e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(5); 422-429

Original Research Article

Phenotypes in Acute Exacerbation of COPD

Sanjay Tandon[1], Harshit Agarwal[2]

[1]Professor and Head, Department of Pulmonary Medicine, People's College of Medical Sciences and Research Centre

[2]PG 3rd Year Resident, Department of Pulmonary Medicine, People's College of Medical Sciences and Research Centre

Received: 27-02-2023 / Revised: 30-03-2023 / Accepted: 30-04-2023

Corresponding author: Dr. Sanjay Tandon

Conflict of interest: Nil

Abstract

Background: We studied the severity of exacerbations, response to standard therapy and length of hospital stay in patients with eosinophilic and non-eosinophilic phenotypes of acute exacerbations of COPD.

Methodology: The study was conducted as an observational cohort study on patients with AECOPD admitted at our centre over a period of 18 months. Blood and sputum counts were done based on which exacerbations were either classified as eosinophilic or non-eosinophilic.

Results: 82 patients with AECOPD presented during the study period. The mean age was 65.38±9.91 years. Based on sputum and absolute blood eosinophil count, 32.9% and 58.5% cases had eosinophilic AECOPD respectively. We found a significant association of severe to life-threatening AECOPD with sputum eosinophilia. 18 patients out of 27 eosinophilic AECOPD had severe to life threatening exacerbations while 14 patients out of 55 non-eosinophilic AECOPD had severe to life threatening exacerbations ($p<0.05$). We did not find any association of sputum and blood eosinophilia with LOHS [sputum (eos vs non-eos,9.22 and 8.84 days, $p = 0.77$), AEC (eos vs non-eos, 8.40 and 9.76 days, $p = 0.27$] and relief of symptoms to standard therapy at day 5 ($p>0.05$). We found a weak positive correlation of peripheral blood eosinophilia with sputum eosinophilia in acute exacerbation of COPD ($r=0.423$; $p<0.05$).

Conclusion: Non-eosinophilic exacerbations were twice as common as eosinophilic exacerbations. No difference in LOHS was seen in eosinophilic and non-eosinophilic phenotypes. Although, sputum eosinophilia was associated with more severe exacerbations, there was no difference in response to standard therapy between the two phenotypes.

Keywords: AECOPD, Eosinophilia, Sputum, Outcome, Response, Severity.

Introduction

Exacerbations are common in COPD patients. Acute exacerbations of COPD patients have increased amounts of inflammatory cells such as neutrophils, eosinophils, macrophages, and lymphocytes. The different phenotypes of airway inflammation are reflected in the different types of inflammatory cells found in AECOPD. [1] Neutrophilic airway inflammation is associated with AECOPD in more than half of patients. [2] Eosinophilia has been found in 10% to 40% of patients with AECOPD. [3,4]

According to the literature, eosinophilia in the blood of AECOPD patients can be used as a reliable indicator of eosinophilia in sputum. [5] As in asthma, it is unclear how eosinophilic inflammation affects risk stratification and prognosis of COPD patients; therefore, more attention has been paid to this issue recently. [6]

According to recent studies, the response to systemic corticosteroids in AECOPD is better in eosinophilic AECOPD [7,8]. Therefore, categorizing patients according to phenotype may be useful and help to individualize therapy.

The percentage of eosinophils in sputum is a more reliable estimate for determining eosinophilia in AECOPD, as this method is a direct and reliable way to assess airway inflammation. However, it has certain limitations, such as the need for expertise and non-availability at most centers. Therefore, determination of eosinophil count in peripheral blood is used as an alternative method because it is simple, minimally invasive, and readily available. With this in mind, the present study was conducted at a tertiary care center to compare the severity of exacerbations, response to standard therapy, and length of hospital stay in patients with eosinophilic and non-eosinophilic phenotypes of acute exacerbations of COPD. We also determined the relationship between the peripheral blood eosinophil counts and eosinophil percentage in sputum.

