

Children with severe persistent asthma have disparate peripheral blood and lower airway eosinophil levels

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Clinical Implications

- Peripheral blood cell counts are often used when considering candidacy for biologic therapies. Our study of paired peripheral blood and bronchoalveolar lavage eosinophil levels from children with severe persistent asthma supports that blood levels are not an accurate proxy for lower airway counts.

TO THE EDITOR:

The growing availability of biologics for the treatment of asthma makes it increasingly important to accurately characterize asthma endotypes so that therapy can be appropriately prescribed to improve asthma control.¹ In children, this may be more challenging given the temporally limited history of their asthma compared with adults, and the varied mixture of allergic and inflammatory influences on pediatric asthma. Control of asthma, particularly of severe asthma in children, may also prevent morbidity and confer long-lasting benefit into adulthood. Guideline-based therapy of severe asthma in children is based primarily on data from adult studies, however, and the dynamics of exacerbations, lung function, and response to medication differ between children and adults.² Advancing our understanding of asthma endotyping in children can improve our ability to predict response to asthma treatment, particularly to biologics that target specific endotypes.¹

Characterizing asthma as eosinophilic or neutrophilic is one way to endotype asthma.¹ Marked by high levels of eosinophils in peripheral blood, eosinophilic asthma is the most common endotype found among severe asthmatics and is thought to be more corticosteroid responsive.¹ In contrast, neutrophilic asthma is marked by elevated peripheral blood neutrophils (>7000 cells/ μ L in patients aged 6-12 years, or >8000 cells/ μ L for those 12 years and older) and is commonly corticosteroid nonresponsive.^{3,4} Although elevated peripheral blood levels of eosinophils and neutrophils have both been associated with severe asthma,⁵ the direct role of these circulating eosinophils and neutrophils on airway inflammation remains poorly understood.⁶ In theory, circulating levels of eosinophils and neutrophils could reflect their levels in the lungs, but this has not been well investigated in children with severe asthma. In this study, we assessed the agreement between eosinophil levels in peripheral blood and bronchoalveolar lavage (BAL) fluid in children with severe asthma.

We studied 25 children with a primary diagnosis of severe persistent asthma who underwent flexible bronchoscopy as part

TABLE I. Baseline characteristics of children with severe persistent asthma who underwent bronchoscopic evaluation (N = 25)

Characteristic	Mean $\pm$ SD or n (%)
Age (y)	12.8 $\pm$ 4.4
Sex (female)	11 (44%)
Age at asthma diagnosis (y)	3.7 $\pm$ 4.3
Emergency department visits for asthma in the past year	4.3 $\pm$ 5.0
Hospitalization for asthma in the past year	2.6 $\pm$ 4.3
Symptoms (d/wk)	5.0 $\pm$ 2.3
Nighttime awakenings (d/wk)	2.1 $\pm$ 2.7
Short-acting β -agonist (SABA) use (d/wk)	6.5 $\pm$ 6.7
Asthma Control Test score	12.4 $\pm$ 4.7
Race	
Caucasian	6 (24%)
African American	9 (36%)
Asian	2 (8%)
Other	8 (32%)
Medications before bronchoscopy*	
SABA	25 (100%)
Inhaled corticosteroid (ICS) only	6 (24%)
ICS + long-acting β -agonist (LABA)	15 (60%)
Leukotriene receptor antagonist	16 (64%)
Allergic rhinitis	16 (64%)
Eczema	13 (52%)

Results reported as mean $\pm$ standard deviation or count (%).

*Four patients self-discontinued ICS or ICS-LABA because of perceived lack of efficacy or adverse reaction.

of their clinical care. These children were a subset of a larger institutional review board–approved study of asthma biomarkers that enrolled subjects with varying severity of asthma. Parents of all pediatric subjects provided written informed consent, and child subjects provided assent, including the use of their data in studies not directly related to the primary study. All children had reversible obstruction (forced expiratory volume in 1 second $\geq$ 12%) and/or positive methacholine challenge (provocation concentration $\leq$ 10 mg/mL) as enrollment criteria for the primary study. The baseline characteristics of the cohort are summarized in Table I. Paired peripheral blood and BAL samples were obtained from all children. BAL was performed in the right middle lobe using 3 successive aliquots of 1 mL/kg body weight, with the maximum aliquot of 30 mL. All children had normal airway anatomy on bronchoscopic examination and were free of subacute infection based on routine bacterial and fungal BAL cultures.

