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The Relationship of Parasite Allergens to Allergic Diseases

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Abstract

Purpose of Review Helminth infections modify the natural history of allergic diseases, by either decreasing or increasing their symptoms. Several helminth components are involved in the increasing of the allergic response and symptoms, overcoming the concomitant immunosuppression of helminthiases. However, the role of individual IgE-binding molecules in this process remains to be defined.

Recent Findings We updated the list of helminth allergens and IgE-binding molecules, their effects on asthma presentation, and their impact on allergy diagnosis. Data from genetic and epigenetic studies of ascariasis are analyzed. A new species-specific *A. lumbricoides* allergen has been discovered, with potential use in molecular diagnosis.

Summary Most helminth IgE-binding components are not officially classified as allergens in the WHO/IUIS database, although there is evidence of their influence increasing allergic manifestations. Further immunological characterization of these components is needed to better understand their mechanisms of action and evaluate the ways in which they can influence the diagnosis of allergy.

Keywords Helminth · Asthma · Allergy · House dust mites · *Ascaris* · IgE

Introduction

Most parasite allergens come from helminths, including those causing soil-transmitted infections (*Ascaris lumbricoides*, *Strongyloides stercoralis*, *Trichuris trichiura*, and the hookworms *Necator americanus* and *Ancylostoma duodenalis*), filarial nematodes (*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*), and platyhelminth flukes (*Schistosoma haematobium*, *S. mansoni*, *S. japonicum*). During infection, helminths produce a variety of molecules for their metabolism and survival as parasites, some of them stimulate the synthesis of specific IgE, and a small number induce allergic symptoms and/or increase the frequency and severity of allergic diseases. The clinical effects of this pro-allergenic activity depend on the modulation of host immunity exerted by the parasites, which means that they must overcome the concomitant immunosuppression to be apparent.

The degree of immunosuppression varies with the type of parasite and host genetic background; in addition, it has been associated with the severity of infection, but the reasons why some people develop severe infections, while others do not, remain to be defined. The contemporary version of the hygiene hypothesis proposes that, among other factors, the reduction of helminth infections across the world (i.e., reduction of immunomodulation) has led to an increase in allergic diseases [1]. Therefore, the potentiating effect of helminthiases on allergic responses is just an aspect of the complex host-parasite interactions between humans and those organisms. Studies of these interactions have been fundamental for understanding basic aspects of both allergy and parasitology; in addition, they have unveiled interesting clinical repercussions that deserve consideration in our medical practice. In this review, we describe the role of some helminthiases and helminth allergens as potentiators of the allergic response, mainly in the tropics, where they are endemic. We will also discuss the impact of helminth immunity on the diagnosis of allergic diseases such as asthma. A detailed review of *Anisakis* spp. allergens can be found elsewhere [2] and will not be included in this review.

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Helminthiases and Allergic Diseases

The first observed allergy-like manifestations induced by helminths were symptoms of respiratory distress or hives in children suffering *A. lumbricoides* infection (ascariasis); however, these and other clinical manifestations also occur during other helminthiases. These infection-induced symptoms are present in a minority of the population, probably because it is genetically predisposed to overreact to parasitic infection, and the degree of concomitant immunosuppression is not sufficient to reduce the manifestations of allergy, especially if the infection is acute and mild. Numerous studies have evaluated the pro-allergenic effects of helminthiases on allergic diseases, and a recent meta-analysis concluded that helminth infections may increase the risk of bronchial hyperreactivity in children and atopy in adults; most of these effects associated with *A. lumbricoides* infection [3••]. However, the role of individual helminth allergens as potentiators of the allergic response has been little explored.

Helminthiases have been controlled in most developed countries but are still endemic in tropical regions; for example, ascariasis has decreased during the last 60 years in industrialized countries, and currently, the most severe infections are present in some rural tropical villages. In tropical urban areas, hygienic conditions are better and regular deworming campaigns are carried out, which diminish the frequency and intensity of infections. Therefore, the effects of helminth allergens on allergic diseases are mostly observed in urban zones of developing countries, although they could also be present in some temperate regions [4•]. Urbanization in developing countries has had several effects [5•], such as providing better conditions for house dust mite (HDM) proliferation and better hygiene conditions associated with less helminth exposure, which supports the high HDM sensitization and allergy (Fig. 1). Moreover, current trends of climate change are expected to expand the geographical extent of HDM growth and sensitization [6].

