

Pediatric Hypereosinophilia: Characteristics, Clinical Manifestations, and Diagnoses



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What is already known about this topic? Data on pediatric hypereosinophilia are limited, and the differential diagnosis is broad.

What does this article add to our knowledge? Pediatric hypereosinophilia commonly occurs in association with other diseases.

How does this study impact current management guidelines? Pediatric hypereosinophilia is not uncommon, highlighting a need for its identification and thorough evaluation.

BACKGROUND: Eosinophilia is associated with various conditions, including allergic, infectious, and neoplastic disorders. The diagnostic differential is broad, and data on hypereosinophilia in pediatric patients are limited.

OBJECTIVE: The objectives of this study were to identify cases of hypereosinophilia in a tertiary pediatric medical center, determine clinical characteristics and disease associations, and estimate the incidence of hypereosinophilia in the hospital and geographic populations.

METHODS: A retrospective chart review included patients younger than 18 years presenting to a tertiary pediatric medical center (January 1, 2008, to May 31, 2017) with absolute eosinophil counts (AECs) greater than or equal to 1.50 thousand eosinophils/microliter (K/ μ L) recorded on at least 2 occasions at least 4 weeks apart (N = 176). Clinical characteristics, laboratory values, treatment course, and associated diagnoses were evaluated.

RESULTS: The most common cause of hypereosinophilia in this cohort was secondary hypereosinophilia. Atopic dermatitis,

graft-versus-host disease, sickle cell disease, and parasitic infections were the most common conditions associated with hypereosinophilia. Median age at diagnosis was 4.6 (interquartile range, 1.5-10.5) years. Median peak AEC was 3.16 (2.46-4.78) K/ μ L. Hypereosinophilia occurred most frequently in patients aged between 6 and 11 years (24.4%) and younger than 1 year (18.2%). Patients with neoplasms and immune deficiencies had significantly higher peak AECs than did patients with overlap hypereosinophilic syndrome and atopic diseases ($P < .0001$).

CONCLUSIONS: Pediatric hypereosinophilia has an incidence of 54.4 per 100,000 persons per year, with children younger than 1 year and aged 6 to 11 years accounting for most affected patients. Pediatric hypereosinophilia is not uncommon and remains underrecognized, highlighting a need for clinicians to identify patients who meet criteria for hypereosinophilia and to pursue a thorough evaluation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2750-8)

Key words: Eosinophilia; Hypereosinophilic syndrome; Eosinophil

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INTRODUCTION

Eosinophilia is defined as an increase in the number of eosinophils in the blood, observed in absolute eosinophil counts (AECs) above the upper limit of normal. Peripheral blood eosinophil levels vary by age, with upper reference limits being higher in younger children.^{1,2} Traditionally, the degree of eosinophilia can be classified as mild (AEC, 0.50-1.49 thousand eosinophils per microliter [K/ μ L]), moderate (AEC, 1.50-5.00 K/ μ L), or severe (AEC, >5.00 K/ μ L). Although mild or transient eosinophilia is observed relatively frequently within the pediatric population, it is generally clinically insignificant. Conversely, marked and persistent eosinophilia is less common and should prompt additional clinical evaluation. The term hypereosinophilia has been reserved for patients with moderate

Abbreviations used

AEC- Absolute eosinophil count
A/I- Allergy and Immunology
ALT- Alanine aminotransferase
EGID- Eosinophilic gastrointestinal disorder
GvHD- Graft-versus-host disease
HES- Hypereosinophilic syndrome
K/ μ L- Thousand eosinophils/microliter

to severe, persistent eosinophilia recorded on at least 2 occasions with a minimum time interval of 4 weeks apart.³ Patients with persistent eosinophilia can have a spectrum of clinical consequences, ranging from relatively benign conditions to diseases associated with organ dysfunction and potentially life-threatening sequelae.⁴ Although the clinical manifestations and underlying etiologies of hypereosinophilia in adults have been well characterized, little is known about the clinical presentation, final diagnosis, treatment response, and prognosis of pediatric patients with hypereosinophilia.^{5,6} Evaluation and treatment of pediatric patients with hypereosinophilia is challenging, because the etiology is often difficult to discern. The differential diagnosis is broad, and workup can ultimately be extensive and costly; thus, it is important to identify underlying conditions at which treatment can be directed rather than directing treatment at the eosinophilia itself.

The aims of this study were to (1) identify patients meeting the laboratory criteria for hypereosinophilia at a tertiary pediatric medical center; (2) evaluate their demographic and clinical characteristics; (3) determine disease associations; and (4) estimate the prevalence and incidence rates of hypereosinophilia in the hospital and geographic populations.

METHODS

A retrospective chart review was completed by searching the electronic medical record (Epic, Verona, Wis) with a computer script generated to identify all records of individuals younger than 18 years presenting to a tertiary pediatric medical center from January 1, 2008, to May 31, 2017, in the outpatient or inpatient setting and meeting laboratory criteria for hypereosinophilia. Hypereosinophilia was defined as having at least 2 peripheral blood AECs greater than or equal to 1.50 K/ μ L recorded at least 4 weeks apart³ and no more than 6 months apart, with no intervening AEC less than 1.50 K/ μ L. Two AEC levels were specifically collected from the electronic record, the AEC at diagnosis and the highest (peak) AEC level on or before the diagnosis date. Diagnosis date was defined as the date that the second AEC (≥ 1.50 K/ μ L) was obtained and the individual satisfied the criteria for hypereosinophilia. Data on demographic characteristics were collected, including sex, age at diagnosis, race, ethnicity, and geographical residence. Clinical and laboratory data were also recorded, when available. Parameters previously shown or suspected to have prognostic significance in HES were recorded, when available, including peak eosinophil count, serum tryptase, serum IgE, vitamin B₁₂ level, serum IL-5, *FIP1L1/PDGFR* mutation status, T-cell phenotype (assessed by flow cytometry), and clonality (assessed by T-cell receptor rearrangement studies).⁷⁻¹⁰ Parameters included in the initial diagnostic workup for hypereosinophilia were recorded, when available, such as liver and kidney function tests and stool/serology for parasites.^{4,11} Tests to evaluate

for end-organ involvement and/or tissue eosinophilia (such as computed tomography of the chest, abdomen, and pelvis; electrocardiogram; echocardiogram; pulmonary function test; and pathology from bone marrow, gastrointestinal tract, lung, and/or liver) were reviewed, when available.^{4,11}