Peripheral blood samples from the 25 children showed a mean eosinophil level of 449 cells/ μ L (standard deviation [SD], 538 cells/ μ L), and BAL fluid samples had a mean eosinophil fraction of 5.5% (SD, 8.6%). Mean neutrophil levels were 4869 cells/ μ L (SD, 2514 cells/ μ L) in peripheral blood and 15.9% (SD, 22.9%) in BAL fluid. Serum total IgE levels were relatively high with mean 718 kU_A/L (SD, 772 kU_A/L).

Peripheral blood levels and BAL eosinophil percentages were weakly correlated without statistical significance (Spearman's ρ ,

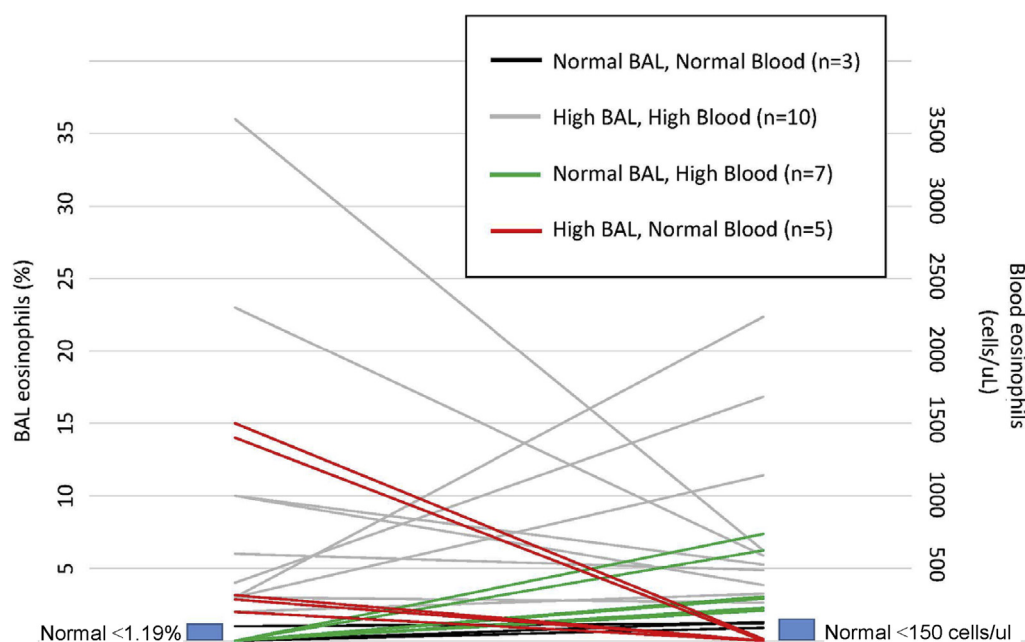


FIGURE 1. Relationship between BAL eosinophil percentage and peripheral blood eosinophil level in paired samples from 25 pediatric subjects with severe persistent asthma. There was a weak correlation between the measures (Spearman's rho, 0.14; $P = .50$) and poor agreement (Cohen's kappa, -0.03 ; $P = .86$) between high vs normal categories of BAL and peripheral blood eosinophils. BAL, Bronchoalveolar lavage.

