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Title: Blood eosinophils and outcomes in severe hospitalised exacerbations of COPD

Short title: Blood eosinophils in severe exacerbations

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Key words: Chronic obstructive pulmonary disease, eosinophils, hospitalisation, length of stay

Abstract

Background Patients with moderate exacerbations of chronic obstructive pulmonary disease (COPD) and the eosinophilic phenotype have better outcomes with prednisolone. Whether this is the case in patients hospitalised with a severe exacerbation of COPD is unclear. We investigate the rate of recovery of eosinophilic and non-eosinophilic exacerbations from subjects participating in a multi-centre randomised control trial assessing health outcomes in hospitalised exacerbations (clinical trial registration ISRCTN05557928).

Methods: Subjects were recruited at presentation to hospital with an exacerbation of COPD and stratified into eosinophilic exacerbations if the peripheral blood eosinophil on admission was ≥200 cells/μL and/or ≥2% of the total leukocyte count. Admission details, serum CRP, length of stay and subsequent re-hospitalisation were compared between groups.

Results: We recruited 243 COPD subjects (117 males) with a mean age (range) of 71 years (45-93). The inpatient mortality rate was 3% (median time to death 12 days, range 9-16). The median absolute eosinophil count was 100 cells/μL (range 10 to 1500 cells/μL) and 25% met our criteria for an eosinophilic exacerbation. In this population, the mean length of stay was shorter than in patients with non-eosinophilic exacerbations (5.0 (1-19) vs. 6.5 (1-33), p=0.015) following treatment with oral corticosteroids and independent of treatment prior to admission. Readmission rates at 12 months was similar between the groups.

Conclusions: Patients presenting to hospital with a severe eosinophilic exacerbation of COPD have a shorter length of stay. These exacerbations are usually not associated with an elevated CRP, suggesting that better treatment stratification of exacerbations can be utilised.

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Key words: exacerbations, COPD, treatment, hospitalisations, eosinophils, C reactive protein

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Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) requiring hospitalisation are associated with poorer outcomes, including accelerated lung function decline(1) and a significant risk of mortality.(2) More recently, epidemiological studies have suggested that the risk of hospitalisation increases with the number of previous admissions.(3) Current guidelines for the treatment of an exacerbation advocate systemic corticosteroids and antibiotic therapy (4, 5) with responses aimed at reducing treatment failure events and shortened length of stay. However, corticosteroid therapy is not without harm (6) associated with increased adverse events compared to placebo including significant hyperglycaemia in 50%.(6)

It has long been recognised that a sputum eosinophilia is a marker for corticosteroid responsiveness in stable COPD with an associated improvement in lung function, symptoms and exercise capacity (7, 8). The peripheral blood eosinophil count is a respectable surrogate for sputum eosinophilic airway inflammation during an exacerbation of COPD (9) and there is increasing evidence to suggest that in moderate exacerbations there is a subgroup with eosinophilic inflammation defined as a peripheral blood eosinophil count ≥2% of the total leukocyte count who particularly benefit from systemic corticosteroid therapy.(10, 11) However, whether this is the case in patients hospitalised with a severe exacerbations of COPD is unclear. We have investigated whether clinical outcomes, including length of hospital stay, readmission rate and mortality differ by admission blood eosinophil count in patients admitted to hospital with a severe exacerbations of COPD who participated in a prospective two-centre randomised acute rehabilitation clinical trial (clinical trial registration ISRCTN05557928) in a post-hoc analysis.(12) This is an important question as morbidity and mortality following a hospital admission is considerable and the benefits of better risk stratification and treatment targeting may be particularly important.

Materials & Methods

Data from COPD subjects entering a prospective two centre randomised clinical trial investigating whether early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease were analysed.(12) In brief this was a randomised clinical trial of a progressive, exercise based recovery intervention delivered immediately following unscheduled hospital admission, in subjects presenting to hospital with an acute exacerbation of chronic respiratory disease, including those with a known physician diagnosis of COPD with a relevant smoking pack year history of >10. The intervention comprised individualised involuntary and voluntary exercise training techniques modified to suit the environment of acute illness together with an education and self-management programme. Clinical data outcomes were collected at admission (baseline), at discharge from

hospital, six weeks, three months and 12 months. The original trial was negative for its primary outcome, with no differences in readmission to hospital in the following 12 months whether randomised to intervention or standard care. In this sub-group analysis data is analysed for exacerbation inflammatory phenotypes alone and not corrected for intervention arm.

