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REVIEW ARTICLE

# From evidence to practice: A systematic review-based diagnostic algorithm for paediatric eosinophilia across socioeconomic context

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## Abstract

**Aim:** Paediatric eosinophilia is a common clinical dilemma, often leading to resource- and time-consuming assessments. We aim to evaluate the main aetiologies of eosinophilia in children from different socioeconomic settings and propose a diagnostic algorithm.

**Methods:** A systematic literature review was conducted through PubMed, Embase and the Cochrane Library. Studies published from January 2012 to June 2023 reporting the incidence and aetiology of peripheral eosinophilia in children were included. Evidence from studies on children originating from low- or high-income countries was compared.

**Results:** A total of 15 observational studies, encompassing 3409 children, were included. The causes of eosinophilia varied based on the children's origin and the eosinophilia severity. In children from high-income countries, allergic diseases were the leading cause, with a prevalence of 7.7%–78.2%, while parasitosis ranged from 1.0% to 9.1%. In children from low-income countries, parasitosis was predominant, ranging from 17.7% to 88.3%, although allergic diseases were found in 2.5%–4.8% of cases. Concerning severity, allergic diseases were the leading cause of mild-to-moderate eosinophilia; parasitosis was associated with moderate-to-severe eosinophilia, while immunological disorders were mostly found in severe cases.

**Conclusion:** We developed a step-up diagnostic algorithm that considers the child's origin and eosinophilia severity and could optimise resource allocation.

KEYWORDS
allergic disorders, diagnostic algorithm, eosinophilia, low-income countries, parasitosis

**Abbreviations:** AEC, absolute eosinophil count; ICOG-EO, International Cooperative Working Group on Eosinophil Disorders.

## 1 | INTRODUCTION

Eosinophils are involved in inflammatory processes, tissue injury, remodelling and fibrosis.[1] An increase in eosinophils in peripheral blood is defined as eosinophilia. Relative eosinophilia is defined by an eosinophil count exceeding 6% of leukocytes, while absolute eosinophilia is determined by an absolute eosinophil count (AEC) higher than 500 cells/mL.[2,3]

Several classifications of eosinophilic disorders have been proposed. The International Cooperative Working Group on Eosinophil Disorders (ICOG-EO) categorised peripheral eosinophilia as mild ($0.5–1.49\times10^9$/L), moderate hypereosinophilia ($1.5–5.0\times10^9$/L), and severe hypereosinophilia ($>5.0\times10^9$/L).[4] Eosinophilia may be transient, episodic, or persistent. According to a recent update of the ICOG-EO classification, the term 'persistent' should apply to hypereosinophilia recorded at least on two examinations with a minimum interval of 2 weeks.[3] If persistent hypereosinophilia is associated with organ damage, assuming other disorders or conditions have been excluded as possible aetiologies, it is defined as hypereosinophilic syndrome.[3] Organ damage is defined as organ dysfunction with marked tissue eosinophil infiltrates and/or extensive deposition of eosinophil-derived proteins, regardless of marked tissue eosinophils, and at least one of the following alterations: fibrosis of lung, heart, digestive tract, skin or other tissues; thrombosis with or without thromboembolism; skin or mucosal erythema, oedema/angioedema, ulceration, itching or eczema; peripheral or central neuropathy with chronic or recurrent neurologic deficit.[4]

Eosinophilia has a broad range of possible aetiologies, from benign conditions to severe diseases requiring urgent investigations and therapy.[5] It can be of primary or clonal origin, resulting from underlying haematological neoplasm, or secondary or reactive origin. Numerous conditions, namely allergic and immunological disorders and infectious and gastrointestinal diseases, can manifest with a reactive increase in AEC. Drug hypersensitivity should always be considered as a possible cause. Its clinical spectrum varies from mild eosinophilia, with or without skin rash, to more severe manifestations, such as drug reaction with eosinophilia and systemic symptoms syndrome, occurring with skin rash and systemic symptoms including liver damage, temperature dysregulation, and lymphadenopathy. Immunodeficiency and rheumatologic disorders are rare causes of eosinophilia, although it is a characteristic of eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss vasculitis.[6,7] Both in high- and low-income countries, parasitosis is one of the leading causes of eosinophilia. In the last decades, migratory flow from resource-limited regions has increased. At the beginning of 2022, around 6.6 million children were registered as migrants in the European Union, accounting for 8.2% of the total number of children living in the European Union.[8] It is crucial to consider children's nationality and migration history when addressing eosinophilia aetiology in this population.

**Key Notes**

- Paediatric eosinophilia is a common clinical dilemma leading to resource- and time-consuming assessments.
- The prevalence of parasitosis and allergic disorders varies according to children's origin and eosinophilia severity; particularly, in children from low-income countries parasitosis is the primary cause, although allergic diseases were found in 2.5%–4.8% of cases.
- A step-up approach based on the child's origin and severity of eosinophilia could optimise the diagnostic assessment and resource allocation.