0.14; $P = .50$). Based on current guidelines for anti-IL5 therapy (≥ 150 eosinophils/ μL in peripheral blood considered high),⁷ and a threshold of $\geq 1.19\%$ eosinophils for high eosinophils in BAL fluid,³ 12 of the 25 subjects in our cohort had discordantly categorized levels. Specifically, 5 children had elevated BAL eosinophil percentages with normal blood eosinophil counts, and 7 children had normal BAL eosinophil percentages with elevated blood eosinophils (Figure 1). Reflecting these discordant measures, there was poor agreement (Cohen's kappa, -0.03 ; $P = .86$) and no evidence for association (odds ratio, 0.86; 95% confidence interval, 0.10-6.35; Fisher's exact test $P = 1$) between peripheral blood eosinophil category (high vs normal) and BAL eosinophil percentage category (high vs normal).

Our results show that peripheral blood eosinophil levels do not correlate well with BAL eosinophil fractions in children with severe persistent asthma, and that classifying children based solely on peripheral blood will not capture a substantial proportion of subjects who have disparately low or disparately high eosinophils in their BAL fluid. Importantly, consideration of anti-IL5 therapy is based primarily on the peripheral blood eosinophil level.⁸ In this regard, our cohort included 5 children for whom anti-IL5 therapy was initially not considered based on their low blood eosinophil levels (0-12 cells/ μL). All 5 of these patients required oral corticosteroids at minimum every 3 months, which may have contributed to the low levels. Of these 5 patients, 1 patient qualified for and is successfully maintained on anti-IgE therapy (BAL eosinophils 2%); 2 patients qualified for but failed to improve with anti-IgE therapy and were changed to anti-IL5 therapy with clinical improvement (BAL eosinophils of 14% and 3%); 1 patient qualified for but failed to improve with anti-IgE therapy and is managed with chronic oral corticosteroids (BAL eosinophils 15%); and 1 patient is not a candidate for anti-IgE or anti-IL5 therapy based on blood levels and

is currently managed on chronic oral corticosteroids (BAL eosinophils 3%, anti-IL5 therapy denied). For the 2 patients changed from anti-IgE to anti-IL5 therapy, each required only 0 and 1 course of oral corticosteroids during the entire subsequent year.

Our findings, like those from a prior study by Ullman et al,³ suggest that peripheral blood eosinophil levels should not be considered an absolute proxy of lower airway eosinophilia. To maximize the relevance of our findings to current practice, we defined high peripheral blood eosinophils based on current recommendations for anti-IL5 therapy, where ≥ 150 eosinophils/ μL ⁷ are considered high. The earlier study by Ullmann et al³ used ≥ 100 cells/ μL as their cutoff for high peripheral blood eosinophils. We used the same parameters as Ullmann et al to define BAL eosinophilia. In addition, the prior investigation did not report on response to monoclonal therapy, whereas our report suggests that consideration of BAL results when selecting initial therapy for patients with elevated BAL/normal blood eosinophils could be beneficial, particularly considering the 3 patients who were candidates for but failed to improve with anti-IgE therapy. It is unclear from our cohort whether patients with high blood/normal BAL eosinophils are less likely to respond to anti-IL5 therapy, in which case BAL might similarly influence therapy when criteria for alternate biologic agents are also met. We acknowledge that our sample size limits such analysis, and that future studies with larger cohorts of patients are required. We also acknowledge that differences between blood, BAL, sputum, and tissue eosinophils were not addressed in our report. Certainly, analysis of sputum eosinophils is less invasive compared with bronchoscopy, and although there are existing data regarding sputum analysis for initiating mepolizumab in adult patients,⁹ we are unaware of similar studies for children.

This study was a focused examination of children with severe persistent asthma who underwent bronchoscopy during their clinical evaluation, and our findings may not be generalizable to those with less severe asthma. Furthermore, because asthma differs among adults and children, our findings may be specific to pediatric asthma. In this regard, our report seems particularly important, because studies that incorporate bronchoscopy in children with severe asthma are challenging to execute and therefore rarely performed. Indeed, our sample size reflects that bronchoscopic examination of children with asthma is not commonly undertaken. However, as we have shown here, doing so can provide information distinct from peripheral blood measurements and may potentially influence the choice of biologic therapy for selected children.

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