

Eosinophilia during intestinal infection

Thomas Löscher* MD

Elmar Saathoff¹ MD

Department of Infectious Diseases and Tropical Medicine, Ludwig-Maximilians-University of Munich, Leopoldstrasse 5, D-80802 Munich, Germany

Eosinophilia is a common finding in tropical developing countries, and is mainly caused by chronic helminth infections, predominantly of the gut. Although only a minority of infections is symptomatic, development during childhood can be impaired, and in some patients serious complications and sequelae may occur. Eosinophilia in helminth infection is typically associated with a strong Th2 immune response, and eosinophils can effectively kill or damage larvae and adult worms in vitro. However, in vivo, eosinophils are only partly effective in the control of helminth infection, and recent research has shown that eosinophils are involved in a range of immunomodulatory effects, such as increased production of the down-modulatory cytokines interleukin 10 and tumour growth factor β , as well as stimulation of regulatory T cells and alternatively activated macrophages. Increasing evidence suggests that immunomodulation favours parasite survival and reduces immune pathology. On the other hand, immunomodulation induced by helminth infections may contribute to protection from allergic and autoimmune responses, as proposed by the 'hygiene hypothesis' to explain the increase in allergic diseases in the industrialised world. The predictive value of eosinophilia for the presence of helminth infections is limited and depends on the epidemiological background and the extent of the eosinophilia. It increases considerably in populations with a high prevalence of parasitic infections, as in developing tropical countries or in travellers to those areas.

Key words: eosinophil; intestinal infection; helminth; immunomodulation.

Blood and tissue eosinophilia is common in infections by helminth parasites.¹ In contrast, most viral, bacterial and fungal infections are not associated with eosinophilia, but typically cause eosinopenia and may suppress eosinophilia from other causes. However, there are some exceptions to this rule, and significant eosinophilia can be observed in patients with HIV infection and a few other infections.²

* Corresponding author. Tel.: +49 89 2180 3517; Fax: +49 89 336 112.

E-mail addresses: loescher@lrz.uni-muenchen.de (T. Löscher), saathoff@lrz.uni-muenchen.de (E. Saathoff).

¹ Tel.: +49 89 21803830; Fax: +49 89 336112.

From a clinical point of view, eosinophilia is a rather unspecific sign, and in addition to helminth infections it may be seen in a large variety of non-infectious diseases (Table 1), such as allergies including asthma, drug hypersensitivity reactions, neoplasm, connective-tissue disorders, primary hypereosinophilic syndromes, and transplant rejection.^{3,4} However, in areas with a high prevalence of parasitic infections, such as rural areas in developing countries, or in travellers returning from such areas, blood eosinophilia may be the first or only indication of a condition with potentially serious sequelae, such as schistosomiasis or strongyloidiasis, and is often useful in guiding the diagnostic evaluation in symptomatic patients.^{5,6} Extensive eosinophilia can be an important diagnostic feature in several tissue-invasive helminth infections. However, the incidence and extent of infection-related eosinophilia do not depend only on the type, intensity and stage of infection; other factors such as individual differences in innate and adaptive immune responses, epidemiological background, age at first exposure, underlying conditions, etc are important as well.

Eosinophils exert a range of biological effects not only against helminth parasites and the surrounding host tissue but also (in some allergic and autoimmune diseases) leading to inflammation and damage of affected tissues. Eosinophilia in helminth

Table 1. Diseases and disorders associated with eosinophilia.

Infectious diseases	Helminth infections (see Table 2) Viral: HIV infection, HTLV 1/2 infection Bacterial: resolving scarlet fever; chronic tuberculosis Fungal: coccidioidomycosis, bronchopulmonary aspergillosis Protozoal: isosporiasis, dientamoebiasis, sarcocystosis Ectoparasitic: scabies, myiasis
Allergic disorders	Asthma Atopic disorders (e.g. dermatitis, rhinitis) Drug hypersensitivity
Neoplasm	Lymphoma, especially Hodgkin's Leukaemia; myelogenous, eosinophilic Carcinoma of the bowel, lung, ovary or other organs
Connective tissue disorders	Churg-Strauss vasculitis Systemic lupus erythematosus Rheumatoid arthritis
Hypereosinophilic syndromes	Myeloproliferative variants (F/P positive/negative) Lymphocytic variants (clonal, polyclonal) Eosinophil-associated gastrointestinal disease (EGID) Chronic eosinophilic pneumonia Eosinophilia myalgia syndrome Familial hypereosinophilia Cyclical angio-oedema and eosinophilia Kimura's disease
Other	Hypoadrenalism Cholesterol embolisation Sarcoidosis Pemphigus vulgaris, bullous pemphigoid Systemic mastocytosis Inflammatory bowel disease Transplant rejection

HIV, human immunodeficiency virus; HTLV, human T-cell leukaemia virus; F/P, FIP1L1/PDGFR α mutation.

infections, as well as in allergic diseases (including asthma), is typically associated with a pronounced Th2 immune response including the production of interleukin-4 (IL-4), IL-5, and IL-13, as well as immunoglobulin E (IgE) and the expansion and mobilisation of other specific effector cells, such as mast cells and basophils.⁷ Until recently, eosinophils have been regarded mainly as end-stage effector cells with cytotoxic activities consequent upon release of the toxic cationic proteins stored in their secondary granules. These non-specific killing abilities are thought to have evolved as a host defence mechanism against large non-phagocytosable parasites. However, eosinophils, in addition to their role in host protection against helminth parasites, are pleiotropic multifunctional leukocytes involved in developmental processes, initiation and propagation of various inflammatory responses, remodelling/repair processes, and modulation of innate and adaptive immunity.⁴

Today, in most industrialised countries parasitic infections have become rare while allergic and autoimmune disorders have risen considerably, whereas in the developing world helminth infections are still highly endemic.⁸ It has been proposed that the increase in allergies may be due to the lack of acute and chronic stimulation of the Th2 immune response during childhood by helminth antigens, which leads to increased Th2 responses against various allergens (hygiene hypothesis). However, recent research has identified several immunomodulatory mechanisms elicited by helminth infections which seem to favour parasite survival and to decrease immune pathology associated with helminth infection, and which also may contribute to protection from allergic and autoimmune responses.^{7,9}

EOSINOPHIL DEVELOPMENT AND TRAFFICKING INTO THE GASTROINTESTINAL TRACT

Eosinophils are produced in the bone marrow from pluripotent stem cells, which differentiate by an interplay of at least three different classes of transcription factors, including GATA-1 (a zinc finger family member), PU.1 (an ETS family member), and C/EBP members (CCAAT/enhancer-binding protein family).^{4,10} In addition to this highly regulated transcriptional control, further proliferation and differentiation of eosinophils is promoted by IL-3, IL-5, and granulocyte-monocyte colony-stimulating factor (GM-CSF) (Figure 1). All three cytokines contribute to eosinophil development, endothelial adhesion, activation and survival, and act on progenitor cells as well as on mature cells at distal sites. IL-5 is of particular importance within the bone marrow, as IL-5 expression is restricted to eosinophils and basophils; IL-5 also stimulates the release of eosinophils from the bone marrow into the peripheral circulation. The critical role of IL-5 in regulating eosinophils in humans has been demonstrated in clinical trials of anti-IL-5 antibodies that dramatically lowered eosinophilia in blood and, less markedly, also in tissues.^{11–13}

Under baseline conditions most eosinophils traffic into the gastrointestinal tract where they normally reside within the lamina propria of all segments except the oesophagus. Baseline recruitment of gastrointestinal eosinophils is mainly regulated by the constitutive expression of eotaxin-1, a member of the eotaxin family of chemokines that are produced especially by epithelial cells, but also by mast cells, alveolar macrophages, eosinophils, airway smooth muscle and vascular endothelial cells. The eotaxins signal exclusively through the CC chemokine receptor 3 (CCR3) that is primarily expressed on eosinophils, basophils, mast cells and Th2 cells.⁴ In addition to the gastrointestinal tract, eosinophils home onto the thymus, mammary gland and uterus,