The causes of eosinophilia are comparable across age groups, although they display different prevalence rates. A retrospective study on 291 subjects (37 children) with hypereosinophilia reported helminth infection as the most common aetiology in children and adults (60% vs. 40%). Primary immunodeficiencies were found to be more prevalent in children (5% vs. 0.4%, $p=0.04$). On the contrary, neoplasm-associated eosinophilia was documented in 3% of adult cases and in none of the children.[9]

To date, some algorithms for the evaluation of eosinophilia have been proposed; however, they are primarily based on data from adults and mainly focused on haematological disorders.[2,10–13] Consequently, the paediatric workup and management of this condition are still challenging, costly, and often not standardised. Therefore, we conducted systematic research on the literature regarding the aetiology of eosinophilia in children from different settings. Our aim was to propose a workup algorithm tailored to the children's origin in order to optimise the diagnostic process in outpatient and inpatient services.

## 2 | METHODS

### 2.1 | Design

We systematically reviewed the literature through PubMed, Embase and the Cochrane Library for papers available from January 2012 to the 30 of June 2023, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline recommendations.[14] References to all relevant articles were also evaluated, and pertinent articles were included in the review. The following search terms were used: eosinophilia, hypereosinophilia, children, paediatric, and paediatric.

### 2.2 | Inclusion and exclusion criteria

The research was restricted to the English language. Articles including patients with peripheral eosinophilia or hypereosinophilia

younger than 18 years old and reporting the incidence and aetiology of eosinophilia were included. The study design was not an exclusion criterion. However, articles without original data or including less than 10 patients were excluded, as were studies evaluating eosinophilia as a prognostic or risk factor for specific diseases.

Due to the limited number of pertinent studies, the definition of eosinophilia used among studies was not restricted to the one proposed by ICOG-EO (AEC > 500/L). However, the cut-off value to determine eosinophilia was evaluated and reported for each of the included studies.

### 2.3 | Data extraction

Duplicate publications were removed, and then two authors (RP and ET) separately screened the titles and abstracts and included relevant articles according to the inclusion and exclusion criteria. Each article was categorised according to the study type. The following information was extracted and analysed: study setting, children's demographic characteristics, including nationality/race, eosinophilia definition, AEC at presentation, severity and aetiology of eosinophilia. Countries were ranked as high-, upper middle, and low-income according to the 2022 World Bank classification.[15]

### 2.4 | Quality assessment

The quality of the selected studies was evaluated through the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Heart, Lung, and Blood Institute.[16]

## 3 | RESULTS

### 3.1 | Study characteristics and quality

The literature research retrieved 1738 articles; after duplicate removal, 1316 records were screened and selected, and 15 studies were included in the review, as reported in Figure 1. All the studies were observational: five were cross-sectional,[17–21] and there were four prospective[22–25] and six retrospective cohort studies.[2,5,9,26–28] The quality of the studies, evaluated through the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, is reported in Appendix S1—figure A1.

Overall, 3409 children with eosinophilia were assessed; the median age ranged from 2.8 to 16.2 years and the median percentage of males was 56.5%.[19,21] Most of the studies were conducted in high- or upper to middle-income countries (three in the USA,[2,5,9] three in Turkey,[21,27,28]

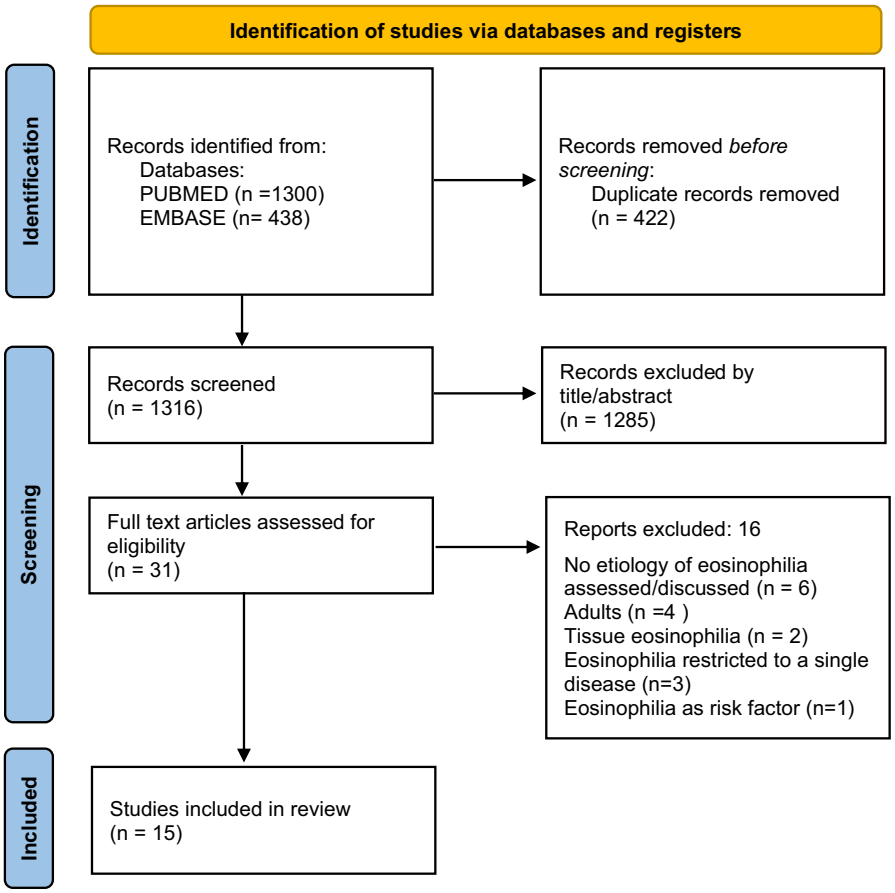


FIGURE 1 Flow diagram of literature search and data extraction.