Subjects

Adults aged 40 and over, presenting to the acute medical ward at the Glenfield Hospital, Leicester and Kettering Hospital, Kettering, with an acute exacerbation of a chronic lung disease were recruited to the study. The respiratory diagnoses were physician defined and included COPD, chronic asthma, bronchiectasis or interstitial lung disease with previous corroborative spirometry, or imaging. Subjects were excluded from the study, if the acute admission was related to a cardiac event, including heart failure, unstable angina or acute coronary syndrome, confirmed by specialist cardiology opinion; or the presence of significant musculoskeletal, neurological or psychiatric co-morbidity that would preclude the provision of informed consent or ability to perform the intervention rehabilitation programme. Subjects with a history or evidence suggesting an acute venous thromboembolic event or pneumothorax were also excluded. Subjects with greater than 4 hospitalisations in the previous 12 months for any cause were also excluded from the study. Only subjects with a confirmed diagnosis of exacerbation of COPD were studied in this sub-group analysis and analysed further. All subjects provided informed written consent and the study was approved by the local Research Ethics Committee (09/H0403/76).

Measurements

Clinical and demographic data was collected at the time of the admission. Spirometry at stable state was recorded as per standard guidelines (13) and venous blood was taken for measurement of a full blood count and serum C reactive protein (CRP). Length of stay, mortality and hospital admissions from any cause in the follow up 12-month period were captured using hospital databases and General Practice records. A chest radiograph (CXR) was performed on all patients and independently reviewed by a senior radiologist and respiratory physician who were blinded to both the intervention and admission exacerbation inflammatory phenotype (including haematological/biochemical inflammatory indices).

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc; Chicago, Illinois) and PRISM version 6 (GraphPad, San Diego, CA). Parametric data were expressed as mean (standard error of the mean, SEM), non-parametric data as median (interquartile range, IQR)

and log normally distributed data as geometric mean (95% confidence interval). Unpaired parametric and non-parametric groups were compared using the Student t-test and Mann Whitney test respectively. The paired t-test was used to compare matched exacerbation and stable recovery measures of lung function and symptom status. For comparison of 3 or more groups, the one-way analysis of variance (ANOVA) was used with repeated ANOVA for paired data. The chi-squared test (χ^2) was used to compare proportions between groups. The eosinophilic exacerbation phenotype was defined as one where the peripheral blood eosinophil count on admission was ≥200 cells/μL and/or ≥2% of the total leukocyte count.(9) The t-test and log-rank Mantel-Cox test was used to compare length of stay and time to next admission between eosinophilic and non-eosinophilic exacerbations in the primary analysis and repeated excluding subjects with CAP. There were no differences in intervention allocation between the inflammatory phenotypes and no correction for multiple analysis was made. A p-value of <0.05 was taken as the threshold of significance for all statistical testing.

Results

Between January 2010 and September 2011, 389 subjects were recruited to the acute intervention study. Of these, a diagnosis of COPD was confirmed in 243, with available venous blood for a differential full blood count taken within a 12 hours of admission (figure 1).

The population consisted of 48%% men, with a mean age (range) of 71 (45 to 93) years. All subjects were current (23%) or ex-smokers (77%) with a mean (range) pack year history of 48 (10 to 210). The baseline mean (SD) FEV_1, FEV_1 % predicted and FEV_1/FVC ratio for the group was 0.93 L (0.47), 42% (18) and 47% (13) respectively. There were 45 subjects (19%) that were prescribed oral corticosteroids within the 4 weeks prior of the admission event. For all subjects admitted, both oral corticosteroids and antibiotic therapy was administered in 79.4%; oral corticosteroids alone in 11.5%; oral antibiotics alone in 7.4%; and 1.6% received neither. Treatment of the exacerbation occurred on day zero of the admission. The mean (range) length of hospital stay was 6.3 days (1 to 33) and 6 subjects (3%) died during this index admission (median time to death 12 days, range 9-16).