Methodology

This was an observational cohort study done at a tertiary care center in central India over a period of 18 months from January 2021 to April 2022 on patients with acute exacerbation of COPD admitted in Pulmonary Medicine ward. All patients over 40 years of age diagnosed with acute exacerbation of COPD were included, while COPD patients with pneumonia, pneumothorax, cardiac disease, Asthma COPD overlap syndrome, on systemic corticosteroid within the past 1 month and those not giving consent were excluded from the study.

After approval from the Institute's ethics committee, all patients who met the inclusion criteria were enrolled in the study, and written informed consent was obtained from all the study participants. A detailed history was obtained on sociodemographic variables, symptoms, duration of COPD, and risk factors (such as smoking and its duration). Blood samples were collected and sent for a complete blood count. Patients were divided into two groups based on the absolute eosinophil count in peripheral blood (Eosinophilic ≥200 cells/mm3 and non-eosinophilic < 200 cells/mm3).

Furthermore, the sputum of all patients was collected at the time of admission. If patients did not expectorate sputum, sputum induction with hypertonic saline (3%) was done. Collected sputum was centrifuged, smeared, and stained with Leishman's stain to obtain differential cell counts. Patients were stratified into two groups (sputum eosinophil ≥2% and <2%). Patients were also subjected to routine investigations such as sputum for AFB, Chest X-ray, stool for ova cysts and parasites, blood peripheral smear to rule out diseases like active tuberculosis, parasitic infestations, eosinophilic pneumonias, malignancy, and chronic eosinophilic leukemia. Burge S *et al*. classification (2003) was used to classify severity of AECOPD exacerbations into moderate, severe, very severe, and life-threatening. [13] mMRC dyspnea scale was used to asses response to standard therapy at day 5, which included steroids, antibitiocs and bronchodialtors. LOHS was determined for each admitted patients.

Statistical Analysis

Data was compiled using MS-Excel and analyzed using IBM SPSS Software version

20 (IBM Corp. Illinois, Chicago). Based upon eosinophil count, patients were categorized into two groups and then they were compared with respect to severity of exacerbations and response to standard therapy using Chi square test and for mean Length of Hospital Stays (LOHS) using independent T test. Association of peripheral blood eosinophilia with sputum eosinophilia was also determine using Chi-square test. Correlation between sputum eosinophil and AEC was done using Pearson correlation coefficient. P value of less than 0.05 was considered statistically significant.

Results

The present study was conducted on a total of 82 patients with AECOPD presenting at our Institute over a period of 18 months from January 2021 to April 2022 with mean age of 65.38±9.91 years.

Table 1: Distribution of patients according to baseline variables

Baseline variables		Frequency (n=82)	Percentage
Sex	Male	76	92.7%
	Female	6	7.3%
Age (years)	≤50	11	13.4%
	51-60	13	15.9%
	61-70	34	41.5%
	71-80	21	25.6%
	>80	3	3.7%
Smoker's	Current smoker	39	47.6%
	Ex-smoker	38	46.3%
	Non smoker	5	6.1%
Comorbidities	Diabetes	15	18.2%
	Hypertension	4	4.9%
	Healed Pulmonary tuberculosis	3	3.7%
	None	60	73.2%

Mean age of patients with AECOPD was 65.38±9.91 years. Majority of patients in our study were elderly i.e. above 60 years of age. There was male predominance with male:female ratio of 12.7:1. 47.6% patients with AECOPD were current smokers, whereas 46.3% cases were ex-smokers. Only 6.1% patients with AECOPD enrolled in our study were nonsmokers. The most common associated comorbid condition in patients with AECOPD was diabetes (18.2%), followed by hypertension (4.9%), and healed pulmonary tuberculosis (3.7%).

Table 2: Distribution according to eosinophil count

Eosinophil count		Frequency (n=82)
Sputum Eosinophil count	<2%	55(67.0%)
	≥2%	27(32.9%)
Absolute blood Eosinophil count	<200	34(41.4%)
	≥200	48(58.5%)

Based upon sputum eosinophil percentage, 67.0% and 32.9% cases had non eosinophilic and eosinophilic AECOPD respectively. Based on blood eosinophil count, a higher numbers of eosinophilic exacerbations were detected(58%).

