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Review

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# The Determinants of Eosinophilia in Patients With Severe Asthma

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## Abstract

**Background:** Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease characterized by chronic airway inflammation. The pathogenesis of the disease is better understood with the comprehension of immunological pathways. These pathways differ by the type of recruited cells and released interleukin (IL). Thus, asthma can be classified into subtypes based on the underlying immune mechanism: eosinophilic asthma (EA) and non-eosinophilic asthma (NEA). Patients with EA tend to respond better to inhaled corticosteroid as compared to those with NEA. The distinction of EA is very important in the light of emergent type 2 inflammation targeted therapies.

**Methods:** We performed a 1-year (2018) retrospective cohort analysis of the Nationwide Inpatient Database (NIS). We included all adult patients presenting with severe asthma. Patients were stratified into two groups: eosinophilic severe asthma and non-eosinophilic severe asthma. The primary outcomes measures were the prevalence of chronic steroid use, status asthmaticus, family history of asthma, food, drug and environmental allergies, presence of nasal polyps, allergic rhinitis, allergic dermatitis, need for mechanical ventilation, need for oxygen supplementation, gastroesophageal reflux disease, in-hospital mortality, and length of stay. We performed descriptive statistics. Continuous parametric variables were reported using a mean and standard deviation. Continuous nonparametric variables were reported using a median and interquartile range. To compare the characteristics of the two groups, we used the independent *t*-test for continuous parametric variables and the Mann-Whitney U test for continuous nonparametric variables. The Chi-square test was used to assess differences in categorical variables.

**Results:** A total of 2,646 patients were included, out of which 882 belonged to the eosinophilic group and 1,764 were in the non-eosinophilic group. Comparing EA versus NEA, we have found that eosinophilic group was characterized by higher percentage of steroid use (18.3% vs. 9.5%, $P < 0.001$). This group also had higher rates of status asthmaticus and positive family history ($P = 0.009$ and 0.004, respectively). The presence of allergies, allergic rhinitis, nasal polyps, and allergic dermatitis was higher among patients with eosinophilia. The need for mechanical ventilation and supplemental oxygen was also higher among this group ($P < 0.001$ for both); however, there was no significant difference in mortality rate ($P = 0.347$) and the length of hospital stay was similar in both groups ($P < 0.001$).

**Conclusion:** We showed herein that the eosinophilic subtype of asthma differs widely from the non-eosinophilic phenotype. Clinically, patients with eosinophilia might exhibit different symptomatology, more atopy, and concomitant comorbidities. However, this group might have better response to steroid therapy and might benefit from the new emergent T2 immune targeted therapy. The identification of EA is crucial for better disease control.

**Keywords:** Eosinophilic asthma; Immune pathways; Steroid use; Atopy; Allergy; Eosinophilia; Asthma

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## Introduction

Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease characterized by chronic airway inflammation. Respiratory symptoms include cough, wheezing, chest tightness and shortness of breath [1], hence the Greek origin of the word. It affects 8% of the United States population, out of which up to 20% have uncontrolled symptoms [2]. Asthma has different disease phenotypes which were originally described by Brown in 1958 [3].

The pathogenesis of the disease is better understood with the comprehension of immunological pathways which can be initiated by several environmental triggers, which could be allergens, irritant as smoke, or microbes [4]. These pathways differ by the type of recruited cells and released interleukin (IL). The upregulation of lymphocyte T helper (TH) 1 pathway is led by IL-1, IL-8, IL-17 and is characterized by neutrophilic recruitment [1, 4]; however, TH2 pathway is marked by the presence of different cytokines: IL-4, IL-5, IL-13 and eosino-

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philic predominance with mast cells activation and immunoglobulin E (IgE)-mediated response [3, 4]. TH2 response can be associated with a certain allergen exposure and is called atopic TH2 response, or non-atopic in the absence of a specific trigger. Thus, asthma can be classified into subtypes based on the underlying immune mechanism: eosinophilic asthma (EA) and non-eosinophilic asthma (NEA).

Several non-invasive means have been established to distinguish between the two types: the induced sputum technique where an eosinophilic level is > 2% defines EA, whereas an eosinophilic level < 2% suggests NEA [1, 4]. Similarly, bronchoalveolar lavage can be studied along with other less specific tests such as peripheral blood eosinophilia, measurement of fractional exhaled nitric oxide (FeNO) and reactive oxygen species (ROS) [3, 5, 6]. Both nitric oxide (NO) and ROS are toxic metabolites secreted by eosinophils, and elevated levels correlate with disease severity or poor control. The increase in ROS results in fibroblastic proliferation [6].