Charts were reviewed by 3 physicians (P.C.F., C.E.R., J.T.S.) to determine underlying diagnoses on the basis of diagnostic criteria and clinical history. Several clinical subtypes of HES have been described.^{12,13} Diagnostic categories included the following: hypereosinophilic syndrome (HES; divided into myeloproliferative HES, lymphocytic HES, overlap HES, or idiopathic HES), hypereosinophilia of unknown significance, secondary (or reactive) hypereosinophilia, or probable secondary hypereosinophilia. HES was defined by the presence of peripheral blood hypereosinophilia and evidence of end-organ damage or dysfunction directly attributable to tissue eosinophilia.³ Myeloproliferative HES was defined as HES with myeloproliferative features indicating clonal eosinophilic involvement (eg, patients with myeloproliferative neoplasms and a known mutation, including patients with *FIP1L1/PDGFR*, as well as subjects with HES and myeloproliferative features without a known mutation).¹⁴ Lymphocytic HES was defined as HES with demonstrable clonal or phenotypically aberrant lymphocyte population.¹⁵ Overlap HES was defined as hypereosinophilia with eosinophilic disease restricted to a single organ system (ie, eosinophilic gastrointestinal disorder [EGIDs]) and peripheral hypereosinophilia.⁵ Idiopathic HES was defined as HES of unknown cause not meeting criteria for any of the other categories of HES. Hypereosinophilia of unknown significance was a term reserved for patients who met the criteria for hypereosinophilia and had sufficient clinical workup to determine that there were no clinical or laboratory signs or symptoms suggestive of end-organ damage or dysfunction that could lead to, and thus explain, hypereosinophilia.³ Secondary hypereosinophilia was defined as hypereosinophilia in the setting of an underlying disease known to be associated with eosinophilia. Patients with an underlying condition with uncertain but likely association with the hypereosinophilia were categorized as having “probable” secondary hypereosinophilia. Finally, cases were categorized as “unknown” if there was insufficient information to determine a diagnosis related to the hypereosinophilia, for example, patients lost to follow-up. See Table 1 for a summary of these diagnostic category definitions. Resolution of hypereosinophilia, defined as a decrease to an AEC less than 1.50 K/ μ L at the time of last recorded AEC, was documented in a dichotomous manner (yes/no); notably, a patient may have experienced 1 or more episodes of hypereosinophilia before its resolution. Hypereosinophilia that did not resolve was defined as AEC values that remained greater than or equal to 1.50 K/ μ L at the time of last recorded AEC; this included cases in which no further AEC levels were obtained after the diagnosis date. The number of deaths before resolution of the hypereosinophilia was recorded. Involvement of the Division of Allergy and Immunology (A/I) clinical team (whether the patient was a primary A/I patient, an A/I referral/consultation, or not an A/I patient) and mention of hypereosinophilia in the physician’s note (yes/no) were recorded to determine the rates of recognition of and referral for hypereosinophilia.

To calculate the prevalence and incidence rates of hypereosinophilia in the hospital population, the number of patients who met the case definition of hypereosinophilia was divided by the total number of patients in the hospital population (2008-2017). The 2010 census data for individuals younger than 18 years in Hamilton County of Ohio, the region immediately surrounding the medical

TABLE I. Definitions of diagnostic categories of hypereosinophilia

Diagnosis	Definition
HESs	Peripheral blood hypereosinophilia and evidence of end-organ damage or dysfunction directly attributable to tissue eosinophilia
Myeloproliferative HES	HES with myeloproliferative features indicating clonal eosinophilic involvement
Lymphocytic HES	HES with demonstrable clonal or phenotypically aberrant lymphocyte population
Overlap HES	Hypereosinophilia with eosinophilic disease restricted to a single organ system
Idiopathic HES	HES of unknown cause not meeting criteria for any of the other categories of HES
Hypereosinophilia of unknown significance	Hypereosinophilia with sufficient clinical workup finding no clinical or laboratory signs or symptoms suggestive of end-organ damage or dysfunction that could lead to, and thus explain, hypereosinophilia
Secondary (or reactive) hypereosinophilia	Hypereosinophilia in the setting of an underlying disease known to be associated with eosinophilia
Probable secondary hypereosinophilia	Hypereosinophilia associated with an underlying condition with uncertain but likely association with the hypereosinophilia
Not enough information to determine	Hypereosinophilia with insufficient clinical or laboratory signs or symptoms to explain hypereosinophilia

center, was used to estimate the prevalence and incidence (2010-2017) of hypereosinophilia by geographic region.

Statistical considerations

Demographic and clinical characteristic comparisons were performed using Mann-Whitney test or Kruskal-Wallis test with the Dunn multiple-comparison posttest, when applicable, for continuous variables and chi-square test for categorical variables. Data are expressed as medians with interquartile ranges, unless otherwise noted. Box plots provide visual group comparison with medians, upper quartiles, lower quartiles, maximums, minimums, and individual data points for values more than 1.5 times the interquartile range above the third quartile or below the first quartile. Of note, statistical analysis included all data points. Group comparisons were evaluated using a fixed effect model with the Tukey multiple-comparison posttest, when applicable. Data are expressed as geometric means $\pm$ geometric SD, unless otherwise noted. Creatinine, aspartate aminotransferase, and alanine aminotransferase (ALT) values were analyzed as dichotomous variables (within normal limits: yes/no). Group comparisons for laboratory values beyond AECs were performed for a subset of disease categories because of small sample size. All tests were conducted at $\alpha = 0.05$ (Prism 5.0 software; GraphPad Software, La Jolla, Calif).