Table 3: Length of hospital stay in eosinophilic and non-eosinophilic phenotypes of acute exacerbation of COPD

Length of hospital stay	Sputum Eosinophil		Absolute blood eosinophil	
	<2% (n=55)	**≥2% (n=27)**	**<200 (n=34)**	**≥200 (n=48)**
Mean	8.84 days	9.22 days	9.76 days	8.40 days
SD	4.663 days	4.430 days	4.17 days	3.07 days
P value	0.77		0.27	

There was no difference in LOHS between eosinophilic and non-eosinophilic phenotypes based on sputum and absolute blood eosinophil count.

Table 4: Severity of AECOPD in eosinophilic and non-eosinophilic phenotypes

Severity of AECOPD	Sputum Eosinophil		Absolute blood eosinophil	
	<2% (n=55)	≥2% (n=27)	<200 (n=34)	≥200 (n=48)
Moderate	41 (74.5%)	9 (33.3%)	23 (67.6%)	27 (56.2%)
Severe	8 (14.5%)	11 (40.7%)	6 (17.6%)	13 (27.0%)
Very severe	3 (5.5%)	4 (14.8%)	2 (5.8%)	5 (10.4%)
Life threatening	3 (5.5%)	3 (11.1%)	3 (8.8%)	3 (6.2%)
P value	**0.005**		0.60	

We found a statistically significant association of severe to life threatening AECOPD with sputum eosinophilia ($p<0.05$) but not with peripheral blood eosinophilia ($p = 0.60$).

Table 5: Relief of symptoms at 5th day in eosinophilic and non-eosinophilic phenotypes

Relief of symptoms at 5th day	Sputum Eosinophil		Absolute blood eosinophil	
	<2% (n=55)	**≥2% (n=27)**	**<200 (n=34)**	**≥200 (n=48)**
No	7 (12.7)	2 (2.5)	9 (26.4)	7 (14.5)
Yes	48 (87.2)	25 (92.5)	23 (67.6)	41 (85.5)
P value	0.47		0.14	

There was no significant difference in relief of symptoms to standard therapy at day 5 between eosinophilic and non-eosinophilic phenotypes of acute exacerbations of COPD based on sputum($p= 0.47$) as well as absolute blood eosinophil count ($p = 0.14$).

Table 6: Correlation of peripheral blood eosinophilia with sputum eosinophilia in acute exacerbation of COPD

R	R Square	Adjusted R Square	Std. Error of the Estimate	F	Sig.
0.423	0.179	0.169	0.431	**17.455**	**0.001**

We found a weak positive correlation of peripheral blood eosinophilia with sputum eosinophilia in acute exacerbation of COPD ($r=0.423$; $p<0.05$).

