ORIGINAL ARTICLE

The 2-week time interval criterion may alter the spectrum of disease and patient characteristics in children diagnosed with hypereosinophilia

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ABSTRACT

Background. Diagnostic criteria for hypereosinophilia (HE) have been revised. Accordingly, the minimum interval between the two results with an absolute eosinophil count (AEC) ≥ 1500 cells/μL has been reduced from 4 to 2 weeks. The aims of this study were to identify patients with HE according to the new diagnostic criteria in children and demonstrate the effects of the revised time interval criterion on patient characteristics and disease spectrum.

Methods. Individuals aged ≤ 18 years admitted to a tertiary university hospital were identified using an algorithm based on old and new diagnostic criteria for HE. While patients diagnosed with HE according to old diagnostic criteria were included in group 1, patients who were diagnosed with HE according to the new diagnostic criteria but did not meet the old criteria were included in group 2.

Results. Patients in group 1 were significantly older than patients in group 2 at the time of diagnosis of HE ($p = 0.004$). While the number of patients diagnosed with HE aged 1-5 years was higher in group 1 ($p = 0.01$), the number of patients diagnosed with HE under the age of one year was higher in group 2 ($p = 0.002$). The most common cause of HE in group 1 was allergic disorders (10/40, 25%), while non-parasitic infections (17/36, 47%) were the most common diagnosis in group 2.

Conclusions. The new diagnostic criteria may change the characteristics of pediatric patients with HE and the spectrum of associated diseases.

Key words

Hypereosinophilia; eosinophil; absolute eosinophil count.

Introduction

The term hypereosinophilia (HE) represents the persistence of eosinophilia and according to consensus in 2012, it was defined as an absolute eosinophil count (AEC) ≥ 1500 cells/μL documented on at least two occasions with a minimum time interval of 4 weeks (1). Recently, the diagnostic criteria for HE have been revised. Accordingly, the time interval requirement of 4 weeks between the two results of AEC ≥ 1500 cells/μL has been reduced to 2 weeks. The necessity of this update was based on the gain of more information about the potentially rapid deleterious clinical effects of some genes (particularly those associated with myeloproliferative

diseases and hypereosinophilic syndrome [HES]) and the widespread availability of better diagnostic tests with faster results (2). While this is considered to be a necessary change enabling an earlier diagnosis of myeloproliferative disorders and HES, the requirement of a shorter time interval may, on the other hand, broaden the spectrum of HE-related diseases.

The aims of this study were

1. To describe the characteristics of childhood HE patients according to the new diagnostic criteria
2. To make a comparison between the 2-week and 4-week time interval criterion in patients diagnosed with HE according to the updated diagnostic criteria.

Material and Methods

The study was a retrospective cohort study conducted at a tertiary university hospital in Turkey. Digital medical record registry of xxxxxxxxxxx University was utilized for selection of the participants. Patients aged 0-18 years admitted to any inpatient or outpatient clinics of the hospital between January 1, 2005 and March 31, 2023 were identified. Among them, those with at least one hemogram test were selected. A total of some consecutive conditions designed according to the old and new diagnostic criteria were established to diagnose HE. These conditions included the followings in order:

1. Patients with AEC ≥ 1500 cells/μL
2. Patients with AEC ≥ 1500 cells/μL at least twice in a 6-month period
3. Patients with an interval of at least 4 weeks between any two results (Designed for old diagnostic criteria).
4. Patients with an interval of at least 2 weeks between any two results (Designed for new diagnostic criteria).
5. Patients without AEC < 1500 cells/μL between two results
6. Patients with AEC ≥ 10% of total leukocytes (only for patients diagnosed with acute myeloid leukemia [AML] and chronic myeloid leukemia [CML]) (Designed for new diagnostic criteria)

Group 1 represented patients diagnosed with HE according to the old diagnostic criteria (HEo). After the patients diagnosed with HE according to the revised diagnostic criteria (HEr) were identified, the patients also included in group 1 were excluded. The remaining patients formed group 2. These patients represented the emerging new group of patients according to the revised diagnostic criteria (HEn). The patient flow chart is shown in **Figure 1.**

Definitions

Previously defined terminology used to describe patients with HE and HES (1-2). In addition, hypereosinophilia with at least one AEC result ≥ 5000 cells/μL was defined as severe hypereosinophilia (SHE), while moderate hypereosinophilia (MHE) was defined as hypereosinophilia with no AEC result ≥ 5000 cells/μL. Demographic features of the patients, peak AEC and eosinophil percentage in peripheral blood (PB) differential count at peak AEC; presence of anemia, leukocytosis, leukomoid reaction, leukopenia, thrombocytopenia, severe eosinophilia (AEC ≥ 5000 cells/μL) at initial presentation and hypertransaminasemia were all recorded. In case of resolution of HE with empirical antiparasitic therapy, "probable parasite infection" terminology was used. HE was considered unresolved if AEC was found ≥ 1500

cells/µL at the last follow-up, whereas AEC < 1500 cells/µL at any time during the study was considered resolved.

