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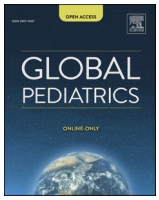

Unraveling the diagnostic puzzle of eosinophilia in children

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ABSTRACT

Eosinophilia is characterized by an increased eosinophil count in peripheral blood, and presents diagnostic challenges in children. Clinical manifestations can range from mild to severe, necessitating a nuanced understanding of its causes and management strategies. This narrative review provides a practice overview of eosinophilia in children, focusing on possible aetiologies and diagnostic workout. The diagnostic process is complex, requiring confirmation of eosinophilia in at least two occasions, and a step-up approach, tailored to the patient's history, symptoms and test results. In case of persistent eosinophilia, it is important that evaluations are executed timely, especially to exclude malignancy. Future research should focus on refining diagnostic algorithms for eosinophilia in children.

Eosinophils play a role in various human processes including inflammation, tissue damage, remodeling, and fibrosis.[1] An elevated level of eosinophils in the blood, known as eosinophilia, is frequently observed in children. This condition can be classified as either absolute eosinophilia, marked by an eosinophil count exceeding 500 cells per microliter in the blood, or relative eosinophilia, characterized by eosinophils constituting over 6 % of the total leukocyte count. Several categorizations of eosinophilic disorders exist, with a widely adopted one being from the International Cooperative Working Group on Eosinophil Disorders (ICOG-EO).[1] This classification system divides peripheral eosinophilia into three categories: mild (500–1499 cell /microL), moderate hypereosinophilia (1500–5000 cell/microL), and severe hypereosinophilia (>5000 cell/microL). Eosinophilia can manifest in various forms: transient, episodic, or persistent. The ICOG-EO's recent update specifies that the term "persistent" should be used for hypereosinophilia documented in at least two examinations spaced a minimum of two weeks apart.[1] A complete cell blood count (CBC) repeated on at least two occasions is needed to confirm eosinophilia.

Eosinophilia can arise from a wide spectrum of causes, such as infections, cancers, immune, and allergic reactions, ranging from mild to severe conditions that necessitate prompt investigation and treatment (Table 1). When persistent hypereosinophilia is linked with organ damage, and no other underlying conditions are identified, it is termed Hypereosinophilic Syndrome (HES). Moreover, eosinophilia can cause damage to various organs, including the lungs, heart, and skin.

While the degree of eosinophilia doesn't necessarily correlate with the extent of organ damage, specific conditions tend to be linked with higher eosinophil levels, such as drug hypersensitivity reactions. On the other hand, asthma and other atopic disorders are often, associated with lower eosinophil counts.[2]

In a retrospective study including 291 patients, clinical hypereosinophilic syndrome (HES) variants occurred similarly in children and adults, while primary immunodeficiencies were more common as a secondary cause of HES in children (5 % vs 0.4 % in adults).[2] Primary immunodeficiencies with eosinophilia include Wiskott Aldrich syndrome, Omenn syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, Netherton's syndrome, ZAP70 deficiency, autoimmune lymphoproliferative syndrome (ALPS), selective IgA deficiency, and adenosine deaminase (ADA), DOCK8 deficiency, hyper-IgE syndrome.

Parasitosis is the leading cause of eosinophilia both in children and adults worldwide. However, there's a noticeable difference in causative factors based on the geographical setting of the studies. In children from low-income or rural areas, including migrants, parasitosis is the most common cause, while in high-income countries, atopic diseases are the most frequently reported cause.[3] Notably, early-stage invasive worm infections, such as Strongyloidiasis, Schistosomiasis, Acylostoma duodenale infection, Filariasis, Ascariasis, Toxocariasis, and Trichinosis, are known to induce significant eosinophilia as the larvae migrate through body tissues. Some of these parasites are prevalent worldwide, and should be taken into account in any child with eosinophilia, regardless of the travel history. For instance, *Strongyloides stercoralis* is frequently observed in warm, moist regions, including parts of the Europe and United States, and can infect individuals through skin contact with soil or water contaminated with human stool. This parasite may remain latent for years, potentially leading to overlooked infections if not

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Table 1
Most relevant causes of eosinophilia in children.