RESULTS

Of 571,071 unique patients younger than 18 years seen at this institution between January 1, 2008, and May 31, 2017, 35,938 patients had at least 2 AECs recorded at least 4 weeks apart but less than 6 months apart. Of these 35,938 patients, 176 unique individuals met criteria for hypereosinophilia (Table II). The median age at diagnosis was 4.6 (interquartile range, 1.5-10.5) years. The median peak AEC was 3.16 (2.46-4.78) K/ μ L, and median AEC at diagnosis was 2.15 (1.82-2.84) K/ μ L. Patients identified as predominantly white (66.5%) followed by black (24.4%). There were 8 deaths in the hypereosinophilia cohort during the study period. Frequency of hypereosinophilia was highest in the spring (March-May, 53 of 176) and summer (June-August, 52 of 176) seasons and was lowest in the winter (December-February, 30 of 176) season.

Of patients with hypereosinophilia, the median age at diagnosis was significantly lower in males than in females (3.4 [1.1-8.6] vs 7.7 [2.0-12.1]; $P = .0033$). Between males and females,

there were no significant differences in peak AECs (3.12 [2.49-5.05] vs 3.19 [2.44-4.55] K/ μ L; $P = .7514$) or AECs at diagnosis (2.18 [1.87-2.71] vs 2.06 [1.78-2.88] K/ μ L; $P = .6103$) (Figure 1, A and B).

TABLE II. Demographic and clinical characteristics for subjects with hypereosinophilia (N = 176)

Characteristic	n (%)
Sex	
Male	97 (55.1)
Female	79 (44.9)
Age at diagnosis (y)	
<1	32 (18.2)
1-2	34 (19.3)
3-5	34 (19.3)
6-11	43 (24.4)
12-17	33 (18.8)
Median age at diagnosis (y) (IQR)	4.6 (1.5-10.5)
Race	
White	117 (66.5)
Black	43 (24.4)
Asian	2 (1.1)
Other	12 (6.8)
Unknown	2 (1.1)
Ethnicity	
Non-Hispanic	165 (93.8)
Hispanic	9 (5.1)
Unknown	2 (1.1)
Residence	
United States	173 (98.3)
Ohio	102 (57.9)
Cincinnati	51 (29.0)
Kentucky	42 (23.9)
Indiana	17 (9.7)
Other states	12 (6.8)
Other country	3 (1.7)
Median AEC at diagnosis (K/ μ L) (IQR)	2.15 (1.82-2.84)
Median peak AEC (K/ μ L) (IQR)	3.16 (2.46-4.78)

IQR, Interquartile range.

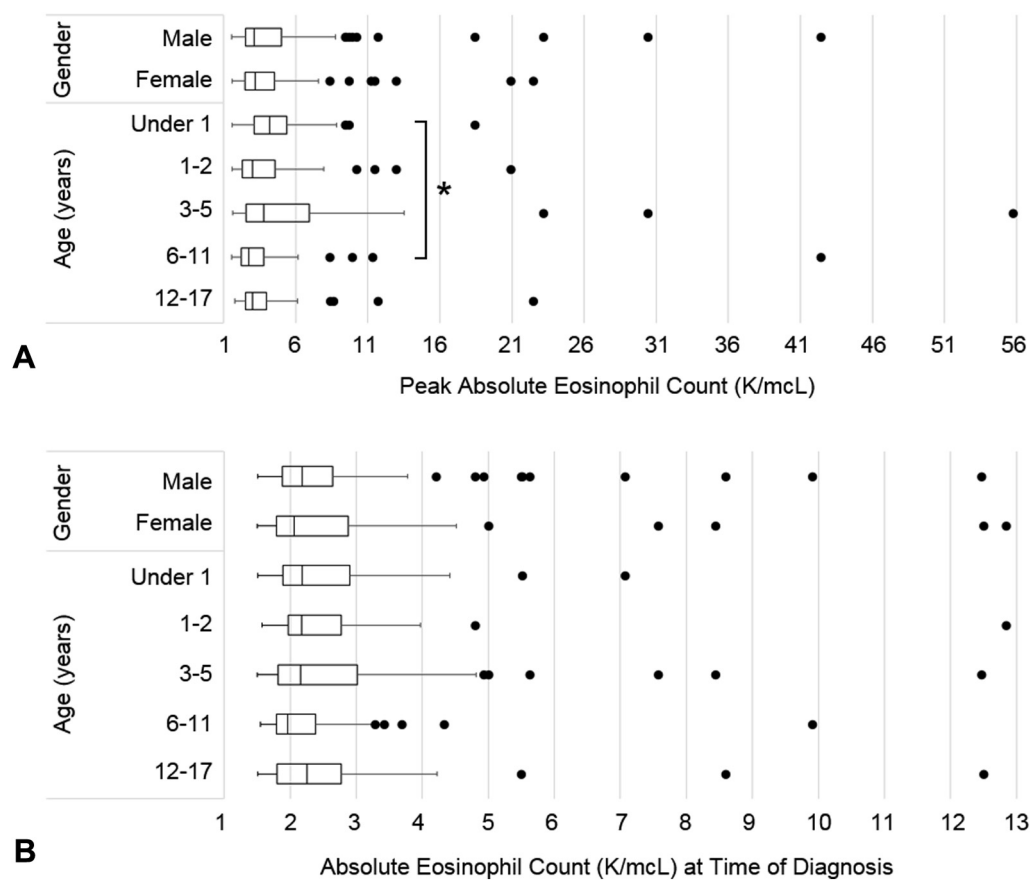


FIGURE 1. AECs by sex and age. **A**, Peak AECs and **B**, AECs at time of diagnosis. Box and whisker plots demonstrate the distribution of the AECs (peak, time of diagnosis) by sex (males: N = 97, females: N = 79) and age categories (<1 year: N = 32, 1-2 years: N = 34, 3-5 years: N = 34, 6-11 years: N = 43, 12-17 years: N = 33) with outliers plotted as individual dots. *Significant difference in peak AECs between age groups ($P < .05$).

Hypereosinophilia occurred most frequently in patients between the ages of 6 and 11 years (43 of 176 [24.4%]). Notably, 32 (18.2%) of the patients with hypereosinophilia were younger than 1 year. There was a significant effect of age group on peak AEC ($P = .0168$), with the Dunn multiple-comparison posttest indicating that the median peak AEC in patients younger than 1 year was significantly higher than the peak AEC in patients aged 6 and 11 years (4.20 [2.98-5.47] vs 2.72 [2.10-3.83] K/ μ L) (Figure 1, A). There were no significant differences in AECs at time of diagnosis among the different age groups (<1 year: 2.18 [1.67-3.00]; $1 \geq$ age < 3 years: 2.16 [1.76-2.91]; $3 \geq$ age < 6 years: 2.16 [1.73-4.82]; $6 \geq$ age < 12 years: 1.96 [1.78-2.68]; $12 \geq$ age < 18: 2.25 [1.67-3.34]; $P = .6533$) (Figure 1, B).