Statistics

SPSS Statistics version 29.0 was used for statistical considerations. Continuous variables were expressed as median with interquartile range (IQR). Chi-square or Fisher's exact tests were used for comparison of categorical variables. While comparisons of continuous variables between two groups were performed using the Mann-Whitney U test or t test, comparisons of three or more groups were performed using the Kruskal Wallis test or the Dunn multiple comparison test. In case of normal distribution of continuous variables, Tukey's Honest Significant Difference (HSD) test was used to assess the difference between three or more groups' means following the finding of a statistically significant difference with one-way ANOVA test. Box plot method was used to show distributions of continuous variables and comparisons of them between multiple groups. A p value of ≤ 0.05 was considered as statistically significant. Ethical approval for the study was taken from the Ethics Committee of xxxxxxxxxx University (Date: 2023/Approval No: 2023/202).

Results

The total number of patients aged 0–18 years admitted to our hospital between January 1, 2005, and March 31, 2023, was 6,278,443. During this period, the total number of hemogram tests performed on these patients was 369,443, and AEC ≥ 1500 cells/µL was detected in 2250 of these tests and in a total of 1162 patients. Of these 1162 patients, 65 had at least two results with AEC ≥ 1500 cells/µL within a 6-month period with a time interval of at least 4 weeks between the two results, while 152 had at least two results with AEC ≥ 1500 cells/µL within a 6-month period with a time interval of at least 2 weeks between the two results. Of these 65 patients, 25 were excluded due to AEC < 1500 cells/µL between the two outcomes, while in the other arm, 73 of 152 patients were excluded, including 72 patients with AEC < 1500 cells/µL between the two outcomes and 1 CML patient with AEC < 10% of total leukocytes. A total of 40 patients were diagnosed with HE according to the old diagnostic criteria and included in Group 1. A total of 79 patients were diagnosed with HE according to the new diagnostic criteria. Four of them were excluded from the study because their medical records could not be accessed. Of these 75 patients, 39 patients who were also included in group 1 were excluded. The remaining 36 patients were included in group 2 (**Figure 1**).

HE Revised

There was a male predominance in HE patients (48/75, 64%). The median age at diagnosis was 16 (IQR:2-96) months. The median peak AEC and eosinophil percentage in PB differential count at peak AEC were 3500 (IQR: 2400-5200) cells/µL and 25% (IQR: 17%-34%), respectively. Demographic characteristics and clinical findings of the patients are shown in **Table I**. There was no significant difference between males and females regarding age at diagnosis (15 [2-93] vs. 32 [2-108] months; $p = 0.44$), peak AEC (3300 [2425-5075] vs. 3500 [2400-5700] cells /µL; $p = 0.52$) and eosinophil percentage in PB differential count at peak AEC (25% [16%-37%] vs. 24% [17%-33%]; $p = 0.83$). While 11 (15%) patients had severe eosinophilia at initial presentation, 21 (28%) patients were diagnosed with SHE. Among age groups, the highest prevalence of HE was observed in children under one year of age (30/75, 40%), followed by 1-5 years (22/75, 29%), 6-11 years (12/75, 16%) and 12-18 years (11/75, 15%). There was no significant effect of age groups on peak AEC ($p = 0.53$) but a significant

effect of age groups on eosinophil percentage in PB differential count at peak AEC was observed (p =0.002) with the Tukey's HSD multiple-comparison posttest indicating that the mean eosinophil percentage at AEC in patients under one year of age was significantly lower than the eosinophil percentage at AEC in patients aged 6-11 years (22.8 ± 9 vs. 37.6 ± 20.3, p = 0.008) **(Figure 2)**.

In the present study including 75 patients with HE identified retrospectively, only one patient was diagnosed with HES who was classified as idiopathic and one patient was diagnosed with HE of unknown significance (HEus). In 12 (16%) patients with HE, information was insufficient to determine an underlying disease associated with HE. Secondary HE was the most common etiologic group in the study (33/75, 44%). The underlying diagnoses in those subjects were parasitic infections (12/75, 16%), allergic diseases (11/75, 15%), inborn errors of immunity (6/75, 8%), neoplastic diseases (3/75, 4%) and autoimmune disease (1/75, 1%). Parasitic infections included hydatid disease (HD) (8 of 12 patients), fascioliasis (2/12), and probable parasitic infections (2/12). Patients with allergic diseases had atopic dermatitis (7/11), asthma (4/11), whereas inborn errors of immunity included combined immunodeficiency (3/6), primary antibody deficiency (1/6), autosomal dominant hyperimmunoglobulin E syndrome (1/6), Omenn syndrome (1/6), and neoplastic diseases included Hodgkin lymphoma (1/3), congenital mesoblastic nephroma (1/3) and hemangioma (1/3). One patient was diagnosed with bullous pemphigoid which manifested in the neonatal period. In 28 (37%) patients, HE was categorized as probable secondary HE (HEps). Non-parasitic infections were the most common cause of HE in these subjects (18/28), including sepsis (11/18), pneumonia (4/18), impetigo (2/18) and urinary tract infection (UTI) in the setting of neurogenic bladder (1/18). The majority of patients with non-parasitic infections (14/18) were under the age of one year and the first 2 months of life were the period in which non-parasitic infections were the most common (12/18). Remarkably, the neonatal period was noted to be the starting point of HE in all patients aged 0-2 months. In addition, 10 of 12 patients with non-parasitic infections in this age group were born prematurely. Other diseases underlying HEps included, nephrotic syndrome (2/28), food protein induced allergic proctocolitis of infancy (2/28), chronic tonsillitis in which HE resolved after tonsillectomy (1/28) necrotizing enterocolitis (1/28), mitochondrial disease (1/28), neurometabolic disease (1/28), feeding intolerance in a preterm infant (1/28) and hereditary spherocytosis (1/28).