four in Spain,[17,22,23,26] one in Germany[20]), and four cohorts were from low-income countries or rural areas.[18,19,24,25] The Spanish and German studies predominantly relied on data from migrant children screened in paediatric infection disease units.[17,20,22,23,26] In contrast, the studies from the USA and Turkey mainly involved resident children.[2,5,9,21,27,28]

### 3.2 | Eosinophilia definition and prevalence

The studies were heterogeneous in terms of inclusion criteria. Some studies exclusively enrolled children with hypereosinophilia,[5,9,27] and one cohort included those with mild eosinophilia yet exhibiting concurrent organ involvement.[24] Furthermore, variations in the definition used for eosinophilia were noted. Most authors used a cut-off value of AEC > 500/μL in peripheral blood to define eosinophilia,[2,17,19–21,25,26,28] while two studies employed a lower threshold of 450/μL.[18,23]

Excluding studies with cohorts restricted to eosinophilic children, the prevalence of absolute eosinophilia varied from 17.4% to 77.2%.[25,26] A lower prevalence of 0.5% was found by Burris et al. assessing hypereosinophilia defined as an AEC > 1500/μL in two determinations obtained at least 4 weeks apart.[5]

### 3.3 | Aetiology of eosinophilia

Overall, parasitosis and allergic disorders were the conditions most frequently associated with eosinophilia. Nevertheless, an income-based analysis of the studies showed a difference in aetiology occurrence, as reported in Figures 2 and 3.

In most high-income countries, allergic disorders were the leading cause of eosinophilia.[2,5,21] The highest prevalence was 78.2% found in a Turkish paediatric allergy unit.[21] In the latter study, a third of the children had at least two allergic disorders simultaneously, often in a clustered manner. Specifically, food allergies tended to occur along with atopic dermatitis, and asthma with allergic rhinitis.[21] Allergic diseases were not evaluated in children living in low-income countries or rural areas. Likewise, only two studies evaluating migrants considered allergic disorders, and the reported prevalence was 2.5% and 4.8%.[23,26] Among allergic disorders, the drug-related eosinophilia prevalence ranged from 1% to 7%, and it was found in three studies, all conducted in high-income countries.[2,5,21] On the other hand, Kulhas Celik et al. reported that 36.6% of children with hypereosinophilia had no other apparent cause for eosinophilia besides the use of medication, even though a clear link was not defined.[27]

Parasitosis was assessed in all the studies and reported a prevalence ranging from 1.0% to 88.3%. According to the children's demographic characteristics, the lowest eosinophilia prevalence was found in those from high-income countries, with a range varying from 1.0% to 9.1%,[2,21] whereas, parasitosis was comparable among children living in rural areas or low-income countries and migrants, with a prevalence range of 15.5%–88.3% and 14.6%–77.1%, respectively.[18,20,23,24] Specifically, prevalence rates of *Strongyloides* spp. ranged from 10.8% to 46.8%,[2,5,22,23,26,29] and *Schistosoma* spp. was identified in 14%–28.9% of cases.[5,18,22,23] A broad variation was observed in the prevalence of *Toxocara canis*, ranging from 7.1% to 100%.[2,5,9,19,26,27,29] The simultaneous presence of at least two parasites occurred in 18.6%–44.6% of the children with parasitosis.[2,17,22,23] The correlation between AEC and the number of detected helminths was statistically significant ($p = 0.003$), although not strong ($\rho = 0.33$).[26] Regardless of the children's origin, helminthiasis was the most reported parasite infestation, with *Toxocara* spp. and *Strongyloides* spp. being the most frequent pathogens.[5,9,14,17,19,24,27] When children's provenience was provided, parasitosis was more common in sub-Saharan African children (68.4% vs. 33.3%, $p = 0.05$), and filariasis was common in this group.[17,22]

Immune disorders were assessed exclusively in children living in middle- to high-income countries, and the prevalence ranged from 1.2% to 8.3%.[2,5,9,21,27,28] Similarly, hypereosinophilic syndrome was found in 46% of the children living in the USA evaluated in a third-level paediatric centre for persistent, unexplained hypereosinophilia.[9] Burris et al. found a lower rate of 12/176 (6.8%), and all except one were further diagnosed with eosinophilic gastrointestinal disorders.[5] Among studies including children from low-income countries, only Shrestha et al. evaluated neoplasm and hypereosinophilic syndrome, which were reported with a prevalence of 1.2% each.[24] Lastly, in a cohort of 26 children with unexplained eosinophilia and respiratory symptoms undergoing diagnostic bronchoscopy, immunodeficiency was the main cause of eosinophilia, with a prevalence of 23.1%, followed by allergy (0.1%), hypereosinophilic syndrome (0.1%), malignancies (0.03%) and parasitosis (0.03%). Interestingly, almost half of the assessed patients were born within consanguineous marriages (46.2%).[28]