In the hospital population, the prevalence of hypereosinophilia was 489.7 per 100,000 persons with a corresponding incidence rate of 54.4 per 100,000 persons per year. Focusing on the general population (Hamilton County, Ohio), the prevalence of hypereosinophilia in persons younger than 18 years was 31.4 per 100,000 persons, with a corresponding incidence rate of 3.5 per 100,000 persons per year.

In the cohort of 176 patients with hypereosinophilia identified retrospectively, 12 patients (7%) were diagnosed with HES. Of

these 12 patients with HES, 11 were further classified as overlap HES (all of whom had EGIDs), and 1 patient was further classified as idiopathic HES. There were no individuals diagnosed with myeloproliferative or lymphocytic variants of HES. One patient was diagnosed with hypereosinophilia of unknown significance. In 60 cases (34.1%), there was not sufficient information to determine a diagnosis related to the hypereosinophilia. Ninety-four patients (53.4%) had secondary hypereosinophilia, and their underlying diagnoses included atopic dermatitis, graft-versus-host disease (GvHD), sickle cell disease, parasitic infections, neoplasms, asthma, adverse drug reactions, immune deficiencies, inflammatory disorders (eg, dermatomyositis), iron deficiency anemia, Netherton syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and inflammatory bowel disease (IBD) (Figure 2, A). Neoplasms included inflammatory myofibroblastic tumors (1 of 6 patients), sacrococcygeal teratoma (1 of 6), relapse of acute myelogenous leukemia status post bone marrow transplant (1 of 6), neuroblastoma (2 of 6), and infantile fibrosarcoma (1 of 6). Infections included *Toxocara canis* (5 of 10 patients), *Strongyloides* (2 of 10), *Histoplasma capsulatum* (1 of 10), and *Sarcoptes scabiei* (1 of 10); 1 patient had coinfection with *Toxocara canis* and *Strongyloides*. In addition, 2 patients were empirically treated

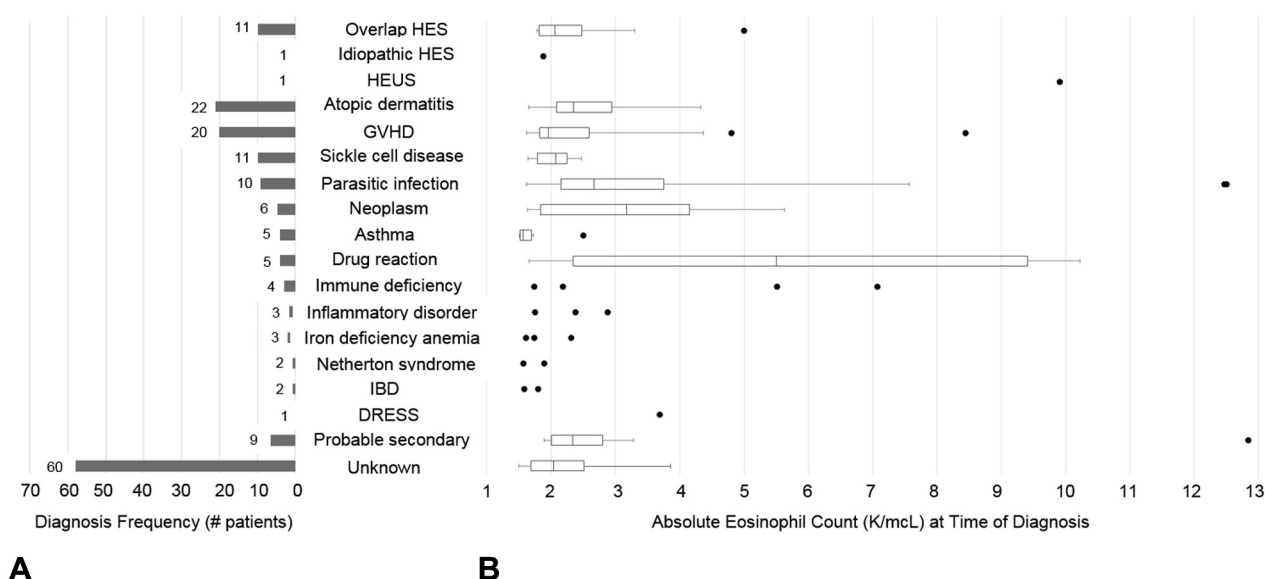


FIGURE 2. Disease categories associated with hypereosinophilia. **A**, Diagnosis frequency (N = 176). There were no individuals diagnosed with myeloproliferative or lymphocytic HES. **B**, AEC at time of diagnosis for each disease category associated with hypereosinophilia. Box and whisker plots demonstrate the distribution of the AEC at the time of diagnosis for each disease category. Individual dots represent outliers. For disease categories with fewer than 5 individuals, dots are used to represent unique AEC levels. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *HEUS*, hypereosinophilia of unknown significance; *IBD*, inflammatory bowel disease; *probable secondary*, probable secondary hypereosinophilia; *unknown*, insufficient information to determine a diagnosis related to the hypereosinophilia.

for parasitic infections with a favorable response to treatment, that is, resolution of hypereosinophilia. Immune deficiencies included Wiskott-Aldrich syndrome (2 of 4 patients), Omenn syndrome in a patient with complete DiGeorge syndrome secondary to diabetic embryopathy (1 of 4), and dedicator of cytokinesis 8 immunodeficiency syndrome (1 of 4). The remaining 9 patients were categorized as having probable secondary hypereosinophilia, which included lead poisoning, *Helicobacter pylori*-induced gastritis, eosinophilic pustulosis of infancy, solid organ transplant-related immunosuppression, food protein-induced allergic proctocolitis of infancy, reactivated tuberculosis, arthropod bite reaction, necrotizing enterocolitis, and fungal peritonitis. Eight patients were deceased, and their diagnoses included GvHD (2 of 8 patients),

immune deficiency (1 of 8; dedicator of cytokinesis 8 immunodeficiency syndrome), inflammatory disorder (1 of 8), neoplasm (1 of 8; relapse of acute myelogenous leukemia status post bone marrow transplant), overlap HES (1 of 8; EGID in the context of a suspected mitochondrial myopathy), and 2 patients with not sufficient information to determine the cause of the hypereosinophilia. For each of the secondary or probable secondary diagnoses, the AEC at time of diagnosis varied widely within the groups (Figure 2, B).

