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Blood eosinophil count and bronchodilator responsiveness in pediatric patients admitted for wheezing attacks

Abbas Fayezi[1*], Mehdi Torabizadeh[2], Naghme Masoomi[3], Farhad Abolnezhadian[1], Mohsen Alisamir[4], Mohammadreza Mirkarimi[4], Mohammad Bahadoram[5]

[1]Department of Allergy and Clinical Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Golestan Hospital Clinical Research Development Unit, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Department of Pediatrics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Department of Pediatrics, Division of Pediatric Pulmonology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Thalassemia and Hemoglobinopathy Research Center, Research Institute of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

***Correspondence to**
Abbas Fayezi, Email: Fayezi-a@ajums.ac.ir, fayeziab@yahoo.com

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Abstract

Introduction: Wheezing episodes are common in infants, younger, and older children which are most commonly caused by asthma or viral bronchiolitis.
Objectives: This study aims to determine the possible correlation between blood eosinophil count and responsiveness to bronchodilators in pediatric patients admitted for wheezing episodes.
Patients and Methods: This cross-sectional study was conducted on 98 patients aged between one month to 12 years (a mean of 2.53 ± 1.12 years) that were admitted because of wheezing at two university hospitals of Jundishapur university of medical sciences, Ahvaz, Iran. The severity of wheezing was defined according to the Preschool Respiratory Assessment Measure (PRAM) classification. The peripheral blood eosinophil count was checked as part of the complete blood count (CBC) in all patients before treatment initiation. Then, the peripheral blood eosinophil count was compared between the two groups of patients based on showing significant or no significant response to bronchodilator treatment.
Results: Of 98 patients, 11 (11.2%) had mild wheezing, 70 (71.4%) had moderate wheezing and 17 (17.3%) had severe wheezing. Significant response to bronchodilator therapy (PRAM reduction) was observed in 68 patients (69.4%) and 30 patients (30.6%) had a partial response to treatment. There was been no statistically significant correlation between the peripheral blood eosinophil count and response to bronchodilator therapy ($P=0.963$). There was also no significant correlation between the peripheral blood eosinophil count and wheezing severity ($P=0.203$).
Conclusion: Our study revealed no correlation between the peripheral blood eosinophil count and the response to bronchodilators in pediatric patients presenting with wheezing attacks. We concluded that the peripheral blood eosinophil count could not be employed as a marker to predict the response to bronchodilator therapy in pediatric patients presenting with wheezing episodes at emergency departments.

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Introduction

Wheezing attacks are common in children. About 50% of children experience a wheezing episode in the first year of life. Recurrent wheezing episodes occur in one-third of the preschool pediatric population. This can also cause economic burden on the health system and families (1). A small degree of bronchoconstriction, especially in infants, could result in airflow limitation and wheezing. Asthma and viral bronchiolitis are the leading causes of wheezing in preschool years. However, about 60% of the cases are asymptomatic up to six years of age and most remain symptom-free between the ages of 11 to 16 years. Early recognition of high-risk children with persistent asthma later in school ages is of utmost importance which leads to better management and prevention of deterioration (2).

Eosinophilic inflammation of the airways is

Key point

Wheezing episodes are common in infants, younger and older children that may be caused by asthma or viral bronchiolitis. In this study, we found that the peripheral blood eosinophil count could not predict the response to bronchodilators in pediatric patients presenting with wheezing episodes at emergency departments.

one of the characteristics of asthma. The blood eosinophil count is considered a marker for eosinophilic inflammation of the airways (3). Increased blood eosinophil count is a laboratory finding in favor of the eosinophilic phenotype of asthma in children and adults. Eosinophils are bone marrow-derived inflammatory cells that are differentiated from myeloid precursors in response to interleukin-3 (IL-3) and granulocyte colony-stimulating factor. The increased production of various cytokines from T-helper 2 cells, such as IL-3, IL-4, and IL-5, which are key elements in allergic asthma leads to increased blood eosinophil count (4). Increased blood eosinophil count occurs late in allergic inflammatory responses. About twenty-four hours following allergen exposure; peripheral blood eosinophilia is considered as a characteristic parameter for asthma and is a marker of eosinophilic inflammation of the airways (5). The blood eosinophil count is a predictor for the responsiveness to inhaled corticosteroids in patients with chronic obstructive pulmonary diseases (6). It is also a predictor for the response rate to anti- IL-5 treatment in patients with asthma. In addition, the blood eosinophil count has been associated with the severity of symptoms (7), degree of airflow limitation, and asthmatic flares. In preschool children, blood eosinophil count has been related to acute wheezing episodes. In some longitudinal studies, increased blood eosinophil count in preschool years has been related to persistent asthma later in school ages. Measuring the blood eosinophil count in different groups of patients may help to find a marker that predicts the severity of wheezing in children (8).