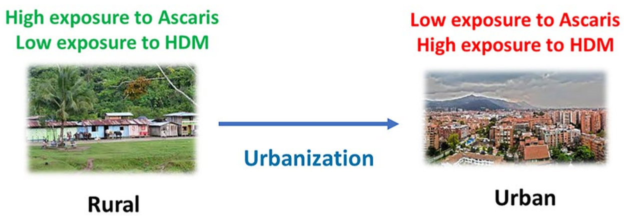


Fig. 1 Urbanization and allergies in the tropics: the influence of helminthiases and house dust mites. If we look at the current situation in the tropics, we can hypothesize that one of the reasons why urbanization leads to an increase in allergy is the reduction of severe forms of helminthiases due to the improvement of hygiene conditions associated with urbanization

Helminth Allergens

Helminth allergens are the result of normal type 2/IgE immune responses during infections. Animal models have shown that specific IgE antibodies, together with eosinophils, can destroy helminth larvae, and other type 2 immune mechanisms have been revealed using diverse helminth species in animal models of infection [7, 2], but their clinical relevance in terms of modifying allergic diseases deserves more investigation. All these molecules are allergenic (they induce and bind IgE), but only few have been investigated for allergenic activity (the capacity to induce allergic inflammation), which is a crucial step in defining their clinical relevance [8]. This consideration is, of course, valid for common allergens but is particularly important for helminths because IgE-binding molecules such as *A. lumbricoides* cystatin (Al-CPI) do not have relevant allergenic activity but strong immunomodulatory effects [9]. In this sense, Table 1 shows the immunological characterization of some helminth IgE-binding molecules.

Ascaris lumbricoides

During larval pulmonary transit, *A. lumbricoides* induces respiratory symptoms similar to asthma, and sometimes Löffler's syndrome. Also, there is epidemiologic evidence that ascariasis increases the frequency and symptoms of asthma. This potentiating effect can be detected at the population level, as it has been repeatedly observed that sensitization to *A. lumbricoides* is associated with a higher prevalence of asthma [10, 11] and asthma severity [4, 12, 13], especially in urban areas with lower exposure and mild infections. These changes are also detected at the cellular and molecular levels, with an increase in several components of the type 2 response, particularly the production of specific and cross-reactive IgE against parasite antigens [11].

Specific IgE to HDM is the most important risk factor for asthma in the tropics. Thus, any condition that increases the allergic response against them could also increase the symptoms and severity of this disease. Since HDM exposure is high and permanent in tropical environments and induces IgE sensitization at a very early age (Fig. 2), the cross-reactivity between several allergens from both sources (e.g., tropomyosins, glutathione S-transferases [GSTs], and other non-characterized components) may explain this potentiating effect of ascariasis [10]. In addition, ascariasis might induce polyclonal nonspecific stimulation of B cells [14]; therefore, it is possible that the implicated components also stimulate HDM allergen-specific memory B cells that are permanently stimulated in the tropics. Furthermore, experimental work suggests that ascariasis can boost IgE/Th2 responses to bystander antigens [15]. These data suggest