In patients for whom a diagnosis related to the hypereosinophilia was able to be determined retrospectively, the most common diagnoses associated with moderate hypereosinophilia, defined as AEC of 1.50–5.00 K/ μ L, were atopic dermatitis, GvHD, overlap HES, sickle cell disease, parasitic infections, and

TABLE III. Most common diagnoses associated with hypereosinophilia by degree of hypereosinophilia

Degree of hypereosinophilia			
Moderate hypereosinophilia (1.50 ≤ AEC ≤ 5.00 K/ μ L) (N = 134)		Severe hypereosinophilia (AEC > 5.00 K/ μ L) (N = 42)	
Diagnosis	n (%)	Diagnosis	n (%)
Not enough information to determine	53 (40)	Not enough information to determine	7 (17)
Atopic dermatitis	19 (14)	GvHD	5 (12)
GvHD	15 (11)	Immune deficiency	4 (10)
Overlap HES*	10 (7)	Neoplasm	4 (10)
Sickle cell disease	9 (7)	Parasitic infection	4 (10)
Parasitic infection	6 (4)	Adverse drug reaction	3 (7)
Asthma	5 (4)	Atopic dermatitis	3 (7)

*All cases of overlap HES in this cohort were EGIDs.

TABLE IV. Most common diagnoses associated with hypereosinophilia by age group

<1 year (N = 32)		1-2 y (N = 34)		3-5 y (N = 34)		6-11 y (N = 43)		12-17 y (N = 33)	
Diagnosis	n (%)	Diagnosis	n (%)	Diagnosis	n (%)	Diagnosis	n (%)	Diagnosis	n (%)
Not enough information to determine	12 (38)	Not enough information to determine	11 (32)	Not enough information to determine	9 (26)	Not enough information to determine	15 (35)	Not enough information to determine	12 (36)
Atopic dermatitis	7 (22)	Atopic dermatitis	5 (15)	GvHD	7 (21)	Atopic dermatitis	5 (12)	GvHD	5 (15)
Probable secondary hypereosinophilia*	4 (13)	GvHD	3 (9)	Neoplasm	3 (9)	GvHD	5 (12)	Atopic dermatitis	3 (9)
Immunodeficiency	3 (9)	Iron deficiency anemia	3 (9)	Overlap HES	3 (9)	Overlap HES	3 (7)	Parasitic infection	3 (9)
Neoplasm	3 (9)	Sickle cell disease	3 (9)	Parasitic infection	3 (9)	Sickle cell disease	3 (7)	Adverse drug reaction	2 (6)
Overlap HES	1 (3)	Adverse drug reaction	2 (6)	Sickle cell disease	3 (9)	Inflammatory disorder	2 (5)	Overlap HES	2 (6)
Parasitic infection	1 (3)	Overlap HES	2 (6)	Atopic dermatitis	2 (6)	Probable secondary hypereosinophilia*	2 (5)	Sickle cell disease	2 (6)
Netherton syndrome	1 (3)	Parasitic infection	2 (6)	Asthma	1 (3)	Adverse drug reaction	1 (2)	Asthma	1 (3)
		Idiopathic HES	1 (3)	IBD	1 (3)	DRESS	1 (2)	IBD	1 (3)
		Netherton syndrome	1 (3)	Probable secondary hypereosinophilia*	1 (3)	HEUS	1 (2)	Inflammatory disorder	1 (3)
		Probable secondary hypereosinophilia	1 (3)			Immunodeficiency	1 (2)	Probable secondary hypereosinophilia*	1 (3)
						Parasitic infection	1 (2)		

DRESS, Drug reaction with eosinophilia and systemic symptoms; *HEUS*, hypereosinophilia of unknown significance; *IBD*, inflammatory bowel disease.

*In patients younger than 1 y, probable secondary hypereosinophilia included eosinophilic pustulosis of infancy (N = 1), fungal peritonitis (N = 1), food protein–induced allergic proctocolitis of infancy (N = 1), and necrotizing enterocolitis (N = 1). In patients aged 1 to 2 y, probable secondary hypereosinophilia included reactivated tuberculosis (N = 1). In patients aged 3 to 5 y, probable secondary hypereosinophilia included lead poisoning (N = 1). In patients aged 6 to 11 y, probable secondary hypereosinophilia included arthropod bite reaction (N = 1) and *Helicobacter pylori*–induced gastritis (N = 1). In patients aged 12 to 17 y, probable secondary hypereosinophilia included solid organ transplant–related immunosuppression (N = 1).