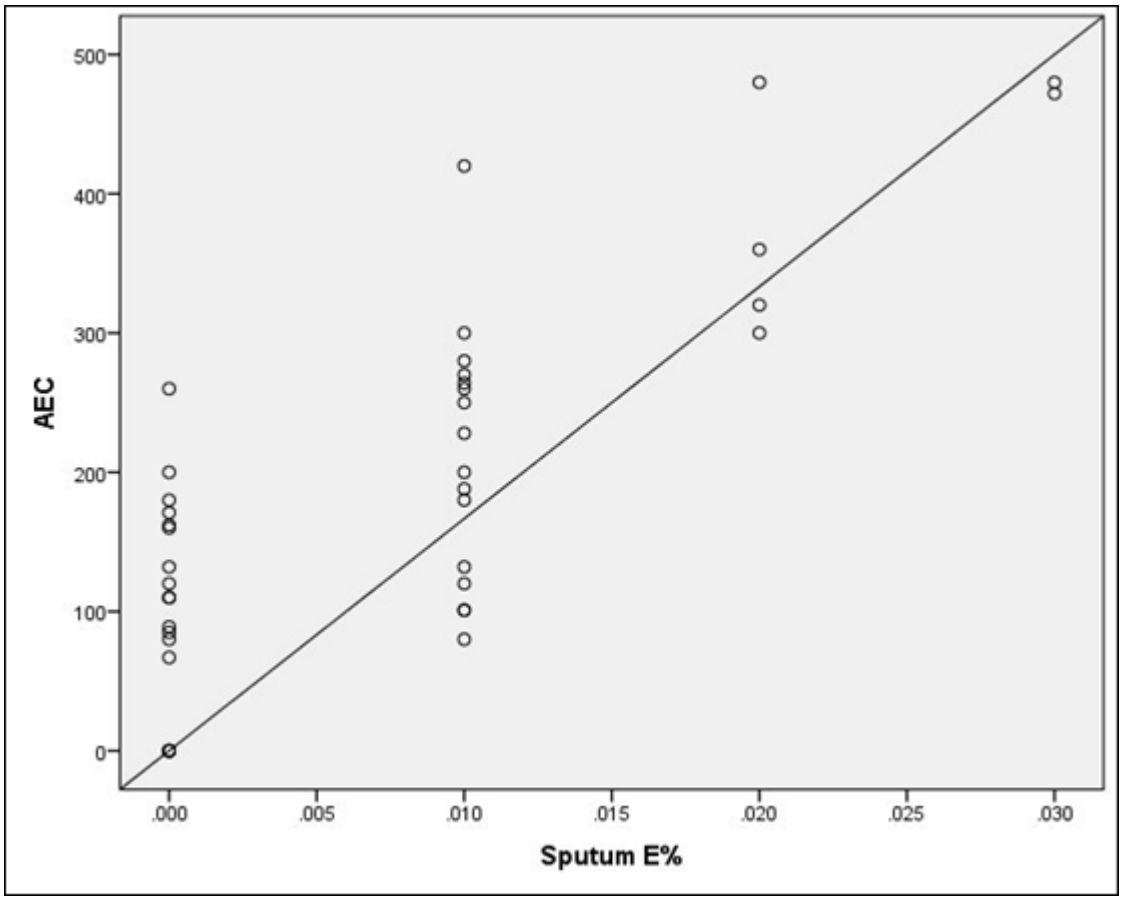

Figure 1

Discussion

AECOPD is usually characterized by neutrophilic inflammation; however, an increase in proportions of other inflammatory cells in sputum, such as eosinophils, macrophages, and lymphocytes, is also observed in a few cases.[2] Eosinophilia in the blood may be considered an important marker reflecting the sputum eosinophil level in patients with AECOPD. Literature suggests that eosinophilic AECOPD is associated with a higher rate of exacerbations, prolonged hospital stay as well as higher mortality. Studies have also reported that patients with eosinophilic COPD show a better response to systemic corticosteroids during exacerbations.[7,8] The present study was conducted on a total of 82 inpatients to compare the severity of exacerbations and clinical outcomes to standard therapy. We also determined the relationship between peripheral blood eosinophil count and sputum eosinophil percentage.

Proportion Of Eosinophilic Exacerbations

We looked for sputum eosinophilia as well as blood eosinophila in AECOPD patients. Sputum eosinophil percentage of ≥2% was considered eosinophilic. A blood eosinophil count of ≥200 cells/mm3 was taken as eosinophilic. In our study, higher number of patients had non-eosinophilic exacerbations than eosinophilic exacerbations by sputum criterion (≥2%). Helala *et al*., based on sputum eosinophils ≥2%, found an equal proportion of eosinophilic (51%) and non-eosinophilic exacerbations.[11] Dai *et al*. also found similar results (Eos: 47.03% vs

Non-Eos: 52.97%).[12] However, in our study, eosinophilic exacerbations were higher by blood counts (≥200 cells/mm3). Duman *et al*. found a higher proportion of non-eosinophilic exacerbations when they defined exacerbations by blood eosinophil >2% of TLC.[13]

Association Of Eosinophilic And Non-Eosinophilic Phenotypes With Length Of Hospital Stay

According to recent studies, the non-eosinophilic phenotype of AECOPD has been linked with prolonged hospital stays. However, we found no such association. When sputum eosinophilia≥2% was considered, mean LOHS by AEC was also similar, 8.40 days in eosinophilic and 9.76 days in non-eosinophilic exacerbations (p =0.27). The mean LOHS in our study was longer than in other studies. Bafadhel *et al*. found LOHS of 5 days in eosinophilic exacerbations and 6.5 days in non-eosinophilic exacerbations [p = 0.015].[1] Similarly, Ho *et al*.[14] and Greulich *et al*.[15] found shorter LOHS in eosinophilic exacerbations than in non -eosinophilic exacerbations.

