ORIGINAL RESEARCH

The association between blood eosinophil percent and bacterial infection in acute exacerbation of chronic obstructive pulmonary disease

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Introduction: The use of antibiotics is based on the clinician's experience and judgment, and antibiotics may often be overused in the treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Eosinophils have been studied as biomarkers of bacterial infection and prognostic factors in chronic obstructive pulmonary disease and AECOPD. Thus, the purpose of this study was to determine whether eosinophils could be used to determine bacterial infection in AECOPD events.

Methods: We retrospectively analyzed the medical records of patients admitted to Korea University Guro Hospital for AECOPD between January 2011 and May 2017. Data pertaining to baseline characteristics, results of previous pulmonary function tests, treatment information during the admission period, and history of pulmonary treatment were collected before admission.

Results: A total of 736 AECOPD events were eligible for inclusion and were divided into two groups based on the eosinophil count: those involving eosinophil counts of less than 2% (546 events) and those involving counts of 2% or more (190 events). In univariate analysis, the only bacterial pathogen identification events and bacterial-viral pathogen co-identification events were significantly more frequent in the group with eosinophil counts of less than 2% ($P=0.010$ and $P=0.001$, respectively). In logistic regression analysis, the rates of only bacterial pathogen identification [odds ratios =1.744; 95% confidence interval, 1.107–2.749; $P=0.017$] and bacterial-viral pathogen co-identification [odds ratios=2.075; 95% confidence interval, 1.081–3.984; $P=0.028$] were higher in the group with eosinophil count less than 2%.

Conclusion: In conclusion, eosinophil counts of less than 2% are potential indicators of a bacterial infection in AECOPD events. Eosinophils could thus serve as a reference for the use of antibiotics in AECOPD treatment.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, bacterial infection, eosinophil

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Introduction

Chronic obstructive pulmonary disease (COPD) is an airway and lung disease that impairs the immune lung defense system making it susceptible to bacterial infections.[1,2] COPD patients may experience acute exacerbations due to these bacterial infections.[3] The global initiatives for chronic obstructive lung disease

(GOLD) guideline recommend the use of antibiotics when a bacterial infection is suspected in events of acute exacerbations of chronic obstructive pulmonary disease (AECOPD).[4] The GOLD guideline also suggests that symptoms such as increase in dyspnea, sputum volume, and sputum purulence are the criteria for antibiotic usage.[5] Since these symptoms are not presented as absolute numerical values, the use of antibiotics is based on clinical experience and judgment. Hence, antibiotics are often overused and stray from the GOLD guidelines, as reported by a study conducted in Europe.[6]

To solve this problem, various biomarkers that distinguish bacterial infections have been studied, which include C-reactive protein (CRP) and procalcitonin. However, CRP commonly elevates in viral infections and hence cannot specifically distinguish bacterial infections.[7,8] Procalcitonin is useful for distinguishing bacterial infections but is expensive and less accessible.[9] Therefore, we need a biomarker that can specifically distinguish bacterial infections, while being cost-effective and user-friendly.

It is known that eosinophils are lowered in pneumonia and other infectious diseases caused by bacteria.[10–12] Eosinophils are a simple test that can be easily measured and are inexpensive to use in the clinical field. Thus, the purpose of this study was to determine whether eosinophils could be used to determine bacterial infection in AECOPD events.

Method
Data recruitment
We retrospectively reviewed and analyzed the medical records of 736 AECOPD events in patients admitted in the Korea University Guro Hospital from January 2011 to May 2017. We searched our electronic medical records database using keywords such as "COPD" and "acute exacerbation". This study was approved by our institutional review board (KUGH16131-002). This study was a retrospective study, so patient consent was not necessary, and we maintained patient confidentiality with the Declaration of Helsinki.

COPD was diagnosed based on the GOLD guidelines, where a ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity was less than 70% in post-bronchodilator spirometry prior to admission, and AECOPD was defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variation and leads to a change in medication".[4,13] All the patients were older than 40 years.