The median (interquartile range) absolute peripheral eosinophil count and percentage eosinophil count was 100 cells/μL (40 to 200 cells/μL) and 0.60% (0.28 to 1.86). The highest recorded absolute and percentage eosinophil count was 1500 cells/μL and 11.8% respectively. An eosinophilic associated COPD exacerbation defined as a peripheral blood eosinophil count ≥200 cells/μL and/or ≥2% of the total leukocyte count occurred in 25% (n=62). A peripheral blood eosinophilia, greater than or equal to 400 cells/μL occurred in 32 subjects (13%). The CRP was significantly lower in eosinophilic compared to non-eosinophilic exacerbations (median (IQR) 13 (5-48) versus 55 (18-139), p<0.001, figure 2). There were no

differences with respect to lung function, smoking history, gender, or treatment at stable state or during the admission between eosinophilic and non-eosinophilic exacerbations, although more subjects with non-eosinophilic exacerbations had consolidation on CXR (table 1). Length of hospital stay following treatment with corticosteroids was shorter in eosinophilic-associated exacerbations compared to non-eosinophilic exacerbations of COPD (mean (range) 5.0 (1-19) vs. 6.5 (1-33), p=0.015, figure 3). The 12 month re-admission rate and time to next exacerbation were not different between the index eosinophilic and non-eosinophilic COPD exacerbation.

A radiological diagnosis of pneumonia (defined as new consolidation on CXR) was detected in 69 (28%) of these subjects. A secondary analysis was performed excluding these subjects, investigating inflammatory cell counts and treatment responses. A total of 174 subjects with an exacerbation of COPD were thus re-analysed. For these subjects, both oral corticosteroids and antibiotic therapy was administered in 78.7%; oral corticosteroids alone in 14.4%; oral antibiotics alone in 4.6%; and 2.3% received neither. These treatment proportions were not different between exacerbations with or without consolidation on CXR. An eosinophilic-associated COPD exacerbation occurred in 31% (n=54) and a peripheral blood eosinophilia, occurred in 30 subjects (17%). The CRP remained to be significantly lower in eosinophilic compared to non-eosinophilic exacerbations (median (IQR) 11 (5-27) versus 37 (14-104), p<0.001). Length of hospital stay following treatment with corticosteroids (excluding those treated with antibiotics alone or neither, n=12) remained to be 1.5 days shorter in eosinophilic associated exacerbations compared to non-eosinophilic exacerbations, although not statistically significant (mean (range) 5.0 (1-19) vs. 6.5 (1-33), p=0.07). These trends were independent of treatment with corticosteroids prior to the admission (given pre-admission prednisolone mean (SD) length of stay eosinophilic exacerbations versus non-eosinophilic exacerbations 5.3 (3.8) vs. 6.9 (6.2), p=0.18; not given pre-admission prednisolone mean (SD) length of stay eosinophilic exacerbations versus non-eosinophilic exacerbations 5.1 (3.5) vs. 6.3 (5.2), p=0.48)

Discussion

We have demonstrated that eosinophilic exacerbations of COPD, defined as 200 cells/μL and/or ≥2% of the total leukocyte count can be identified in severe hospitalised exacerbations of COPD and occur in approximately 25% of hospitalised exacerbations. These exacerbations are clinically indistinguishable from non-eosinophilic exacerbations of COPD, a finding previously demonstrated (9, 10) but associated with a shortened length of stay, irrespective of pre-hospital treatment and the presence of consolidation on CXR. Readmission rate over 12 months were not different between the exacerbation phenotypes studied. This data suggests

that acute events requiring hospitalisation associated with eosinophilic inflammation may show a rapid response to corticosteroid treatment, as has previously been shown,(10, 11) hence requiring a shorter length of hospital stay. Conversely however, this did not impact on long term health outcomes or readmission rates which may be more closely related to the underlying condition of the patient, for example disease severity, frailty,(14) muscle mass(15) and comorbidities.(16)

