The association of blood eosinophil counts to future asthma exacerbations in children with persistent asthma

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Clinical Implications

- Blood eosinophil counts of 300/mm^3 or more in children with persistent asthma may identify children at increased risk for future asthma exacerbations, indicating a possible higher disease burden among these patients.

TO THE EDITOR:

Eosinophilic pulmonary inflammation is a major asthma phenotype associated with exacerbation-driven uncontrolled asthma.[1] We recently reported that high blood eosinophil counts were a risk factor for increased future asthma exacerbations in adults with persistent asthma after controlling for other factors that may confound this relationship.[2] It is unknown whether a similar relationship exists in children with persistent asthma. To address this issue, we conducted a retrospective study (see Figure E1, *A*, in this article's Online Repository at www.jaci-inpractice.org) using administrative data from a large medical care organization to determine whether blood eosinophil levels in children with persistent asthma are an independent risk factor for future asthma exacerbations. Electronic pharmacy and health care data from Kaiser Permanente Southern California identified 2451 children aged 5 to 11 years who met the Health Effectiveness Data and Information Set 2-year criteria for persistent asthma in 2009 and 2010, did not manifest cystic fibrosis and other major illnesses (Figure E1, *B*), and were continuously enrolled health plan members with pharmacy benefit from 2009 to 2011.[2] Of these 2451 identified children, 333 (13.6%) also had a total blood eosinophil count determined from the last complete blood cell count with differential obtained in 2010 (Figure E1, *B*). *Exacerbations*, the study's primary outcome, were defined as asthma outpatient visits requiring systemic corticosteroid dispensing within ±7 days or asthma emergency department (ED) visits or hospitalizations. A period of 8 or more days between episodes was required to define a new exacerbation. Negative binomial and Poisson regression were applied to examine the association between blood eosinophil counts using cutoff points of 150/mm^3, 200/mm^3, 300/mm^3, and 400/mm^3 determined in 2010 and the rate and risk of exacerbations in 2011 after controlling for demographic characteristics, comorbidities, and asthma burden (see this article's Online Repository at www.jaci-inpractice.org).[2] SAS (version 9.2 for Windows, SAS Institute, Cary, NC) was used for all analyses, with the statistical significance level set at $P < .05$, 2-tailed.

Children with (N = 333) compared with those without (N = 2118) eosinophil determinations in 2010 evidenced generally similar demographic characteristics, but more frequent comorbidities, allergist visits, and uncontrolled asthma (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The present study's subgroup with eosinophil determination (N = 333) was aged 7.7 ± 1.9 years, 72% boys, about 75% nonwhite, from households with median incomes of about $63,000, long-term health plan enrollees (6.7 ± 2.4 years), and possessed mainly commercial insurance, with 25.8% covered by Medicaid or other state programs (Table I). During the baseline year (2010), this subgroup had frequent comorbidities, including rhinitis (56.2%), pneumonia (30.6%), and eczema (15.0%), received inhaled corticosteroids (88.9%) and leukotriene modifiers (32.4%), and was Global Initiative for Asthma (GINA) step-care level 3 or higher[2,3] (59.1%). Of the study subgroup with eosinophil determination, 61.9% and 29.1% experienced at least 1 and 2 asthma exacerbations, respectively, and 32.7% required an asthma-related ED visit or hospitalization (Table I). Children with eosinophil counts of less than 300/mm^3 during the baseline year (2010) exhibited generally similar characteristics than did those children with eosinophil counts of 300/mm^3 or more, except that the latter more frequently visited an allergist ($P = .003$) and received inhaled corticosteroid/long-acting β_2-agonist ($P = .001$), but less frequently experienced pneumonia ($P = .002$) (Table I).

The rate of asthma exacerbations in 2011 was 0.64 events per person-year (95% CI, 0.54-0.76). Compared with children with a blood eosinophil count of less than 300/mm^3, children with counts of 300/mm^3 or more in 2010 experienced a higher rate (0.82/y vs 0.53/y; $P = .01$) and risk (49.6% vs 34.3%; $P = .01$) of asthma exacerbations in 2011. However, no difference was found in asthma ED visits or hospitalizations or excessive short-acting β_2-agonist (SABA) dispensings (≥7 canisters dispensed/y) between the 2 stratified eosinophil subgroups (Table II).

We further explored the relationship of blood eosinophil counts in 2010 (yes/no) using cutoff points of 150/mm^3, 200/mm^3, 300/mm^3, and 400/mm^3 with the rate and risk of future asthma exacerbation in 2011. Blood eosinophil counts of 300/mm^3 or more and 400/mm^3 or more were associated with both increased rate (Figure 1, *A*) and risk (% of children) (Figure 1, *B*) for future exacerbations in 2011. After adjusting for age, sex, obesity, geocoded education, ethnicity, GINA step-care level, 7 or more SABA canisters dispensed, and history of asthma exacerbations in 2010,[2] multivariate analyses revealed that an eosinophil cutoff point of 300/mm^3 or more was associated in 2011 with a 52% increase in asthma exacerbation rate (rate ratio, 1.52; 95% CI, 1.12-2.07; $P = .01$) (Figure 1, *A*) and a 40% increase in the frequency of any asthma exacerbation (risk ratio, 1.40; 95% CI, 1.09-1.79; $P < .01$) (Figure 1, *B*). Slightly higher point estimates were observed in terms of the rate or risk ratio when comparing the effects of eosinophils on asthma exacerbations using a cutoff point of 300/mm^3 or more versus a cutoff point of 400/mm^3 or more. However, because of overlap of the 95% CIs, comparisons on the risk of exacerbations between these 2 cutoff points cannot be made (Figure 1, *A* and *B*).