Table 1 Allergenic activity assays of some helminth IgE-binding molecules

Helminth	Molecule	In vivo provocation tests	In vitro provocation tests	Animal models	Association with allergic diseases
A. suum	ABA-1 / Asc s 1	n/d	HR	n/d	n/d
A. lumbricoides	Asc l 3	ST	HR	n/d	Asthma
	Asc l 5	n/d	BAT	sIg, PCA	n/d
	Asc l 13	ST	n/d	n/d	n/d
S. stercoralis	NIE	n/d	HR	n/d	n/d
S. mansoni	SmTAL1	n/d	RBL	n/d	n/d
	SmTAL2	n/d	RBL	n/d	n/d
	SmVAL4	n/d	n/d	sIg, AAI, PCA	n/d
	SmVAL26	n/d	n/d	sIg	n/d
	IPSE/alpha-1	n/d	RBL	n/d	n/d
	SmATPDase2	n/d	n/d	sIg	n/d
	SmCB1	n/d	n/d	sIg	n/d
B. malayi	TTR	n/d	n/d	PA	n/d
	Bm23-25 (γ-GT)	n/d	n/d	sIg	TPE
	BmAl-1	n/d	n/d	sIg	n/d
O. volvulus	OvTrop	n/d	HR	n/d	n/d
N. americanus	Calreticulin	n/d	HR	n/d	n/d
	Na-ASP-2	ST	n/d	n/d	Urticaria
A. caninum	Ac68	n/d	n/d	n/d	Eosinophilic enteritis

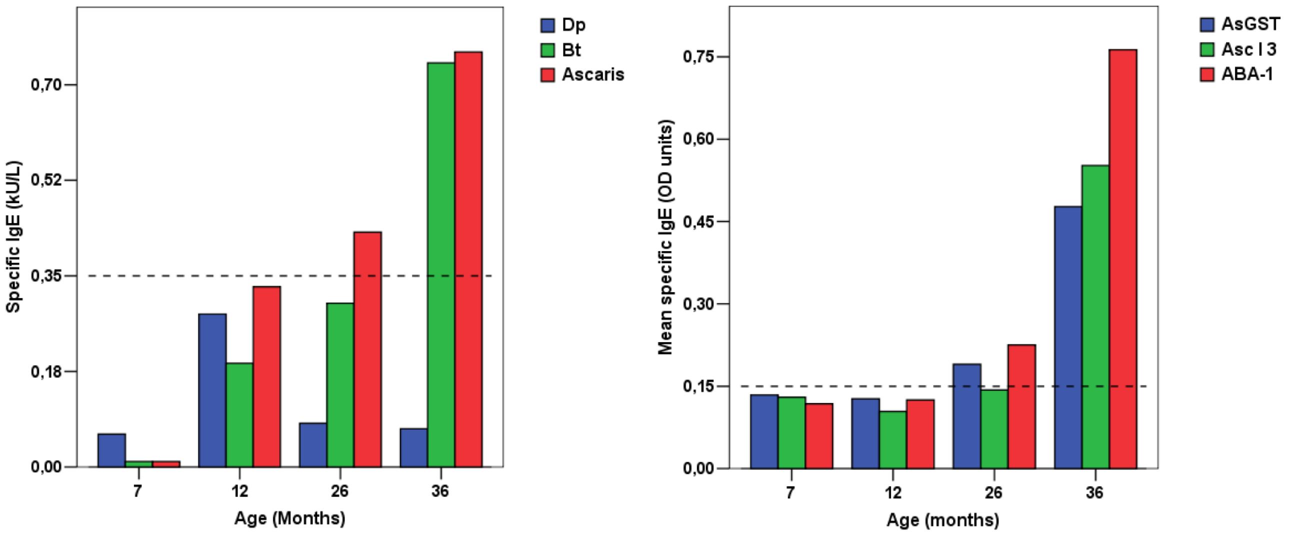
AAI allergic airway inflammation, *BAT* basophil activation test, *HR* histamine release, *PA* passive anaphylaxis, *PCA* passive cutaneous anaphylaxis, *RBL* rat basophil leukemia cells test, *sIg* specific immunoglobulin (IgG1 and/or IgE) response, *ST* skin test, *n/d* no data

that helminthiases can boost the allergic responses to HDM in several ways.

Trying to further explore this boosting effect in human ascariasis, we studied the evolution of the immune responses in children of the FRAAT birth cohort [16], finding that *Ascaris*-sensitized children had stronger IgE to *B. tropicalis* and those sensitized to the *Ascaris* allergen ABA-1 had increased IgE responses to Blo t 5 and Blo t 12, two species-specific allergens of *B. tropicalis*, ruling out the effect of cross-reactivity [17]. This nonspecific boosting was also detected in a large population co-exposed to *A. lumbricoides* and HDM, where subjects sensitized to ABA-1 (a marker of ascariasis) had at least twice the odds of being sensitized to HDM [10]. Furthermore, in another cohort of asthmatic patients, *Ascaris*-sensitized patients had significantly higher IgE levels to the HDM-specific allergens Der p 2 and Blo t 5 [13]. These findings support the idea that the Th2/IgE hyperresponsiveness induced by *A. lumbricoides* infection includes responses not only to helminth antigens but also to HDM allergens. However, the role of *A. lumbricoides* components, the host genetic background, and the epigenetic modifications that influence this boosting effect are only beginning to be unraveled.

