validation is now required.

References

1. Calverley PM Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356: 775-89.
2. Kardos P, Wencker M, Glaab , Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations n severe chronic obstructive pulmonary disease. Am Respir Crit Care Med 2007; 175: 144-9.
3. Wedzicha JA, Calverley PM, Seenmungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008; 177: 19-26.
4. Rello J, Rodriguez A, Torres A, Roig J, Sole-Violan J, Garnacho-Montero J, de la Torre MV, Sirvent JM, Bodi M. Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. Eur Respir J 2006; 27: 1210-16.
5. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J 2006; 28: 346-51.
6. Holguin F, Folch E, Redd SC, Mannino DM, Comorbidity and mortality in COPD-related hospitalisations in the United States. 1979-2001. Chest 2005; 128: 2005-2011.

7. Torres A, Menendez R. Mortality in COPD patients with community-acquired pneumonia: who is the third partner? Eur Respir J 2006; 28: 262-3.
8. Torres A, Dorca J, Zalacaín R, Bello S, El-Ebiary M, Molinos L, Arévalo M, Blanquer J, Celis R, Iriberri M, Prats E, Fernández R, Irigaray R, Serra J. Community-acquired pneumonia in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996; 154: 1456-61.
9. Ruiz De Ona JM, Gomez Fernandez M, Celdran J, Puetu-Maestu L. Pneumonia in the patient with chronic obstructive pulmonary disease. Levels of severity and risk classification. Arch Bronchoneumol 2003; 39: 101-5.
10. Crim C, Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones, PW, Willits LR, Yates JC, Vestbo J. Pneumonia risk in COPD patient receiving inhaled corticosteroids alone or in combination: TORCH study result. Eur Respir J 2009; 34: 641-7.
11. Singanayagam A, Chalmers JD, Hill AT. Inhaled corticosteroids and risk of pneumonia: evidence for and against the proposed association. QJM 2010; 103: 379-85.
12. Singanayagam A, Chalmers JD, Hill AT. Admission hypoglycaemia is associated with adverse outcome in community-acquired pneumonia. Eur Respir J 2009; 34: 932-9/
13. www.goldcopd.com Web Reference. [Accessed 23/03/2010]
14. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58:377–82.
15. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low risk patients with community-acquired pneumonia. NEJM 1997; 336: 243-50.
16. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009; 64: Suppl 3 iii1-55.
17. Halm EA, Fine MJ, Kapoor WN , Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with community acquired pneumonia. *Arch Intern Med* 2002; 162(11):1278-84

18. Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 170: 760.
19. Llewellyn-Jones CG, Harris TA, Stockley RA. Effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema. Am J Respir Crit Care Med 1996; 153: 616.
20. van Overveld FJ, Demkow UA, Górecka D, Zielinski J, De Backer WA.. Inhibitory capacity of different steroids on neutrophil migration across a bilayer of endothelial and bronchial epithelial cells.. Eur J Pharmacol 2003; 477: 261.
21. Malo de Molina R, Mortensen EM, Restrepo MI, Copeland LA, Pugh MJ, Anzueto A.. Inhaled corticosteroid use is associated with lower mortality for subjects with chronic obstructive pulmonary disease and hospitalized with pneumonia. Eur Respir J 2010; 36: 751-7.
22. Salluh JI, Povoa P. Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. Crit Care 2008; 12: R76.
23. Gorman SK, Slavik RS, Marin J. Corticosteroid treatment of severe community-acquired pneumonia. Ann Pharmacother 2007; 41: 1233-7.
24. Van De Garde EM, Oosterheert JJ, Bonten M, Kaplan RC, Leufkens HG. International classification of diseases codes show modest sensitivity for detecting community-acquired pneumonia J Clin Epidemiol 2007; 60: 834-8.
25. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic-obstructive pulmonary disease. A Systematic review and meta-analysis. JAMA 2008; 300: 2407-16.
26. Singh S, Amin AV, Loke YK. Long term use of inhaled corticosteroids and the risk of pneumonia in chronic-obstructive pulmonary disease. A meta-anaysis. Arch Intern Med 2009; 169: 219-29.
27. Woodhead M. Inhaled Corticosteroids Cause Pneumonia….Or Do They? Am J Respir Crit Care Med 2007; 176: 111-2.
28. Rees PJ. Inhaled Corticosteroids do not reduce mortality but increase pneumonia in COPD. Evid Based Med 2009; 14: 74.
29. Sin DD, Tashkin D, Zhang X, Radner F, Sjöbring U, Thorén A, Calverley PM, Rennard SI Budesonide and risk of pneumonia: a meta-analysis of indivudual patient data. Lancet 2009; 374: 712-9.

Acknowledgements

Financial support: J.D.C. is supported by a Clinical Research Training Fellowship from the Medical Research Council (London, United Kingdom).

Potential conflicts of interest: All authors: no conflicts.

Figure 1: Flow chart of patient enrolment into study

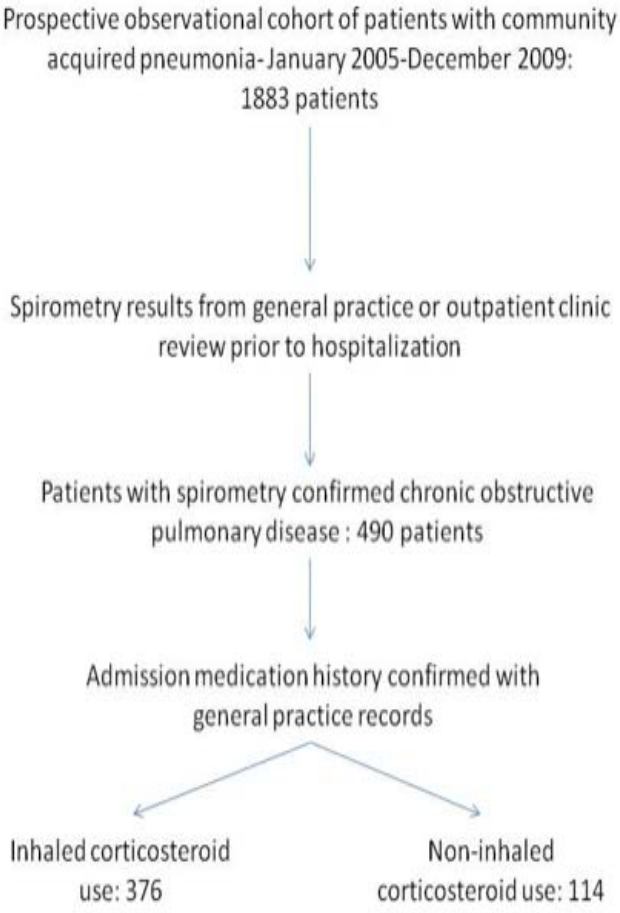

Figure 2: Survival analysis in ICS users and non-ICS users