Of the 8 patients diagnosed with HD, 6 had a single cyst, and 7 had single organ involvement. The liver was the most commonly affected organ (6 of 8 patients), and 5 patients had isolated right lobe involvement. Of the 8 patients with HD, 6 were aged 6-11 years. All cysts were classified as stage 1 or 2 according to the World Health Organization (WHO) hydatid cyst classification (3). Complicated cysts were seen in 5 of 8 patients. In these cases, there was either cyst infection (3/5) or cyst rupture (2/5).

Disease category had no significant effect on peak AEC (p = 0.15) but it was found to be significantly associated with eosinophil percentage in PB at peak AEC (p = 0.03) using Dunn multiple comparison test indicating that the median eosinophil percentage at peak AEC in individuals with parasitic infections was higher than the median eosinophil percentage in individuals with non-parasitic infections (38.5% [24.3%-51.3%] vs. 21.5% [16.8%-28.3%] p = 0.03) but not significant after Bonferroni correction was made. The distribution of peak absolute eosinophil counts and eosinophil percentages at peak absolute eosinophil counts for each disease group were illustrated in **Figure 3**. There was no statistically significant difference among disease categories in terms of gender but a significant effect of disease category on age at diagnosis was observed ($p < 0.001$) with Dunn multiple comparison test indicating that the

median age at diagnosis in patients with parasitic infections was significantly higher than the median age at diagnosis in patients with non-parasitic infections (119 [87-132] vs. 2 [1-6.5] months, $p < 0.001$). According to age groups, non-parasitic infections and atopic dermatitis were the most common diagnoses in patients aged less than one year and 1-5 years, respectively, whereas parasitic infections were the most common diagnosis in patients aged 6-11 and 12-17 years (**Table II)**. The most common diseases causing SHE were parasitic infections. On the other hand, non-parasitic infections were the most common diagnoses in patients with MHE.

Regardless of treatment, HE resolved in the majority of patients (63/75, 84%), as evidenced in their last registered AEC. Individuals with unresolved HE were noted to have the following disorders: inborn errors of immunity (3/7, 1 patient with combined immunodeficiency, 1 patient with autosomal dominant hyper-IgE syndrome, 1 patient with Omenn syndrome), atopic dermatitis (2/7) and asthma (2/7). Of note, patients with atopic dermatitis were carefully investigated for the presence of an underlying primary immunodeficiency and other genetic disorders associated with atopic dermatitis. On the other hand, all patients with inborn errors of immunity with unresolved HE had atopic dermatitis. Four patients died. The patient with Omenn syndrome died due to cytomegalovirus infection after stem cell transplantation. One patient had severe asthma and died following an asthma exacerbation requiring invasive mechanical ventilation. Two other patients died of sepsis.

Group 1 and 2

Patients in group 1 were significantly older than patients in group 2 at the time of diagnosis of HE ($p < 0.01$). While the number of patients diagnosed with HE aged 1-5 years was higher in group 1 ($p = 0.01$), the number of patients diagnosed with HE under the age of one year was higher in group 2 ($p < 0.01$). In group 1, 43% of patients were aged 1-5 years, whereas 58% of patients in group 2 were under the age of one year. Twenty of 30 patients under the age of one year clustered in the period of first three months of life. This clustering was more pronounced in group 2 ($p < 0.001$). There was no statistically significant difference between the two groups in terms of the number of patients aged 6-11 years and 12-17 years **(Table III)**.

No significant difference was observed between the groups regarding the peak AEC and eosinophil percentage in PB differential count at peak AEC ($p = 0.09$ and $p = 0.3$, respectively). SHE was more common among patients in group 1 at initial presentation ($p = 0.03$), whereas there was no significant difference between the groups in terms of the degree of HE ($p = 0.31$) **(Table III)**.

In group 1, the most common causes of HE were allergic diseases (10/340, 25%) followed by inborn errors of immunity (6/40, 15%) and parasitic infections (5/40, 13%). In group 2, non-parasitic infections were the most common diagnosis (17/36, 47%) followed by parasitic infections (7/36, 19%). All patients with inborn errors of immunity were in group 1, while the majority of patients with non-parasitic infections were in group 2. There were statistically significant differences between the groups in terms of the frequency of allergic diseases ($p = 0.05$), non-parasitic infections ($p < 0.001$) and congenital immune defects ($p = 0.03$). Sepsis was the most common diagnosis (10/36, 28%) in group 2 and bacterial infections were the most prevalent culprit in non-parasitic infections (16/18, 89%) **(Table III)**.

Leukocytosis was significantly more frequent in group 1 ($p = 0.003$). The frequency of thrombocytopenia and hypertransaminasemia did not differ between the groups ($p = 0.67$, $p =$

0.09, respectively). HE resolved in great majority of patients in group 2 and in most of the patients in group 1, and there was a significant difference between the groups in terms of resolution of HE ($p = 0.01$) **(Table III)**.