Patients were excluded 1) if the cause of admission was not AECOPD, for example, acute heart failure, acute pulmonary edema, acute pulmonary embolism, pneumothorax, or arrhythmia; or 2) if they had a co-morbidity that could affect the eosinophilic count, for example, cancer, allergic disorder, autoimmune disease, or hematologic disease; or 3) if they had no clinical data, such as pulmonary function test (PFT), laboratory test, and culture test results.

Medical records were reviewed and analyzed for the following data: age, gender, smoking history, comorbidities, treatment information during admission period, laboratory test, culture test, polymerase-chain-reaction (PCR) assay, previous PFT, and pulmonary-related treatment before admission. Laboratory test, culture test, and PCR assay were conducted within 24 hrs after admission. Blood, sputum, and urine culture were conducted for identification of the bacterial infection. Sputum PCR assay was conducted for identification of viral infection. Sputum PCR assays were performed using nasopharyngeal aspiration by a trained doctor. And sputum PCR assay can detect influenza virus, respiratory syncytial virus, parainfluenza virus, coronavirus, rhinovirus, enterovirus, adenovirus, bocavirus, and metapneumovirus. We defined "maintenance oral steroid" as using steroid for more than three weeks and "short-term oral steroid use" as using steroid for three weeks or less.

Statistical analysis
Data were analyzed by SPSS 20 software (SPSS for windows, SPSS Inc., Chicago, IL, USA). Data were reported as mean ± standard deviation or number and percent of each group. We divided the two groups with respect to eosinophil count of 2%. Continuous variables were compared using the Mann–Whitney test or independent t-test, while categorical variables were compared using the chi-square test or Fisher`s exact test. Variables with P-value <0.05 on univariate analysis were tested in logistic regression analysis. When analyzing logistic regression analysis, white blood cell (WBC) and CRP were converted into binary variables based on the optimal cut-off values, and these optimal cut-off values were calculated using receiver operating characteristic. The cut-off values of WBC and CRP were 10,450.0 cells/mm^3 and 44.7 mg/L, respectively.

The logistic regression analysis was assessed by the Hosmer–Lemeshow test, with P-value <0.05 considered statistically significant. Multivariate analysis was performed in three different models. Model-1 analyzed only bacterial pathogen identification, bacterial-viral pathogen co-identification, and laboratory findings (WBC, CRP). Model-2 analyzed all other factors that were statistically significant in the univariate analysis except for the no-pathogen identification factor. Model-3 analyzed the age and gender along with the factors of model-2.

Results

Baseline characteristics

With respect to the exclusion criteria, only 736 AECOPD events were eligible. Out of these, 546 events with eosinophil counts less than 2% and 190 events with eosinophil counts of 2% or more were analyzed. Table 1 shows baseline characteristics of the total events and the two groups.

There were statistically significant differences between the two groups: length of hospital stay ($P<0.001$), experience of intensive unit care ($P=0.045$), WBC ($P<0.001$), eosinophil percent ($P<0.001$), eosinophil count ($P<0.001$), CRP ($P<0.001$), and FEV$_1$ (liters) ($P=0.003$). There were no statistically significant differences in the other factors (P-value for all other variables >0.05) (Table 1).

Pulmonary-related treatment before admission

We analyzed any past treatment associated with pulmonary conditions before admission. There was a statistically significant difference between the two groups for maintenance oral steroid ($P=0.006$), but no statistically significant differences in the other factors were noted (P-value for all other variables >0.05) (Table 2).

Isolated pathogen

We classified all events into four groups according to bacteria or virus identification: only bacterial pathogen identification, only viral pathogen identification, bacterial-viral pathogen co-identification, and no-pathogen identification. The only bacterial pathogen identification events and bacterial-viral pathogen co-identification events were significantly more frequent in the group with eosinophil counts of less than 2% ($P=0.010$ and $P=0.001$, respectively). The no-pathogen identification events were significantly more frequent in the group with eosinophil counts of 2% or more ($P<0.001$). The

frequency of only viral pathogen identification events did not show any statistically significant difference between the two groups ($P=0.302$; Table 3).

