Global issues in allergy and immunology: Parasitic infections and allergy

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Date of Original Release: November 2017. Credit may be obtained for these courses until October 31, 2018.

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: A. A. Cruz has board memberships with GlaxoSmithKline, AstraZeneca, Novartis, Mylan, and Boehringer Ingelheim; has consultant arrangements with Boehringer Ingelheim; has given expert testimony on behalf of Boehringer Ingelheim; has received grants from GlaxoSmithKline; has received payment for lectures from EUROFARMA, AstraZeneca, Novartis, CHIESI, Boehringer Ingelheim, and Mylan; has received payment for manuscript preparation from Mylan and Merck Sharp & Dohme; and has received travel support from Boehringer Ingelheim. The rest of the authors declare that they have no relevant conflicts of interest. Z. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To learn T_H2 immune responses are the primary mediators in helminth infections.
2. To explore structural homology between allergens derived from parasites and aeroallergens.
3. To learn similar immune mechanisms exist between atopic conditions and helminth infections.
4. To discover the potential negative association between helminth infection and allergy.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The exam authors disclosed no relevant financial relationships.

Allergic diseases are on the increase globally in parallel with a decrease in parasitic infection. The inverse association between parasitic infections and allergy at an ecological level suggests a causal association. Studies in human subjects have generated a large knowledge base on the complexity of the interrelationship between parasitic infection and allergy. There is evidence for causal links, but the data from animal models are the most compelling: despite the strong type 2 immune responses they induce, helminth infections can suppress allergy through regulatory pathways. Conversely, many helminths can cause allergic-type inflammation, including symptoms of "classical" allergic disease. From an evolutionary perspective, subjects with an effective immune response against helminths can be more susceptible to allergy. This narrative review aims to inform readers of the most relevant up-to-date evidence on the relationship between parasites and allergy. Experiments in animal models have demonstrated the potential benefits of helminth infection or administration of helminth-derived molecules on chronic inflammatory diseases, but thus far, clinical trials in human subjects have not demonstrated

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C.A.F., N.M.A.-N., M.L.B., and A.A.C. receive investigator grants from the Brazilian Research Council (CNPq).

Received for publication August 9, 2017; revised September 19, 2017; accepted for publication September 21, 2017.

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0091-6749/$36.00

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https://doi.org/10.1016/j.jaci.2017.09.005

unequivocal clinical benefits. Nevertheless, there is sufficiently strong evidence to support continued investigation of the potential benefits of helminth-derived therapies for the prevention or treatment of allergic and other inflammatory diseases. (J Allergy Clin Immunol 2017;140:1217-28.)

Key words: *Allergy, asthma, parasite infection, helminths, epidemiology, pathogenesis*

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The frequency of allergic disease has been increasing in urban and urbanizing populations,[1] whereas an overall decrease in rates of infections has been observed. Studies of the inverse association between parasitic infections and allergy suggest the existence of a causal link.

Although human subjects can be infected with some 300 species of worms and more than 70 species of protozoa,[2] we will focus on soil-transmitted helminths (STHs), also called geohelminths. Worldwide, it is estimated that 1.5 billion human subjects are infected with one of these species.[3] We will also refer to *Schistosoma* species, which infect human subjects through contact of skin with water infested with larvae and are estimated to infect 230 million persons.[4]

For example, Fig 1 shows typical features of a rural household in a village of Conde, northeast Brazil, from 2005, in which the prevalence of helminth infections was 83.5%.[5] In the city of Salvador, 185 km away, the frequency of helminth infection among children was less than 20%.[6] An ecological study including all Brazilian municipalities reported that hospitalization rates for asthma were lower in those endemic for *Schistosoma mansoni* or STH parasites.[7] A typical urban underserved neighborhood of Salvador is presented in Fig 2.[6]

The purpose of this narrative review is to inform clinicians and researchers of the most current evidence on the interrelationship between parasitic infections and allergy from epidemiologic studies to mechanisms and molecules identified in helminths that are candidates for novel therapeutics.

GLOBAL TRENDS IN PARASITE INFECTIONS AND ALLERGY

Global trends

Allergic diseases are among the most common chronic diseases,[1] particularly in populations undergoing urbanization.[8] Individual allergy risk is considered to reflect a complex interaction between genetic predisposition and environmental exposures over the life course.[9] Geographic differences in the prevalence of allergy between and within populations is more likely to reflect exposures to common environmental factors that can either increase or decrease risk. The most consistent environmental exposures considered to reduce allergy risk are those associated with rural residence and include farming, animal exposure,[10] and infections with parasites.[11]

Protective immunity against STHs is mediated through type 2 immune mechanisms,[11] and parasites can survive to cause chronic infections by modulating these allergic inflammatory responses. The prevalence of STH infections is decreasing worldwide. This reflects a combination of factors leading to reductions in transmission of these infections, including reductions in extreme poverty and improvements in the living environment (potable water and disposal of feces) and the wide availability of anthelmintic drugs. Reductions in STH prevalence, although beneficial, might raise concerns in case of being causally associated with allergy.

Abbreviations used
AAMΦ: Alternatively activated macrophage
ES: Excretory-secretory
FOXP3: Forkhead box protein 3
GWAS: Genome-wide association study
ILC: Innate lymphoid cell
ILC2: Type 2 innate lymphoid cell
SNP: Single nucleotide polymorphism
SPT: Skin prick test
STH: Soil-transmitted helminth
tIgE: Total IgE
Treg: Regulatory T

Epidemiologic evidence for associations between parasites and allergy

There is evidence in support of protection against allergy by STH infections, but many studies in human populations present discordant effects.

Meta-analyses of observational studies have shown differences in effects on asthma symptoms for different parasites: although *Ascaris lumbricoides* was associated with an increased risk of asthma, hookworm infection was associated with a reduced risk.[12] In contrast, studies that have measured the presence of *Ascaris* species–specific IgE, which is recommended by some as a marker of infection in areas of low prevalence[13] but is perhaps more appropriately used as a marker of allergic sensitization to *Ascaris* species, have shown consistently positive associations with asthma symptoms and even disease severity.[14,15]

In the case of atopy, which is generally measured based on allergen skin prick test (SPT) reactivity, most cross-sectional studies have shown inverse associations with STH infections.[16] A meta-analysis of cross-sectional studies showed that current STH infections were protective against atopy, an effect that was consistent for all 3 of the most common STH infections and also schistosomiasis.[16] Although *Ascaris* species infections can be associated inversely with atopy, they are often associated directly with wheezing, as mentioned in the previous paragraph. STH infections are not alone in attenuating atopy. A cross-sectional study showed that several different childhood infections were associated independently and inversely with reactivity to SPTs, including the visceral worm *Toxoplasma gondii*, *Herpes simplex*, and EBV infections.[6] This observation raises the possibility that rather than mediating protection directly, STH infections might be markers of poor environmental conditions that mediate protection through alternative mechanisms. Interestingly, in the study mentioned above, *T gondii* was the only organism associated with a reduction in allergen-specific IgE levels in this population.[6]

Few prospective studies have explored the effects of geohelminths on allergy development. It has been suggested that the key effects of protective environmental exposures occur during early life, during which there might be a limited window of opportunity for such exposures to mediate their effects.[9] If this is

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