Investigating eosinophilia in patients returned from the tropics

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In patients who have returned from the tropics, eosinophilia usually signifies infection with worms. This paper gives an approach to investigating these patients systematically. The key element is a good travel history leading to targeted investigations.

With travel to exotic destinations increasing, infection acquired in the tropics is likely to follow the same pattern. Two of the most common presentations of tropical infections are those with fever (Felton and Bryceson, 1996) and eosinophilia. In the returned traveller, eosinophilia usually indicates worm infection. Most of these will be asymptomatic and self-limiting, but worm infections acquired in the tropics can remain latent for decades (schistosomiasis, onchoceriasis) or even a lifetime (strongyloides) if untreated.

Worm infections can cause serious pathology, with varied presentations such as fits (Roman et al, 2000), acute tetraplegia (Anonymous, 1996), bowel obstruction (Wasadikar and Kulkarni, 1997), blindness (Addis, 1998), septicaemia (Lessnau et al, 1993), limb oedema (Waddell, 1999), cancer (Mastafa et al, 1999) and death (Eye et al, 1997). Worm infections are common: in Africa and Asia, the majority of children have worms (Brooker et al, 1999). In asymptomatic travellers returned from the tropics 13% may have evidence of worm infection (Carroll et al, 1993). Often eosinophilia is the only clue that an infection is present, and it should be investigated systematically.

PHYSIOLOGY

Eosinophils are one of a host of cells produced in bone marrow and involved in the immune response to antigenic stimuli (Rothenberg, 1997). Normally, eosinophils account for between 1–3% of peripheral leucocytes and eosinophilia can be considered when absolute values exceed 0.5 x 10^9/l. They play an important role in the engulfment of antigen–antibody complexes and release of peptides that can damage parasitic helminths, although their importance in fighting helminthic infections is controversial (Meeusen and Balii, 2000).

CAUSES OF EOSINOPHILIA

In a traveller, eosinophilia is most commonly caused by helminth infection. Any patient presenting with an eosinophilia should, however, first be assessed for the possibility of a non-infectious cause of eosinophilia, since these are as likely as in those who have not travelled. The most important non-infectious causes are listed in *Table 1*, and a few of the (very long) list of rare non-infectious causes in *Table 2*. Often a careful history and examination suffices to rule out a non-infectious aetiology for eosinophilia. Eosinophilia associated with non-infectious causes is usually mild. Exceptions include drug reactions, blistering skin diseases, lymphoma and vasculitides; in such cases, the eosinophil count may rise to above 5.0x 10^9/l.

TABLE 1.
Important non-infectious causes of eosinophilia

Allergic disorders	Asthma
	Eczema
	All drug reactions
	Allergic bronchopulmonary aspergillosis
Systemic disorders	Vasculitis (especially polyarteritis nodosa)
	Inflammatory bowel disease
	Blistering skin disorders
Malignancy	All malignancies, but especially lymphoma, leukaemia and colorectal carcinoma

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INFECTIOUS CAUSES OF EOSINOPHILIA

Helminthic parasite infection is the most common cause of eosinophilia in the traveller returning from the developing world. The most common group of worms are those that live within the lumen of the host's gut and are transmitted faeco-orally; these are outlined in *Table 3*. All the common gut-lumen worms have a worldwide distribution, and in many tropical countries the majority of children and a large minority of adults will be carrying worms in the gut. For gut worms, simple stool microscopy is usually sufficient for diagnosis (see below).