Logistic regression analysis

In all multivariate models, the only bacterial pathogen identification events and bacterial-viral co-identification events showed statistically significant differences between the two groups (Table 4). Table 4 shows odds ratio, 95% confidence interval, and P-value by logistic regression analysis.

Discussion

This study was the first to analyze whether bacterial infections can be differentiated based on the eosinophil percent of 2% in AECOPD patients in Korea. Our results showed that only bacterial pathogen identification events and bacterial-viral pathogen co-identification events are significantly more frequent in groups with eosinophil counts of less than 2%. Since some studies used eosinophil percent of 2% as a cut-off value to predict the prognosis and treatment response in COPD, we also used the same cut-off value. For example, some studies analyzed the prognosis of steroid inhaler response and treatment in COPD based on the 2% value,[14,15] while some analyzed the pneumonia risk and stability in stable COPD based on the 2% value.[11,16]

Eosinophils, which make up 1–6% of the total WBCs, have several receptors on their cell surface and secrete various cytokines and mediators.[17] Research in eosinophils was initially focused on helminth infection and allergic disorders.[18] As research progressed, it was found that eosinophils performed various functions in the human body such as regulation of innate and adaptive immunity and responses to infection and inflammation.[19,20] Since animal studies showed that eosinophil count decreased with acute bacterial infection, eosinophils have been studied as a marker of bacterial infections.[12,21] The reason for the decrease in peripheral eosinophils count in acute bacterial infection was the accumulation of eosinophils at the inflammatory site and inhibition of egress from the bone marrow.[22] Additionally, bacterial infection in lungs affects the cytokine and chemokine release from the airway smooth muscle cells (ASMC).[23] Bacterial infections activate human ASMC to release C-X-C motif chemokine (CXCL)-8 that increases neutrophil recruitment.[24] On the other hand, bacterial infections inhibit the release

Table 1 Baseline characteristics

	Eosinophil count of less than 2% events (N=546)	Eosinophil count of 2% or more events (N=190)	P-value
No. of exacerbation events/patients	546/379	190/152	
Age (years)[‡]	72.5±8.9	71.6±10.5	0.292
Gender, no. of exacerbations			
Male[*]	378 (69.2%)	140 (73.7%)	0.247
Female[*]	168 (30.8%)	50 (26.3%)	
Smoking history, no. of exacerbations			
Current-smoker[*]	78 (14.3%)	30 (15.8%)	0.433
Ex-smoker[*]	319 (58.4%)	115 (60.5%)	
Non-smoker[*]	149 (27.3%)	45 (23.7%)	
Pack/year history[‡]	42.2±22.0	44.0±28.0	
Comorbidities, no.			
Hypertension[*]	289 (52.9%)	87 (45.8%)	0.090
Diabetes[*]	135 (24.7%)	37 (19.5%)	0.141
Coronary artery disease[*]	83 (15.2%)	36 (18.9%)	0.227
Cerebrovascular accident[*]	23 (4.2%)	11 (5.8%)	0.372
Treatment information during admission period			
Length of hospital stay (days) [‡]	11.2±10.5	8.0±5.9	<0.001
Experience of intensive unit care, no.[*]	73 (13.4%)	15 (7.9%)	0.045
Mortality (in hospital)[*]	28 (5.1%)	4 (2.1%)	0.078
Laboratory findings			
WBC (cells/mm^3) [‡]	12,163.6±5,506.9	8,652.1±3,046.3	<0.001
CRP (mg/L)[‡]	97.2±95.5	36.2±59.8	<0.001
Baseline spirometry after bronchodilation			
FEV$_1$ (liters) [‡]	1.2±0.5	1.3±0.5	0.010
FEV$_1$ (% of predicted value) [‡]	50.0±19.6	50.9±18.0	0.566
Ratio of FEV$_1$ to FVC (%)[‡]	48.3±12.4	49.1±12.0	0.477
Severity of COPD, no. of exacerbations			
GOLD I[*]	44 (8.1%)	13 (6.8%)	0.227
GOLD II[*]	197 (36.1%)	84 (44.2%)	
GOLD III[*]	234 (42.9%)	73 (38.4%)	
GOLD IV[*]	71 (13.0%)	20 (10.5%)	