The peripheral blood eosinophil count has been shown to be an independent predictor of mortality in patients with an exacerbation of COPD complicated by pneumonia(17, 18) but it remains unclear whether patients with eosinophilic COPD have different exacerbations. Our data suggests that a simple blood biomarker can identify patients who may have a different and immediate response to systemic corticosteroids during a severe exacerbation. Guidelines for corticosteroid therapy during an exacerbation suggest that the benefits are short-term,(19) with improvements over placebo for symptoms of dyspnoea, improvement of lung function and ventilation-perfusion mismatch in the first 72 hours of care.(5) However, the number needed to treat (NNT) is 10, albeit with a number needed to harm (NNH) of 6.(5). Data from our group (9) and others (20) have shown that the peripheral blood eosinophil count has utility as a marker of corticosteroid responsiveness and may reduce treatment failure rates in COPD exacerbations. A raised blood eosinophil count may also identify a group that are at greatest risk from harm without corticosteroids(11) whereas an eosinopenia may identify those with higher hospital mortality.(17)

In our study we found that a proportion of patients had already been treated with corticosteroids and antibiotics in the community, whether by their General Practitioner (GP), community nurse or by usage of their standby packs as part of the National Institute for Clinical Excellence (NICE) management of COPD exacerbation quality standards.(4) A single dose of prednisolone at doses between 0.5-1mg/kg can reduce the peripheral blood eosinophil count by 50%(21) with effects on eosinophil endothelial adherence occurring as early as 4 hours and returning to normal by 24 hours.(22) It remains unknown what proportion of these patients were non-eosinophilic at the index exacerbation event and whether delivery of eosinophil guided prednisolone may have prevented or delayed an admission. In our study we could not identify any differences in clinical characteristics in patients that were eosinophilic or non-eosinophilic at the time of the exacerbation, further replicating previous work.(10) Available near patient differential cell counts would be promising for use in improving outcomes for patients with COPD. Our in-patient hospital mortality was lower than national audit findings(23) and lower than that previously found by others,(24) but is likely to reflect the near-immediate access to respiratory COPD specialists in the participating centres(25) and the nature of a clinical trial where very sick patients would decline or not be recruited to enter interventional

studies. We observed that approximately 25% of patients admitted with an exacerbation had evidence of community acquired pneumonia (CAP) from plain chest radiography consistent with published literature.(17, 25) Moreover, it is recognised that CXR examination is likely to under-represent the true proportion of COPD exacerbations with significant consolidation and infection (26, 27). Despite having similar treatment, we found that the difference in length of hospital stay between eosinophilic and non-eosinophilic exacerbations was similar when CAP cases were excluded, albeit not statistically significant (p=0.07). This implies a type 2 statistical and remains an important finding.

One limitation of this study is that this is a sub-group analysis within a large randomised clinical trial. The original study(12) was not powered to investigate recovery and clinical outcomes in eosinophilic COPD exacerbations; and the study design could not determine if a hastened recovery in eosinophilic exacerbations was truly as a result of oral corticosteroids as this was not a randomised control trial of corticosteroids in eosinophilic COPD exacerbations. Our findings are thus not definitive, but suggest that further clinical studies are warranted. A second limitation is that we excluded some subjects with COPD from the original study due to the unavailability of haematology results within 12 hours of admission. This has reduced the number of subjects analysed and may bias our results to select out patients that may have been viewed by the admitting clinical team to not warrant a blood test or admission, perhaps with a less severe exacerbation. However, we did not find any differences in length of stay, hospitalisation rate or mortality rates in COPD subjects with haematology results or not (data not shown). Furthermore, we accept that length of stay following an acute admission encompasses both physical and social well-being which together with the presence of co-morbidities, deconditioning and the individual's personal social and family support network will impact on discharge decision. The degree of disease severity, measured by spirometry, the presence of co-morbidities and the proportion that died were not different in the two studied exacerbation phenotypes, and the peripheral blood eosinophil count remained a discriminatory factor for hospital length of stay. In this study we did not have information relating to microbes in determining if these exacerbations were virus or bacteria associated, where there is often an increased length of stay irrespective of treatment.(28)

Conclusion

To conclude, eosinophilic severe hospitalised exacerbations of COPD have shortened length of stay but no difference in longer term mortality or re-hospitalisation. These exacerbations are usually not associated with an elevated CRP, suggesting that better treatment stratifications of antibiotics and corticosteroids during exacerbations can be utilised.