On the same page, pathological samples, when bronchoscopy is obtained, differ between the two phenotypes: in EA, the mucosa has eosinophilic predominance with a median number of 23 cells/square millimeter ($mm^2$) versus 4.4 cells/$mm^2$ in NEA that can have neutrophilic infiltrates and lack airway eosinophilia [5]. Another pathological difference reported by Berry et al is the thickening of the subepithelium that is much more pronounced in EA secondary to eosinophilic induced airway inflammation [5].

The clinical distinction between the two types is crucial because it has an impact on asthma severity, quality of life, and therapeutic modalities. EA which accounts for 50% of people with severe asthma according to GINA [1, 3] is correlated with an increase in asthma severity, later onset of disease, and an increase in associated atopy [2]. Patients with EA tend to respond better to inhaled corticosteroid (ICS) as compared to those with NEA who seem to be steroid-resistant and might have poorer control [2, 3, 5]. The distinction of EA is very important in the light of emergent type 2 inflammation targeted therapies: anti-IL-5 and anti-IgE. These immunomodulators are shown to be effective in asthma control and are replacing systemic corticosteroid, which is now reserved for advanced steps in GINA guidelines [2, 6].

Of importance, the eosinophilic type of asthma has to be more illustrated based on patients' characteristics, comorbidities, atopies, and asthma-associated features. A better stratification of EA is a sensitive key for a better quality of life and disease control.

## Materials and Methods

### Data source

We performed a 1-year (2018) retrospective cohort analysis of the Nationwide Inpatient Database (NIS). The NIS is provided by the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available inpatient care database in the United States. It contains data on more than 7 million hospital visits. Its large sample size allows for analyses of rare conditions, uncommon treatments, and special populations. This study was exempt from institutional review board (IRB) approval because the NIS contains deidentified patient data.

### Inclusion and exclusion criteria

We included all adult patients between the age of 18 and 90 years presenting with a primary diagnosis of severe asthma (J45.5), based on the International Classification of Diseases (ICD)-10th Revision-Clinical Modification diagnostic codes. Severe asthma is defined by the presence of one or more of the following symptoms: 1) continuous daytime symptoms; 2) frequent nighttime symptoms; and 3) a peak flow while exhaling of less than 60% of the predicted age. We excluded patients who have restrictive or other types of obstructive lung diseases, patients who developed eosinophilia in the context of diseases not directly related to asthma (parasitic infection, leukemias or lymphoproliferative disorders, hyper eosinophilic syndrome), patients with allergic bronchopulmonary aspergillosis, and patients declared dead on arrival based on the ICD-10th Revision-Clinical Modification diagnostic codes. Patients were stratified into two groups based on the presence of eosinophilia defined as serum eosinophil count at least 150 cells/µL or above 2%: eosinophilic severe asthma vs. non-eosinophilic severe asthma.

### Data points

The following data points were abstracted for each patient: patient demographics (age, sex, race, ethnicity, primary payer method, and household income), patient comorbidities (current cigarette smokers and obesity). We also analyzed the following data points: admission characteristics (weekday admission, elective admission, and transfers).

### Outcomes measured

The primary outcomes measures were the prevalence of chronic steroid use, status asthmaticus, family history of asthma, food, drug and environmental allergies, allergy to non-steroidal anti-inflammatory drugs (NSAIDs), presence of nasal polyps, allergic rhinitis, allergic dermatitis, need for mechanical ventilation, need for oxygen supplementation, gastroesophageal reflux disease (GERD), and in-hospital mortality. Secondary outcomes were discharging disposition (routine home discharge, transfer to another facility, home with healthcare), hospital charges, and length of stay (LOS). The following variables (need for mechanical ventilation and need for oxygen supplementation) were defined based on the International Classification of Diseases (ICD)-10th Revision-Clinical Modification procedure codes.

### Statistical analysis

We performed descriptive statistics. Continuous parametric


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**Table 1.** Baseline Characteristics of Studied Population

| Variable | N = 2,646 | Asthma with eosinophilia (n = 882) | Asthma without eosinophilia (n = 1,764) |
|---|---|---|---|
| Age, years, mean ± SD | 48 ± 21 | 48 ± 21 | 48 ± 21 |
| Sex, female, n (%) | 1,562 (59%) | 514 (58.3) | 1,048 (59.4) |
| White, n (%) | 1,490 (56%) | 480 (54.4) | 1,010 (57.3) |
| Black, n (%) | 568 (21%) | 192 (21.8) | 376 (21.3) |
| Hispanic, n (%) | 404 (15%) | 139 (15.8) | 265 (15.0) |
| Current smokers | 277 (10%) | 101 (11.5) | 176 (10.0) |
| Obesity | 504 (19%) | 182 (20.6) | 322 (18.3) |