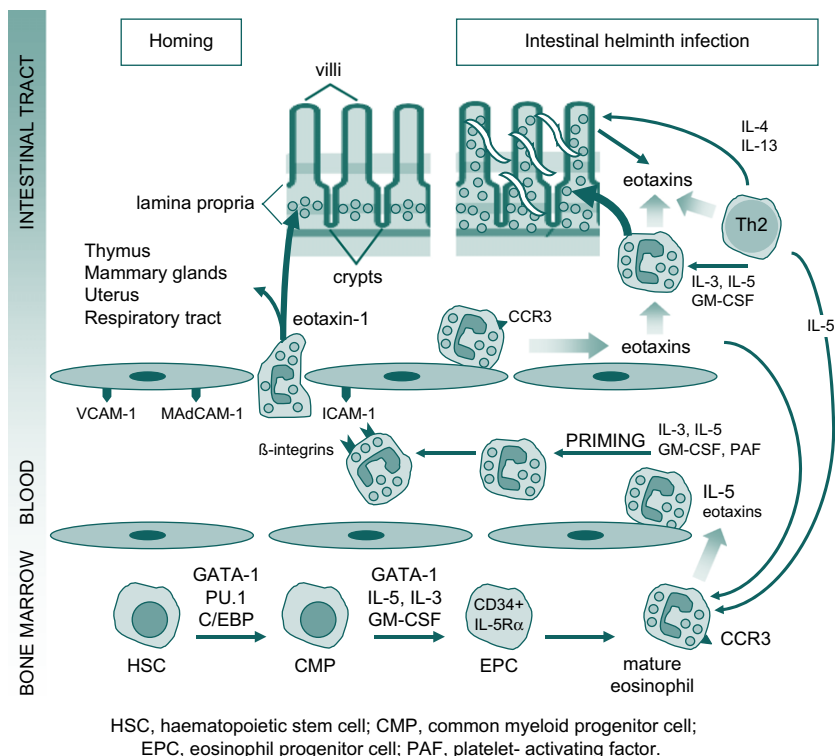


Figure 1. Schematic representation of eosinophil development, trafficking and function in the intestinal tract.

also under the regulation of eotaxin-1 (Figure 1). Eosinophils are several-hundred-fold more abundant in tissues than in blood, and eosinophil numbers are greatest in those tissues with a mucosal epithelial interface with the environment, including the gastrointestinal, respiratory, and lower genitourinary tracts.¹⁴ The life span of eosinophils is longer than that of neutrophils, and eosinophils may survive for weeks in tissues.¹⁵ As normal constituents of the mucosal immune system, particularly in the gastrointestinal tract, eosinophils exchange signals with virtually all kinds of resident cells, and are likely to have a physiological function. Besides their well-known role in adaptive immunity and inflammation, they have been implicated in innate immunity as an early and possible instrumental source of cytokines (e.g. IL-4), and recent research suggests that eosinophils are initial responders to cell death and tissue damage, participating in remodelling/repair processes as well as in immunomodulation.^{4,10,16}

EOSINOPHIL ACCUMULATION AND ACTIVATION IN INTESTINAL INFECTION

The trafficking of eosinophils into inflammatory sites of the gastrointestinal tract is dependent on the coordinated actions of numerous cytokines (in particular Th2 and endothelial cell products IL-4, IL-5, and IL-13), adhesion molecules, and chemokines (Figure 1). IL-5, produced by Th2 CD4⁺T lymphocytes as well as by other cells

(including eosinophils), provides an essential signal for the expansion and mobilisation from the bone marrow after exposure to both allergens and helminth infections.¹⁷ The critical role of IL-5 has been clearly demonstrated in animal models, including transgenic and knockout mice infected with a wide variety of intestinal and tissue helminths.^{18,19} In humans, enhanced eosinophilopoiesis requires over a week to increase blood eosinophilia. However, IL-5 may also act more rapidly to increase circulating eosinophils by mobilising a marginated pool of preformed eosinophils.²⁰ Whereas IL-5 alone is sufficient to cause helminth infection-mediated eosinophilia and eosinophil activation, a number of other cytokines (e.g. IL-4 and IL-3) and chemokines (e.g. RANTES and eotaxin) appear to be necessary for the recruitment of eosinophils to the tissues.¹⁷

Eotaxins play an important role as eosinophilic chemoattractants in directing eosinophil recruitment in tissues – especially into the lung in asthma but also into the gastrointestinal tract – following intestinal helminth infection.^{4,21} The finding that the Th2 cytokines IL-4 and IL-13 are potent inducers of eotaxins by a STAT6-dependent pathway provides an integrated mechanism to explain the eosinophilia associated with Th2 responses.²¹ In patients with asthma, eotaxin-1 and eotaxin-2 mRNA are increased, and following allergen challenge, eotaxin-1 is induced early, correlating with early eosinophil recruitment, whereas eotaxin-2 and eotaxin-3 seem to account for late and persistent eosinophilia.¹⁰

Eotaxins interact synergistically with IL-5 to recruit and prime circulating eosinophils, which increases their capacity for migration, adhesion and degranulation. Eosinophils subsequently interact with the endothelium by processes involving rolling, adhesion, and diapedesis.¹⁰ Several adhesion receptors (e.g. β -integrins) are highly expressed on partially primed eosinophils and bind to general endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) as well as to the mucosal addressin cell adhesion molecule (MAdCAM-1) expressed by vascular endothelium in the gastrointestinal tract.^{4,10} Evidence from CCR3 knock-out (KO) mice indicates that the binding of eotaxin with eosinophil CCR3 is mainly responsible for the migratory process beyond the subendothelial space.²² Eosinophil CCR3 undergoes prolonged ligand-induced receptor internalisation, and eotaxin responses also include inhibitory events such as desensitisation of the receptor.²³ In addition to eotaxins, CCR3 also recognises RANTES, macrophage inflammatory protein 1 α (MIP-1 α), and monocyte chemoattractant proteins-2, -3 and -4 (MCP-2, -3, and -4); these chemokines act via a variety of receptors and are not as selective as eotaxins for the recruitment in eosinophils. CCR3 may also deliver powerful inhibitory signals to eosinophils, depending on the ligands engaged.²⁴

In addition, eosinophils modulate the immune microenvironment by cell autonomous mechanisms that promote the recruitment and local survival of eosinophils themselves.¹⁶ They express an array of cell-surface receptors that are critical to their own survival, recruitment, and activation, including cytokine receptors (e.g. IL-5R, IL4R, IL-13R, GM-CSFR, c-kit), chemokine receptors (e.g. CCR3), complement receptors, immunoglobulin receptors (e.g. Fc ϵ RII), leukotriene receptors, and receptors for growth factors such as tumour growth factor β (TGF- β).²⁵ Eosinophils are also robust sources of the ligands that bind these receptors, suggesting local autocrine and paracrine regulatory loops. Studies in *Schistosoma mansoni* infection demonstrated the importance of the Th2 cytokines IL-4 and IL-5 in eosinophil-dependent autoregulation.²⁶

Eosinophils in the blood and tissues of helminth-infected patients and experimental animals exhibit morphological and functional changes associated with eosinophil activation in vitro. These include decreased density, up-regulation of surface activation

molecules (e.g. CD69, CD25, CD44, and HLA-DR), enhanced cellular cytotoxicity, and release of granule proteins, cytokines, leukotriens and other mediators of inflammation.¹⁷

EOSINOPHILS AND IMMUNE RESPONSE TO HELMINTH INFECTIONS

Eosinophils frequently accumulate in tissues soon after helminth invasion. This happens also in hosts immunologically naïve to the invading parasite, a fact suggesting that eosinophils play a role in innate defence against this type of pathogen.^{27,28} This rapid and non-specific eosinophilic response might be a barrier limiting mechanism active against the invasion of many tissue-dwelling helminths. Some findings, such as the capacity of Sephadex beads embolised into the lungs to elicit eosinophilia,²⁹ suggest that eosinophilia may develop not only in response to specific antigens but also to large particulate objects.

Most helminth infections stimulate Th2-like T-cell responses, including stimulation of eosinophilia and of parasite-specific as well as polyclonal IgE synthesis. Several heat- and protease-stable glycan moieties – from *Schistosoma mansoni* egg antigen (SEA) as well as from different filarial nematodes – have been found to induce Th2 stimulation. However, various unrelated glycoproteins and non-glycosylated proteins from SEA, the filaria *Dirofilaria immitis*, and from a variety of intestinal nematodes used in murine models are also able to stimulate a Th2 response.⁷ It has also been shown that eosinophils can function as antigen presenting cells (APCs), and that they can process and present various microbial antigens, including parasite antigens, to CD4⁺T cells.³⁰ In addition, eosinophils secrete an array of cytokines capable of promoting T-cell proliferation and Th1/Th2 polarisation.⁴