Discussion

In this retrospective cohort study, we sought to identify the characteristic features of childhood HE by establishing a diagnostic algorithm based on the new criteria for HE diagnosis. It is the first study not only to examine childhood HE using the new diagnostic criteria but also to evaluate the effects of the time interval criterion between the two AECs ≥ 1500 cells/L, which is a controversial issue in HE diagnostic criteria (1).

Secondary HE was the most common cause of HE in our study. This included in decreasing order of frequency parasitic infections, allergic diseases, and inborn errors of immunity which is consistent with the literature (4-7). HD which is caused by the parasite *Echinococcus granulosus* was the most common parasitic infection in our study contrary to some previous reports based on the old diagnostic criteria (5,7). Another important reason of this discrepancy may be the higher prevalence of the disease in our region. HE in HD cases usually develops as a result of rupture of the cyst and invasion of its contents into the vascular system (8-10). In our study, cyst rupture developed in only 3 patients. A total of 17 HD patients with at least one AEC ≥ 1500 cells/L were identified (data not shown) and only 8 of them met the diagnostic criteria for HE. Regardless of the treatment, only 2 cases were included in group 1 because the remaining 6 patients did not fulfil the 4-week time interval criterion between the two AECs ≥ 1500 cells/L. This suggests that HD-associated HE is relatively short-lived compared to other parasites invading tissues as previously reported (11).

There were differences in terms of disease categories between groups.The higher prevalence of allergic diseases and inborn errors of immunity in group 1 could be explained by the chronic nature of such conditions, making more probable the detection of HE by hemograms performed at a longer time interval (i.e. 4 weeks). On the other hand, the higher frequency of non-parasitic infections in group 2 may be explained by the shorter duration of common infections due to easier diagnosis and early treatment.

The reduction of the time interval requirement between two AEC ≥ 1500 cells/L results from 4 weeks to 2 weeks was intended to increase the chance of catching HE-associated myeloproliferative diseases, while the requirement of ≥10% eosinophils in PB differential count was added to exclude non-HE-associated myeloproliferative diseases (2). In large retrospective cohort studies including childhood HE cases using the 4-week time interval criterion for recruitment, no patient was diagnosed with HE-associated myeloproliferative disease (5,7). In the present study, only one patient with an HE-related myeloproliferative disease was identified. That patient met only the old diagnostic criteria. During the recruitment period, 6 patients with at least one AEC ≥ 1500 cells/L and diagnosed either with a myeloproliferative disease or AML were detected. Three of them were diagnosed with CML. Only one CML patient met the old HE diagnostic criteria, but did not pass the 10% eosinophil percentage requirement of the new criteria. All these CML cases had AECs above 10,000 cells/μL and *BCR-ABL* fusion gene defects. On the other hand, three patients were diagnosed with AML. They had all peak AECs above 10,000 cells/μL and ≥10% eosinophils in PB

differential count, however, HE regressed within two weeks following therapy initiation in these cases, so, none of them fulfilled the two-week interval criterion. We attributed this observation not only to the rapid regression of HE with therapy initiation but also the possible lack of a previous hemogram test between the onset of the disease and the detection of HE.

As demonstrated in cohort studies involving patients with both HE alone and with eosinophilia, HES in childhood is a rare and most commonly an idiopathic disorder (5,7). In our study, one patient had HES that was considered to be idiopathic. A 9-year-old boy presented with fever, abdominal pain and anorexia accompanied by red-purple rashes on both legs and diffuse joint pain. The patient had severe eosinophilia (AEC: 12,300 cells/μL, 66% of total leukocytes in PB). Malignancy was considered in the differential diagnosis because of accompanying thrombocytopenia. Bone marrow examination revealed a marked increase in cells of eosinophilic lineage (60% of all nucleated cells) but no blastic cells were observed. Abdominal imaging showed thrombosis extending from the superior vena cava to the portal vein. A skin biopsy taken from a purpuric eruption revealed intense eosinophilic leukocytes and inflammatory infiltration in the dermis involving the capillary vessel wall and its surroundings and continuing in the periadnexal areas. Although the histopathological findings were consistent with necrotizing small vessel vasculitis and associated eosinophilic leukocyte infiltration, the diagnosis of eosinophilic granulomatosis with polyangiitis was excluded because the patient did not meet the diagnostic criteria (12). Cytogenetic analysis revealed no *BCR-ABL* or *PDGFRA-FIP1L1* gene fusions, inv (16) or *JAK2* mutation. Serology for parasites and antineutrophil cytoplasmic antibodies were also negative. A diagnosis of idiopathic HES was made.

We hypothesized that the percentage of eosinophils in PB differential count would be a more reliable indicator of eosinophil predominance in a disease, so we also analyzed this variable not only in individuals with CML or AML, but in all patients diagnosed with HE. We noticed indeed the percentage of eosinophils to be above 10% in all patients fulfilling HE criteria. Although we did not observe a difference in median peak AECs between various age groups, the mean eosinophil percentage was significantly lower in patients under one year of age compared to those aged 6-11 years. We also observed that patients with parasitic infections had a higher mean percentage of eosinophils at peak AEC than patients with non-parasitic infections, indicating that parasitic infections stimulate eosinophil production more potently than non-parasitic infections in HE patients.