Severity Of Aecopd In Eosinophilic And Non-Eosinophilic Phenotypes

We observed that the eosinophilic phenotype of AECOPD by sputum eosinophilia was associated with more severe illness compared to non-eosinophilic AECOPD. Hastie *et al*. observed a significant association between raised sputum eosinophil ≥2% and increased severity of exacerbations. In our study, such association could not be observed with absolute blood eosinophil count.[16] Helala *et al*. observed a significant association between absolute blood eosinophil count ≥300 cells/mm3 and increased severity of exacerbations.[17] Contrary to the result of our study, Jabarkhil *et al*. using blood eosinophil count found that non-eosinophilic phenotype was associated with more severe exacerbations as compared to the eosinophilic phenotype.[18]

Response To Standard Therapy

Response to standard therapy was assessed with relief of symptoms at the end of day five. We observed that the majority of patients in both groups had symptom relief at day five. There was no difference between the two phenotypes with the degree of relief of symptoms to standard therapy on 5th day. Bafadhel *et al*. reported a better response following treatment with ICS in eosinophilic phenotype having absolute blood eosinophil count ≥ 200 cells/mm3 as compared to non-eosinophilic AECOPD.[21] Greulich *et al* observed that patients with severe COPD exacerbations with absolute blood eosinophil count<300 cells /mm3 were less responsive to systemic corticosteroids.[15]

Association Of Sputum Eosinophilia With Peripheral Blood Eosinophilia

Determining peripheral blood eosinophil count is an easy, minimally invasive, and readily available method that may potentially be used as an alternative to sputum eosinophil percentage to determine the prognosis and treatment response in patients with AECOPD.[21] In our study, we found a weak positive correlation of peripheral blood eosinophilia with sputum eosinophilia ≥2% (r = 0.423; p<0.05). Correlation between blood AEC and sputum eosinophilia has been reported in stable COPD.

Singh *et al*. reported significantly high blood AEC of ≥257cells/mm3 in eosinophilic patients characterized by a sputum eosinophil percentage of ≥3%, and the authors showed a moderate correlation between sputum eosinophilia with peripheral blood eosinophils count (r=0.54,p<0.0001).[19] Hastie *et al*. performed ROC analyses and demonstrated a weak relationship of blood eosinophils count of ≥250 cells/mm3 to predict sputum eosinophils≥2%.[16]Negewo

et al. showed a moderate correlation between AEC and sputum eosinophilia (ρ=0.535; P<0.0001).[20] While other studies have shown a correlation between sputum eosinophilia ≥2% and blood eosinophil count of ≥ 200 cells/mm3 in stable COPD, we have found a similar association in AECOPD.

Conclusion

Non-eosinophilic exacerbations were twice as common as eosinophilic exacerbations. No difference in LOHS was seen in eosinophilic and non-eosinophilic phenotypes. Although, sputum eosinophilia was associated with more severe exacerbations, there was no difference in response to standard therapy between two phenotypes.