There is ample evidence from experimental data that Th2 immune responses are involved in immunity in many different helminth infections. In animal models, IL-3/IL-9-stimulated mast cells, IL-4R-stimulated intestinal muscle cells, and IL-13-stimulated epithelial goblet cells are each essential for resistance to different nematode infections of the gut.⁷ Probably the most effective immunity is against incoming helminth larvae, both from species which remain in the tissues or blood (such as schistosomes or filarial worms) and those which migrate onward to the intestinal tract. Here, eosinophils seem to play a major role as effector cells and, in vivo, activated eosinophils aggregate and degranulate in the local vicinity of damaged parasites.^{7,17} In vitro, cellular toxicity has been demonstrated against various helminths involving antibody-induced release, complement-induced release, or both, of toxic granule proteins and reactive oxygen intermediates by activated eosinophils.¹⁷ From several models of immunity to reinfection and challenge after vaccination with irradiation-attenuated larval vaccines, good evidence exists to argue that both eosinophils and antibodies are required.⁷

However, most data are from in-vitro experiments and animal models. In humans, the most compelling association between eosinophilia and protective immunity comes from post-treatment reinfection studies in schistosomiasis that demonstrated a direct relationship between the lack of reinfection and the level of peripheral blood eosinophils in patients from areas endemic for both *Schistosoma mansoni* and *S. haematobium*.^{31,32} There is consensus that in a number of human intestinal helminth infections, such as schistosomiasis and intestinal nematode infections, effective immunity may evolve against infective larval stages.⁷ However, efficient immunity against adult worms is usually low or nil in established infections. With few exceptions

(e.g. strongyloidiasis, capillariasis), there is no multiplication of adult worms within the human host, and infection intensity depends only on the number of incoming larvae completing their maturation successfully. Therefore, limiting reinfection and superinfection by damaging and partly destroying infectious larval stages will control parasite load and as a consequence limit morbidity and mortality of the host, which also is in favour of the parasite.⁷ Even in strongyloidiasis, where, due to continuous autoinfection, the parasite load may increase independently from renewed infection, larval development is immunologically controlled, with eosinophils being the prominent effector cells in vitro and in vivo.^{27,28} Although, this control is not able to eradicate the chronic persistent infection, it avoids life-threatening hyperinfection which may evolve in immunosuppression.³³

EOSINOPHILS AND IMMUNE PATHOLOGY IN HELMINTH INFECTIONS

Eosinophils also play a role in the pathogenesis of helminth infections. Eosinophils can cause tissue damage through a number of different mechanisms, including direct cytotoxicity, physical damage caused by tissue infiltration (space-occupying), and thromboembolic phenomena caused by eosinophil-induced hypercoagulability. However, it is the release of eosinophil granule proteins and other cytotoxic substances that has been best correlated with helminth-induced tissue damage.¹⁷ Eosinophilic cationic proteins – including major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN) – are toxic to various normal tissues and cells. Other potentially toxic inflammatory mediators that are released by activated eosinophils include leukotrienes, platelet-activating factor, reactive oxygen species, and lysosomal hydrolases. These mediators not only damage the parasites and surrounding tissues but also play a role in the perpetuation of the local inflammatory reaction (e.g. stimulation and activation of mast cells, basophils, and neutrophils) and subsequent damage to tissues and organs.^{4,10} This is evident, for example, in onchocerciasis where inflammation in sclerosing keratitis and in post-treatment dermatitis is closely related to eosinophil infiltration and deposition of eosinophil granule proteins at the sites of microfilarial degeneration.^{34,35} A primary role of eosinophils has also been demonstrated in the pathogenesis of trichinellosis, toxocariasis, loiasis, and lymphatic filariasis.¹⁷ However, the possibility that recruitment of eosinophils occurs secondarily in response to damaged or killed parasites cannot be excluded. Furthermore, eosinophils present in pathological lesions must not always be essential to their development. Liver granulomas in intestinal schistosomiasis typically contain a high percentage of activated eosinophils, a major source of Th2-associated cytokines in the granuloma milieu.³⁶ However, anti-IL-5-treated mice as well as eosinophil lineage-ablated mice infected with *Schistosoma mansoni* produce normal-sized granulomas, despite the absence of eosinophils.^{37,38}

EVASION AND MODULATION OF THE IMMUNE SYSTEM BY HELMINTH INFECTIONS

In contrast to the vigorous immune response against tissue-dwelling stages of parasitic helminths, most of these infections, when left untreated, are able to persist for years, or sometimes decades within their hosts. Helminths are masters of immune evasion and have developed an impressive variety of strategies to escape the various lines of

defence of both the innate and adaptive immune systems.⁷ Immunity might be circumvented by parasite differentiation, as most helminths present different developmental stages during infection, and the host might be repeatedly exposed to larval-, adult-, or egg-stage antigens. In addition, various stages might change tissue tropism, and adult intestinal helminths which have completed their tissue-dwelling larval migration and maturation, usually lodge in a protected niche, the lumen of the gut. Some tissue parasites are sequestered from the host's immune system; for example, trichinella larvae are encysted within the musculature, and metacestode larvae in echinococcosis or cysticercosis are separated from host immune responses by a strong, multilaminated cyst membrane. Adult schistosomes live for years within the blood and protect themselves from a highly active immune response by molecular mimicry through the absorption of host proteins to the tegument. In addition, this tegument is composed of a unique, syncytial double plasma membrane, which might be changed rapidly when required.

However, the escape of larval tissue stages from immune attack during repeated infection, or the long-term survival of filarial adult worms in blood and tissues, has remained largely unexplained. In recent years, increasing evidence has evolved for immunomodulation as an important factor contributing to survival of larval and adult stages in various helminth infections. In chronic human schistosomiasis and filariasis, antigen-specific T-cell responses are compromised, most evident as a lack of in-vitro proliferation and diminished IL-2, IL-5 and interferon γ (INF- γ) responses to antigen challenge.³⁹⁻⁴¹ The suppression therefore extends to both Th1- and Th2-type responses. It depends on the presence of parasites, and T-cell responses are restored after treatment.⁷

Recently, the significance of regulatory T cells (Treg) for the down-regulation of parasite-specific immune responses could be demonstrated in both chronic schistosomiasis and onchocerciasis.⁷ Naturally occurring Tregs arise in the thymus early during development in the process of T-cell selection, and have fundamental functions in the control of other immune cells by suppressing their functional activity to prevent autoimmunity, but also influence the immune response to allergens as well as against tumour cells and pathogens. Adaptive regulatory Tregs can develop extrathymically from conventional T helper cells, and their development in general is driven by IL-10 and TGF- β , tolerating conditions such as suboptimal antigenic stimulation, and some immunosuppressive or anti-inflammatory molecules.⁴² Tregs produce down-modulatory cytokines, IL-10 and TGF- β , which switch off inflammatory and protective immune responses and interfere with effector-T-cell activation in a contact-dependent manner (Figure 2). In a murine model of filarial infection with *Litomosoides sigmodontis*, the inhibition of Treg activity resulted in parasite clearance and increased immune responsiveness towards parasite antigens.⁷ In suppressed filarial- or schistosome-specific T effector cells from infected patients, reactivity could be restored in vitro by antibodies to IL-10 and TGF- β .⁷ Interestingly, also eosinophils may express IL-10 and TGF- β as well as indoleamine 2,3-dioxygenase (IDO), and can thereby modulate local adaptive Treg activities and prevent the polarisation of naïve Th0 lymphocytes to either the Th1 or Th2 phenotype.^{16,43} Recently, it has been proposed that eosinophils may also participate in thymocyte education, and a close temporal and spatial relationship has been demonstrated between thymic eosinophil accumulation and T-cell selection during the neonatal period.^{16,44}

In addition to Treg, helminth infections have been shown to activate alternatively activated macrophages (AAMs).^{7,45} These macrophages exhibit an activated surface marker phenotype but are diametrically opposed to 'classically activated' macrophages,

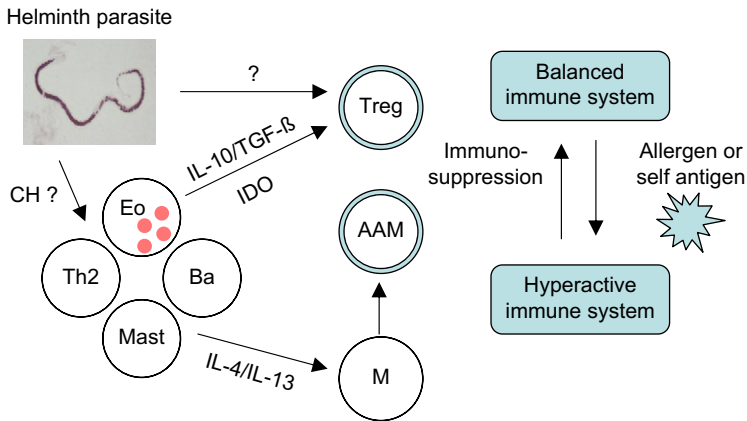


Figure 2. Immunomodulation by helminth infection and hypothetical mechanisms for suppression of immune responses against allergens and self antigens. CH, carbohydrates, chitin, or other parasitic structures; Eo, eosinophils; Ba, basophils; Mast, mast cells; Th2, T2 helper cells; Treg, regulatory T cells; M, monocytes/macrophages; AAM, alternatively activated macrophages; IL, interleukin; TGF- β , tumour growth factor β ; IDO, indoleamine 2,3-dioxygenase.