Category	Examples
Infectious diseases	Helminthiasis (strongyloidiasis, trichinellosis, filariasis, toxocariasis, schistosomiasis, *Ancylostoma duodenale* infection), Scabies, Protozoan infections (isosporiasis, sarcocystis myositis), fungal infection (coccidiomycosis, allergic bronchopulmonary aspergillosis, histoplasmosis), viruses (EBV, HIV-1)
Allergic disorders	Atopic diseases (atopic dermatitis, asthma, allergic oculo-rhinitis)
Drug hypersensitivity	DRESS (drug reaction with eosinophilia and systemic symptoms), eosinophilia-myalgia syndrome, interstitial nephritis, eosinophilic hepatitis
Immunologic disorders	Wiskott Aldrich syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, and Netherton's syndrome. ZAP70 deficiency, autoimmune lymphoproliferative syndrome (ALPS), selective IgA deficiency, adenosine deaminase deficiency Immunodeficiencies (DOCK8 deficiency, hyper-IgE syndrome, Omenn syndrome), Autoimmune and idiopathic disorders (sarcoidosis, inflammatory bowel disease, other connective tissue disorders)
Neoplastic disorders	Primary hypereosinophilic syndromes, Acute or chronic eosinophilic leukemia, other myeloid neoplasms including chronic myeloid leukemia, systemic mastocytosis, lymphoid malignancies (B cell lymphoma, B or T lymphoblastic leukemia/lymphoma, adult T cell leukemia/lymphoma, cutaneous T cell lymphoma/Sézary syndrome), solid tumors (adenocarcinoma, squamous carcinoma)
Eosinophilic disorders	Idiopathic hypereosinophilic syndrome, Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), Eosinophilic gastrointestinal disorders
Miscellaneous	X-Ray exposre, rebound after steroid therapy, hypoadrenalism,

IgE: immunoglobulin E: human immunodeficiency virus- type 1; FGFR1: fibroblast growth factor receptor 1; FIP1L1-PDGFRA: FIP1-like-1-platelet-derived growth factor receptor alpha; FIP1L1-PDGFRB: FIP1-like-1-platelet-derived growth factor receptor beta; DOCK8: dedicator of cytokinesis 8.

routinely tested for. *Toxocara canis* and *cati*, causing visceral larva migrans, are also globally endemic, transmissible through soil or food contaminated with dog or cat feces. Toxocariasis is especially prevalent in young children, with pica, making them more susceptible to ingesting contaminated soil.

Apart from helminths, other infections can also cause eosinophilia in children. Scabies should be considered in cases presenting with an itchy skin rash. Fungal infections and allergic bronchopulmonary aspergillosis in children with chronic lung conditions (such as asthma or cystic fibrosis). Systemic Coccidioidomycosis and Histoplasmosis, may also be associated with eosinophilia. HIV-1 infection, though rare in children, are other potential cause of eosinophilia. and should be considered in cases with unexplained eosinophilia and relevant risk factors. Contrarily, protozoal parasites, like *Giardia spp,* usually do not lead to peripheral eosinophilia.

Currently, there are several proposed algorithms for assessing eosinophilia, but these primarily rely on adult data and tend to concentrate on blood disorders. As a result, the approach to diagnosing and managing eosinophilia in pediatric patients remains complex, expensive, and lacks a uniform standard.[4]