SD: standard deviation.

variables were reported using a mean and standard deviation. Continuous nonparametric variables were reported using a median and interquartile range. Categorical variables were reported as counts and proportions. To compare the characteristics of the two groups, we used the independent *t*-test for continuous parametric variables and the Mann-Whitney U test for continuous nonparametric variables. The Chi-square test was used to assess differences in categorical variables. To ascertain the association between the presence of eosinophilia in the setting of severe asthma on desired outcomes while adjusting for measurable confounding factors, we performed propensity score matching using a 1:2 matching ratio. The following variables were accounted for: demographics and medical comorbidities. A logistic regression model was used to generate a propensity score (ranging from 0 to 1) for each patient. A nearest-neighbor model match, using a caliper width of 0.1, was performed to identify patients who were subsequently included in the post-match analysis. We considered a P value of less than 0.05 ($P < 0.05$) to be statistically significant. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, version 26; SPSS, Inc.).

## Results

### Demographics and descriptive analysis

After matching patients within the two groups based on their baseline characteristics, the total number (N) of studied patients was 2,646. The control group had 1,764 patients whereas patients with eosinophilia were 882. The mean age was 48 with female predominance of 59%. The majority (56%) belonged to the white ethnicity. Smokers were 10% of the population, and obesity which was defined as body mass index (BMI) > 30 kg/m$^2$ was reported as 19% (Table 1).

### Comparing EA and NEA cases

Comparing EA versus NEA, we found that eosinophilic group was characterized by higher percentage of steroid use (18.3% vs. 9.5%, $P < 0.001$). This group also had higher rates of status asthmaticus (10.4% vs. 7.4%, $P = 0.009$) and positive family history (4.4% vs. 2.4%, $P = 0.004$) (Table 2).

When it comes to associated atypia, the percentage of allergies, allergic rhinitis, nasal polyps, and allergic dermatitis was higher among eosinophilic group with $P < 0.001$. There was no significant difference when it comes to NSAIDs' allergy or the concomitant presence of GERD between the two groups (2.5% vs. 1.6%, $P = 0.106$; 23.4% vs. 20.9%, $P = 0.142$, respectively) (Table 2).

The need for mechanical ventilation and supplemental oxygen was higher among patients with eosinophilia (6.2% vs. 3.4%, $P < 0.001$ and 12.9% vs. 6.1%, $P < 0.001$); however, there was no significant difference in mortality rate ($P = 0.347$) and the LOS was similar in both groups ($P < 0.001$) (Table 2).

## Discussion

Worldwide, 95-100% of asthmatic patients develop mild to moderate symptoms, controlled with long-acting beta-2 receptor agonist (LABA) and ICS. However, a subgroup of these patients clinically worsen and need escalation in treatment with either biologics or oral corticosteroids (OCS), and this subgroup is entitled "severe asthmatics with eosinophilia", which include patients with symptoms that are not controlled with LABA and high dose of ICS or require OCS for multiple months yearly [7]. Biologics constitute targeted therapies against IL-5 and IL-4, and they have proven great efficacy in improving lung function and decreasing asthma exacerbations [6]. Whether early introduction of biologics in the treatment of mild to moderate asthmatics will prevent them from developing severe asthma remains unclear.

In our study, severe asthmatics with eosinophilia experienced more episodes of status asthmaticus and required more mechanical ventilation and oxygen supplementation compared to severe asthmatics with no eosinophilia, with statistically significant difference (10.4% vs. 7.4%, $P = 0.09$; 6.2% vs. 3.4%, $P < 0.001$; 12.9% vs. 6.1%, $P < 0.001$, respectively). Several studies showed that severe asthma can lead to respiratory distress and eventually necessitating invasive mechanical ventilation (IMV). The associated mortality varies noticeably between studies; the largest retrospective study, conducted by Gupta et al, found that the mortality rate of intubated patients