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Statement of work performed: MB, NJG, JEAW, TCH-D, SFH, SJS, IDP, CEB, MDM and MCS contributed to the design of the study. NJG, JEAW, TCH-D, SFH, SJS and MCS recruited the participants into the study. MB, NJG and MCS contributed to data analysis and all authors contributed to data interpretation and to the writing of the manuscript. All authors have reviewed and approved the final draft for submission.

Table 1 Clinical characteristics of COPD subjects entered into acute exercise intervention study, categorised into eosinophilic (≥200 cells/μL and/or ≥2% of the total leukocyte count) and non-eosinophilic COPD exacerbations defined using admission peripheral blood eosinophil count

	Eosinophilic COPD n=62	Non-eosinophilic COPD n=181	p-value
Male, n (%)	35 (56)	81 (54)	0.54
Age, years¥	72 (48-89)	71 (45-93)	0.61
Current smoker, n (%)	14 (23)	42 (23)	0.54
Pack years smoked¥	49 (14-204)	48 (10-210)	0.86
Stable state FEV_1 L	1.00 (0.05)	0.91 (0.03)	0.15
Stable state % FEV_1 predicted	44.9 (1.9)	40.7 (1.4)	0.13
Stable state FEV_1/FVC, %	46.6 (1.9)	46.7 (1.1)	0.99
Proportion using ICS/LABA/LAMA, n (%)	33 (53)	84 (46)	0.38
Proportion using LABA/ICS, n (%)	14 (23)	42 (23)	1.00
Proportion using LAMA/ICS, n (%)	3 (5)	18 (10)	0.30
Pre-admission any prednisolone use, n (%)	10 (16)	35 (19)	0.36
Admission any prednisolone use, n (%)	57 (92)	164 (91)	0.49
Admission only antibiotic use, n (%)	4 (7)	14 (8)	0.74
Consolidation on X-ray, n (%)	8 (13)	61 (34)	<0.01
Peripheral blood eosinophil count, cells/μL ᵒ	400 (350 - 460)	50 (50 – 60)	<0.01
% peripheral blood eosinophil count¥	4.4 (0.8-11.8)	0.5 (0.1-1.99)	<0.01
C reactive protein, mg/L‡	13 (5-48)	55 (18-139)	<0.01
Presence of any co-morbidities, n (%)	42 (68)	133 (73)	0.39
Cardiovascular co-morbidity	29 (47)	80 (44)	0.73
Diabetes	9 (15)	13 (7)	0.08
Depression	16 (26)	33 (18)	0.20
Gastro-oesophageal reflux disease, on treatment	22 (36)	77 (43)	0.33
Length of stay, days¥§	5.0 (1-19)	6.5 (1-33)	0.015
Died during admission, n (%)	2 (3)	4 (2)	0.48
Died within 12 months, n (%)	12 (19%)	32 (18%)	0.85
Hospitalisation rate in following year¥	1.5 (0-9)	1.5 (0-16)	0.88

Data presented as mean (SEM) unless specified. ᵒgeometric mean (95%CI); ‡median (IQR); ¥ mean (range). FEV_1 Forced expiratory volume in 1 second; FVC Forced vital capacity, SGRQ St Georges Respiratory Questionnaire, scores range from 0 to 100 where a lower score indicates a better health status; CRQ Chronic Respiratory Questionnaire where a higher score indicates a better respiratory health status. §any corticosteroid treatment groups (prednisolone alone, both antibiotics and corticosteroids); n=57 in eosinophilic and n=164 in non-eosinophilic groups