The patients in our study were significantly younger than those reported in previous studies that used the old diagnostic criteria for HE (5,13,14). The median age at diagnosis was 16 months in the present study. Unlike the aforementioned studies, in our cohort, the group under one year of age included the highest number of patients (30/75, 40%). This noteworthy clustering was particularly pronounced in the period of 0-3 months of age, which included 67% (20/30) of patients under the age of one year and 27% (20/75) of all patients with HE. It was notable that almost all (19/20) patients aged 0-3 months were in group 2, which consisted of patients with HE who did not meet the 4-week time interval criterion, a component of the old diagnostic criteria. In addition, we noted that the starting point of HE in majority (12/20, 60%) of patients aged 0-3 months was the neonatal period. Previous studies have shown that eosinophilia is more common in newborn infants and there is a negative correlation between gestational age and eosinophil counts. Infections during the neonatal period, especially sepsis, have been reported to be associated with higher eosinophil counts (15,16). Among the patients aged 0-3 months in

our study, 11/20 (55%) were born prematurely, 8/20 (40%) had sepsis as the underlying diagnosis followed by pneumonia in 4/20 (20%) cases. Non-infectious diseases were present in 8/20 patients (40%), and in five of them (5/8), the onset of HE was in the neonatal period. These observations suggest that not only infections but also non-infectious diseases can induce eosinophilia in newborns who are already prone to develop eosinophilia, and this induction may be stronger and longer-lasting than in older age groups, but usually does not exceed 4 weeks. We also used the term "probable secondary HE" for uncertain secondary causes of HE (5). Of the 27 patients with probable secondary HE, 17 (63%) were in the 0-3 months age group (data not shown). These results also suggest that the use of the new criteria for HE may be associated with the first two months of life being a confounder in HE diagnosis.

One of the limitations of our study is that the disease spectrum may be biased because it is a single-center study. Due to the methodology used in patient selection, we may have found the number of patients lower than it should be. This may be due to the fact that hemogram records other than the study hospital's records were not evaluated and HE may have rapidly regressed following appropriate therapy initiation in some cases. The results of the present study should be interpreted with caution due to the lack of similar studies to compare its results.

Conclusion

In this study, we aimed to evaluate how patient characteristics and disease spectrum may change using the new HE diagnostic criteria. In particular, we observed a significant clustering of patients in the 0-3 months age group due to the shortening of the time interval requirement for HE diagnosis between two AEC results from 4 weeks to 2 weeks. We suggest that this is due to the characteristics of the first months of life, especially neonatal period, during which the cases are more prone to eosinophilia and certain diseases, especially non-parasitic infections.

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Conflict of Interest: The author has no conflicts of interest to declare.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Suleyman Demirel University School of Medicine (Date: 2023/Approval No: 2023/202).

Informed consent: Informed consent was not required.

Authors' contributions: Material preparation and data collection were performed by ICM. Data analysis was performed by ICM. The first draft of the manuscript was written by ICM. The author read and approved the final manuscript.

Competing interests: The author has no relevant financial or nonfinancial interests to disclose.

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Figure 1. Patient Flow Chart in the Study