In a search for genetic variants supporting the IgE hyperresponsiveness of ascariasis, we found that SNPs of the genes coding for acidic mammalian chitinase (*CHIA*) and chitinase 3 like 1 (*CHI3L1*) were significantly enriched in high IgE responders to the resistance marker ABA-1; in addition, SNPs in the tumor necrosis factor superfamily member 13b gene (*TNFSF13B*) encoding the cytokine B cell activating factor were associated with high levels of total IgE [18]. We then investigated the histone 4 acetylation (H4Ac) of these and other immune genes in *A. lumbricoides*–infected and non-infected subjects, finding significant associations between H4Ac levels in the *IL4* and *CHI3L1* genes and IgE levels to *A. lumbricoides.* In addition, the levels of specific IgE antibodies to HDM were associated with H4Ac levels in the *TNFSF13B* gene. These results suggest that acariasis induces histone acetylation of immune response genes, which in turn increases the IgE response to both helminth and HDM allergens [19•]. Therefore, regarding the boosting effects of ascariasis on the allergic response, we hypothesized that patients predisposed to asthma, with a strong pro-Th2 genetic background, parasitized at an early age, under regular deworming campaigns (followed by re-infections), and permanently exposed to mite allergens, have a stronger IgE response to allergens and more severe asthma clinical symptoms.

Immunochemistry analyses of *A. lumbricoides* extract suggest that it has high cross-reactivity with *B. tropicalis* and *D. pteronyssinus*, and that this nematode has at least nine IgE-binding components [20]; however, only three



	7	12	26	36
Total IgE (kU/L)	22.4	163	123	347.23

Fig. 2 An example of allergic sensitization in a child living in the tropics. Specific IgE against *D. pteronyssinus* (Dp), *B. tropicalis* (Bt), and *Ascaris* extracts were measured using ImmunoCAP™ 100. Specific IgE to *A. lumbricoides* GST (AsGST), tropomyosin (Asc l 3), and ABA-1 were measured by ELISA. Samples were collected at 7, 12, 26, and 36 months. Data on the child's total IgE levels at these time points are also included. Figure obtained from data of the FRAAT cohort (reference 16)

have been characterized and listed in the official WHO/IUIS site. Two of these, Asc l 3 (tropomyosin) and Asc l 13 (GST), cross-react with their HDM group 10 and group 8 homologs [21, 22]. More recently, we discovered a third *A. lumbricoides* allergen, Asc l 5; the evaluation of its allergenic activity included determination of IgE-binding frequency (in two populations: 254 children and 298 all-age subjects), CD203c-based basophil activation tests, and a passive cutaneous anaphylaxis mouse model [23••]. Further analyses of this allergen, employing immunoblotting and mass spectrometry of *A. lumbricoides*, *B. tropicalis*, and *D. pteronyssinus* extracts, suggest that it is *A. lumbricoides* species-specific [24].