**Table 2.** Measured Outcomes

| Outcomes | Asthma with eosinophilia (n = 882) | Asthma without eosinophilia (n = 1,764) | P value |
|---|---|---|---|
| Chronic steroid use | 161 (18.3) | 168 (9.5) | < 0.001 |
| Status asthmaticus | 92 (10.4) | 131 (7.4) | 0.009 |
| Family history of asthma | 39 (4.4) | 42 (2.4) | 0.004 |
| Allergies | 183 (20.7) | 304 (17.2) | 0.028 |
| Allergy to NSAIDs | 22 (2.5) | 28 (1.6) | 0.106 |
| Nasal polyps | 17 (1.9) | 1 (0.1) | < 0.001 |
| Allergic rhinitis | 35 (4.0) | 22 (1.2) | < 0.001 |
| Allergic dermatitis | 33 (3.7) | 7 (0.4) | < 0.001 |
| Mechanical ventilation | 55 (6.2) | 60 (3.4) | < 0.001 |
| Oxygen supplementation | 114 (12.9) | 108 (6.1) | < 0.001 |
| GERD | 206 (23.4) | 368 (20.9) | 0.142 |
| In-hospital mortality, n (%) | 7 (0.8) | 21 (1.2) | 0.347 |
| Hospital length of stay, days, median (IQR) | 3 (2 - 6) | 3 (2 - 5) | < 0.001 |

GERD: gastroesophageal reflux disease; IQR: interquartile range; NSAIDs: non-steroidal anti-inflammatory drugs.

secondary to severe asthma in intensive care unit was 15% [8]. Three other recent studies, which also followed patients with severe asthma requiring IMV, reported a mortality rate ranging between 0% and 15% [9-11].

In addition, our study showed statistically significant differences regarding characteristics associated with severe asthma with eosinophilia versus non-eosinophilia. Indeed, the former had more concomitant nasal polyps, allergic rhinitis, allergic dermatitis, and family history of asthma (1.9% vs. 0.1, $P < 0.001$; 4% vs. 1.2%, $P < 0.001$; 3.7% vs. 0.4%, $P < 0.001$; 4.4% vs. 2.4%, $P < 0.001$, respectively). This can be attributed to the fact that eosinophils are the main players in the immunologic processes of these diseases. In patients with chronic rhinosinusitis with nasal polyps and/or allergic rhinitis, eosinophils are considered a pathologic landmark, using the TH2-driven lymphocyte immune pathway [12, 13]. Also, patients with atopic dermatitis have peripheral eosinophilia along with eosinophil granule proteins deposited in the skin. These findings establish a pivotal role of eosinophils in the pathogenesis of atopic dermatitis [14].

Individuals with mild to moderate asthma with associated diseases whose pathogenesis consists of eosinophilia, such as rhinosinusitis with nasal polyps, allergic rhinitis, and allergic dermatitis, should be considered as possible candidates for monoclonal antibodies to decreased morbidity and mortality. One case report describing a 31-year-old male with allergic dermatitis and mild asthma controlled on demand with inhaled salbutamol was admitted for asthma exacerbation [15]. The hospital course was complicated by respiratory distress, despite methylprednisolone (2 mg/kg) and salbutamol nebulizers, with eventual orotracheal intubation and venovenous extracorporeal membrane oxygenation (VV-ECMO) placement. Blood eosinophil count kept increasing and BAL cytology showed predominance of eosinophils. The patient was given mepolizumab (IL-5 monoclonal antibody) with dramatic clinical improvement within 48 h. Similar two cases have been described. One patient, with severe EA placed on VV-ECMO, was treated with IL-5 monoclonal antibody. And another patient with severe EA on IMV received mepolizumab with successful clinical improvement [11, 15].

Our study has two major limitations. Firstly, data rely on ICD-10 codes for disease identification, which may exclude individuals with severe asthma, eosinophilic and non-eosinophilic. Secondly, several studies showed that severe EA had less atopy or dermatitis. And this fact has been attributed to the routine use of OCS and biologics in this subgroup, suppressing the severity of associated conditions [2, 3]. Further studies are needed to complement our results.

## Conclusion

Although asthma is a disease that affects the airways, the immune dysregulation or upregulation can target different organs in the body such as skin and gastrointestinal. The immune targeted therapy is not only effective in asthma treatment, but also is shown to be effective in addressing other symptoms and manifestation. Asthma control and response might also be reflected by the remission of other diseases that share the same pathophysiology. We showed herein that EA is associated with an increase in atopy, higher severity, and an increase in steroid use. Early implementation of biologics in the treatment of mild to moderate EA, specifically with associated eosinophilic characteristics, might prevent the progression into severe asthma and reduce morbidity and mortality.

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## Conflict of Interest

The authors declare that there is no conflict of interest.

## Informed Consent

Not applicable.

## Author Contributions

Racha Abi Melhem, Marc Assaad, Khalil El Gharib, Hussein Rabah, Ali Kassem, Jordyn Salak, and Saif Abu-Baker helped writing the manuscript. Ahmad Itani is responsible for supervision and concept. Racha Abi Melhem is responsible for concept and data analysis. Marc Assaad is responsible for editing.

## Data Availability

The authors declare that the data supporting the findings of this study are available within the article.

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