The first step in evaluating a patient should focus on identifying clinical signs that might be related to eosinophilia and determining its root cause. Gathering the **patient's histor**y is crucial to uncover symptoms indicating eosinophil-related organ involvement. This includes medical and family history, and information include country of origin of the subject/family; travel abroad, with particular attention to tropical areas, atopy in the subject/family members, intake of raw meat/fish, lake or river bathing in countries at risk of schistosomiasis. Moreover, history should aim to identify potential causes of eosinophilia such as asthma, atopic conditions, rheumatologic disorders, infections, cancer. Patients should be inquired about fever, night sweats, unexplained weight loss, fatigue, skin signs or symptoms (eczema, itching, hives, angioedema, rash, ulcers), heart-related issues (dyspnoea, cough, chest pain, palpitations, heart failure signs), respiratory problems (nasal/sinus issues, wheezing, cough,), gastrointestinal symptoms (weight loss, abdominal pain, difficulty swallowing, nausea, vomiting, diarrhoea, changes in bowel habits); neurological symptoms (including mood changes, vision changes, numbness, weakness, pain), lymphadenopathy or hepatosplenomegaly, ocular problems, genitourinary symptoms, muscle or joint pain, anaphylaxis. A detailed review of current and past medications is essential since eosinophilia can be triggered by various drugs.

The **physical examination** includes careful examination for skin rash or lesions, lymphadenopathy or hepatosplenomegaly, nasal/sinus findings, cardiac and respiratory abnormalities, or neurologic signs. Among **laboratory test,** review of previous CBCs can provide information on the duration and time course of eosinophilia. Eosinophilia may appear as an isolated blood count abnormality or with other blood test alterations, which may suggest different pathological conditions. A peripheral blood smears should be performed to examine the morphology of the eosinophils and other possible haematological anomalies. Further testing should be tailored to each patient based on clinical presentation and initial test results. Such investigations should include serum cardiac troponin in children with possible cardiac involvement, and serum vitamin B12 and tryptase levels in cases of suspected mastocytosis.

Infectious disease investigations are recommended in any case particularly in children originating from areas highly endemic for parasitic infection.[4] Parasitic infections are the most widespread in these children. According to an Italian multicenter study, 44.5 % of children adopted from abroad, originating from Africa, displayed a parasitic infection, and cases of co-infection with multiple parasites were frequent (about 20 %). *Giardia lamblia* (61.4 %) and *Toxocara spp*. (16.7 %) were the most commonly detected parasites, followed by *Hymenolepis nana, Ascaris lumbricoides, Entamoeba histolytica, Strongyloides stercoralis, Taenia solium/cysticercus, Trichuris trichiura, Schistosoma* spp.[4] Hyper-eosinophilia is common in helminthic infections, while it is rarer in protozoan infections. For example, it is typically absent in cases of infections by *Giardia lamblia* or *Entamoeba histolytica*, while it is common in infections by *Toxocara, Strongyloides, Schistosoma, Filaria, Ancylostoma,* and *Echinococcus*. In most cases, hyper-eosinophilia is entirely asymptomatic, but such infections, if untreated, can have severe long-term consequences. The parasitological examination of feces should preferably be performed on 3–5 samples collected on different days. Serologic investigations for *Toxocara* spp. and *Strongyloides* spp. should be performed in all children, while serologies for *Cysticercosis, Trypanosoma cruzi*, or *Schistosoma* may be executed in selected children originating from endemic areas for these parasites. In selected cases, fecal antigens for *Cryptosporidium*, and *Ameba*, nocturnal and diurnal microfilariae, and uroparasitological examination for *Schistosoma haematobium* may also be performed (Table 2).

Radiological investigations (i.e. chest x-ray or chest computed tomography) should be performed in children of respiratory symptoms. ECG and heart ultrasound scan is useful in order to investigate cardiac damage, while abdomen ultrasound scan may give information regarding organ involvement, cysts, abscesses or other lesions. Ocular fundus evaluation, and central nervous system (CNS) imaging is needed to evaluate possible ocular or CNS helminthic localization.

In case of persistent eosinophilia, it is important that these evaluations are executed timely, especially to exclude malignancy. In a recent US study,[5] the authors suggested a proactive approach, despite the low incidence of malignancy as a cause of paediatric eosinophilia (less than 1 % in the study group). In cases of moderate to severe eosinophilia, especially if accompanied by any form of cytopenia, atypical findings in blood smear, splenomegaly, or symptoms suggestive for systemic mastocytosis (i.e. urticaria, anaphylaxis, rash, or abdominal pain), authors

Table 2
Helminthiasis possibly associated with eosinophilia (from ref 6, modified).