Tropomyosin, a well-known pan-allergen, is involved in *Ascaris*-HDM cross-reactivity [20, 25]. Specific IgE levels to Asc l 3 are significantly higher in asthmatic patients than in healthy controls, which suggests that it may be a risk factor for asthma symptoms in the tropics [10], as it is the only helminth allergen directly associated with an allergic disease. More detailed information about this pan-allergen can be found in reference [26]. Although the allergenic activity of *Ascaris* GST (Asc l 13) has not been properly defined, its recombinant form induces skin wheal and flare reaction in subjects with ascariasis. The frequency of IgE reactivity to this molecule is low (< 20%) but may be clinically relevant in cases where there is also sensitization to mite and cockroach GSTs [22]. The allergenic cross-reactivity between GSTs from *Ascaris* and other allergenic sources is supported by the structural homology between Asc l 13 and allergenic GSTs in cockroaches (Bla g 5) and HDM (Der p 8 and Blo t 8) [27]. A comprehensive review of GST allergens from different sources has been published elsewhere [28•]. The first allergen to be reported from *Ascaris* spp. was ABA-1 (Asc s 1), discovered in *Ascaris suum.* It is a polyprotein abundant in the pseudocelomic fluid of both *A. suum* and *A. lumbricoides*. In humans, IgE and IgG responses to ABA-1 have been associated with protection [29] rather than allergy symptoms. In addition, since it has no cross-reactivity with any HDM component, it is considered a marker for *Ascaris* infection.

Strongyloides stercoralis

Strongyloidiasis can be asymptomatic [30], but in some cases can elicit allergic respiratory or cutaneous manifestations. Murine models show that this parasite induces airway hyperreactivity with asthma-like characteristics, such as eosinophilic inflammation, mucus hypersecretion, and bronchial wall thickening [31]. In humans, the infection can manifest with chronic cough, mimic asthma exacerbations, or worsen stable asthma, thus complicating the evolution and management of this disease [32, 33•, 34]. Localized skin eruption (i.e., larva currens) and urticaria are among the cutaneous manifestations of strongyloidiasis [35]. However, the individual components that induce these allergic symptoms or changes in the natural history of allergic diseases remain unknown.

Immunity to *S. stercoralis* involves type-2 pathways, including IgE antibodies. Both somatic antigens and excretory/secretory products (ESPs) are recognized by IgE, trigger IgE-dependent histamine release from basophils, and induce positive skin test reactions [36]. However, few individual IgE-binding molecules have been studied. For instance, NIE is a larval component recognized by human IgE that induces histamine release from basophils in 90% of patients with strongyloidiasis [37], and shares a cross-reacting C-terminal epitope with the Hymenoptera venom allergens Ves v 5 and Pol a 5 [37, 38]. Strongylastacin is another excretory/secretory metalloprotease with IgE reactivity that helps larvae penetrate the skin [39]. Anti-strongylastacin IgE was present in 93% of infected subjects but not in healthy or *Wuchereria bancrofti*–infected individuals [39]. Finally, the *S. stercoralis* IgE-binding recombinant protein rA133 is recognized by IgE from 100% of infected patients but not from healthy controls or individuals infected with other parasites [40].

Schistosoma spp

Schistosomiasis has been regarded as a protective factor against atopy and asthma [41, 42], depending on the parasite burden and chronicity of the infection [43]. However, some studies have shown that anti-schistosome IgE is positively associated with specific sensitization (e.g., to mites or cockroaches) and allergic diseases [3, 44, 45]. In addition, in vivo models have used sensitization and challenge with *Schistosoma* eggs to induce type-2 inflammation [46], suggesting the presence of components with allergenic activity.

Some *Schistosoma* components are recognized by IgE, including a 22.6-kDa molecule from *S. mansoni* (Sm22.6, currently known as SmTAL1) that is associated with human resistance to reinfection [47], and the antigens Sj22.6 and Sh22.6 from *S. japonicum* and *S. haematobium* respectively [48, 49]. Two Sj22.6 IgE-binding epitopes showed sequence similarity with known IgE-binding epitopes from fish and grass pollen allergens [49]. Genome searches identified 13 *S. mansoni* tegumental-allergen-like proteins (TALs) that are differentially expressed throughout the parasite lifecycle [50]. In terms of allergenic activity, a luciferase-based test using a humanized rat basophilic leukemia cell line showed that SmTAL1 and SmTAL2 induce basophil activation [51].

