Title

COPD Exacerbation Phenotypes in a Real-World Five Year Hospitalisation Cohort

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ABSTRACT

Introduction: COPD exacerbation phenotypes have been defined in research populations by predominantly infective or inflammatory aetiology . We sort to characterise this in patients admitted to our centre.

Materials and Methods: Case-notes of consecutive patients discharged alive after treatment for acute COPD exacerbations between December 2012 and January 2017 were analysed. Data were collected on treatment, length of stay, C-reactive protein (CRP), eosinophil count and bacterial sputum culture positivity for potentially pathogenic microorganisms (PPM).

Results: 1029 exacerbations were included. There was an inverse correlation between CRP and eosinophil count (rho=-0.277, $p<0.01$). The proportion of eosinophilic exacerbations (eosinophils $\geq 0.3 \times 10^9$/L) was low (157, 15%). Median length of stay was longer in patients with a CRP >100mg/L (4d [3,8] vs 4d [2,7], $p<0.01$) or when given antibiotics (4d [2,8] vs 3d [1,6], $p<0.001$) and shorter if receiving corticosteroids (4d [2, 6] vs 6d [3,7], $p<0.001$). Being sputum culture positive on first exacerbation was associated with sputum culture positivity in subsequent exacerbations. Patients with PPM in sputum culture had a significantly higher median CRP than culture negative patients (38mg/L [18.75, 57] v 18mg/L [8.5,45.5] $p<0.05$). Length of stay, eosinophil count and CRP were significantly correlated between exacerbation pairs.

Conclusions: This real-world population found eosinophilic and high CRP exacerbations to be distinct and significantly stereotyped within individual patients across recurrent exacerbations. High CRP exacerbations are associated with greater healthcare utilisation and chance of sputum positivity with PPM. Eosinophilic exacerbations were associated with lower rate of readmission. Phenotype-driven treatment warrants further investigation in this population.

INTRODUCTION

The management of COPD exacerbations has changed little over the course of the last 20 years, with continued prescription of inhaled bronchodilators, oral corticosteroids and often overuse of antibiotics.[1] Recent research has focussed on using biological markers to delineate between exacerbation groups, with research populations defining exacerbations as predominantly bacterial, viral, eosinophilic or pauci-inflammatory.[2] Particular emphasis had been made on the targeted use of oral corticosteroids in exacerbations, where there is increasing evidence that subsets of patients presenting with lower eosinophil counts may have worse outcomes with such standardised protocols.[3] However, phenotype targeted treatment protocols have not been established in inpatient clinical practice. Indeed phenotypic evaluation has focussed largely on outpatient cohorts with little data on hospitalised patients.

We sought to investigate this by retrospectively reviewing patients admitted with acute exacerbations of COPD over a five-year period to a North London Hospital.

MATERIAL AND METHODS

We completed a retrospective observational casenote study of patients admitted between December 2012 and January 2017 to Barnet Hospital with history of COPD and diagnosed as having an exacerbation as their primary medical diagnosis made by the treating physician and who were discharged alive after treatment.

Consecutive surviving patients who saw the respiratory nurse prior to discharge from hospital were included. Readmissions within two weeks were presumed to be ongoing episodes and excluded. Data were collected on treatment with antibiotics and systemic corticosteroids, length of stay, serum C-reactive protein (CRP), serum eosinophil count and sputum bacterial cultures. Samples were analysed as standard in the hospital laboratory. Patients were defined as having high CRP if admission CRP was ≥100 mg/L, while patients were defined as having high eosinophils if the absolute

eosinophil count was ≥0.3 x10^9/L. Potentially pathogenic microorganisms (PPMs) were defined as *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumonia, Pseudomonas species, E.coli and Klebsiella species.*

Data were assessed for normality and analysed using the Wilcoxon signed-rank test, Spearman's rho and the chi-squared test as appropriate. Averages were expressed as median (interquartile range [IQR]). Analysis was carried out using SPSS Statistics (IBM Corp) and R Statistics version 3.4.1.

RESULTS

CRP and Eosinophil Count

A total of 1029 exacerbations were included from 825 patients. Men made up 51% (n=525) of the cohort. The mean age at admission was 74.4 years [± 9.9]

Using an eosinophil count cut-off of ≥0.3 x10^9/L, we found that 15% (n=157) were eosinophilic exacerbations, while 25% (n=256) had a high CRP (CRP>100 mg/L); 588 (57%) had neither and only 28 exacerbations (3%) had both high eosinophils and high CRP (χ^2 p<0.001). (Table 1). There was a significant inverse correlation between CRP and eosinophil count (Spearman's rho= -0.277, p<0.001).

There was a negative correlation between length of stay and eosinophil count (rho = -0.083, p<0.01) and a positive correlation between CRP and length of stay (rho = 0.127, p<0.001). Length of stay (LoS) was longer in patients who had high CRP (4d [3,8] vs 4d [2,7], p<0.01) or were given antibiotics (4d [2, 8] vs 3d [1, 6], p<0.001). Length of stay was shorter if patients had received corticosteroids (4d [2, 6] vs 6d [3,7], p<0.001). Patients with raised eosinophils were significantly more likely to have been given oral corticosteroids (OR 1.64 95% CI (1.06, 2.56)).