as they do not up-regulate inducible nitric oxide synthase (NOS) but instead up-regulate the cross-regulatory enzyme arginase.⁴⁶ AAMs very efficiently suppress T-cell proliferation, reduce pro-inflammatory chemokines (e.g. MIP-1 α , MIP-1 β , MIP-2), further promote the Th2 response, and mediate tissue repair and remodelling, probably by expression of arginase 1.⁴⁵ Differentiation of monocytes to AAMs depends on both IL-4 and IL-13, and STAT6.⁴⁶ Although, Th2 cells and basophils are major sources of IL-4, eosinophils show increased IL-4 expression upon helminth infection and, in addition, promote IL-4 and IL-13 secretion of CD4⁺ cells.⁴ The mechanisms of AAM-mediated T-cell suppression and anti-inflammatory action are largely unknown (Figure 2). However, AAMs in helminth infection suppress proliferation of neighbouring cells only in the context of a Th2 environment.⁷

IMMUNOMODULATION, COINFECTIONS, ALLERGIC AND AUTOIMMUNE DISORDERS

Helminth-induced immunomodulation not only favours parasite survival, it also mitigates immune pathology.⁴⁷ In addition, immunomodulation may extend to other pathogens and non-cognate antigens, with variable consequences. For example, in heavily infected onchocerciasis patients, T-cell mitogen responsiveness is compromised, as are responses to third-party antigens and common vaccines.⁷ Several experimental models have shown established helminth infections to promote parasite load and persistence of superinfections with other helminths.^{7,9} Mice infected with *Schistosoma mansoni* developed significantly higher parasitaemias when infected with *Plasmodium chabaudi*, and this was accompanied by reduced TNF α .⁴⁸ However, *P. chabaudi* is not a model for cerebral malaria, and suppression of Th1-associated TNF α production may be beneficial in other infections, as outlined in the *P. berghei* model where mice exposed to filarial infection by *Brugia pahangi* were protected from cerebral malaria.⁴⁹ A case-control study in humans also showed significantly less cerebral malaria in patients with

intestinal helminth infection.⁵⁰ Recent epidemiological studies have demonstrated a strong association between eosinophilia and progression to active tuberculosis in Ugandan adults co-infected with HIV and tuberculosis,⁵¹ which in part has been associated with intestinal schistosomiasis.⁵² However, further data are needed to assess such associations, and to investigate possible confounders in more detail and in different geographical areas and settings.

Possible associations between helminth-associated immunomodulation and allergies have received much attention during recent years. To explain the continuous rise of allergic diseases in the industrialised world the 'hygiene hypothesis' was first formulated by Strachan in 1989, with the initial postulation that the decline of viral and bacterial infections due to improved hygiene and vaccinations leads to insufficient Th1 stimulation of the immune system during early childhood, and that Th2-associated pathologies such as allergies (including asthma) become more prevalent.⁵³ However, in tropical countries with high levels of Th2-driving helminth infections, allergies are less common, and experimental evidence as well as several studies in humans have shown that helminth infections significantly protect from the development of allergies.⁵⁴ Now, helminth-induced immunomodulation provides an explanation for the prevention of allergies by strengthening the physiological roles of Treg and AAMs to inhibit immune responses against self and innocent antigens (Figure 2).^{7,55} Meanwhile the hygiene hypothesis has been extended to autoimmune disorders such as rheumatoid arthritis, Crohn's disease, or multiple sclerosis, which in fact are also significantly less common in tropical developing countries.^{8,56} Interestingly, it has been demonstrated recently that patients with Crohn's disease can be treated successfully with larvae of the pig whipworm *Trichuris suis*,⁵⁷ and that patients with multiple sclerosis have a significantly slower progression when there is concomitant helminth infection.⁵⁸ Currently, intensive research is going on to better define the molecular mechanisms of helminth immunomodulation, and identifying responsible genes and pathways may help to develop new strategies for the treatment and prevention of allergic and autoimmune disorders.

GLOBAL EPIDEMIOLOGY OF EOSINOPHILIA AND INTESTINAL INFECTION

Worldwide, helminth infections are by far the leading cause of infection-associated eosinophilia, and probably of eosinophilia of all causes. Intestinal infections account for the majority of all helminth infections, and the global burden is estimated by WHO as more than 2 billion infected people.⁵⁹ Due to behavioural aspects, partial immunity, and other factors, prevalence rates and infection intensity (parasite loads) are usually highest in children. However, relative to most other pathogens, helminths have a long life span, often measured in years or decades, and under poor socioeconomic conditions continuous reinfection often persists during adulthood. Consequently, blood eosinophilia is common in tropical developing countries, and population-based studies in rural areas have demonstrated eosinophilia in up to 50% of children and adults.⁶⁰ A recent study in Kenya revealed eosinophilia in 18.8% of adult blood donors in a rural area versus 8.5% in an urban area.⁶¹ Eosinophilia due to helminth infection is also observed more frequently in refugees and in travellers or expatriates returning from developing countries.^{6,62} Blood eosinophilia is much less common in populations residing in temperate and industrialised countries, and if present, it is mainly due to allergies and other non-infectious disorders.

CLINICAL SIGNIFICANCE OF EOSINOPHILIA IN INTESTINAL INFECTION

Blood eosinophilia usually is defined as eosinophils in excess of 500 cells/ μ L of blood.^{2,6} Increased percentages of eosinophils in the differential blood count (e.g. >7% of all leukocytes) are also used, but can be misleading due to leukopenia. Other cut-offs for blood eosinophilia have been proposed to adjust for improved sensitivity and specificity in certain epidemiological and diagnostic settings, such as 600 eosinophils/ μ L in tropical areas with a high prevalence of parasitic infections, or 450/ μ L in travellers returning from those areas.^{5,60}

The predictive value of eosinophilia for the presence of helminth infections is limited and depends largely on the epidemiological background. It is low in industrialised countries, and increases considerably in populations with a high prevalence of parasitic infections, as in developing tropical countries, or in travellers to those areas. In a population-based study in a rural area of Brazil, intestinal helminth infection was present in 86% of children and adults with eosinophilia, in contrast to 25% in those without eosinophilia.⁶⁰ A study in more than 14,000 travellers returning from developing countries showed that in 18.9% of travellers with eosinophilia a helminth infection could be detected; in travellers with hypereosinophilia (>15% of the total white blood cell count) this figure increased to 46.6%.⁶

Although, helminth infections are a common cause of eosinophilia, various studies in different populations have shown that 20–50% of patients with documented helminth infection did not have eosinophilia at the time of diagnosis.^{6,60,63,64} Therefore an evaluation of patients for the presence of helminth infections is warranted independently from eosinophilia due to other epidemiological and clinical clues.

Helminth infections can cause serious acute and chronic disease, but the majority of individuals with intestinal helminth infections are asymptomatic. Helminth infections are typically over-dispersed, with patterns of intense infections being confined to minorities within the general population.⁵⁹ Therefore, overt clinical disease and severe sequelae are especially seen in those with more severe infection. However, even moderately intense infections have been shown to significantly impair the cognitive development of children – for example in chronic trichuriasis, hookworm infection, or intestinal schistosomiasis.^{59,65,66} In highly endemic areas, multiple infections with several species of intestinal helminths and with other parasites are extremely common, especially in children, and combine to result in anaemia, hypoproteinaemia, malnutrition and immunosuppression, causing significant chronic morbidity as well as increased morbidity and mortality of intercurrent diseases such as malaria, pneumonia, or acute diarrhoea.^{59,65} In the individual patient, even light infections (as typically seen in travellers from non-endemic areas) can lead to severe complications (e.g. acute schistosomiasis, aberrant localisation of *Ascaris* in biliary or pancreatic ducts, aberrant migration of larvae to the central nervous system).