Eight studies failed to ascertain the underlying cause of eosinophilia in 5.4% to 70.2% of the children. The highest rate of unexplained eosinophilia was reported in a Nepalese study, probably due to a low-resource setting and a non-systematic diagnostic approach. Notably, only eight children out of 84 underwent parasite serological tests.[24] Similarly, Ness et al. found 35.5% of children with eosinophilia of unknown origin. Many of them had an incomplete diagnostic workup: only 45% underwent a stool test and 17% a serological test for *Toxocara* spp. and *Strongyloides* spp.[2] In the study by Bustamante et al. the aetiology remained undetermined in 40.5% of cases despite performing second-stage diagnostic tests. Particularly, age ≤2 years, absence of symptoms and mild eosinophilia were identified as independent risk factors for the unexplained aetiology.[26]

### 3.4 | Severity of eosinophilia: definitions and aetiologies

The severity of eosinophilia was considered in eight studies,[2,5,20,21,23–26] of which only three assessed it according to the ICOG-EO classification.[5,21,25] In six out of eight studies, most children presented with mild eosinophilia, ranging from 12.6% to 80.8% of the entire cohort.[2,20,21,23,25,26] On the other hand, Burris et al. found moderate hypereosinophilia (AEC: 1500–5000/μL) in 76%

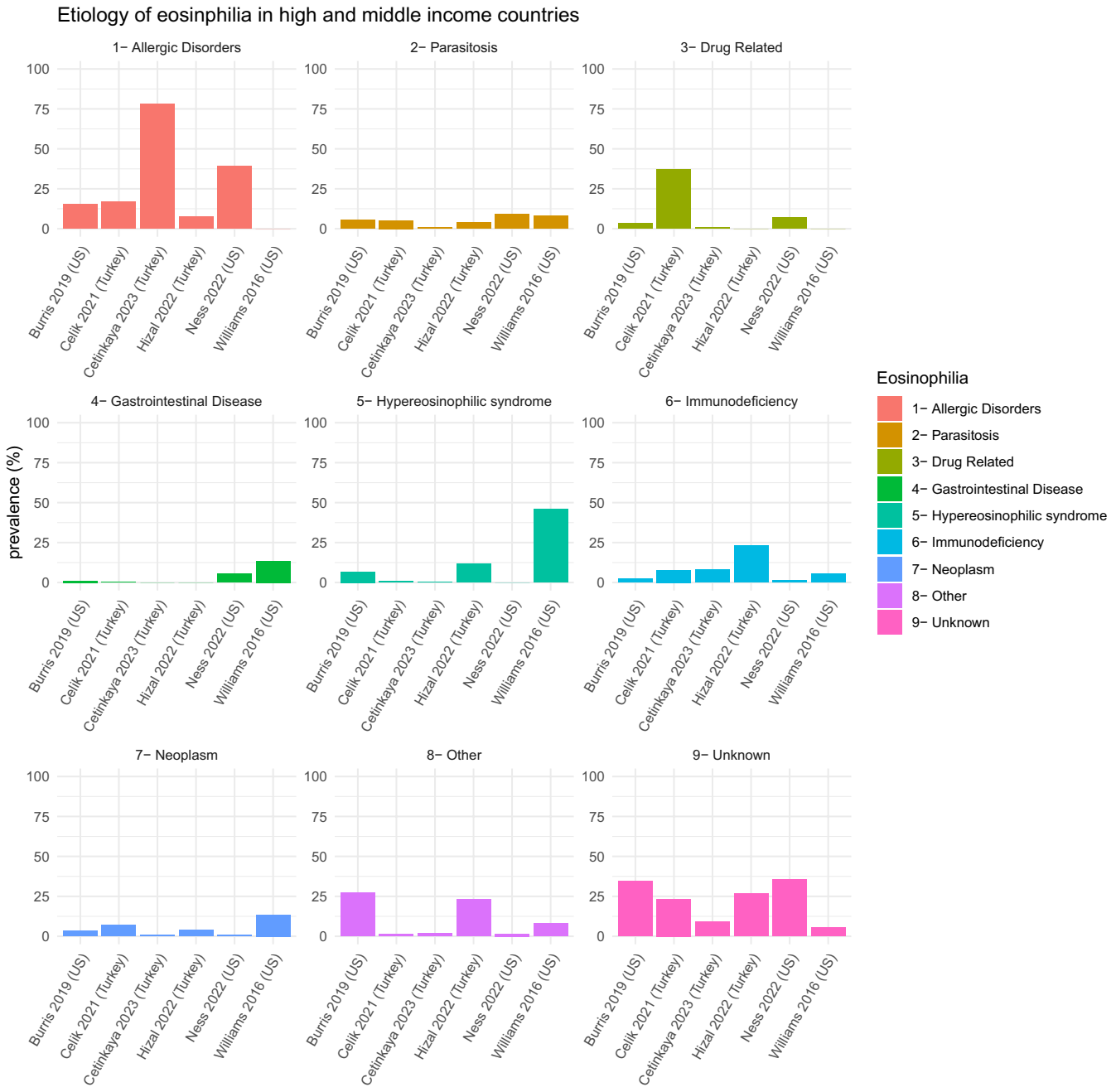


FIGURE 2 Aetiology of eosinophilia in high- and middle-income countries.