Trematode “venom allergen-like proteins” (VALs) are similar to the wasp venom allergen Ves v 5. SmVAL6 is recognized by IgE from *S. mansoni*–infected individuals, with a higher IgE-binding frequency after anthelmintic treatment [52]. Besides, SmVAL4 induced IgE production in immunized BALB/c mice, generating allergic airway inflammation and passive cutaneous anaphylaxis, supporting the allergenic activity of this protein [53]. Other *S. mansoni* IgE-binding proteins are the IL-4-inducing principle from *S. mansoni* eggs (IPSE/alpha-1), a glycoprotein that induces IL-4 release from basophils [51, 54], and kappa-5, produced by the egg and miracidium stages, with a 45% IgE-binding frequency among patients infected with *S. mansoni* and 0% in uninfected controls [55].

In addition, *S. mansoni* ATP diphosphohydrolases (SmATPDases) also have allergenic properties [56], and some cysteine proteases of this parasite, such as cathepsin B1 (SmCB1), are similar to mite allergen Der p 1 [57, 58]. Furthermore, IgE from infected individuals recognizes antigens from schistosomula, including the extracellular vesicle-enriched larval extracellular vesicle protein 1 (SmLEV1) [59]. It is also important to note that *S. mansoni* has IgE-binding homologs to well-known allergens like tropomyosin, GSTs, profilin, lipocalin, cyclophilin, and phosphoglycerate kinase [52].

Toxocara spp

There is experimental and epidemiological evidence that toxocariasis increases asthma susceptibility [60]. A meta-analysis revealed that children infected with *Toxocara spp.* are more likely to have asthma compared to non-infected children [61]. Human specific IgE antibodies detect several components in the ESPs of *T. canis* [62]; however, the identification of individual IgE-binding components from this parasite remains to be done.

Hookworms

Most studies about these nematodes suggest that they are more associated with immunosuppression than with an increase in allergic symptoms [63], although some reports show positive associations between current or past hookworm infection and allergic rhinoconjunctivitis or wheezing [64, 65]. Hookworms can induce allergic inflammation in humans during their lifecycle, and the passage of larvae through the lungs can cause Löffler syndrome. In addition, *N. americanus* can induce basophil activation and degranulation in the absence of detectable specific IgE, probably due to early basophil sensitization or an effect mediated by hookworm-secreted proteases [66, 67]. Furthermore, larvae of animal hookworms, such as *Ancylostoma caninum*, can penetrate human skin and produce an intensely pruritic, erythematous, serpiginous eruption that is characterized histologically by an important eosinophilic infiltration, called larva migrans [68]. Although the presence of specific IgE against hookworm antigens has been demonstrated by serological assays, skin tests, and basophil histamine release, few of their IgE-binding components have been identified [69, 71]. One of these is the *N. americanus* calreticulin, which induces basophil histamine release and has little cross-reactivity with its human counterpart [72, 73].

Another hookworm IgE-binding molecule, *Na*-ASP-2, is abundantly secreted by *N. americanus* larvae upon entry into the host and is structurally similar to vespid venom allergens and SmVALs [74, 76]. *Na*-ASP-2 can elicit positive skin test results [77], supporting its allergenic activity. Both calreticulin and *Na*-ASP-2 have been studied as anti-hookworm vaccines [74, 78], but their allergenic properties have impeded these efforts. *Na*-ASP-2 induced generalized urticaria in three of seven individuals who received a single dose of a recombinant version of this protein, all of which had pre-existing *Na*-ASP-2-specific IgE [77]. Regarding *A. caninum*, Ac68 and Ac-ASP-1 are IgE-binding molecules from this parasite [79, 80].

Filariae

Human filariasis has been associated with allergic manifestations and atopic sensitization. Microfilaria of *W. bancrofti* in the lungs can cause an allergic reaction that resembles asthma, a rare condition known as tropical pulmonary eosinophilia (TPE), which presents with cough, dyspnea, wheezing, chest pain, systemic manifestations (including fever and weight loss), peripheral blood eosinophilia > 3000/μL, and elevated total IgE > 1000 IU/mL. Patients with TPE have higher levels of filarial-specific IgE than those with other manifestations of filarial infection [81], and this condition can lead to irreversible pulmonary hypertension, pulmonary fibrosis, and chronic respiratory failure. Animal models of filariasis show that helminth-induced airway hyperresponsiveness is dependent on IL-4, IL-5, and eosinophil recruitment and degranulation, consistent with type 2 immune-mediated inflammation [82, 83].