Chronic persistent eosinophilia has also been associated with endomyocardial fibrosis and peripheral neuropathy, which have both been observed significantly more commonly in some populations with a high prevalence of chronic helminth infections.^{2,67} However, in certain areas these complications are rare despite a high prevalence of chronic parasite-associated eosinophilia, and other as yet ill-defined factors seem to be important in the pathogenesis of these possible sequelae. The influence of persistent eosinophilia, of chronic helminth infection, or of both, on concurrent or secondary infections is a topic of current discussion.⁷ Several studies are under way

to further elucidate the influence of chronic eosinophilia on the progression to active tuberculosis in HIV infection and on other co-infection dynamics.⁵²

HOST FACTORS AND PATTERNS OF EOSINOPHILIA IN INTESTINAL INFECTIONS

Many host factors influence peripheral-blood eosinophil levels, including diurnal variation with a peak in the early morning when endogenous corticosteroid levels are low. Eosinophil counts are higher in the neonatal period and decline with age. Levels may be lowered by oestrogens; they also fall during pregnancy, and are especially low during delivery. Corticosteroids inhibit blood and tissue eosinophils, probably by several mechanisms, including promotion of eosinophil apoptosis.⁶⁸ Epinephrine causes a sharp decrease in peripheral eosinophils, whereas beta-blockers can block this effect and may increase eosinophil counts by 30%.² In addition, a variety of drugs can cause eosinophilia that may be associated with pathological changes and dysfunction of various tissues and organs (e.g. rash, pulmonary infiltrates, asthma, hepatitis, interstitial nephritis, myocarditis, vasculitis, eosinophilia-myalgia syndrome).

The eosinophilic response may also vary considerably according to the age at first exposure, the epidemiological background, and the frequency and timing of reinfection and superinfection. In highly endemic areas, helminth infections usually begin early during childhood, and even an exposure to helminth antigens in utero (e.g. in filarial infection of the mother) is common in some regions.⁷ Typically, eosinophilia is less frequent and less prominent in residents of those areas, whereas non-immunes, such as travellers or immigrants, often have pronounced eosinophilia following first exposure, and show more severe signs and symptoms, such as the Katayama fever syndrome in acute schistosomiasis.⁶⁹

In immunocompromised patients, helminth infection may cause high-grade eosinophilia, for example due to strongyloides hyperinfection. However, eosinophilia is often low or absent despite single or multiple helminth infection, even when the parasite load is high.¹

INTESTINAL INFECTIONS ASSOCIATED WITH EOSINOPHILIA

Helminth infections

Blood and tissue eosinophilia are common in intestinal helminth infections with tissue-invasive development stages. However, in infections with intestinal helminths, whose entire life cycle in the human host takes place in the lumen of the gut (such as the nematode parasites *Enterobius*, *Trichuris*, and *Trichostrongylus*, or most of the intestinal trematodes and cestodes), eosinophilia in the majority of patients is absent or low. In addition to 'classical' intestinal helminths, many other – primarily extraintestinal – helminths may involve the gastrointestinal tract during some stages of their development (Table 2).

Intestinal nematode infections

Infection with the pinworm *Enterobius vermicularis* is acquired by swallowing embryonated (i.e. larva-containing) eggs. The adult female worms move on the epithelial surface of the caecum and other parts of the colon, and migrate out onto the perianal skin

Table 2. Helminth infections and eosinophilia.

Disease/parasite	Main body site	Possible cause of	
		Marked eosinophilia (>3000/ μ L)	Chronic eosinophilia (>2 years)
Angiostrongyliasis, cerebral	CNS	+	
Angiostrongyliasis, abdominal	GI	+	
Anisakiasis	GI		
Ascariasis	GI, lung (larvae)	+ (early)	
Clonorchiasis/opisthorchiasis	Hepatobiliary	+	+
Capillariasis, hepatic	Hepatobiliary		
Capillariasis, intestinal	GI	+	
Coenurosis	CNS, other		
Cutaneous larva migrans	Skin, subcutaneous		
Cysticercosis	CNS, soft tissue, other		+
Dicrocoeliasis	Hepatobiliary		
Diphyllobothriasis	GI		
Dirofilariasis	Lung, subcutaneous		
Echinococcosis	Liver, lung, CNS, other		+
Echinostomiasis	GI		
Enterobiasis	GI		
Fascioliasis	Hepatobiliary	+	+
Filariasis, lymphatic	Lymphatics, blood	+	+
Gnathostomiasis	Subcutaneous, other tissue	+	+
Heterophyiasis	GI, rarely: heart, CNS		
Hookworm infection	GI, skin + lung (larvae)	+	+
Hymenolepiasis	GI		
Loiasis	Subcutaneous, eye	+	+
Mansonelliasis	Blood, skin, body cavities	+	+
Metagonimiasis	GI, rarely: heart, CNS		
Onchocerciasis	Skin, eye	+	+
Paragonimiasis	Lung, CNS, subcutaneous	+	
Schistosomiasis, intestinal	GI, mesenteric veins, liver	+	+
Schistosomiasis, urogenital	Urinary tract, vesical veins	+	+
Sparganosis	Subcutaneous		+
Strongyloidiasis	GI, lung (larvae), skin, CNS	+	
Taeniasis, saginata/solium	GI		
Trichinellosis	GI (early), muscle, heart, CNS	+	
Trichostrongyliasis	GI		
Trichuriasis	GI		
Visceral larva migrans	Liver, eye, lung, CNS, other	+	+

CNS, central nervous system; GI, gastrointestinal tract.

to deposit eggs, which may cause anal pruritus. Occasionally, when adults are causing appendicitis, or when the mucosa is damaged due to other causes, worms may be found in mucosal granulomas, and tissue and/or slight to moderate blood eosinophilia has been described in some of these patients.⁷⁰

Whipworm infection, caused by *Trichuris trichiura*, is common in children, who ingest embryonated eggs from soil or contaminated food. The anterior part of the adults is firmly lodged in the colon mucosa, causing small ulcerations surrounded by an

eosinophilic infiltration. In severe infections, not uncommon in highly endemic areas, chronic dysentery with anaemia and hypoproteinaemia may evolve, often accompanied by moderate and sometimes marked blood eosinophilia.^{6,65}

In ascariasis and hookworm (*Ancylostoma duodenale*, *Necator americanus*) infection, an initial migration through various host tissues, including the lung, is obligatory for the development of the larvae, which enter the body either through the gut (*Ascaris lumbricoides*, *A. duodenale*) or through the skin (*A. duodenale*, *N. americanus*). Depending on the number of larvae and the immune reaction of the host (including sensitisation by prior infections), the migration through the lung may cause marked eosinophilia and pneumonitis beginning 1–3 weeks after infection. In ascariasis, and less commonly in hookworm infection, this is often accompanied by migratory pulmonary infiltrates, non-productive cough, and low-grade fever (Loeffler's syndrome). Symptoms resolve when larval migration is finished (within 1–2 weeks) and the adult worms have reached the gut. In ascariasis, eosinophilia usually subsides completely within several weeks, whereas in hookworm infection low to moderate eosinophilia often persists. Diagnosis is complicated by the fact that eggs may be not apparent in the stool for many weeks, and in hookworm infection sometimes for months. Consequently, finding ascariasis eggs in stool of patients with eosinophilia should rather prompt a search for other causes of eosinophilia.^{2,5}

In strongyloidiasis, there is also an initial tissue migration of larvae after penetration of the skin, and the passage through the lung can cause pulmonary symptoms, such as in ascariasis or hookworm infection. However, larvae of *Strongyloides stercoralis* hatch from the egg directly after being deposited by the adult worms in the small bowel, and are able to mature within the host into infective third-stage (filariform) larvae which may reinvade the mucosa of the colon or penetrate the skin, mostly in the perianal region. This ongoing reinfection (i.e. autoinfection) enables the parasite to persist for decades. Strongyloidiasis may present with intermittent creeping eruption (larva currens), urticaria, and gastrointestinal symptoms, but is often asymptomatic. More importantly, in immunocompromised hosts disseminated, potentially fatal disease (hyperinfection syndrome) may develop, presenting as haemorrhagic enterocolitis, pneumonia, and sometimes also with CNS invasion. Treatment with corticosteroids, haematological malignancies, solid organ transplantation, and infection with HTLV-I are known risk factors, whereas hyperinfective strongyloidiasis is not a common opportunistic infection in patients with AIDS.^{33,71} Eosinophilia is frequent and can be extensive, even in asymptomatic cases, but may be absent in hyperinfection.³³ In some groups, such as travellers and immigrants, strongyloidiasis has been found as a frequent cause of unexplained eosinophilia.^{6,62,63} The diagnostic sensitivity of stool investigations is limited, since concentration of strongyloides larvae by usual methods is not very effective, and larvae may be excreted only sporadically and in small numbers.¹ Therefore, more efficient methods (e.g. Baermann concentration, coproculture) and repeated investigations may be necessary. In addition, serology (enzyme-linked immunosorbent assay, ELISA) is a useful screening test, but sensitivity and specificity are limited, and antibodies may be undetectable in immunodeficient patients.³³