Objectives

There have been limited studies that have evaluated a possible correlation between the blood eosinophil count and bronchodilator responsiveness in pediatric patients with acute wheezing episodes. Additionally, efforts to develop a reliable marker to predict the severity, the disease course, and the response rate to treatment has not been much successful. The main objective of this study is to determine whether the blood eosinophil count could be used to predict the response to bronchodilator therapy in children presenting with acute wheezing.

Patients and Methods

Study design

This study included pediatric patients aged between one month to 12 years that presented with acute wheezing at Aboozar and Golestan University hospitals over 12 months (March 2020 to March 2021). At admission, the parents were interviewed for the patients' medical histories and physical examination was conducted on patients by the senior pediatric resident. However, in critically ill patients, a thorough interview and physical examination were conducted after initial stabilization. The patients were excluded from the study if the medical history or physical examination suggested heart failure, or any congenital or acquired heart disease, foreign body aspiration, any other underlying medical illness, or anatomical defects.

The severity of respiratory symptoms at admission and one hour after receiving the standard care and bronchodilators was evaluated with the PRAM (Preschool Respiratory Assessment Measure) scores, using blood O_2 saturation, suprasternal retraction, scalene muscle contraction, air entry to lung fields, and wheezing characteristics (9). The complete blood count including absolute blood eosinophil count was checked for all patients. All interventions were planned according to patients' respiratory condition from admission to discharge from the hospital. In addition, informed consent was taken from the parents to use the data in our study.

Data collection

The demographic and clinical data including age, gender, history of wheezing episodes or any past underlying illness, and atopic history including eczema, food allergy, skin or systemic allergy-related reactions were taken and documented. In addition, the history of bronchodilator and inhaled corticosteroid treatment and previous chest imaging were reviewed and documented. The patients were re-assessed one hour after the initiation of bronchodilator therapy for the changes in the respiratory features and the PRAM score that were all documented. The patients were divided into two groups according to whether significant bronchodilation was observed, and the blood eosinophil count of each group was compared. The patients were followed up until discharge and the final diagnosis was documented.

Statistical analysis

In this study, the descriptive statistics of the qualitative and quantitative variables were explained by the frequency (percentage) and mean ± standard deviation, respectively. To compare the bronchodilator response in the different age groups, the chi-square test was used and the results were evaluated. A *P* value less than 0.05 was considered as the significant level. All statistical analysis were performed with the SPSS 18 software.

Results

Ninety-eight patients aging from one month to 12 years (a mean of 2.53 ± 1.12 years) were included in the study. The clinical data of the patients are shown in Table 1 and Figure 1. Of 98 patients presenting with acute wheezing episodes, 68 patients (69.4%) had significant bronchodilator response within one hour, and 30 patients (30.6%) had partial or no response to treatment within the same time.

The age group younger than one-year-old, which is mostly admitted with viral bronchiolitis or viral pneumonia, contained only one infant with a measured blood eosinophil count of more than 10% of the total WBC count.