of children assessed in a tertiary paediatric centre in the USA.[5] However, a Nepalese study evaluating children with organ involvement symptoms reported severe hypereosinophilia (AEC > 5000/μL) in 46.6% of cases.[24]

Only four of the abovementioned studies discussed the aetiology of eosinophilia, depending on the severity of eosinophilia.[2,5,21,26] Allergic diseases were the leading cause in children with mild to moderate eosinophilia, especially in children from high- or middle-income countries.[2,5,21] Among allergic children, those with drug-induced eosinophilia had a higher median AEC than other allergy disorders.[2] Parasitosis was more frequently associated with moderate or severe eosinophilia; particularly, children with helminthiasis had a higher AEC than those with protozoan infestation (median, 2663.4 cells/μL vs. 1205 cells/μL).[2] This is in line with the multivariate analysis by Bustamante et al. showing that an AEC >1000/μL is a risk factor for helminthiasis.[26] Lastly, immunological disorders were mostly found in children with severe eosinophilia.[5,21]

## 3.5 | Proposed diagnostic algorithm in children with eosinophilia

Numerous diagnostic algorithms concerning eosinophilia are available. However, they are primarily derived from adult data and often

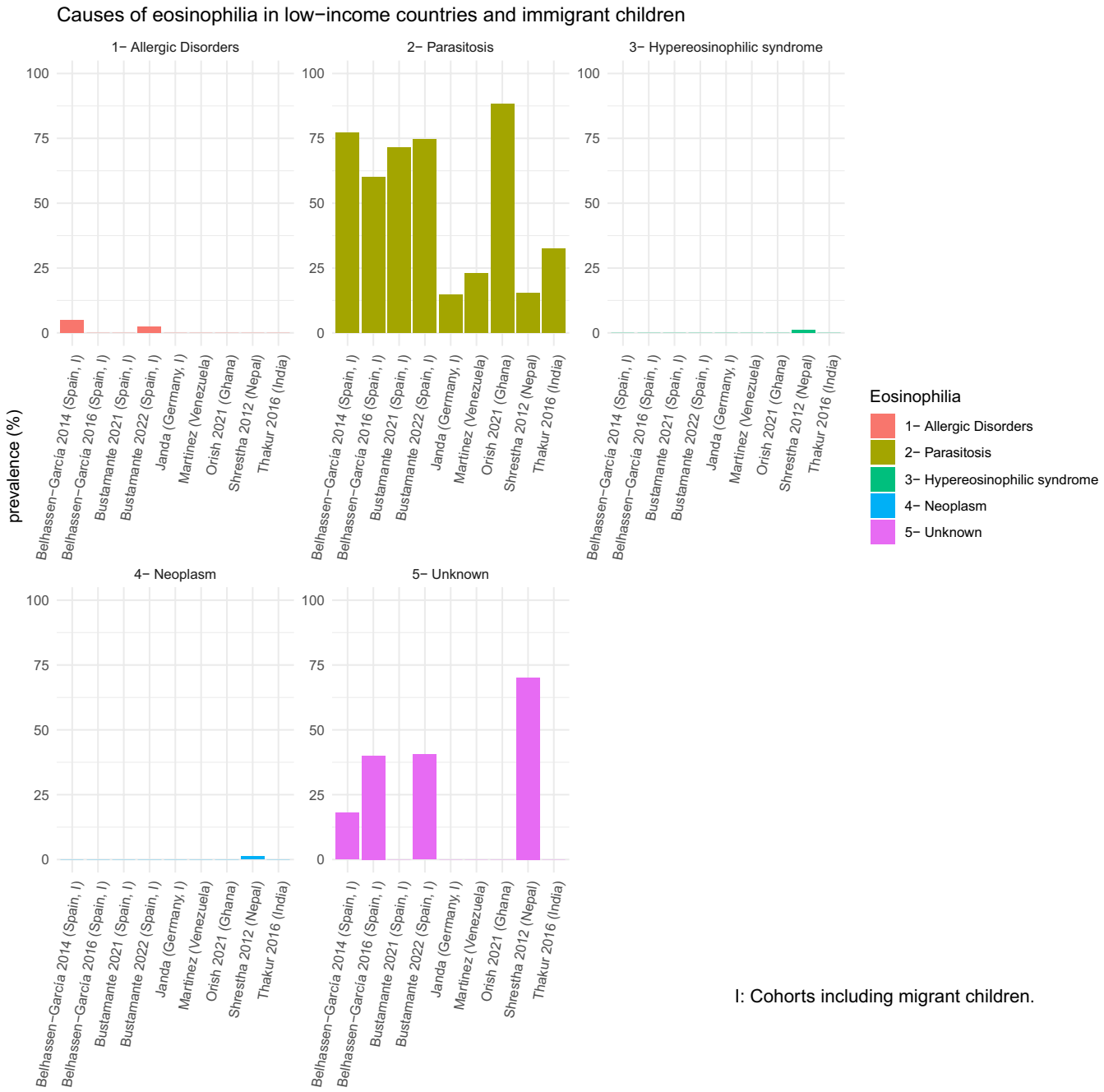


**FIGURE 3** Aetiology of eosinophilia in low-income countries and migrant children.

focus on specialistic disorders. Further, the setting and origin of the patient are rarely considered.[7,10–13]