Intestinal capillariasis is a rare but potentially life-threatening human infection caused by the ingestion of *Capillaria philippinensis* larvae with raw or undercooked fish. After maturing to adults within the gut, eggs are produced from which in turn new larvae may hatch within the bowel, and mature to new adults. Similarly to strongyloidiasis, the ongoing endogenous autoinfection can lead to very high parasite loads associated with severe diarrhoea and malabsorption. Most patients show peripheral eosinophilia, which may be extreme in some patients.⁷²

Occasionally the canine hookworm *Ancylostoma caninum* has been found as a cause of eosinophilic enteritis which manifests with abdominal pain, peripheral eosinophilia and focal or diffuse eosinophilic inflammation within the gastrointestinal tract. This is due to a hypersensitivity reaction to antigens from the zoonotic hookworm larvae which cannot complete their tissue migration in man.⁷³

Intestinal cestode infections

Infections with intestinal tapeworms whose entire life in human hosts is in the lumen of the gut, such as the beef and fish tapeworm, *Taenia saginata* and *Diphyllobothrium latum*, cause no, or only a few, intestinal symptoms, despite impressive size and longevity of the adult worms. They are usually not associated with eosinophilia. The pork tapeworm *Taenia solium*, however, may affect humans not only as definite host, with the adult tapeworm in the gut, but also as intermediate host, with the cystic metacestode larvae in tissues (cysticercosis). In disseminated cysticercosis, the cysts are mostly in the musculature, and mild to moderate eosinophilia is frequently present, in contrast to neurocysticercosis where the parasitic cysts are usually well sequestered from the host's immune system.

In infections caused by the dwarf tapeworm *Hymenolepis nana*, both adults and metacestodes (cysticercoids) develop in the human gut, resulting in endogenous auto-infection. This may lead to high parasite loads, especially in children, often accompanied by abdominal pain, diarrhoea and moderate eosinophilia. Due to the development of immunity, most infections subside spontaneously during childhood or adolescence.

Intestinal trematode infections

Although the large intestinal fluke *Fasciolopsis buski* has no tissue-invasive development in the human host, a high parasite load may be associated with eosinophilia and leukocytosis. The adult flukes attach with their suckers to the gut mucosa and cause chronic inflammation with small ulcerations and increased mucus secretion, leading to malabsorption and protein-losing enteropathy in severe infection. Other intestinal flukes usually do not cause eosinophilia. However, some small intestinal flukes, such as *Heterophyes heterophyes* and *Metagonimus yokogawai*, may occasionally lodge in the intestinal wall, and this rarely can lead to haematogenous spread of the minute eggs to extraintestinal sites (e.g. heart, CNS), causing embolic eosinophilic granulomas and blood eosinophilia.

Intestinal schistosomiasis

Blood eosinophilia is most pronounced during acute schistosomiasis, when considerable numbers of cercarial larvae have entered the body through the skin, and complete larval migration through lung and liver before reaching the final destination of adult worm pairs in the mesenteric veins. The acute stage (Katayama syndrome) shows an incubation period of 2–12 weeks, usually 4–6 weeks, and is characterised by fever, anorexia, myalgia, dry cough, abdominal pain, nausea, and diarrhoea. In more severe infections there is often hypereosinophilia and leukocytosis; occasionally severe complications such as myocarditis or CNS involvement (transverse myelitis, coma, convulsions) occur. Katayama syndrome is uncommon in residents of endemic areas and is seen primarily in non-immune travellers or immigrants after single or multiple

exposures within a short time to fresh waters contaminated with cercariae of *Schistosoma mansoni* or *S. japonicum*. Acute schistosomiasis is uncommon in infections with other pathogens causing intestinal schistosomiasis, i.e., *S. intercalatum* and *S. mekongi*, and in urogenital schistosomiasis (*S. haematobium*).

Although the acute symptoms resolve spontaneously with 1–4 months, eosinophilia may persist for years. In the chronic phase of intestinal schistosomiasis, pathology and clinical presentation predominantly depend on the deposition of eggs in the intestinal wall and other organs (liver, lung) which cause a surrounding eosinophilic granuloma associated with chronic inflammation, tissue damage, and fibrosis (Figure 3). However, approximately half of the patients with chronic intestinal or urogenital schistosomiasis do not present with peripheral eosinophilia.

The gold standard for the diagnosis of intestinal schistosomiasis remains the detection of the characteristic eggs in stool or in biopsies from the colon or rectosigmoid. The sensitivity of stool investigations is limited, even when effective concentration methods are used repeatedly, and in as many as 50% of patients with chronic schistosomiasis and in most patients with acute schistosomiasis no eggs will be detected.^{64,69} Serology is much more sensitive, especially during the prepatent period of 1–3 months before egg excretion may start in a newly infected patient.⁶⁹

Larval helminth infections that may cause intestinal symptoms

In trichinellosis, hypereosinophilia often accompanied by leukocytosis is common during the acute haematogenous dissemination phase of the infection. During the first week, larvae of *Trichinella spiralis* (or other *Trichinella* species), ingested with contaminated meat, mature to adult worms in the small bowel (initial intestinal phase), and diarrhoea may occur in some patients. In 1–3 weeks after infection, larval production starts, and larvae invading the gut mucosa cause eosinophilic inflammation of the intestinal wall. Peripheral eosinophilia increases rapidly with haematogenous spread and larval invasion of the skeletal musculature. Myalgia with raised CK, fever, conjunctivitis, facial and periorbital oedema are typical clinical features during this stage of the

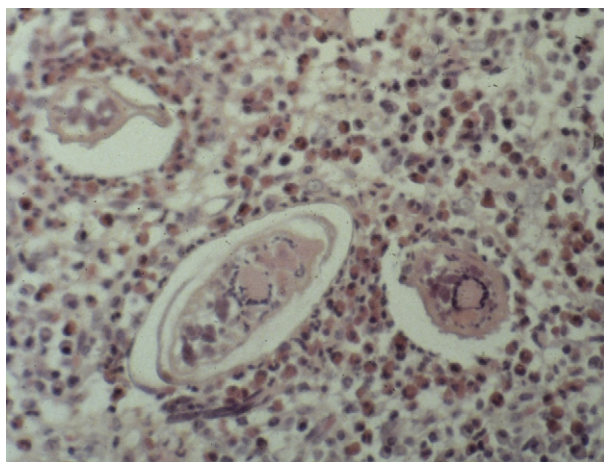


Figure 3. Eosinophils in the granulomas surrounding *Schistosoma mansoni* eggs in the gut wall.

disease. In severe infections, peripheral eosinophil counts may reach extreme values of $>10,000/\mu\text{L}$.² Around migrating larvae there is an intensive inflammatory reaction with oedema and eosinophilic and neutrophilic infiltration. The diagnosis can be made by detection of larvae in muscle biopsies or sometimes in the blood. However, during the early stage of the infections as well as in light infections, serology may provide the only clue to diagnostic confirmation. During the initial intestinal phase, adults and/or larvae are only rarely detected in the stool.

Several infections by larval stages of zoonotic nematodes that do not mature to adult worms in humans may cause eosinophilia (Table 2). Anisakiasis has been reported particularly from Japan and some other countries where consumption of raw or marinated fish is common. Larvae of the herring worm *Anisakis simplex* or the codworm *Pseudoterranova decipiens* penetrate the gastric or small-bowel mucosa and may cause local inflammation with eosinophilic and neutrophilic infiltration associated with acute gastritis or enteritis, or with a more chronic tumour-like inflammation of the intestinal wall leading to intermittent diarrhoea, abdominal pain, and obstruction. Peripheral eosinophilia is not present in all cases. Rarely, larvae can migrate to other organs such as peritoneum, liver, pancreas or lung. Mucosal larvae are sometimes detected during endoscopy, and larvae in tissues may be seen in biopsies. Serology is of limited diagnostic value. Endoscopic or surgical removal of larvae may be required. Allergic reactions (urticaria, asthma) due to thermostable antigens of anisakis larvae have been reported, which have been severe in some cases (anaphylaxis) and which may be associated with eosinophilia, a positive prick test and specific IgE antibodies to anisakis antigens. This has been observed independently from infection after consumption of thoroughly cooked fish and seafood containing anisakis larvae, and after eating meat of chicken fed with fishmeal.⁷⁴

Abdominal angiostrongyliasis, an infection caused by the rat nematode *Angiostrongylus costaricensis*, predominantly occurs in parts of Central and South America. The infective larvae are ingested with contaminated food or water, migrate to mesenteric lymph nodes, and mature to adults which lodge in mesenteric arteries. Eosinophilic granulomas of the intestinal wall and arteritis with thrombosis may cause eosinophilic enteritis and acute abdominal symptoms often mimicking appendicitis. Eosinophilic leukocytosis is common,⁷⁵ and, together with the clinical picture, often is the only clue to diagnosis which may be further confirmed by serology. Although adult worms sometimes reach sexual maturity in man, eggs or larvae are not excreted in the stool, but may occasionally be found within eosinophilic granulomas in intestinal biopsies.