Notes: [*]Numbers are presented as N (%). [‡]Numbers are presented as mean ± Standard deviation.
Abbreviations: WBC, white blood cell; CRP, C-reactive protein, FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; GOLD, the global initiatives for chronic obstructive lung disease.

of eotaxin-1 that is proven to induce blood eosinophilia in studies on mice.[25]

Many studies have been conducted on the relationship between eosinophil and COPD and AECOPD. In COPD analysis, it was thought that sputum eosinophilia could be indirectly predicted by the peripheral blood eosinophils,[26] and blood or sputum eosinophil count were inversely related to the bacterial load.[10] In AECOPD analysis, eosinopenia is predicted to have a poor prognosis. Eosinopenia group based on eosinophil count of 40/mm^3 is associated with long hospital day and high mortality.[27] Our results suggested that the eosinopenia group showed an increase in the mortality rate and duration of hospitalization because the rate of bacterial infection was higher than the eosinophilia group.

Studies on the relationship between eosinophils and viral infection have shown heterogeneous results. There

Table 2 Pulmonary-related treatment before admission

	Eosinophil count of less than 2% events (N=546)	Eosinophil count of 2% or more events (N=190)	P-value
Inhaler			
LABAs[*]	4 (0.7%)	4 (2.1%)	0.465
LAMAs[*]	65 (11.9%)	26 (13.7%)	
LABAs+LAMAs[*]	91 (16.7%)	30 (15.8%)	
ICS/LABAs[*]	47 (8.6%)	10 (5.3%)	
Triple therapy (ICS/LABAs+LAMAs) [*]	211 (38.6%)	73 (38.4%)	
None	128 (23.4%)	47 (24.7%)	
Oral medication			
β2 oral agonist	80 (14.7%)	18 (9.5%)	0.070
N-acetylcysteine[*]	52 (9.5%)	17 (8.9%)	0.814
Roflumilast[*]	46 (8.4%)	10 (5.3%)	0.157
Mucolytic agent[*]	299 (54.8%)	107 (56.3%)	0.711
Leukotriene-receptor antagonist[*]	59 (10.8%)	23 (12.1%)	0.624
Maintenance oral steroid[*]	27 (4.9%)	1 (0.5%)	0.006
Short-term oral steroids[*]	13 (2.4%)	5 (2.6%)	0.790
Oral antibiotics[*]	27 (4.9%)	10 (5.3%)	0.863
Oxygen therapy at home[*]	135 (24.7%)	32 (16.8%)	0.025
Pneumococcal vaccination[*]	159 (29.1%)	56 (29.5%)	0.830

Note:*Numbers are presented as N (%).
Abbreviations: LABAs, long-acting B agonist bronchodilator; LAMAs, long-acting antimuscarinic agent bronchodilator; ICS, inhaled corticosteroids.

Table 3 Identified pathogens

	Eosinophil count of less than 2% (N=546)	Eosinophil count of 2% or more (N=190)	P-value
Only bacterial pathogen identification[*]	162 (29.7%)	38 (20.0%)	0.010
Only viral pathogen identification[*]	123 (22.5%)	36 (18.9%)	0.302
Bacterial-viral pathogen co-identification[*]	93 (17.0%)	14 (7.4%)	0.001
No-pathogen identification[*]	168 (30.8%)	102 (53.7%)	<0.001

Note: *Numbers are presented as N(%).