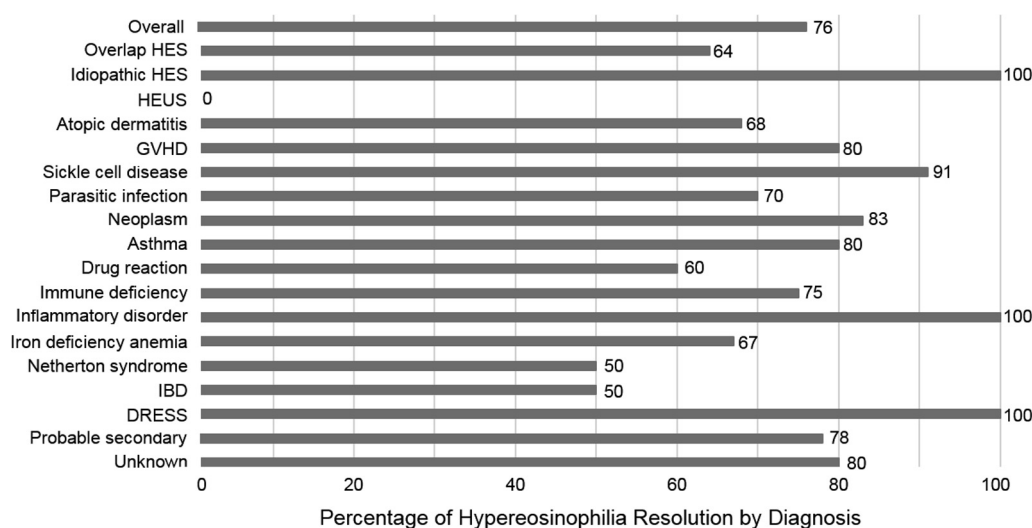


FIGURE 3. Outcome of hypereosinophilia by diagnosis category. Resolution of hypereosinophilia was defined as a decrease to an AEC less than 1.50 K/ μ L at the time of last recorded AEC. Hypereosinophilia that did not resolve was defined as AEC values persistently greater than or equal to 1.50 K/ μ L at the time of last recorded AEC; this included cases in which no further AEC levels were obtained after diagnosis date. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *HEUS*, hypereosinophilia of unknown significance; *IBD*, inflammatory bowel disease; *probable secondary*, probable secondary hypereosinophilia; *unknown*, insufficient information to determine a diagnosis related to the hypereosinophilia.

asthma (Table III). The most common diagnoses associated with severe hypereosinophilia, defined as AEC greater than 5.00 K/ μ L, were GvHD, immune deficiencies, neoplasms, parasitic infections, adverse drug reactions, and atopic dermatitis. Notably, in patients with moderate and severe hypereosinophilia, 40% and 17% of patients, respectively, did not have sufficient information in their medical record to determine a diagnosis related to the hypereosinophilia (Table III). Similarly, across all age groups, most patients did not have sufficient information in their medical record to determine the cause of hypereosinophilia. In patients in whom a diagnosis related to the hypereosinophilia was able to be determined retrospectively, the most common diagnoses associated with hypereosinophilia by age group were as follows: atopic dermatitis in patients younger than 2 years, GvHD in patients aged 3 to 5 years, atopic dermatitis and GvHD in patients aged 6 to 11 years, and GvHD in patients aged 12 to 17 years (Table IV).

There was a significant effect of disease category on peak AEC ($P < .0001$), with the Tukey multiple-comparison posttest indicating that patients with neoplasms and immune deficiencies had higher peak AEC (2-3-fold) than did patients with overlap

HES and atopic disease (asthma and atopic dermatitis combined) (7.91 ± 2.74 and 10.26 ± 2.68 vs 2.70 ± 1.32 and 2.96 ± 1.46 K/ μ L). There was a significant effect of disease category on AEC at diagnosis ($P = .0258$), with the Tukey multiple-comparison posttest indicating that patients with parasitic infections had higher AEC at diagnosis than did patients with sickle cell disease (3.9 ± 2.11 vs 2.01 ± 1.14 K/ μ L). There were no statistically significant differences in sex distribution or age at diagnosis among the disease categories.

Overall, patients had limited laboratory and diagnostic evaluation for hypereosinophilia (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) and nonspecific clinical characteristics (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Although group comparisons were not performed because of small sample size in several disease categories, associations with laboratory findings beyond the AECs in a subset of diagnoses were examined. Among patients with overlap HES, atopic disease, GvHD, sickle cell disease, and parasitic infections, there was a significant effect of disease category on serum IgE level ($P = .0059$), with the Tukey multiple-comparison posttest indicating that patients with atopic disease had higher IgE levels than did patients with GvHD (1387.0 ± 11.6 vs 32.7 ± 20.3 IU/mL). Among the disease categories, there were no significant differences in abnormal creatinine, abnormal aspartate aminotransferase, IL-5, tryptase, or vitamin B₁₂ levels. There was a significant effect of disease category on abnormal ALT level ($P = .0387$), with the Dunn multiple-comparison posttest indicating that a higher proportion of patients with GvHD had abnormal ALT levels than did patients with parasitic infections.

For a subset of individuals with multiple AECs recorded, there were characteristic trends in AEC for distinct diseases. For example, atopic individuals had consistently elevated AECs, which often failed to resolve to the normal range (see

TABLE V. Recognition of and referral for hypereosinophilia*

Involvement of the A/I service	Hypereosinophilia documented	Hypereosinophilia not documented
Primary A/I patient	21 (30.0)	10 (9.4)
A/I referral/consultation	13 (18.6)	4 (3.8)
Not an A/I patient	36 (51.4)	92 (86.8)
Total	70 (39.8)	106 (60.2)

*Involvement of the A/I service (whether the patient was a primary A/I patient, an A/I referral/consultation, or not an A/I patient) and mention of hypereosinophilia in the physician's note (yes/no) were recorded to determine the rates of recognition of and referral for hypereosinophilia.

Figure E1, A, in this article's Online Repository at www.jaci-inpractice.org). Individuals with sickle cell disease demonstrated elevated AECs around the onset of symptoms associated with infection (Figure E1, B). In addition, patients with sickle cell disease who underwent monthly transfusion visits demonstrated variable AEC levels. Interestingly, 3 patients who had a history of lead toxicity subsequently developed hypereosinophilia, and subsequent workup identified underlying *Toxocara* infections. Two of these patients also had a history of pica and iron deficiency anemia preceding the development of hypereosinophilia, which may have contributed to their development of lead toxicity. After treatment with antiparasitic medication, their hypereosinophilia resolved. Another patient with a history of iron deficiency anemia and pica developed hypereosinophilia, which led to the identification of an underlying *Toxocara* infection. Another patient who had a history of lead toxicity presented with hypereosinophilia, but additional information was not available because the patient was lost to follow-up.