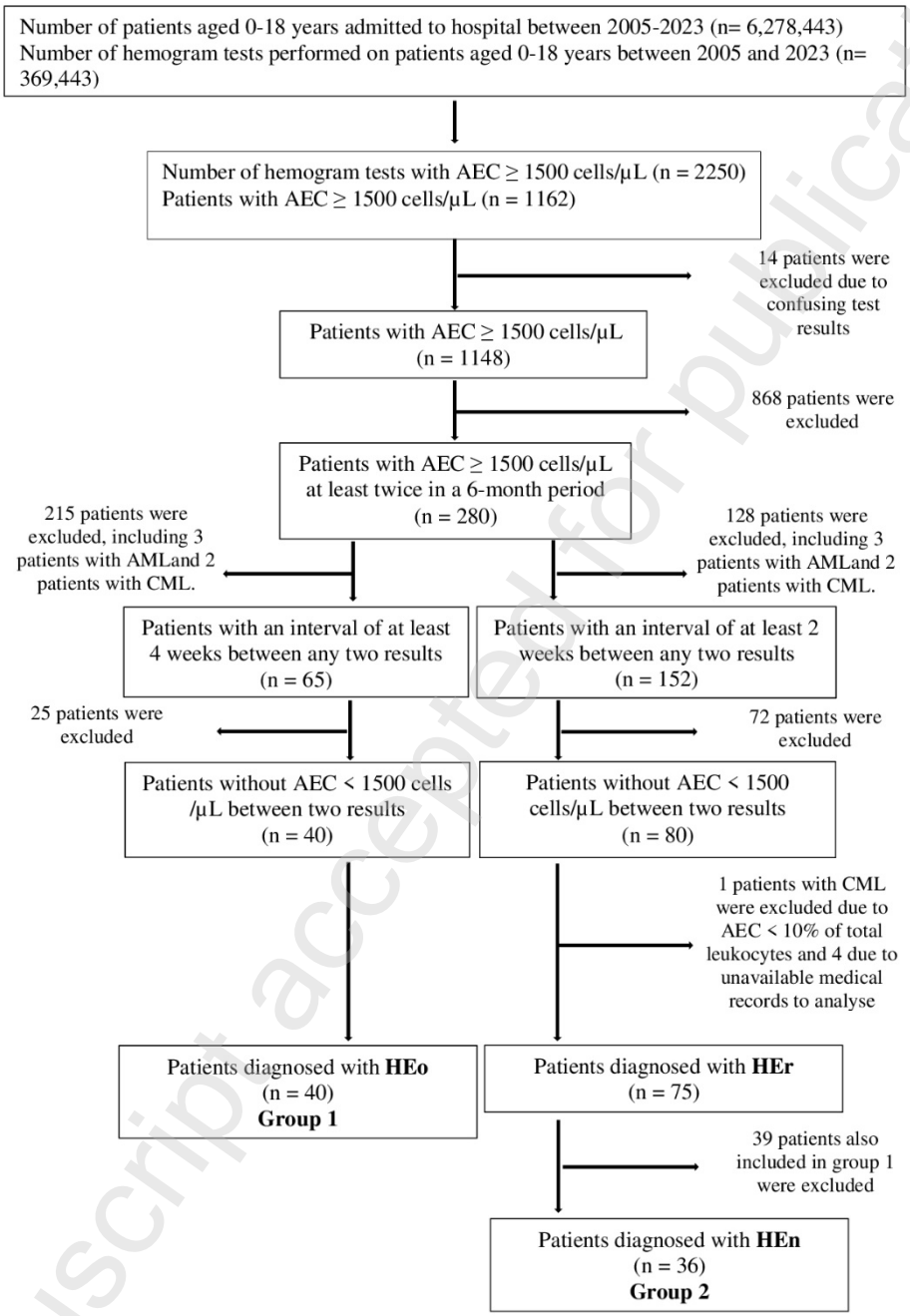

Figure 2. Age Groups Associated with Hypereosinophilia

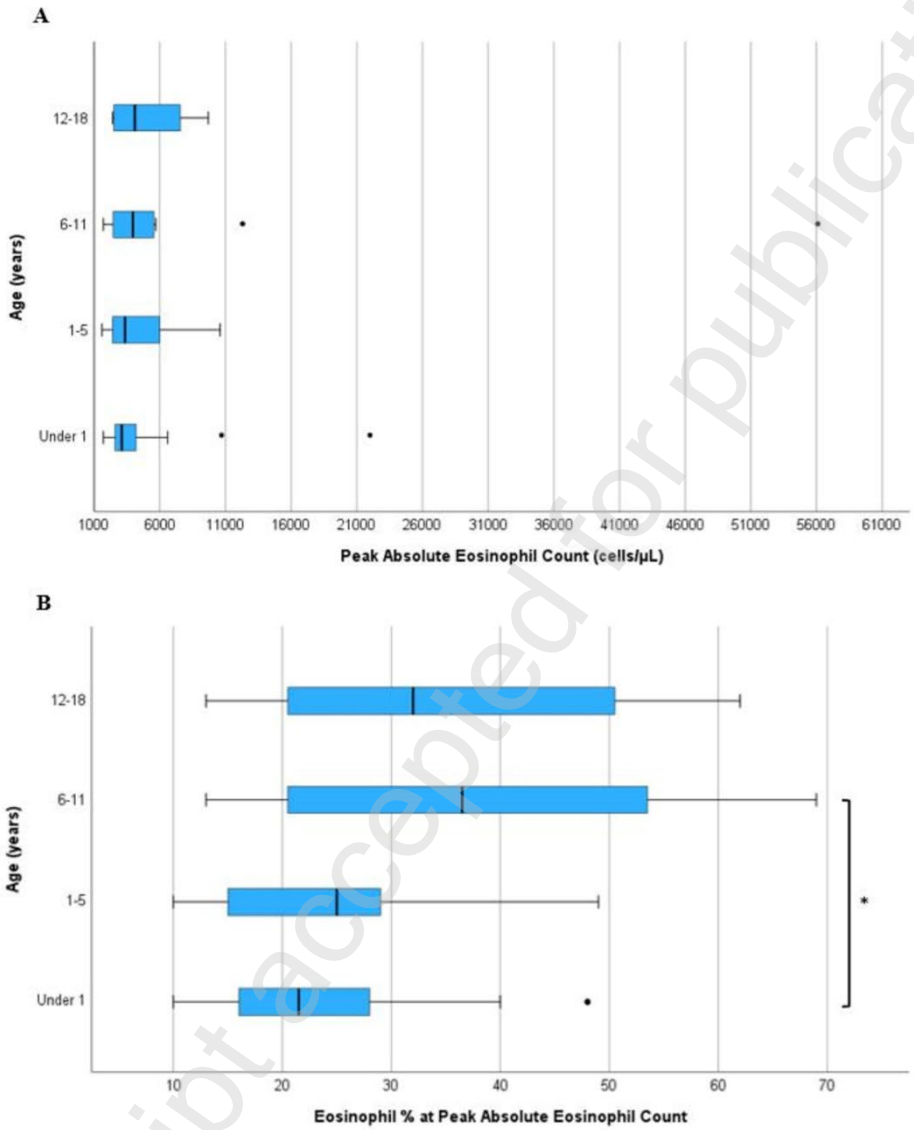

Figure 3. Disease Groups Associated with Hypereosinophilia

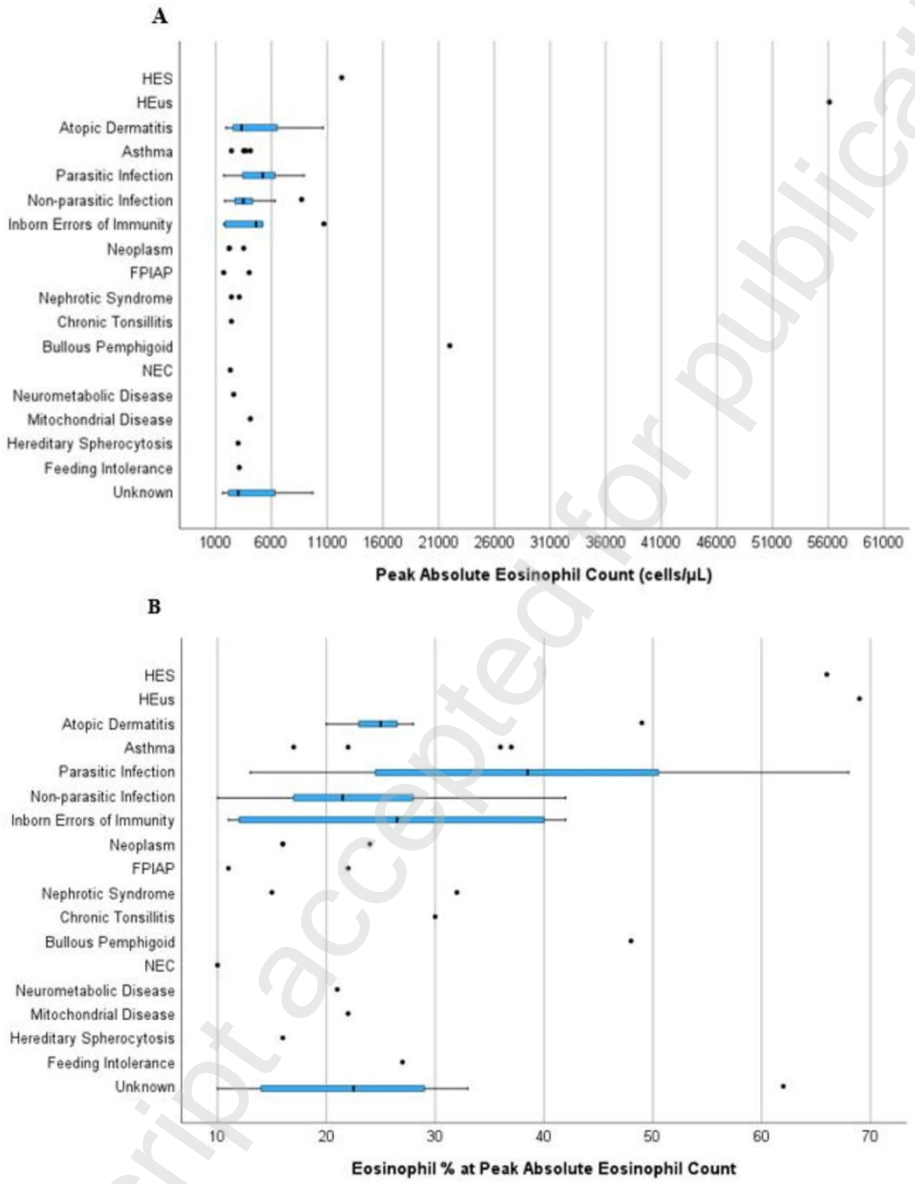

Table I. Demographic and Clinical Characteristics of Children with Hypereosinophilia

	HE (n = 75)
Gender (M) (n/%)	48 (64)
Age at diagnosis (months) (median/IQR)	16 (2-96)
Peak eosinophil count (cells/μL) (median/IQR)	3500 (2400-5200)
Eosinophil percentage at peak AEC (% of total leukocytes) (median/IQR)	25 (17-34)
Severe eosinophilia at initial presentation (n/%)	11 (15)
SHE (n/%)	21 (28)
Age groups (n/%)	
Under 1 year	30 (40)
0-3 months	20 (27)
4-12 months	10 (13)
1-5 years	22 (29)
6-11 years	12 (16)
12-18 years	11 (15)
HE etiology (n/%)	
HE Secondary (or Reactive)	33 (44)
HE Probable Secondary	28 (37)
HEus	1 (1)
Unknown (Not enough information to determine)	12 (16)
HES	1 (1)
Presence of infection (n/%)	30 (40)