According to the bronchodilator response in the group

Table 1. Basic characteristic of the studied patients

Variable	Group	No. (%)
Gender	Female	41 (41.8)
	Male	57 (58.2)
Past history of wheezing attack		53 (54.1)
History of attacks leading to hospitalization		30 (30.6)
Number of attack in each patient	First	45 (45.9)
	Second	9 (9.2)
	Third	16 (16.3)
	More than three times	28 (28.6)
Past history of bronchodilator use and good response to it		48 (49.0)
Any history in favor cell mediated food allergies*		4 (4.1)
History of skin or mucosal symptoms or any other repeated systemic reactions after a special food		9 (9.2)
Total number of Infants		41 (41.8)
Consumed milk in infants	Breast fed	20
	Formula fed	11
	Both breast and formula fed	10
History of respiratory allergy** in siblings		19 (19.4)
History of respiratory allergies** in parents		33 (33.7)
Existence of background disease		28 (28.6)
Atopic background ***		48 (49.0)
Passive smoker		46 (46.9)
Severity of wheezing attack	Mild	11 (11.2)
	Moderate	70 (71.4)
	Severe	17 (17.3)
Type of received Bronchodilator	Ventolin	87 (88.8)
	Atrovent	1 (1.0)
	Both	10 (10.2)
Corticosteroid treatment in the first hour of admission along with bronchodilator nebulization		51 (52.0)
Chest radiographic findings	Normal	26 (26.5)
	Hyperaeration	43 (43.9)
	Any consolidation	20 (20.4)
	Other abnormal findings	9 (9.2)
Early impression	Severe asthma	50 (51.0)
	Pneumonia	17 (17.3)
	Bronchiolitis	31 (31.6)
Final diagnosis	Severe asthma	34 (34.7)
	Pneumonia (viral and bacterial)	36 (36.7)
	Bronchiolitis	28 (28.6)

* Food allergies in the form of bloody streaked stools or any repeated gastrointestinal symptoms after eating a particular food.
** Respiratory allergy in the form of allergic rhinitis or asthma.
*** Defined as history of eczema and allergic rhinitis in the patient.

of younger than one years of age with different levels of blood eosinophil counts. Patients with a measured blood eosinophil count between 4% to10%, and with below 4% of total WBCs, exhibited partial or no response to the bronchodilator drugs within the first hour of admission (Table 2). Moreover, no significant association between eosinophil levels and clinical response to bronchodilator therapy was observed.

In the age group of one to five years of age, both two patients had blood eosinophils of more than 10% of the total WBC count, along with about 67% of patients with blood eosinophil levels between 4% to 10% of the total WBC count and about 65% of the patients with blood eosinophil levels below 4% of the total WBC count had a significant response to bronchodilator medications (Table 3). Although the responses to bronchodilators in this age group found to be more prominent in patients with higher blood eosinophil levels; however, it was not statistically significant.

Finally, in the age group of 6 to 12 years of age, both two children with blood eosinophil counts above 10% of the total WBC count, along with about 66% of children with blood eosinophil counts between 4% to 10% of the total WBC count, and about 88% of the children with blood eosinophil counts below 4% of the total WBC count, had a significant response to bronchodilators (Table 4). No correlation between blood eosinophil counts and response to bronchodilator could be found in this age group.

Discussion

Few studies have evaluated the association between the response to bronchodilators in asthmatic patients and different levels of blood eosinophil count. Most studies have evaluated the associations with other treatment modalities such as corticosteroids and biologic agents.

According to our findings, no statistically significant correlation between peripheral blood eosinophil count and bronchodilator response in patients presenting with wheezing and different severities was detected.

The blood eosinophil count has been suggested to be a useful biomarker in predicting glucocorticoid response in inflammatory airway diseases and has been used successfully in the management of adult patients with asthma. In one study, the blood eosinophil count decreased following the administration of different doses of omalizumab, and a correlation was detected between the blood eosinophil count and clinical improvement in patients receiving omalizumab (10). Another study revealed asthma control following mepolizumab, a monoclonal antibody against IL-5, that was associated with blood eosinophil levels (11).

The blood eosinophil count is not a reliable marker for airway eosinophilia. A study evaluated the blood and airway eosinophil levels in pediatric patients with severe and treatment-resistant asthma, 86% of the children had normal blood eosinophil counts while 84% had airway

Table 2. Bronchodilator response in the group of younger than one years of age with different levels of blood eosinophil counts

Eosinophil percentage	Significant response	Partial or no response	*P* value
Less than 4%	21(65.6%)	11 (34.4%)	0.328
4% to 10%	6 (75%)	2 (25%)	
More than 10%	0 (0%)	1 (100%)	

Table 3. Bronchodilator response in the group of 1 to 5 years of age with different levels of blood eosinophil counts

Eosinophil percentage	Significant response	Partial or no response	*P* value
Less than 4%	15 (65.2%)	8 (34.8%)	0.597
4% to 10%	11 (68.75%)	5 (31.25%)	
More than 10%	2 (100%)	0 (0%)	

Table 4. Bronchodilator response in of 6 to 12 years of age with different levels of blood eosinophil count

Eosinophil percentage	Significant response	Partial or no response	*P* value
Less than 4%	7 (87.5%)	1 (12.5%)	0.471
4% to 10%	4 (66.6%)	2 (33.4%)	
More than 10%	2 (100%)	0 (0%)	

eosinophilia. Therefore, it was concluded that normal blood eosinophil count does not rule out the eosinophilic phenotype of asthma and bronchoalveolar lavage was suggested in pediatric patients with severe or treatment-resistant asthma (12).