Intestinal symptoms may also be observed in visceral larva migrans (toxocariasis) due to *Toxocara canis* or, less commonly, to other zoonotic ascarids. Infections occur worldwide and are most common in young children who ingest embryonated eggs in soil contaminated with faeces of dogs or other definite hosts. The larvae are released in the intestine, migrate through the bowel wall and spread haematogenously to the liver, lungs, CNS and other organs where they cause eosinophilic granulomas. Infection may be subclinical or may result in fever, rash, respiratory symptoms, ocular involvement, hepatomegaly, adenopathy, or neurological disturbances. Eosinophilia is common and may persist for months or years. Since detection of larvae in tissue biopsies is rare, diagnosis is usually confirmed by serology. However, sensitivity and specificity of available tests are limited, and it may be difficult to distinguish between past and current infection.⁷⁶

Human gnathostomiasis, most frequently caused by *Gnathostoma spinigerum*, occurs predominantly in Southeast Asia and is acquired by eating raw or undercooked fish, poultry or pork. Third-stage larvae, penetrating the gut, cannot complete their

development in humans, but may cause a subcutaneous or visceral larva migrans syndrome lasting for weeks to months before larvae spontaneously die off. Typically, intermittent subcutaneous migratory swellings do occur, often accompanied by intensive pruritus and pronounced oedema. However, migration of larvae to ocular, neural or visceral tissues is also possible and may lead to serious complications. Migration of larvae to the intestinal wall, causing abdominal pain, has been described in some cases. Blood eosinophilia is common and often pronounced.⁷⁷ Since the detection of larvae from tissue specimens is difficult, diagnosis often has to rely on the clinical picture and confirmation by serology.

Helminth infections of the liver and the lung

Several helminth parasites residing in the liver and/or biliary tree (Table 2) may cause intestinal symptoms. Fascioliasis can manifest as acute or recurrent cholangitis or cholecystitis. The infectious metacercarial larvae of the large liver flukes *Fasciola hepatica* or *F. gigantica* usually encyst on water plants, and infection is typically acquired by consumption of raw water cress. The larvae penetrate the bowel and the capsule of the liver and migrate through liver parenchyma, causing local necrosis and eosinophilic inflammation, before they enter the bile ducts where they mature to adult flukes; these produce eggs that are released into the bile and passed in the faeces. Peripheral eosinophilia is often pronounced during the acute migration phase, and may wax and wane when infection becomes chronic.

Infections with small liver flukes (*Clonorchis/Opisthorchis* species) are endemic in eastern and southeastern Asia. They are acquired by ingestion of raw or undercooked fish harbouring infectious metacercariae, and usually have a chronic course with recurrent cholangitis and an increased incidence of cholangiocarcinoma. Peripheral eosinophilia is usually mild and may be absent during chronic infection.² Obstruction of the biliary system may also be caused by echinococcal cysts or aberrant migration of an adult ascaris entering the bile duct and causing acute obstruction, pancreatitis, or liver abscess.

Intestinal symptoms may also occur in paragonimiasis, an infection caused by the lung fluke *Paragonimus westermani* (and other *Paragonimus* species). The metacercarial larvae are ingested with raw freshwater crayfish or crabs, excyst in the duodenum, penetrate the gastrointestinal wall, migrate within the peritoneal cavity, then penetrate the diaphragm to migrate and mature within the pulmonary parenchyma. During the migration phase, fever and intestinal symptoms such as abdominal pain and diarrhoea are common. These symptoms disappear after a few days to some weeks, and during chronic infection usually pulmonary symptoms prevail. Occasionally, there is an aberrant larval migration and flukes may lodge at extrapulmonary sites such as the abdominal wall, diaphragm, peritoneum, pleura, liver, intestinal wall, heart, musculature, or brain. Eosinophilia during the migration phase is often high-grade, and may wax and wane during chronic infection.⁷⁸ Diagnosis by detection of eggs in stool, sputum, or tissues can be difficult, and serology may be helpful, especially during the acute phase when egg production has not yet begun (Table 2).

Other infections

Intestinal protozoal infections, including giardiasis and amoebiasis, do not cause eosinophilia. The only exception is the intestinal coccidian parasite *Isospora belli*, which

causes diarrhoea and malabsorption. Mild to moderate blood eosinophilia has been reported in up to 50% of immunocompetent patients.⁷⁹ Immunocompromised patients, such as those with AIDS, often develop severe and chronic isosporiasis. However, eosinophilia seems to be less frequent. Other protozoal infections in which eosinophilia has been described in a few reports include intestinal infection with *Dientamoeba fragilis*, acute symptomatic eosinophilic myositis in association with the coccidian parasite *Sarcocystis*, and toxoplasmosis.^{2,5,80}

Intestinal infections by agents other than helminths and isospora are usually not associated with eosinophilia. However, there are some extraintestinal or systemic infections that may be associated with eosinophilia (Table 1). During longitudinal cohort studies, blood eosinophilia has been found to occur significantly more commonly in patients with HIV infection.^{2,81} No single consistent cause has been identified, and eosinophilia in HIV-infected patients may be due to allergic drug reactions, adrenal insufficiency caused by infection with cytomegalovirus (CMV) or other agents, opportunistic infections such as coccidioidomycosis or strongyloidiasis, or the relative preservation of the eosinophil cell line while other cell lines decline with decreasing CD4⁺ count.² However, in advancing HIV infection there is a shift to a Th2 type of response, and increased production of IL-4 and/or IL-5 has been demonstrated in some patients.⁸¹ In highly endemic areas of HIV/AIDS in the developing world, helminth coinfections are common, and may also cause eosinophilia and a shift towards a Th2 response.

EVALUATION OF PATIENTS WITH EOSINOPHILIA AND INTESTINAL INFECTION

The evaluation of patients with blood and/or tissue eosinophilia and suspected intestinal infection (Figure 4) is directed by the patient's epidemiological background, history, clinical signs and symptoms, and the results of additional investigations.

Obviously, the probability of intestinal infections as a cause of eosinophilia is much higher in patients living in areas with a high prevalence of parasitic infections, as in developing tropical countries, or in travellers returning from those areas. Nevertheless, even in industrialised countries a parasitic infection should be excluded in patients with eosinophilia of unknown origin. Depending on the stage and severity of intestinal parasitic infection, intestinal symptoms are absent in a considerable number of patients, and systemic or extraintestinal symptoms may prevail in others. Even in entirely asymptomatic individuals a diagnostic work-up may be warranted to identify treatable diseases that could cause future problems.

The history should include targeted questions of possible exposures (Table 3) and a detailed travel history. The anamnesis should also address pre-existent medical problems that may be associated with eosinophilia (e.g. asthma, atopic disorders), as well as a detailed drug history, including over-the-counter medications, vitamins and dietary supplements, and drugs or other agents known to be associated with eosinophilia should be discontinued if possible.

Knowledge of the geographical distribution of various parasitic diseases is essential, and several important tropical helminth infections – such as schistosomiasis, filarial infections, or clonorchiasis/opisthorchiasis – are confined to distinct endemic areas.

Taking account of the characteristic time intervals between exposure and onset of symptoms (i.e. incubation period) or the beginning of the presence of diagnostic forms of parasites in stool or other diagnostic material (i.e. patency period) is essential to guide diagnostic procedures.

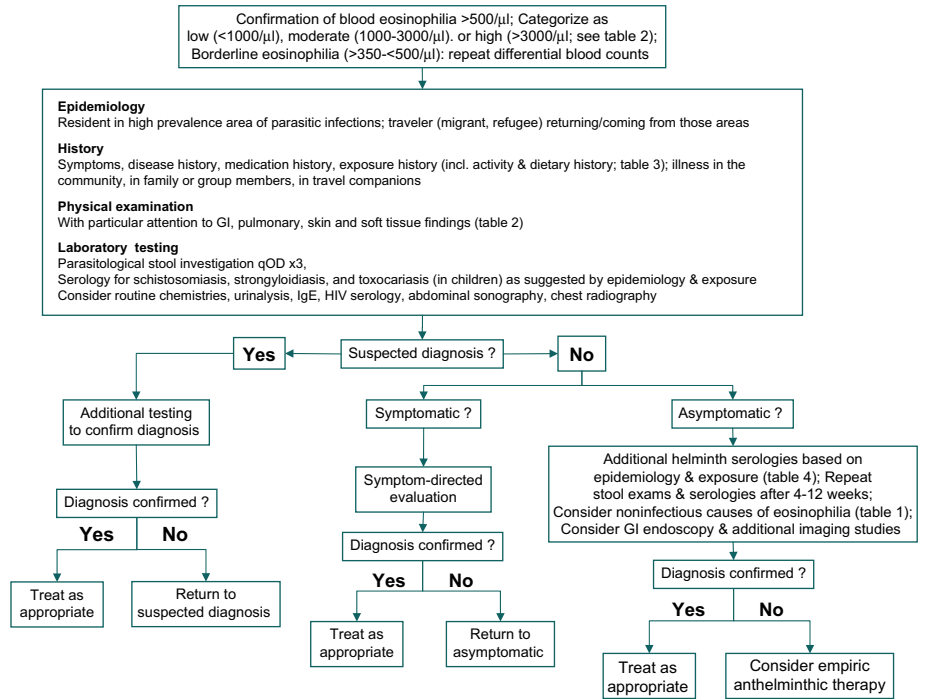


Figure 4. Evaluation of patients with eosinophilia and suspected intestinal infection. Modified from Klion (2003), *Travel Medicine*. In Keystone J et al. (ed.) Baltimore: Elsevier, pp. 517–525) with permission.