Parasitic infection (n/%)	12 (16)
Hydatid disease	8 (11)
Fasciola	2 (3)
Probable parasitic infection (n/%)	2 (3)
Non-parasitic infection (n/%)	18 (24)
Bacteria	16 (21)
Fungi	2 (3)
Sepsis (n/%)	11 (15)
Pneumonia (n/%)	4 (5)
Cutaneous infection (n/%)	2 (3)
UTI (n/%)	1 (1)
Neoplasm (n/%)	3 (4)
Inborn errors of immunity (n/%)	6 (8)
Allergic disease (n/%)	11 (15)
Atopic dermatitis	7 (9)
Asthma	4 (5)
Anemia (n/%)	35 (47)
Leukocytosis (cells/μL) (n/%)	25 (33)
≥ 50.000	1 (1)
Leukopenia (n/%)	1 (1)
Thrombocytopenia (n/%)	5 (7)
Hypertransaminasemia (n/%)	13 (17)
Resolution of HE (n/%)	63 (84)
Spontaneous	11(15)
With treatment	52(69)
No Information About Resolution (n/%)	6(8)

HE, hypereosinophilia; HEus, hypereosinophilia of unknown significance; HES, hypereosinophilic syndrome; IQR, interquartile range; M, male; SHE, severe hypereosinophilia; UTI, urinary tract infection. HEus, hypereosinophilia of unknown significance; HES, hypereosinophilic syndrome.