Sputum Microbiology

215 sputum samples were sent for analysis at the time of admission, PPM were found in 11% of sputum cultured . Median CRP was higher in those exacerbations where a PPM was present (69/214,

32.2%) than when other organisms were isolated (38 mg/L [18.75, 57] vs 18 mg/L [8.5, 45.5], p <0.05]). There were no differences in eosinophil count by whether the bacteria isolated were pathogenic or not (0.0 $x10^9$/L [0.0, 0.03] v 0.0 $x10^9$/L [0.0, 0.3]).

Recurrent exacerbations

After excluding non-recovered events, 114 paired recurrent admissions were analysed. Length of stay, eosinophil counts and CRP were significantly correlated between exacerbation pairs. Patients whose first exacerbations were culture positive were more likely to be culture positive at the second exacerbation. Administration of antibiotics was associated with a reduced risk of readmission (OR 0.75 95% CI [0.39, 0.87]), as was an eosinophil count ≥ 0.3 OR 0.54 (95% CI [0.32, 0.92]).

DISCUSSION

This study examined COPD phenotypes in a real-world cohort of hospitalised patients in the UK. We found that exacerbations were significantly stereotyped, with few presenting with a mixed high eosinophil and high CRP presentation. This is likely to be secondary to the aetiology of exacerbation, CRP is a key acute phase protein most significantly associated with bacterial infections,[4] while eosinophils mediate a predominantly TH2 response which previous groups have suggested may inhibit acute phase response. [5] Patients with eosinophilic exacerbations (15%) comprised a lower proportion of the total than have been presented elsewhere, [2, 6], although the prescription of corticosteroid treatment prior to admission may have reduced this proportion. These patients had a significantly shorter average length of hospital stay and lower risk of readmission than bacterial exacerbations. This difference was present regardless of antibiotic or corticosteroid therapy. Bacterial exacerbations defined by high CRP were also associated with the presence of airway bacteria on sputum analysis, which supports the use of this biomarker in exacerbation classification. Eosinophilic and bacterial exacerbations therefore appear to be distinct sub-populations and display clinically important differences.

Our analysis of paired exacerbations also suggests that exacerbation subtypes are stereotyped within patients, although undiagnosed bronchiectasis may explain some paired bacterial exacerbations. Individual patients' previous exacerbation phenotypes may therefore guide future management, particularly in the context of emerging biologically targeted therapies.[7] Eosinophilic exacerbations were associated with a lower readmission rate, which may reflect that these events are milder and more treatment-responsive than bacterial events. The administration of antibiotic therapy was associated with a reduced rate of future readmissions, although this finding should be treated with caution.

Corticosteroid use was associated with a shorter length of stay regardless of eosinophil count, a finding that is in agreement with meta-analysis elsewhere [8]. However there is evidence that steroids may not be of benefit in exacerbations associated with bacterial infection [2, 3].

The retrospective nature of this study limits its applicability. Treatment duration of antibiotics or oral corticosteroids and the frequency of inhaled bronchodilators were at the discretion of the treating clinician while compliance and duration of completed therapy could not be ascertained. Furthermore, we were unable to control for patient's lifestyle factors, co-morbidities or the frequency of community exacerbations.

CONCLUSIONS

In summary, we have shown that hospitalised COPD exacerbations can be usefully characterised into bacterial and eosinophilic phenotypes and that these are stereotyped within patients across recurrent events. Phenotype-driven treatment warrants further investigation in this population.

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CONFLICT OF INTERESTS

The authors have no competing interests to declare.

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Table 1. Treatment and length of stay of exacerbations separated by CRP and Eosinophil Status

n = 1029	Total Cohort		Low Eosinophil (<0.3 x109/L)				High Eosinophil (≥0.3 x109/L)			
			Low CRP (≤100 mg/L)		High CRP (>100 mg/L)		Low CRP (≤100 mg/L)		High CRP (>100 mg/L)	
	N =		**588**	**57%**	**256**	**25%**	**157**	**15%**	**28**	**3%**
CRP (mg/L)	36	(11, 108)	25	(9, 46)	187	(137, 264)	12	(5, 27)	150.5	(5, 27)
Eosinophil ($x10^9$/L)	0.1	(0, 0.2)	0	(0, 0.1)	0	(0, 0.1)	0.5	(0.3, 0.7)	0.4	(0.3, 0.53)
Length of Stay (days)	4	(2, 7)	4	(2,7)	4	(3, 8)	4	(2, 6)	4	(3, 7.5)
Treatment										
Corticosteroids (n)	807	78%	479	82%	172	67%	137	87%	19	68%
Antibiotics (n)	915	89%	512	87%	253	98%	122	78%	28	100%
Both (n)	693	67%	403	69%	169	66%	102	65%	19	68%

All averages are displayed as medians with corresponding Inter quartile range.