In the vast majority of patients (134 of 176 [76.1%]), hypereosinophilia resolved, as noted in their last recorded AEC, regardless of treatment (Figure 3). Of 134 patients with resolution of hypereosinophilia, 70 (52.2%) patients had resolution of hypereosinophilia in absence of any documented therapy (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Hypereosinophilia was documented in the medical record of 70 (39.8%) cases (Table V). In patients with noted hypereosinophilia (N = 70), 21 (30.0%) patients were regularly followed by an A/I physician, 13 (18.6%) were evaluated for hypereosinophilia by an A/I physician as a referral/consultation, and 36 (51.4%) patients were not evaluated by an A/I physician. In 106 (60.2%) patients, hypereosinophilia was not documented in the medical record. Of this subset of patients with no noted hypereosinophilia (N = 106), 10 (9.4%) patients were regularly followed by an A/I physician, 4 (3.8%) were evaluated for hypereosinophilia by an A/I physician as a referral/consultation, and 92 (86.8%) patients were not evaluated by an A/I physician.

DISCUSSION

The overall prevalence of hypereosinophilia within the pediatric population was previously unknown, because no population-based studies have been completed. A recent study identified eosinophilia (AEC > 1.00 K/ μ L) in 357.8 per 100,000 persons who had 1 complete blood cell count with differential in a primary care setting.¹⁶ The existing data on pediatric hypereosinophilia are largely composed of case reports or case series.^{5,6,17-19} To our knowledge, this is the first study to provide data on the prevalence of pediatric hypereosinophilia in the general population. In addition, we believe this is the largest study to date to evaluate pediatric patients with hypereosinophilia seen at a single center, providing data on both initial presentation and long-term follow-up.

The most common cause of hypereosinophilia in our pediatric cohort was secondary (reactive) hypereosinophilia. Atopic dermatitis, GvHD, sickle cell disease, and parasitic infection were the most common disease entities associated with hypereosinophilia. There was not enough information to determine the cause of hypereosinophilia for approximately one-third of the patients. This may be due to lack of workup to determine the

cause, loss to follow-up, or an inability to identify a known cause of hypereosinophilia.

The significant effect of age group on peak AEC, with the peak AEC of patients younger than 1 year being significantly higher than the peak AEC of patients aged 6 to 11 years, may be attributable to the natural variation in blood eosinophil levels by age.^{1,2} Notably, patients with neoplasms and immune deficiencies had higher peak AEC levels than did patients with atopic disease or EGID, which likely reflects the severity of the underlying pathology. Classically, the degree of eosinophilia is rarely helpful for identifying the cause, except at extremes of eosinophil counts; for example, mild eosinophilia in adults can be associated with atopic disease, and very severe eosinophilia is more likely to be caused by a myeloproliferative neoplasm. Among this cohort of pediatric patients with hypereosinophilia, the extremes are populated by EGIDs and other atopic disorders (mild) versus immune deficiencies and neoplasms (severe). In addition, the highest incidence of hypereosinophilia occurs during the spring and summer seasons, highlighting the possible effect of environmental exposures on pediatric hypereosinophilia.

There were noticeable trends in AEC levels. Individuals with atopy tended to have persistently high AECs, whereas individuals with sickle cell disease tended to have variable elevations in their AECs, with peaks occurring around the development of symptoms associated with infection. Sickle cell disease has not been previously reported as a cause of pediatric hypereosinophilia, but there is evidence of a potential role for eosinophils in vaso-occlusive crises.^{20,21} In addition, though the association between helminth infections and eosinophilia is well known, it was interesting to note that the subsequent workup of patients with a history of pica and/or lead poisoning presenting with hypereosinophilia identified underlying *Toxocara* infections. These are patterns and clinical histories that may be useful in guiding the diagnostic approach for the child who presents with unexplained hypereosinophilia.

Apart from the AEC, clinical features that were notable included the serum IgE level, which was higher in patients with atopic disease than in patients with GvHD, and whether patients had abnormal ALT levels, which was more common in patients with GvHD than in patients with parasitic infections. These differences can be attributed to the nature and severity of the underlying disease pathology, respectively. Given the paucity of laboratory data, the study was not sufficiently powered to detect additional differences in clinical laboratory features among the disease categories. It is likely that many of these parameters were not performed in most patients because there was no clinical concern for HES as most cases of hypereosinophilia were not even noted.

The treatment response and prognosis of pediatric patients with hypereosinophilia has not previously been well characterized. In this cohort, hypereosinophilia resolved in the last AEC in 76% of individuals, regardless of treatment (Figure 3). Furthermore, in the absence of documented therapy, 52% of patients had resolution of their hypereosinophilia (Table E3). Overall, these data suggest that hypereosinophilia can resolve with treatment plans targeting underlying associated diagnoses. Potential explanations for resolution of hypereosinophilia include removal of an offending agent (ie, transient exposure), clearance of an infection, resolution of the driving stimulus (such as an inflammatory process), and downregulation of host responses (eg, in the setting of chronic helminth infections). Because the length of time for absence of hypereosinophilia was not defined for

resolution, it is important to note that our resolution rate may be an overestimate because of inclusion of individuals with transient resolution. Interestingly, hypereosinophilia was more likely to be documented in the medical record when the A/I service was involved in the care of the patient.

Limitations to this study include the lack of inclusion of patients with hypereosinophilia lasting less than 1 month or who only have 1 AEC recorded. Patients meeting these criteria are likely to be cases with severe hypereosinophilia who were recognized and treated early or who were seen as a consult in clinic for a second opinion. For example, it is important to highlight that cases of pediatric myeloproliferative HES have been reported in the literature,⁵ but such cases were possibly not captured in the electronic medical record query used to identify patients for inclusion in this study if they were seen once in clinic as a second opinion and had only 1 AEC recorded before treatment. In addition, individuals with high AECs that were obtained more than 6 months apart were not included in the analysis because it is possible that these individuals do not have persistent hypereosinophilia. Conversely, it is possible that lack of recognition of an elevated AEC and lack of follow-up AECs limits the ability to identify individuals with persistent hypereosinophilia compared with those with intermittently elevated AECs. Another limitation is that this study was conducted at a single tertiary medical center, which may lead to referral bias. In addition, our definition of resolution of hypereosinophilia is limiting because it requires another AEC to be performed. Some cases may have had resolution of hypereosinophilia, but it could not be confirmed without an additional AEC completed at our institution, thereby possibly underestimating the number of cases with resolution of hypereosinophilia. Despite these limitations, our data suggest that hypereosinophilia is not uncommon in the pediatric population and remains underrecognized. Although these data suggest that most cases of hypereosinophilia resolve, the differential diagnosis remains broad and inclusive of disorders that require specific treatments, highlighting a need for medical providers to identify patients who meet criteria for hypereosinophilia and to pursue a thorough evaluation.