Based on the findings of our review, we suggest a diagnostic process for the initial evaluation of eosinophilia in paediatric patients (Figure 4). Elevated AEC should be confirmed on at least two occasions before initiating diagnostic investigations, especially in mild eosinophilia cases. The physical examination and a thorough patient history, including any symptoms, drug therapy, and travel history, should always be assessed and guide the diagnostic process. In addition, for migrant children, information about the migration route could be helpful. It is common to find eosinophilia in asymptomatic children with no anamnestic clues. In the latter case, the severity of eosinophilia and the child's origin are fundamental to guide the workup. Therefore, the proposed algorithm has been designed to reflect these two crucial factors.

It is pertinent to assess children living in high-income countries according to the severity of eosinophilia, as defined in the ICOG-EO classification.[3] In this setting, allergies as the primary cause should be investigated in cases with mild or moderate eosinophilia as well as in those with severe eosinophilia. AEC > 1500/μL may be associated with symptoms in allergic patients. Nevertheless, severe eosinophilia is rarely associated with allergic disorders except for rare severe atopic dermatitis, which needs an immune-allergological evaluation.[21] Once allergies have been ruled out, in children with

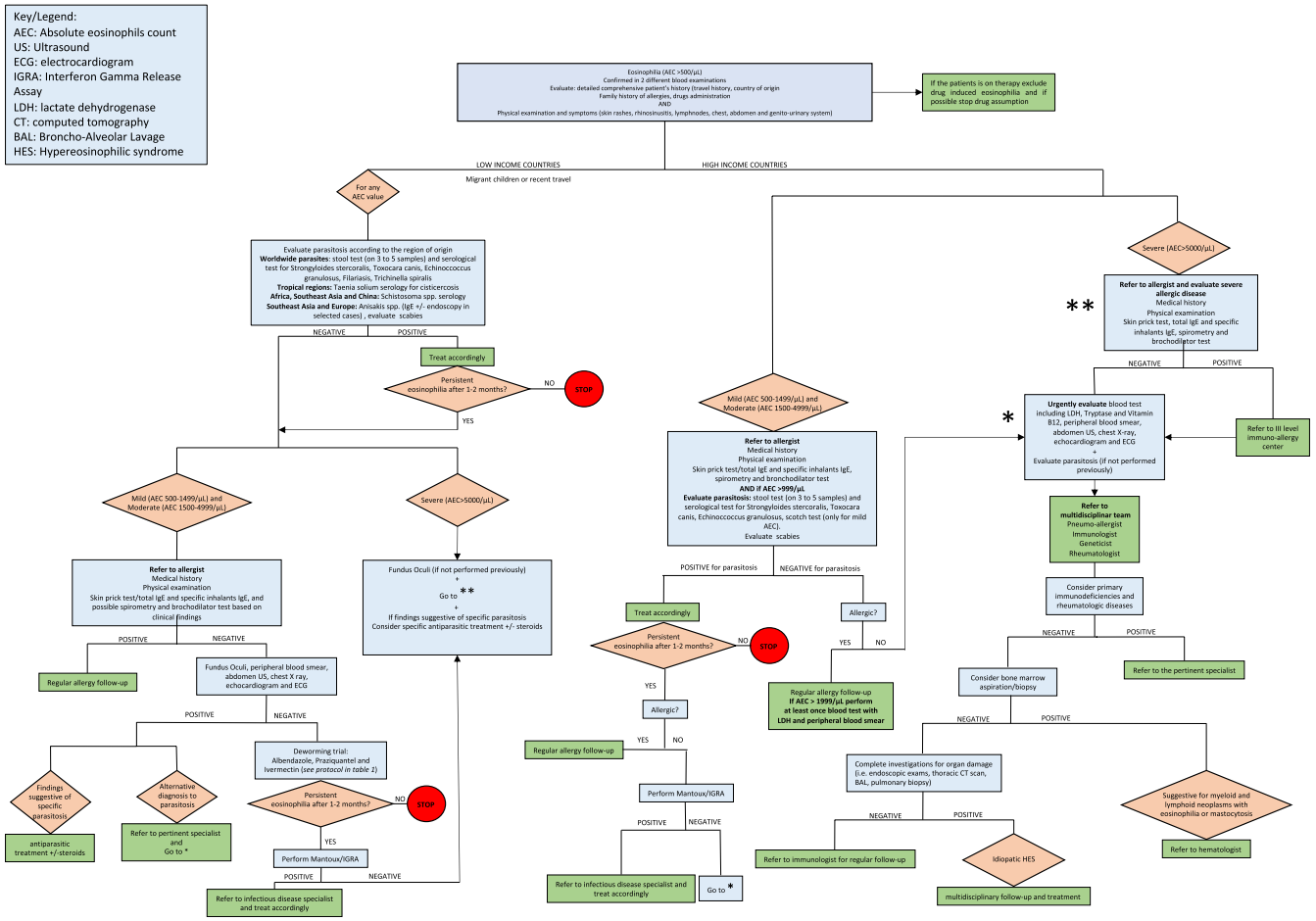


**FIGURE 4** Step-up approach to paediatric eosinophilia in children from low- and high-income countries.

mild eosinophilia and AEC > 999/µL, the most common parasitosis should be considered.