TABLE 2.
Examples of rarer non-infectious causes of eosinophilia

Addison's disease
Cholesterol emboli
Wiskott–Aldrich syndrome
Heavy metal poisoning
Bacterial endocarditis
Eosinophilic endomyocardial disease
Churg–Strauss disease
Idiopathic hypereosinophilia syndrome

TABLE 3.
Worms that live in the gut lumen

Name	Common name	Transmission	Distribution
Ascariasis lumbricoides	Roundworm	Faeco-oral	Worldwide
Ancylostoma duodenale	Hookworm	Cutaneous	Worldwide
Trichuris trichiura	Whipworm	Faeco-oral	Worldwide
Cestodes	Tapeworm	Faeco-oral	Worldwide
Strongyloides stercoralis	Strongyloides	Cutaneous	Worldwide
Enterobius vermicularis	Threadworm, pinworm	Faeco-oral	Worldwide

TABLE 4.
Common worms that live in tissues outside the gut

Tissue	Worm or fluke	Geography
Liver	*Schistosoma mansoni*	Africa (common), South America (rare)
Liver	*Schistosoma japonicum*	East Asia
Liver	Liver flukes (various)	Worldwide, especially East Asia
Blood/lymph	*Wuchereria bancrofti*	Africa, Asia
Blood/lymph	*Brugia malayi*	Asia
Blood	Loa loa	West Africa
Bladder	*Schistosoma haematobium*	Africa
Skin	*Onchocerca volvulus*	West Africa

When trying to identify worms that live outside the gut, a detailed geographical history is essential. The more common ones presenting in travellers and immigrants are outlined in *Table 4*. Most have clear-cut geographical boundaries, and a patient with unexplained eosinophilia who has travelled or lived in West Africa will have a completely different set of possible infections from one from Southern Africa or South-East Asia.

Tests for tissue worms have to be directed specifically at identifying the worm you are looking for; if you ask the wrong question, you will get the wrong answer. This is important because many patients have several different worm species simultaneously, and it is tempting to stop looking once you find one or two. However, infections with half a dozen or more separate species are not uncommon. A good travel history allows the physician to ask for all the relevant symptoms and tests and to avoid unnecessary investigations, which are often difficult and expensive to obtain even in large teaching hospitals.

CLINICAL PRESENTATION

History

In investigating a patient with eosinophilia, a good geographical history cannot be overstressed. Occasionally, patients will describe symptoms that are pathognomonic of a particular worm and diagnosis can be made on history alone. Common examples are:

1. Tapeworm (worm seen or felt on defecation, or proglottid wriggling out through anus)
2. Ascariasis (worm seen after defecation)
3. Loa loa (worm crossing the eye)
4. Cutaneous larva migrans (worm seen moving slowly in the skin).

Other symptoms may be indicative in the right clinical context, although there is a wide differential. These include:

1. Itch (onchocerciasis)
2. Haematuria (*Schistosoma haematobium*)
3. Limb oedema (filariasis)

However, most patients will have either mild symptoms or no symptoms at all (Whitty et al, 2000).

Physical examination

This is usually unrewarding (Whitty et al, 2000), with the exception of cutaneous larva migrans and the now rare Guinea worm.

Investigations

Most worms are diagnosed by investigations but these have to be guided by the geographical his-

tory. A broad division of which species to consider from different locations is given in *Table 5*.

All patients require a concentrated stool microscopy for ova and parasites, since the gut-lumen worms are found all over the world. Three stools are adequate for identifying most clinically relevant gut infections except *Strongyloides stercoralis*. This important pathogen (see below) can often be missed in light infections; if it is suspected, specific tests are required (Sato et al, 1995). For most other worm, species-specific tests are needed. Since most of these are only available from specialist laboratories, it is advisable to telephone these laboratories first in advance. In rough order of importance:

Schistosomiasis: This should be looked for microscopically in urine (*Schist. haematobium*) and stool (*Schist. mansoni*, *Schist. japonicum*, *Schist. intercalatum*). There is a sensitive and specific serological test that works for all species (Tosswell and Ridley, 1986). Serology should also be sent, but only becomes reliable if taken 3 or more months after last exposure.