Studies suggested the blood eosinophil count as an easily measurable marker of airway inflammation which could be used as guidance in the management of asthmatic patients (13,14). Other studies evaluated the association of blood eosinophil count and asthma severity, no one could confirm any relation between asthma severity and blood eosinophil count (15,16) but increased blood eosinophil count may be detected in moderate to severe asthma (17).

Increased blood eosinophil count has been reported in asthmatic patients compared to normal control subjects (18). Another study reported a correlation between blood eosinophil counts and the severity of bronchoconstriction (19). In patients suffering from asthma, high blood eosinophil count may be caused by factors such as allergen exposure, associated allergic rhinitis, or parasitic infections (20). Although blood eosinophils can be easily measured and have been confirmed to have a role in the inflammatory pathways of asthma, using this marker to determine the phenotype of asthma has some limitations. Some of these limitations include lower specificity than sputum eosinophil count, influential effects of parasitic infections and allergen exposure, and the baseline steroid treatment (21). Eosinophils remain in the intravascular space for a short time (22) which may be the result of rapid distribution to inflamed tissues and indicates a transient and inconsistent connection between the blood and airway eosinophil levels (23).

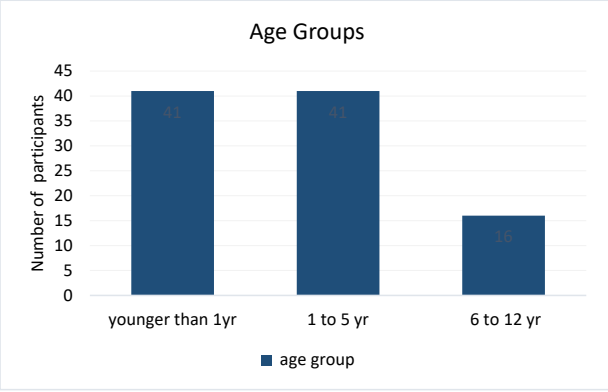

Figure 1. Distribution of the participants in three distinct age groups.

There has been a modest sensitivity and specificity report of blood eosinophil counts (about 55%) in predicting the airway inflammation phenotype in adult patients compared to controlled asthma patients (24). Therefore, it has been concluded that blood eosinophil count alone could not be reliable to assess the airway inflammation and help to choose the treatment option. In a systematic meta-analysis review of 32 articles (24 articles on adults and 8 articles on children), the blood eosinophil count was reported to have a modest diagnostic and prognostic value that if used to monitor and assess patients with asthma leads to increased diagnostic errors (25). There were modest changes in the blood eosinophil count within the one-year follow-up, despite the patients being consistently controlled with stable pulmonary function and no flares. The cause of the changes in blood eosinophil levels was not clearly understood but as noted earlier, other factors such as daily changes, exercise, and steroid medications could have a role. In our study, no correlation was found between the blood eosinophil count and the severity of wheezing attacks on admission.

Conclusion

The blood eosinophil count does not seem to be a reliable marker to predict the extent of clinical improvement

following bronchodilator therapy in patients with asthma exacerbation. Further studies with larger sample sizes and inclusion of other potential inflammatory markers are required.

Limitations of the study

There are some noticeable shortcomings in our study. Some of these limitations include the relatively small sample size, lack of manual WBC differential to re-check the eosinophil count, the uncertain effectiveness of nebulization methods and drug delivery difficulties in small children and infants. These limitations should be considered in future studies.

Authors' contribution

AF, NM, and MT were the principal investigators of the study. FA, MA, MM, and MB were involved in the preparation of the concept and design. FA, MT, and AF revisited the manuscript and critically evaluated the intellectual contents. All authors participated in the preparation of the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of all parts of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study (IR.AJUMS.REC.1398.965). Accordingly, informed consent was taken from all of the parents of the participating children before any intervention. This study was extracted from the pediatric residency thesis of Naghme Masoomi at this University (Thesis #330096503). In addition, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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