Table 4 Multivariate analysis by logistic regression analysis

Parameter	Odds ratio	95% confidence interval	P-value
Model 1[a]			
Only bacterial pathogen identification	1.960	1.256–3.057	0.003
Bacterial-viral pathogen co-identification	2.281	1.194–4.358	0.013
Model 2[b]			
Only bacterial pathogen identification	1.653	1.045–2.614	0.032
Bacterial-viral pathogen co-identification	2.072	1.075–3.993	0.030
Model 3[c]			
Only bacterial pathogen identification	1.744	1.107–2.749	0.017
Bacterial-viral pathogen co-identification	2.075	1.081–3.984	0.028

Notes: [a]Adjusted for only bacterial pathogen identification, bacterial-viral pathogen co-identification, and laboratory findings (white blood cell, C-reactive protein). [b]Adjusted for forced expiratory volume in 1 s (liters), maintenance oral steroid, oxygen therapy at home, length of hospital stay, experience of intensive unit care, and factors of model 1. [c]Adjusted for age, gender, and factors of model 2.

have been studies of the relationship between viral infections and eosinophil in children and infants, but not with COPD. Although these studies were not conducted for COPD patients, it was reported that respiratory viral infections showed various cytokines and eosinophil activation depending on the type of virus.[28,29] Furthermore, in the murine asthma model study, airway eosinophil infiltration increased following a rhinovirus infection unlike that in the control mice.[30] In conclusion, eosinophil is expected to show various patterns depending on the virus type and airway reactivity. However, additional studies are needed because of the lack of studies in COPD patients.

Biomarkers should be such that they are quick and easy to perform, and cost-effective despite medical and economic levels. However, CRP and procalcitonin are difficult to perform in all hospitals, including primary care hospitals. On the other hand, eosinophil test, belonging to complete blood count test, is easily accessible anywhere and is inexpensive. A disadvantage of using eosinophil as a biomarker is that there are many factors that affect eosinophils, such as hematologic disorders, cancer, allergy diseases, medications, and steroids.[31] In this study, patients with diseases that could affect eosinophil were initially excluded and the use of inhaled corticosteroids or oral steroid was analyzed using univariate and multivariate analysis.

In pulmonary-related treatment before admission, the use rate of β2 oral agonist was high. Korean COPD patients prefer oral medicines over inhalers. Also, previous epidemiological studies on the use of medications in COPD patients in Korea show a low use rate of inhalers. Because there was no difference in the use rate of β2 oral agonist between the two groups, we think that it will not affect the results of the study.

This study had several limitations. First, it had a retrospective design and was a single center study. We wanted to analyze other biomarkers like procalcitonin, but only half the patients were tested for procalcitonin and hence, could not evaluate the procalcitonin together. Second, colonization and contamination could not be distinguished in the analysis of isolation. To compensate for this as much as possible, we also analyzed the condition bronchiectasis that was known to be highly colonized, and the difference between the two groups was not apparent. Additionally, culture test and PCR assay were performed by trained doctors. Third, we could not analyze the effect of the steroid

dose and type. In the inhaled corticosteroids group, different doses and different kinds of inhalers were used, and the dose varied between 10 and 30 mg in the oral steroid use group. Fourth, eosinophil may be affected by various conditions and diseases. Although eosinophil has the advantage of being cheap and easy to use in practice, it is dangerous to decide alone by eosinophil percent whether to use antibiotics in AECOPD. It would be useful to use it as a reference.

Although this study was a retrospective and single-center study, we analyzed various factors in a large-scale group, and multiple factors that affected eosinophil count were analyzed. However, an additional large-scale multicenter, randomized control study will be required to demonstrate our results better.

Conclusion

Eosinophil count of 2% may be an indicator to distinguish various bacterial infections in AECOPD patients. Furthermore, by predicting the presence or absence of bacterial infection, a more reliable antibiotic treatment can be determined.

Abbreviation list

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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