In the case of severe eosinophilia, after a prompt allergy assessment, organ involvement and parasitosis should be excluded. A multidisciplinary team should be involved, including a pneumoallergist, immunologist, geneticist and rheumatologist. If the cause of eosinophilia remains unexplained, second-level investigations should be performed, including a bone marrow aspiration to investigate neoplasms with eosinophilia.

Most of the individuals affected by parasitosis live in tropical regions. However, many pathogens, such as *Echinococcus granulosus*, *Strongyloides stercoralis*, and *Toxocara canis*, are spread worldwide.[30–32] These data were in line with our findings, showing that *Toxocara* spp. and *Strongyloides* spp. were the most reported parasites, regardless of children's provenience.[5,9,14,17,19,24,27] However, other helminths, such as *Trichinella spiralis*, *Trichuris trichiura* and *Filarial* worm infection, are found worldwide and should be considered in the differential diagnosis according to the child's history and clinical presentation.[31] On the contrary, schistosomiasis is predominantly diffuse in sub-Saharan Africa, Southeast Asia and China.[33] Still, local European outbreaks have been sporadically described due to the introduction of schistosomes in southern European freshwater, where snail hosts are present.[31,34] Consequently, parasitosis should also be investigated in eosinophilic children living in high-income countries with mild to moderate unexplained eosinophilia, and travel history should always be ascertained since it can guide parasitological tests. The *Taenia solium* infection, for instance, should be excluded if the child has travelled to tropical regions, while *Anisakis*-specific immunoglobin E should be assessed in the case of travel to Asia.[31] Nowadays, *Anisakis* spp. is widely diffused in Europe and should be considered in cases of ingestion of possibly contaminated foods. In cases of suggestive history and gastrointestinal symptoms, the definitive diagnosis is based on digestive endoscopy demonstrating the presence of the parasite. On the other hand, if allergic symptoms prevail, the assessment of specific immunoglobin E may be sufficient.[35,36]

In children from low-income countries or rural areas, parasitosis is the primary cause of eosinophilia, both in mild and severe cases. Therefore, we recommend prioritising parasite investigation regardless of the AEC level in this population. Nonetheless, in this context, prompt exclusion of severe immune allergic conditions is crucial in patients with severe eosinophilia lacking evidence of parasitic infection.

Besides the above-mentioned parasitological tests, further investigations can be performed according to the native country and migration route. Screening through serological tests for filariasis is

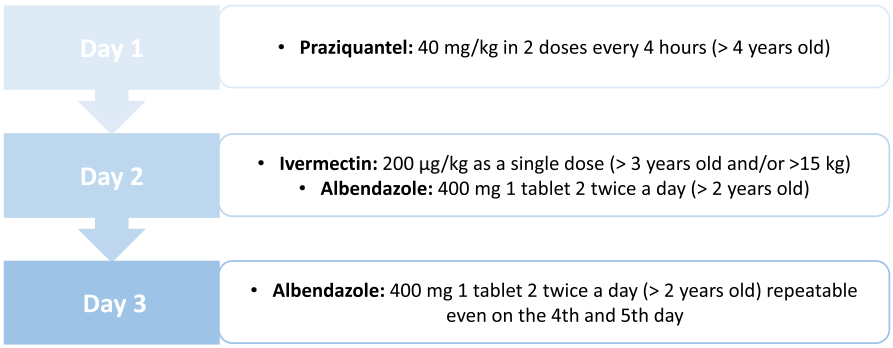


**FIGURE 5** Broad-spectrum antiparasitic therapy according to the Italian Society of Tropical Medicine and Global Health.

suggested in children from Africa, particularly those from western and central regions where there is a higher risk of transmission. Examination of blood smears for microfilariae could aid the diagnosis, considering that a nocturnal blood sample could increase the diagnostic accuracy since some species tend to have a nocturnal periodicity. Moreover, in the case of haematuria, urine microscopy for parasites is indicated to exclude the presence of *Schistosoma haematobium*.[31]

Diagnostic tests are not always easily accessible, as they are often performed only in specialised laboratories, particularly in areas with limited resources. Furthermore, most serological tests become positive after 4–12 weeks from the infection.[29,31,32] Consequently, due to the high prevalence of parasitosis, an antiparasitic trial treatment could be administered to children from low-income countries with eosinophilia, despite negative parasitological tests. The trial antiparasitic treatment should be based on the therapeutic protocol proposed by the Italian Society of Tropical Medicine and Global Health (Figure 5). We suggest investigating organ involvement before starting the treatment to determine if steroid or targeted therapy is needed. If eosinophilia persists after 1–2 months following empirical antiparasitic treatment (Figure 5), allergic disorders, immunodeficiency and neoplasms must be excluded, especially in hypereosinophilia and in symptomatic children. Furthermore, it is advisable to screen children for tuberculosis since associations with eosinophilia have been described.[24,37]

## 4 | DISCUSSION

The current evidence on paediatric eosinophilia is scarce and predominantly based on case reports and case series.[5] Our review included 3409 children with eosinophilia from 15 observational studies, of which five were cross-sectional, four were prospective cohort studies and six were retrospective. Two-thirds of the studies were based on children living in low-income countries and migrants.