Filariae induce a long-lasting IgE response and contain several IgE-binding components that are poorly characterized [84] such as the *O. volvulus* molecules Ov27, OvD5B, and OvGalBP [85, 86]. *W. bancrofti* and *B. malayi* components trigger histamine release from human basophils, whereas *B. malayi* antigens also induce positive skin test reactions [81, 84, 87]. Fourteen IgE-binding ESPs of *B. malayi* have been identified, including transthyretin-related protein (TTR), WbSXP-1, macrophage migration inhibitory factor, and gp15/400 [88•]. Interestingly, proteins belonging to the TTR family are the most dominant filarial antigens targeted by the human IgE response [88•]. Sensitization with TTR-binding IgE monoclonal antibodies induces anaphylaxis in mice upon challenge with TTR proteins [88•]. Bm23-25 is a *B. malayi* IgE-binding component with a potential role in the pathogenesis of TPE given that it is recognized by IgE present in the bronchoalveolar lavage fluid and serum of patients with this condition [89]. Bm23-25 is a homolog of mammalian γ-glutamyl transpeptidase (γ-GT) that induces a specific antibody response (including IgG1 and IgE) in BALB/c mice and exhibits cross-reactivity with human airway epithelium γ-GT [89, 90]. In addition, patients with TPE, but also healthy individuals from a filaria-endemic area, have elevated specific IgE levels against *B. malayi* γ-GT [91].

Many filarial proteins have homologs in allergenic sources such as mites and cockroaches, which can lead to cross-sensitization [92, 93]. For example, *B. tropicalis* trypsin (Blo t 3) shares amino acid sequence similarity with its *W. bancrofti* counterpart [93]. In addition, there is considerable amino acid sequence identity, 3D structure similarity, and cross-reactivity between mite and filarial tropomyosins (i.e., Der p 10 from *D. pteronyssinus* and OvTrop from *O. volvulus*), as well as between cockroach and filarial GSTs (i.e., Bla g 5 from *Blattella germanica* and WbGST from *W. bancrofti*) [94, 95]. Furthermore, vespid venom allergen homologs are present in *B. malayi* and *W. bancrofti* (e.g., Bm-VAL-1 and WbVAH) [96, 97].

Helminth Allergens and Allergy Diagnosis

Since allergic responses and helminth immunity have several similarities, it is possible that some diagnostic parameters for allergy can be confounded by helminthiases. In rural areas of the tropics, severe helminthiases can diminish allergen skin testing results [98, 99], even in the presence of serum allergen-specific IgE [100]. In tropical urbanized settings, when using allergen extracts for skin testing or serodiagnosis, cross-reactivity between *A. lumbricoides* and HDM allergens (tropomyosin and GST) may confuse the diagnosis because sensitization to both organisms is very frequent [101]. In addition, there is evidence that this could also be important in some temperate zones [4, 102]. Fortunately, today it is possible to differentiate co-sensitization vs cross-reactivity between the two sources using molecular diagnosis [103]. Another constraint of serologic allergy diagnosis in patients with helminthiases is the presence of the carbohydrate epitope galactose-α1,3-galactose (α-Gal), which is expressed in non-primate mammalian proteins, such as the cat allergen Fel d 5 (cat IgA) and *A. lumbricoides* [104, 105].

Helminthiases could also limit the usefulness of type 2 asthma markers such as total IgE, fractional exhaled nitric oxide (FeNO), and blood eosinophils, which can impact decisions regarding the use of biologics for treatment. Both