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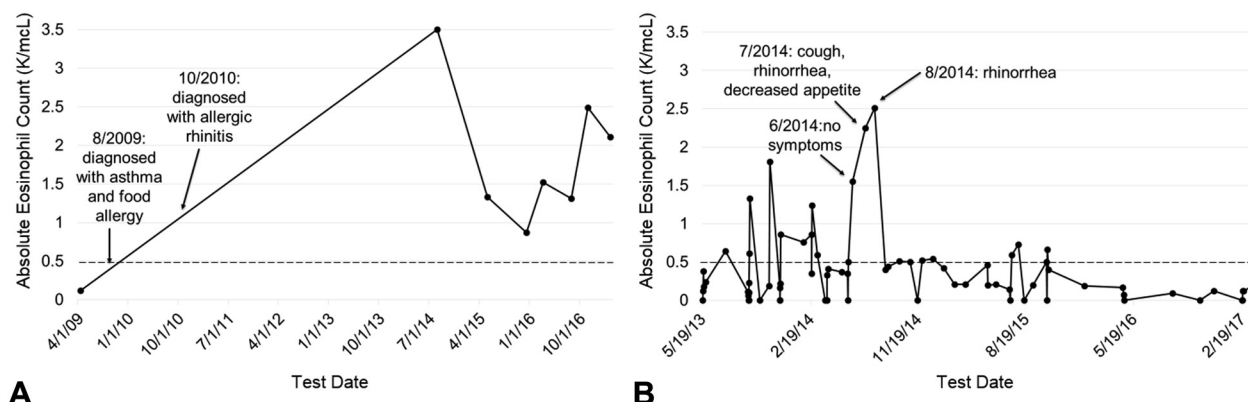


FIGURE E1. Disease-specific trends in AECs. **A**, AEC trend for an individual, aged 10 years at time of diagnosis with hypereosinophilia, with atopic dermatitis, and subsequently diagnosed with asthma, food allergy, and allergic rhinitis. This trend of a consistently high AEC, which fails to resolve to the normal range, was typical for atopic individuals. The dashed line demarcates the upper limit of a normal AEC of 0.50 K/ μ L. Individual dots represent dates when the AEC was measured. **B**, AEC trend for an individual, aged 1 year at time of diagnosis with hypereosinophilia, with sickle cell disease. Individuals with sickle cell disease commonly demonstrated elevated AEC levels around the time of development of symptoms associated with infection, as this individual's trend demonstrates. The dashed line demarcates the upper limit of a normal AEC of 0.50 K/ μ L. Individual dots represent dates when an AEC was measured.

TABLE E1. Laboratory tests performed in subjects with hypereosinophilia

	Subjects (N = 176)	Subjects with abnormal results (% total subjects)
Laboratory test		
Serum creatinine	162 (92)	18 (11)
Serum AST	160 (91)	49 (31)
Serum ALT	156 (89)	33 (21)
Serum IgE	86 (49)	54 (63)
Serum vitamin B ₁₂	42 (24)	14 (33)
Serum IL-5	27 (15)	2 (7)
Stool/serology for parasites	16 (9)	4 (25)
Serum tryptase	13 (7)	3 (23)
T-cell phenotype/clonality	6 (3)	0 (0)
<i>FIP1L1/PDGFRA</i> mutation status	4 (2)	0 (0)
Diagnostic test		
Echocardiogram	26 (15)	
Electrocardiogram	21 (12)	
Pulmonary function test	9 (5)	
CT scan	5 (3)	
EGD	24 (14)	
Bone marrow biopsy	19 (11)	
Bronchoscopy	5 (3)	
Liver biopsy	1 (1)	
Any biopsy confirmed eosinophil infiltrate		20 (11)

AST, Aspartate aminotransferase; EGD, esophagogastrroduodenoscopy; CT, computed tomography.
Values are n (%).

TABLE E2. Clinical characteristics in subjects with hypereosinophilia

Characteristic	n (%)
Medical history	
Any atopy	66 (38)
Atopic dermatitis	47 (27)
Allergic rhinitis	28 (16)
Asthma	23 (13)
Bone marrow transplant	25 (14)
Poor weight gain	20 (11)
Feeding difficulty	15 (9)
Immunodeficiency	14 (8)
GvHD	8 (5)
Epilepsy	6 (3)
Allergies	
Any allergy	71 (40)
Food allergy	38 (22)
Environmental allergy	30 (17)
Medication allergy	11 (6)
Signs/symptoms	
Rash	63 (36)
Poor weight gain	26 (15)
Abdominal pain	23 (13)
Vomiting	16 (9)
Diarrhea	15 (8)
Anemia	14 (8)
Fever	12 (7)
Feeding difficulty	10 (6)
Cough	9 (5)

TABLE E3. Resolution of HE in the absence of therapy

Diagnosis	Patients with resolution of HE, n (%)	Patients with resolution of HE in absence of any therapy, n (%)
Overall	134 (76)	70 (52)
Overlap HES	7 (64)	0 (0)
Idiopathic HES	1 (100)	0 (0)
HEUS	0 (0)	—
Atopic dermatitis	15 (68)	0 (0)
GvHD	16 (80)	3 (19)
Sickle cell disease	10 (91)	10 (100)
Parasitic infection	7 (70)	0 (0)
Neoplasm	5 (83)	0 (0)
Asthma	4 (80)	0 (0)
Drug reaction	3 (60)	2 (67)
Immune deficiency	3 (75)	0 (0)
Inflammatory disorder	3 (100)	1 (33)
Iron deficiency anemia	2 (67)	2 (100)
Netherton syndrome	1 (50)	0 (0)
IBD	1 (50)	0 (0)
DRESS	1 (100)	0 (0)
Probable secondary	7 (78)	6 (86)
Unknown	48 (80)	46 (96)

DRESS, Drug reaction with eosinophilia and systemic symptoms; *HE*, hypereosinophilia; *HEUS*, hypereosinophilia of unknown significance; *IBD*, inflammatory bowel disease.