References

1. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002;57(10):847-52.
2. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925-31.
3. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67(11):957-63.
4. NICE. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre: Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English. 2010.
5. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2014;9:Cd001288.
6. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA : the journal of the American Medical Association. 2013;309(21):2223-31.
7. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. American journal of respiratory and critical care medicine. 1998;158(5 Pt 1):1511-7.
8. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2000;356(9240):1480-5.
9. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. American journal of respiratory and critical care medicine. 2011;184(6):662-71.
10. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. American journal of respiratory and critical care medicine. 2012;186(1):48-55.
11. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. The European respiratory journal. 2014.
12. Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. Bmj. 2014;349:g4315.

13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. The European respiratory journal. 2005;26(2):319-38.
14. Agboado G, Peters J, Donkin L. Factors influencing the length of hospital stay among patients resident in Blackpool admitted with COPD: a cross-sectional study. BMJ open. 2012;2(5).
15. Greening NJ, Harvey-Dunstan TC, Chaplin EJ, Vincent EE, Morgan MD, Singh SJ, et al. Bedside Assessment of Quadriceps Muscle Using Ultrasound Following Admission for Acute Exacerbations of Chronic Respiratory Disease. American journal of respiratory and critical care medicine. 2015.
16. Kon SSC, Patel MS, Canavan JL, Clark AL, Jones SE, Nolan CM, et al. Reliability and validity of 4-metre gait speed in COPD. European Respiratory Journal. 2013;42(2):333-40.
17. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax. 2012;67(11):970-6.
18. Steer J, Norman EM, Afolabi OA, Gibson GJ, Bourke SC. Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. Thorax. 2012;67(2):117-21.
19. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet. 1999;354(9177):456-60.
20. Aaron SD, Vandemheen KL, Maltais F, Field SK, Sin DD, Bourbeau J, et al. TNFalpha antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. Thorax. 2013;68(2):142-8.
21. Wardlaw AJ, Moqbel R, Kay AB. Eosinophils: biology and role in disease. Advances in immunology. 1995;60:151-266.
22. Altman LC, Hill JS, Hairfield WM, Mullarkey MF. Effects of corticosteroids on eosinophil chemotaxis and adherence. The Journal of clinical investigation. 1981;67(1):28-36.
23. Stone RA, Holzhauer-Barrie J, Lowe D, Searle L, Skipper E, Welham S, et al. COPD: Who cares matters. National Chronic Obstructive Pulmonary Disease (COPD) Audit Programme: Clinical audit of COPD exacerbations admitted to acute units in England and Wales 2014. Executive summary. London: RCP, February 2015.
24. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003;124(2):459-67.
25. Price LC, Lowe D, Hosker HS, Anstey K, Pearson MG, Roberts CM, et al. UK National COPD Audit 2003: Impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. Thorax. 2006;61(10):837-42.
26. Rutschmann OT, Cornuz J, Poletti P-A, Bridevaux P-O, Hugli OW, Qanadli SD, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? Thorax. 2007;62(2):121-5.

27. Shapira-Rootman M, Beckerman M, Soimu U, Nachtigal A, Zeina AR. The prevalence of pulmonary embolism among patients suffering from acute exacerbations of chronic obstructive pulmonary disease. Emerg Radiol. 2015;22(3):257-60.
28. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. American journal of respiratory and critical care medicine. 2006;173(10):1114-21.

Figure Legends

Figure 1

Subject consort algorithm

Figure 2

CRP levels in subjects without consolidation on CXR (red outline) and with consolidation on CXR (blue outline) according to the inflammatory exacerbation phenotype. Data presented as median (interquartile range). Significant difference in CRP in non-CAP eosinophilic versus non-eosinophilic exacerbations ($p<0.0001$). No difference in CRP in CAP associated eosinophilic versus non-eosinophilic exacerbations ($p=0.989$).

Figure 3

Length of hospital stay in eosinophilic and non-eosinophilic COPD exacerbations treated with systemic corticosteroids ± antibiotics; panel A horizontal bar chart; panel B Kaplan-Meier chart