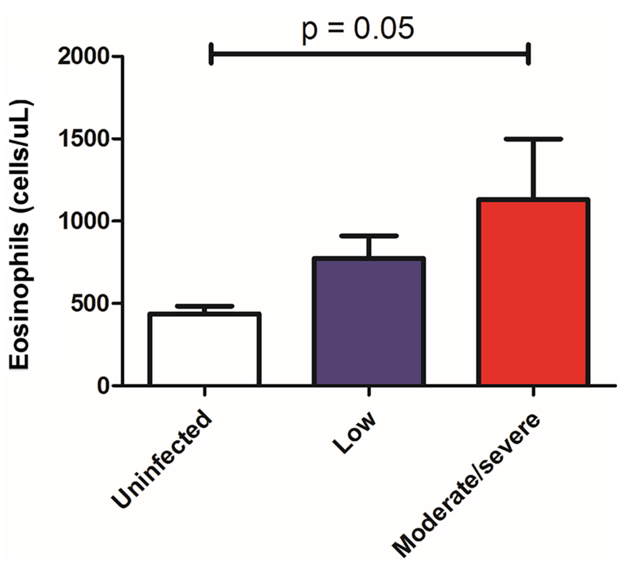


Fig. 3 Blood eosinophil counts increase with the severity of *A. lumbricoides* infection. The number of eosinophils is expressed as absolute cell counts/μL. Low infection < 2500 eggs/g. Moderate/Severe = equal or > 2500 eggs/g. A total of 82 subjects were included

asthma and helminthiases run with high total IgE levels; in tropical zones, children reach high total IgE levels at the age of 3 years [106] (Fig. 2). Hence, specific IgE detection is a better criterion than total IgE for defining atopy in these locations. Blood eosinophilia has also been described in both asthmatic [107] and parasitized subjects [108]. Indeed, we found that eosinophil counts increased with the severity of *A. lumbricoides* infection [109] (Fig. 3). In addition, a comparison of asthmatic and non-asthmatic subjects living in an endemic tropical village, using a general linear model, showed that eosinophil counts were dependent on ascariasis rather than asthma (Zakzuk J, personal communication). Therefore, investigation of current helminth infection by stool examination can help define the origin of blood eosinophilia in asthmatic patients living in endemic zones of the tropics.

FeNO is an important tool for evaluating lung inflammation [110] and is currently used as a clinical biomarker of Th2 inflammation in asthma [111]. A previous study suggested that FeNO levels are higher in *A. lumbricoides* parasitized children in Ecuador [99]. However, in a cohort of adult asthmatic patients, we found no difference in FeNO levels between *Ascaris*-sensitized and non-sensitized patients [112]. There were also no differences in FeNO levels between children that were IgE-sensitized to the infection marker ABA-1. Since positive IgE reflects parasite exposure but not necessarily active infection, we also compared FeNO levels between parasitized and non-parasitized children ($n = 99$) from a rural village in Colombia. Preliminary unpublished results (Acevedo N, personal communication) showed no difference in FeNO levels between infected and non-infected children. Cases with lung migratory phase parasites, such as *A. lumbricoides* or *A. duodenalis*, had FeNO levels below 20 ppb (see some examples in Table 2). Therefore, although more research about this topic is needed, in tropical environments this important diagnostic tool should also be supported with patient's stool examination.

Conclusions

The allergenic activity of several helminth products (e.g., parasite extract, pseudocelomic fluid, and extracellular vesicles) has been demonstrated experimentally, although more research is needed to identify the molecules involved and the underlying mechanisms. Still, this information supports clinical and epidemiological evidence demonstrating the diverse pro-allergenic effects of helminthiases in humans, especially in areas where helminthiases are frequent. The modifications of the natural history of allergic diseases induced by helminth infections also impact their diagnosis and management.

Table 2 A descriptive of FeNO levels in children infected by nematodes with lung migratory phases in their lifecycle

Subject ID	Age (years)	Nematode detected	Eggs per gram of feces•	FeNO level (ppb)	Blood eosinophil cell counts (eos/µL) ••
LA012	7	*Ascaris lumbricoides*	72	16.5	1090
ST095	8	*Ascaris lumbricoides*	1824	19.5	600
ST093	9	*Ancylostoma duodenalis*	72	4	1930
ST094	7	*Ancylostoma duodenalis*	312	12	760
ST101	9	*Ancylostoma duodenalis*	120	18.5	1450

•As quantified by the Kato-Katz method

••Eosinophilia is considered above 500 eosinophils per microliter of blood

FeNO levels < 20 ppb are considered normal in children

ppb, parts per billion

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Data Availability Acevedo N, personal communication.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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