Other variables selected in the final rate and risk models at the 300/mm^3 eosinophil cutoff point that were associated with an increase in asthma exacerbations were (1) a history of asthma exacerbations in 2010 ($P < .001$ for both ratios), (2) decreasing

TABLE I. Comparison of demographic characteristics, comorbidities, and asthma features at baseline in 2010 among 5- to 11-y-old children with persistent asthma stratified by blood eosinophil levels of 300/mm^3 or more vs less than 300/mm^3*

Demographic characteristic/clinical feature	Blood eosinophils ≥300/mm^3 (N = 123)	Blood eosinophils <300/mm^3 (N = 210)	Total (N = 333)	P†
Age (y), mean ± SD	7.9 ± 2.0	7.6 ± 1.9	7.7 ± 1.9	0.13
Boys	80 (65.0)	126 (60.0)	206 (61.9)	0.36
Race and/or ethnicity				0.34
White	35 (28.5)	47 (22.4)	82 (24.6)	
Black	21 (17.1)	37 (17.6)	58 (17.4)	
Hispanic	55 (44.7)	96 (45.7)	151 (45.3)	
Asian/Pacific Islander	8 (6.5)	16 (7.6)	24 (7.2)	
Multiple, others	4 (3.3)	9 (4.3)	13 (3.9)	
Unknown	0 (0)	5 (2.4)	5 (1.5)	
Median household income by geocoding ($), mean ± SD	62,363 ± 25,626	63,366 ± 26,168	62,995 ± 25,935	0.74
% resident education level ≤grade 12 by geocoding, mean % ± SD	27.0 ± 19.2	29.1 ± 18.8	28.3 ± 18.9	0.23
BMI (percentile), mean ± SD	68.1 ± 30.32	68.0 ± 31.29	68.0 ± 30.89	0.70
Obese (≥95th percentile)	31 (25.2)	59 (28.1)	90 (27.0)	0.57
Smoking status				0.30
Yes	0 (0)	1 (0.5)	1 (0.3)	
Passive	14 (11.4)	33 (15.7)	47 (14.1)	
Quit	3 (2.4)	1 (0.5)	4 (1.2)	
Never	101 (82.1)	170 (81.0)	271 (81.4)	
Missing	5 (4.1)	5 (2.4)	10 (3.0)	
Length of health plan enrollment (y), mean ± SD	7.0 ± 2.5	6.5 ± 2.4	6.7 ± 2.4	0.10
Insurances‡				
Commercial	89 (72.4)	152 (72.4)	241 (72.4)	1.00
Medicaid and other state programs	31 (25.2)	55 (26.2)	86 (25.8)	0.84
Private pay	4 (3.3)	4 (1.9)	8 (2.4)	0.44
Charlson comorbidity index, mean ± SD	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	0.88
Rhinitis	77 (62.6)	110 (52.4)	187 (56.2)	0.07
Gastroesophageal reflux	6 (4.9)	4 (1.9)	10 (3)	0.12
Chronic sinusitis	18 (14.6)	24 (11.4)	42 (12.6)	0.40
Pneumonia	25 (20.3)	77 (36.7)	102 (30.6)	0.002
Eczema	22 (17.9)	28 (13.3)	50 (15.0)	0.26
Nasal polyps	1 (0.8)	0 (0)	1 (0.3)	0.19
Allergist visit	58 (47.2)	65 (31)	123 (36.9)	0.003
12-mo GINA step-care level				0.84
Step 1	10 (8.1)	14 (6.7)	24 (7.2)	
Step 2	38 (30.9)	74 (35.2)	112 (33.6)	
Step 3	51 (41.5)	81 (38.6)	132 (39.6)	
Step 4	24 (19.5)	40 (19.0)	64 (19.2)	
Step 5	0 (0)	1 (0.5)	1 (0.3)	
Any ICS dispensed				0.73
Low dose	56 (45.5)	100 (47.6)	156 (46.8)	
Medium dose	43 (35)	79 (37.6)	122 (36.6)	
High dose	8 (6.5)	10 (4.8)	18 (5.4)	
None	16 (13.0)	21 (10.0)	37 (11.1)	
Any ICS/LABA dispensed				0.001
Low dose	14 (11.4)	5 (2.4)	19 (5.7)	
Medium dose	10 (8.1)	15 (7.1)	25 (7.5)	
High dose	5 (4.1)	2 (1)	7 (2.1)	
None	94 (76.4)	188 (89.5)	282 (84.7)	
Leukotriene modifiers	39 (31.7)	69 (32.9)	108 (32.4)	0.83
Controller equivalent canisters dispensed, mean ± SD§	6.9 ± 6.4	6.8 ± 5.4	6.8 ± 5.8	0.70

(continued)