References

1. Gao J, Chen B, Wu S, Wu F. Blood cell for the differentiation of airway inflammatory phenotypes in COPD exacerbations. BMC pulmonary medicine. 2020 Dec;20(1):1-9.
2. Balzano G, Stefanelli F, Iorio C, De Felice A, Melillo EM, Martucci M, Melillo G. Eosinophilic inflammation in stable chronic obstructive pulmonary disease: relationship with neutrophils and airway function. American journal of respiratory and critical care medicine. 1999 Nov 1;160(5):1486-92.
3. Brightling CE, Bleecker ER, Panettieri Jr RA, Bafadhel M, She D, Ward CK, Xu X, Birrell C, van der Merwe R. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. The Lancet Respiratory Medicine. 2014 Nov 1;2(11):891-901.
4. Eltboli O, Bafadhel M, Hollins F, Wright A, Hargadon B, Kulkarni N, Brightling C. COPD exacerbations severity and frequency is associated with References Page 47 impaired macrophage efferocytosis of eosinophils. BMC pulmonary medicine. 2014 Dec;14(1):1-0.
5. Schumann DM, Tamm M, Kostikas K, Stolz D. Stability of the blood eosinophilic phenotype in stable and exacerbated COPD. Chest. 2019 Sep 1;156(3):456-65.
6. Adir Y, Hakrush O, Shteinberg M, Schneer S, Agusti A. Circulating eosinophil levels do not predict severe exacerbations in COPD: a retrospective study. ERJ open research. 2018 Jul 1;4(3).
7. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, Dolovich J, Hargreave FE. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. American journal of respiratory and critical care medicine. 1998 Nov 1;158(5):1511-7.
8. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, Pavord ID. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. The Lancet. 2000 Oct 28;356(9240):1480-5.
9. National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care. [Internet]. London: Royal College of Physicians (UK); 2010 Jun. (NICE Clinical Guidelines, No. 101.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK65039/
10. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. European Respiratory Journal. 2003 Jun 1;21(41 suppl):46s-53s.
11. Helala LA, AbdelFattah EB, Elsalam HM. Blood and sputum eosinophilia in COPD exacerbations. The Egyptian

Journal of Bronchology.2022Dec;16(1):1-5.
12. Dai G, Ran Y, Wang J, Chen X, Peng J, Li X, Deng H, Xiao M, Zhu T. Clinical differences between eosinophilic and noneosinophilic acute exacerbations of chronic obstructive pulmonary disease: a Multicenter Cross-Sectional Study. Mediators of Inflammation. 2020 Nov 12;2020
13. Duman D, Aksoy E, Agca MC, Kocak ND, Ozmen I, Akturk UA, Gungor S, Tepetam FM, Eroglu SA, Oztas S, Karakurt Z. The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. International journal of chronic obstructive pulmonary disease. 2015; 10:2469.
14. Ho J, He W, Chan MT, Tse G, Liu T, Wong SH, Leung CC, Wong WT, Tsang S, Zhang L, Chan RY. Eosinophilia and clinical outcome of chronic obstructive pulmonary disease: a meta-analysis. Scientific reports. 2017 Oct 18;7(1):1-0.
15. Greulich T, Tüffers J, Mager S, Eder A, Maxheim M, Alter P, Schmeck B, Vogelmeier CF. High eosinophil blood counts are associated with a shorter length of hospital stay in exacerbated COPD patients–a retrospective analysis. Respiratory research. 2020 Dec;21(1):1-8.
16. Hastie AT, Martinez FJ, Curtis JL, Doerschuk CM, Hansel NN, Christenson S, Putcha N, Ortega VE, Li X, Barr RG, Carretta EE. Sputum or blood eosinophil association with clinical measures of COPD severity in the SPIROMICS cohort. The Lancet. Respiratory medicine. 2017 Dec;5(12):956.
17. Helala LA, AbdelFattah EB, Elsalam HM. Blood and sputum eosinophilia in COPD exacerbations. The Egyptian Journal of Bronchology. 2022 Dec; 16(1):1-5.
18. Jabarkhil A, Moberg M, Janner J, Petersen MN, Jensen CB, Henrik Ängquist L, Vestbo J, Jess T, Porsbjerg C. Elevated blood eosinophils in acute COPD exacerbations: better short-and long-term prognosis. European clinical respiratory journal. 2020 Jan 1; 7(1): 1757274
19. Singh D, Watz H, Beeh KM, Kornmann O, Leaker B, Colgan B, Lucci G, Emirova A, Nandeuil MA, Santoro D, Balzano D. COPD sputum eosinophils: relationship to blood eosinophils and the effect of inhaled PDE4 inhibition. European Respiratory Journal. 2020 Aug 1;56(2).
20. Negewo NA, McDonald VM, Baines KJ, Wark PA, Simpson JL, Jones PW, Gibson PG. Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD. International journal of chronic obstructive pulmonary disease. 2016; 11:1495.
21. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JE, Morgan MD, Brightling CE, Hussain SF, Pavord ID, Singh SJ, Steiner MC. Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. Chest. 2016 Aug 1;150(2):320-8.