Table II. Diagnoses of Patients with Hypereosinophilia by Age Group (n/%)

Diagnosis	Age Group			
	Under 1 year (n = 30)	1-5 years (n = 22)	6-11 years (n = 12)	12-18 years (n = 11)
Unknown	1 (3)	8 (36)	2 (17)	1 (9)
Atopic dermatitis	2 (7)	5 (23)	0	0
Asthma	0	1 (5)	2 (17)	1 (9)
Parasitic infection	0	1 (5)	6 (50)	5 (45)
Inborn errors of immunity	3 (10)	3 (14)	0	0
Neoplasm	2 (7)	0	0	1 (9)
Bullous pemphigoid	1 (3)	0	0	0
Idiopathic HES	0	0	1 (8)	0
HEus	0	0	1 (8)	0
Probable secondary HE	21 (70)	4 (18)	0	3 (27)
□ Non-parasitic infection	14 (47)	3 (14)	0	1 (9)
□ Food protein induced allergic proctocolitis of infancy	2 (7)	0	0	0
□ Chronic tonsillitis	0	0	0	1 (9)
□ Nephrotic syndrome	0	1 (5)	0	1 (9)
□ Necrotizing enterocolitis syndrome	1 (3)	0	0	0
□ Feeding intolerance	1 (3)	0	0	0
□ Mitochondrial disease	1 (3)	0	0	0
□ Hereditary spherocytosis	1(3)	0	0	0
□ Neurometabolic disease	1 (3)	0	0	0

Table III. Comparison of Patients Diagnosed with HE According to Old and New Diagnostic Criteria

	Group 1 (n = 40)	Group 2 (n = 36)	*P* value
Gender (M) (n/%)	29 (73)	20 (56)	0.15
Age at diagnosis (months) (median/IQR)	40 (12-96)	2 (1-96)	0.004
Peak eosinophil count (cells/µL) (median/IQR)	3900 (2650-6525)	3100 (2400-4300)	0.09
Eosinophil percentage at peak AEC (% of total leukocytes) (median/IQR)	26 (17-38)	22 (16-29)	0.3
Severe eosinophilia at initial presentation (n/%)	10 (25)	2 (6)	0.03
SHE (n/%)	14 (35)	8 (22)	0.31
Age groups (n/%)			
Under 1 year	9 (23)	21 (58)	0.002
0-3 months	1 (3)	19 (53)	<0.001
4-12 months	8 (20)	2 (6)	0.06
1-5 years	17 (43)	5 (14)	0.01
6-11 years	8 (20)	5 (14)	0.6
12-18 years	6 (15)	5 (14)	1
HE etiology (n/%)			
HE Secondary (or Reactive)	23 (58)	10 (28)	0.01
HE Probable Secondary	4 (10)	24 (67)	< 0.001
HEus	0	1 (3)	
Unknown (Not enough information to determine)	11 (28)	1 (3)	0.004
HES	1 (3)	0	
Presence of infection (n/%)	6 (15)	24 (67)	< 0.001
Parasitic infection (n/%)	5 (13)	7 (19)	0.54
Hydatid disease	2 (5)	6 (17)	0.14
Fasciola	1 (3)	1 (3)	
Probable parasitic infection (n/%)	2 (5)	0	
Non-parasitic infection (n/%)	1 (3)	17 (47)	< 0.001
Bacteria	1 (3)	15 (42)	< 0.001
Fungi	0	2 (6)	
Sepsis (n/%)	1 (3)	10 (28)	< 0.001
Pneumonia (n/%)	0	4 (11)	
Cutaneous infection (n/%)	0	2 (6)	
UTI (n/%)	0	1 (3)	
Neoplasm (n/%)	2 (5)	2 (6)	
Inborn errors of immunity (n/%)	6 (15)	0	
Allergic disease (n/%)	10 (25)	1 (3)	0.05
Atopic dermatitis	6 (15)	1 (3)	0.11
Asthma	4 (10)	0	
Anemia (n/%)	19 (48)	17 (47)	1
Leukocytosis (cells/µL) (n/%)	20(50)	6 (17)	0.003
≥ 50.000	1(3)	1 (3)	
Leukopenia (n/%)	1 (3)	0	
Thrombocytopenia (n/%)	2 (5)	3 (8)	
Hypertransaminasemia (n/%)	4 (10)	9 (25)	0.12
Resolution of HE (n/%)	29 (73)	35 (97)	0.01
Spontaneous	9(23)	2(6)	
With treatment	20(50)	33(92)	<0.001

No Information About Resolution (n/%)	5(13)	1(3)	