Pathogens	Geographic regions
Angiostrongylus cantonensis	Southeast Asia, Pacific Basin, Africa, Caribbean, Central America
Angiostrongylus costaricensis	Central and South America
Anisakiasis	Japan, Europe
Ascariasis	Latin America, Sub-Saharan Africa, Asia, Western Pacific
Baylisascariasis	North America
Clonorchiasis	East Asia
Dirofilariasis	Worldwide
Echinococcus	Worldwide
Fascioliasis	South America, Europe, Asia, Egypt
Fasciolopsiasis	Southeast Asia, Far East
Lymphatic filariasis (*Brugia, Wuchereria*)	Sub-Saharan Africa, Africa, Southeast Asia (including India), Western Pacific
Tropical pulmonary eosinophilia (a manifestation of lymphatic filariasis)	Sub-Saharan Africa, Africa, Southeast Asia (including India), Western Pacific
Loa loa	Central/West Africa
Mansonella ozzardi	Latin America, Caribbean
Mansonella perstans	Sub-Saharan Africa, South America
Mansonella streptocerca	Africa
Onchocerca volvulus	Sub-Saharan Africa
Gnathostomiasis	Southeast Asia, Latin America
Hookworm	Latin America, Sub-Saharan, Africa, Asia, Western Pacific
Hymenolepiasis	Egypt, Sudan, Thailand, India, and Latin American countries
Opisthorchiasis	Southeast Asia, former Soviet Union
Paragonimiasis	United States (*Paragonimus kellicotti*); Southeast Asia, Central/West Africa, Latin America (non-kellicotti)
Schistosomiasis	
Schistosoma haematobium	Sub-Saharan Africa, Middle East, southern parts of Arabian Peninsula
Schistosoma intercalatum	Central and West Africa
Schistosoma japonicum	Indonesia, China, Southeast Asia
Schistosoma mansoni	Sub-Saharan Africa, western South America, some South Caribbean islands
Schistosoma mekongi	Laos, Cambodia
Strongyloidiasis	Worldwide
Trichinosis	Worldwide
Toxocara canis, T. catis	Worldwide

recommend testing for serum vitamin B12 and tryptase levels, to investigate a potential underlying blood disorder or malignancy.

In conclusion, the evaluation of the child with eosinophilia may be complex and should include a comprehensive approach considering a wide spectrum of infectious, allergic, immunologic, and hematologic diseases and drug reaction disorders. Future research should focus on refining diagnostic algorithms for eosinophilia in children.

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CRediT authorship contribution statement

Elena Chiappini: Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Valent P, Klion AD, Roufosse F, et al. Proposed refined diagnostic criteria and classification of eosinophil disorders and related syndromes. *Allergy*. 2023;78:47–59.
2. Williams KW, Ware J, Abiodun A, Holland-Thomas NC, Khoury P, Klion AD. Hypereosinophilia in children and adults: a retrospective comparison. *J Allergy Clin Immunol Pract*. 2016;4:941.
3. Chiappini E, Paba T, Bestetti M, Galli L. Parasitic infections in internationally adopted children: a twelve-year retrospective study. *Pathogens*. 2022;11:354.
4. Chiappini E, Zaffaroni M, Bianconi M, et al. Italian multicentre study found infectious and vaccine-preventable diseases in children adopted from Africa and recommends prompt medical screening. *Acta Paediatr*. 2018. https://doi.org/10.1111/apa.14237. Jan 24.
5. Ness TE, Erickson TA, Diaz V, et al. Pediatric Eosinophilia: a Review and Multiyear Investigation into Etiologies. *J Pediatr*. 2023;253:232–237.
6. Mejia R, Nutman TB. Evaluation and differential diagnosis of marked, persistent eosinophilia. *Semin Hematol*. 2012;49:149.