Strongyloides: In addition to three stools, a hairy-string test can be used. This primitive but effective test involves swallowing a hairy string in a capsule (keeping one end attached to the mouth) and pulling it up the next day and examining it microscopically for *Strongyloides stercoralis*. *Strongyloides* charcoal culture of fresh stool increases yield. There is also a serological test that is fairly sensitive and specific, and useful as a screening test.

Filariasis: There is a generic serological test, but it cannot be relied on in isolation. Loa loa needs to be looked for by microscopy of filtered citrated blood taken at midday, as the microfilaria peak at that time to coincide with peak biting time of the vector. For exactly the same reasons, most strains of *Wuchereria bancrofti* and *Brugei malayi* (the most common causes of lymphatic filariasis) need to be looked for by microscopy of filtered blood (20 ml of citrated blood) taken at midnight. Sensitivity will be much lower in blood samples taken at the wrong time, as the microfilariae disappear from the blood and hide in the lungs where they are less susceptible to immune destruction at these times.

Onchocerciasis: Heavy infections can be diagnosed by skin snips. These are taken from six sites and placed in saline, and the microfilaria will then come out and can be seen microscopically. For light infections, the Mazzoti test, where patients are given a single dose of 50 mg of diethyl carbimazole (DEC) and then examined for a rash can be used. This test is more sensitive (Pryce et al, 1992).

Other rarer causes of eosinophilia caused by parasites also have specific tests, but these are seldom necessary in ordinary hospital practice.

TABLE 5.
Common helminths to expect depending on region travelled to

Region	Common helminths
Worldwide	*Ascaris lumbricoides*, hookworm, *Trichuris trichiura*, strongyloides, tapeworm
All Africa	Schistosomiasis, filariasis
West Africa	Onchocerciasis, Loa loa
Indian Subcontinent	Strongyloides, filarial diseases
South-East Asia	Strongyloides, liver flukes
South America	Liver flukes, schistosomiasis

TREATMENT

Where a diagnosis is made, fast, safe and effective treatment is almost always available. A summary of the appropriate drugs for common worm infections is given in *Table 6*. Treating gut

TABLE 6.
Drugs appropriate for common worm infections

Worm		Treatment
Worms it is reasonable to treat without expert advice	*Ascariasis lumbricoides*	Mebendazole (BNF)
	Hookworm	Mebendazole (BNF)
	Trichuris trichiura	Mebendazole (BNF)
	Tapeworm	Niclosamide (BNF), Praziquantel (better; NPB)
	Strongyloides	Albendazole (BNF), Ivermectin (better; NPB)
	Schistosomiasis	Praziquantel (BNF)
	Cutaneous larva migrans	Albendazole
Worms it is strongly advised to treat only after taking expert advice	Hydatid disease	Albendazole + praziquantel +/- surgery (NPB)
	Filarial worms (including Loa loa)	Diethylcarbamazine (NPB)
	Onchocerca	Ivermectin (NPB)

BNF indicates that details of a good regimen are available in the British National Formulary. NPB= named-patient basis

worms is simple, and sufficiently reliable in most cases that follow-up is not required. For tissue worms (and in particular filariasis, onchocerciasis, and strongyloides in immunocompromised patients) it is worth getting expert advice on treatment, and many of the drugs are only available on a named-patient basis. Advice on any aspects of diagnosis or treatment can be obtained from The Hospital for Tropical Diseases, London (Tel: 020 7387 9300) or The Liverpool School of Tropical Medicine (Tel: 0151 708 9393). HM

Conflict of interest: none.

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KEY POINTS

- In those returning from the tropics, eosinophilia usually signifies worm infection. Untreated, worms can cause serious morbidity.
- Worms infecting humans can live for years, or occasionally for life.
- Intestinal worms generally have a worldwide distribution. Worms living outside the gut have specific geographical distribution; an accurate geographical history is essential.
- Almost all intestinal worms can be diagnosed with simple stool microscopy. Worms living outside the gut require specific tests that have to be guided by geographical exposure.
- Once identified, almost all worms can be treated easily, but different species require different treatment.

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