Careful history and physical examination are essential first steps in directing the evaluation (Figure 4). However, clinical signs and symptoms can be misleading as a means of suspicion of intestinal infection in patients with eosinophilia. Some intestinal helminths have a distinct migratory phase during their larval development and may cause pulmonary and systemic symptoms, as in ascariasis, hookworm infection, or acute schistosomiasis. Even if migration is terminated and adult worms lodge in the gut, intestinal symptoms may be absent, and some patients may present with general

Table 3. Specific exposures and helminthic infections.

Exposure	Helminth infection
Dietary:	
Raw vegetables and salads	Ascariasis, trichuriasis, fascioliasis, fasciolopsiasis
Raw or undercooked meat	Taeniasis, trichinellosis
Raw or undercooked fish	Anisakiasis, fish tapeworm, clonorchiasis/opisthorchiasis
Raw or undercooked snails	Small intestinal trematodes
Freshwater contact	Schistosomiasis
Skin contact with soil (walking barefoot, occupational, military)	Hookworm infection, strongyloidiasis

symptoms or those related to organs other than the gut. For example, in hookworm infection intestinal symptoms may be completely absent despite the development of severe anaemia due to continuous blood loss from blood-sucking adults in the small bowel and bleeding from mucosal ulcerations at their attachment sites.⁵⁹

Intestinal symptoms such as diarrhoea or abdominal pain may result from several mechanism, including e.g. attachment to or penetration of the gut mucosa by larvae or adult helminths, causing irritation, inflammation, and ulceration; migration through the wall or to other adjacent sites (such as biliary or pancreatic ducts); deposition of eggs throughout the intestinal wall (e.g. in intestinal schistosomiasis), causing granulomas and chronic inflammation; intraluminal obstruction by a bolus of worms; and entry into the appendix.²

SPECTRUM AND TIMING OF TESTS

Eosinophilia should be confirmed by an absolute eosinophil count, and previous eosinophil counts, if available, should be considered. The pattern of eosinophilia in helminth infection may differ considerably according to the type of parasite and the stage of infection. High-grade eosinophilia tends to be associated with tissue invasion and is seen in a relatively limited number of helminthiases (Table 2). In intestinal helminth infections with an initial tissue-invasive stage (e.g. ascariasis, hookworm infection, strongyloidiasis, schistosomiasis, trichinellosis) there may be marked eosinophilia during migration of larvae through various host tissues approximately 1–6 weeks after infection. The extent of eosinophilia depends on the number of larvae and the immune reaction of the host, and it usually declines during the chronic stage of the infection. However, chronic persistent eosinophilia does occur in certain infections (Table 2).

If history and physical examination do not point to a specific diagnosis, at least three stool specimens from different days should be examined using sensitive concentration methods (i.e. formalin-ether or sodium acetate-formalin concentration). However, sensitivity of routine stool examinations is low for strongyloidiasis and intestinal schistosomiasis. Tissue parasitoses – including filarial infections, trichinellosis, or infection by larval nematodes (e.g. toxocariasis, anisakiasis, angistrongyliasis) – will also be missed. Therefore, serological testing for the most common helminth infections such as schistosomiasis, strongyloidiasis, filariasis, and toxocariasis (in children) is recommended as suggested by epidemiological background and exposure history (Table 4). However, many serological tests for helminth infections are poorly standardised, have limited sensitivity and specificity, and cross-reactions with related parasites can cause confusion.

In addition, routine chemistries – including liver enzymes, urinalysis, IgE, HIV serology, chest radiography, and abdominal sonography – may be helpful. More specific helminth serologies (Table 4) and other diagnostic procedures such as further imaging studies, gastrointestinal endoscopy, biopsies and additional microbiological investigations should be guided by the patient's history, clinical findings, and the results of additional investigations (Figure 4).

Because of the long prepatent period in some helminth infections, eosinophilia may occur at a time when parasitological diagnosis is difficult or even impossible to obtain. Therefore, stool investigations and other parasitological procedures may have to be repeated (e.g. after 4–8 weeks in most intestinal helminthiases), sometimes several times and after extended periods of time (e.g. in filarial infections after more than

Table 4. Serological testing in helminth infections.

Infection	Tests
Angiostrongyliasis	Antibody (ELISA, IB) ^a
Anisakiasis	Antibody (ELISA) ^a
Clonorchiasis/opisthorchiasis	Antibody (ELISA and other)
Cysticercosis	Antibody (ELISA, IB), antigen
Echinococcosis	Antibody (ELISA and other)
Filariasis	Antibody, antigen
Gnathostomiasis	Antibody (ELISA, IB) ^a
Onchocerciasis	Antibody, antigen
Paragonimiasis	Antibody (ELISA and other)
Schistosomiasis	Antibody (ELISA and other), antigen
Strongyloidiasis	Antibody (ELISA and other)
Toxocariasis	Antibody (ELISA and other) ^a
Trichinellosis	Antibody (ELISA and other), antigen

ELISA, enzyme-linked immunosorbent assay; IB, immunoblot test.
^a May be useful (limited evaluation).

12 months). Also serology may be negative early in infection, and consequently may need to be repeated (usually after 1–4 weeks).

UNDIAGNOSED EOSINOPHILIA AND PRESUMPTIVE TREATMENT

Despite extensive evaluation, up to 50% of patients with blood eosinophilia remain undiagnosed.^{5,6} Many processes, as outlined in Table 1, may need to be considered. Drug hypersensitivity reactions are common and should always be taken into account. In patients with persistent eosinophilia, a comprehensive evaluation for non-infectious aetiologies of eosinophilia is warranted, including neoplasias (e.g. lymphomas, myeloproliferative disorders), connective tissue disorders and primary hypereosinophilic disorders.

In highly endemic areas of helminth infections, or in travellers returning from those areas, empirical treatment with mebendazole, albendazole, or ivermectin may be considered. In asymptomatic travellers, however, eosinophilia resolves in most cases within 3–6 months, with or without anthelmintic treatment.²

PERSPECTIVE

Traditionally, eosinophils have been regarded as effector cells involved in host protection from parasitic helminths, and, more recently, also as part of an unwanted Th2 immune response associated with allergic disorders, including asthma. However, recent studies now suggest that eosinophils are essential components in the homeostasis of the immune system, including inflammatory responses and tissue damage as well as tissue remodelling, repair, and – more importantly – immunoregulation. Eosinophils seem to play a significant role in the immunomodulation seen in chronic helminth infections which has been associated with protection from allergies and autoimmune disorders. Further elucidation of these mechanisms will improve our understanding of helminth-induced immunoregulation and eosinophil functions, and may contribute to

developing new strategies to treat and prevent allergic and autoimmune disorders. Eventually, we could learn from parasites that have managed to escape the human immune system for millions of years.

Practice points

- helminth infections are main causes of eosinophilia during intestinal infection
- the predictive value of eosinophilia for the presence of helminth infection depends largely on the epidemiological background (e.g. inhabitants, migrants, and travellers from developing countries)
- accurate exposure history and knowledge of the geographical distribution of helminth infections are crucial to the evaluation of patients with eosinophilia that may be due to intestinal infection

Research agenda

- epidemiological and clinical studies are necessary to define the interaction between helminth infections, allergic and autoimmune disorders, and major infectious diseases such as HIV/AIDS, tuberculosis and malaria
- the molecular mechanisms of immunomodulation caused by helminth infections need to be elucidated
- understanding helminth-mediated immunomodulation may provide important clues to developing new strategies for treatment and prevention of allergic and autoimmune disorders

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