Although an international classification of eosinophilia is available, the cut off value to define eosinophilia varied among the studies.[3] Likewise, the management was heterogeneous, and the diagnostic strategies lacked systematic consistency. Most children had mild eosinophilia.[2,20,21,23,25,26] The highest rates of moderate and severe hypereosinophilia were found in children with previous non-conclusive first-line investigations assessed in a tertiary paediatric US centre and in symptomatic children with severe manifestation including organ involvement.[5,24]

Many conditions can cause eosinophilia, such as infectious diseases, malignancies, immune disorders and allergic disorders. Among these, parasitosis is considered the most common cause worldwide, both in children and adults.[9,27] Nevertheless, a certain discrepancy in the prevalence of aetiologies has been observed across different settings. The leading cause of eosinophilia in children from low-income countries or rural areas, including migrants, was indeed parasitosis.[18,20,23,24] On the contrary, in high-income countries, eosinophilia was predominantly due to allergic conditions, including drug-related disorders.[2,5,21]

When a severity-based epidemiology analysis was provided, it was shown that children with mild eosinophilia mainly suffered from allergic disorders,[2,5,21] and those with drug-induced eosinophilia had a higher median AEC than other allergic diseases.[2] On the other hand, moderate-to-severe eosinophilia was mainly associated with helminthiasis.[2] In a minority of cases, immunodeficiency or neoplasms were found, mostly in children with persistent hypereosinophilia.[5,9,21]

Unexplained eosinophilia was identified in eight studies, exhibiting a variable prevalence ranging from 5.4% to 70.2%. Eosinophilia of unknown origin was associated with incomplete diagnostic workup in both high- and low-resource settings.[2,24] Nonetheless, Bustamante et al. underlined that slightly less than half of the children remained undiagnosed even after second-stage investigations. Interestingly, age under 2 years, absence of symptoms and mild eosinophilia were reported as independent risk factors for an unexplained aetiology.[26]

Notably, most high-income studies did not routinely assess parasitic diseases, explaining the low prevalence rates, which are stable under 10%.[5,9,14,17,19,24,27] Although most parasitosis are included in the group of Neglected Tropical Diseases, they significantly impact global child health, sometimes leading to chronic disability.[31,32,38] Some pathogens are diffused worldwide, as confirmed in our review showing that *Toxocara* spp. and *Strongyloides* spp. were the most reported parasites regardless of children's provenience.[30–32] Local European cases of schistosomiasis and strongyloidiasis have been documented recently, suggesting an epidemiological change.[30,34] Consequently, it is necessary to maintain a high suspicion of parasitic diseases in children living in high-resource settings, regardless of their tropical travel history.

To provide a more comprehensive approach for the initial assessment of eosinophilia in children, we proposed a diagnostic algorithm

based on the severity of eosinophilia and the children's origin country. The step-up approach makes the diagnostic process easily applicable to outpatient services, including primary care ones.

Our review had some limitations, including that some articles might have been missed. In addition, the diagnostic tests used in the studies were not consistent or systematic, which may have contributed to difficulties in determining the cause of eosinophilia. Stratifying the study according to economic country income could mask migrant children in cohorts from high-resource settings, potentially impacting epidemiological findings. The proposed diagnostic workup was not based on the clinical picture, as symptoms of children with eosinophilia were often not evaluated and data about it were scarcely comparable. Lastly, our algorithm needs to be validated by further clinical studies to assess the algorithm's feasibility in different healthcare settings.

## 5 | CONCLUSION

The conditions associated with eosinophilia are numerous, and the approach to the child with eosinophilia could be time-consuming and costly. We propose an algorithm based on eosinophilia severity and the children's origin country. This could optimise resource allocation, ensure appropriate testing, and improve diagnostic accuracy and the resulting outcomes. Furthermore, its step-up approach makes the algorithm easily applicable in many paediatric settings, including primary care. However, further research and validation studies are needed to assess the algorithm's efficacy and feasibility in different healthcare settings and populations.

### AUTHOR CONTRIBUTIONS

**Roberta Pellegrino:** Writing – original draft; writing – review and editing; data curation; conceptualization. **Mariangela Tosca:** Conceptualization; writing – review and editing; supervision. **Edoardo Timitilli:** Conceptualization; writing – original draft; writing – review and editing; data curation. **Matteo Naso:** Conceptualization; writing – review and editing. **Gian Luigi Marseglia:** Conceptualization; writing – review and editing. **Luisa Galli:** Conceptualization; writing – review and editing. **Michele Miraglia del Giudice:** Conceptualization; writing – review and editing. **Elena Chiappini:** Conceptualization; writing – original draft; writing – review and editing; methodology; data curation; supervision.

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### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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