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CLINICAL GUIDELINES OF THE BRITISH INFECTION SOCIETY

Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management

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KEYWORDS
Eosinophilia;
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Migrant;
Investigation;
Management

Summary Eosinophilia is a common finding in returning travellers and migrants, and in this group it often indicates an underlying helminth infection. Infections are frequently either asymptomatic or associated with non-specific symptoms, but some can cause severe disease. Here the British Infection Society guidelines group reviews common and serious infectious causes of eosinophilia, and outlines a scheme for investigating returning travellers and migrants. All returning travellers and migrants with eosinophilia should be investigated with concentrated stool microscopy and strongyloides serology, in addition to tests specific to the region they have visited. Terminal urine microscopy and serology for schistosomiasis should also be performed in those returning from Africa. Eosinophilia is also a feature of significant non-infective conditions, which should be considered.

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1. Introduction

Eosinophilia occurs commonly in individuals returning from the tropics. In a UK series of 852 asymptomatic returning travellers, 8% had eosinophilia,[1] and in a Canadian series of 1605 individuals returning from the tropics 10% of asymptomatic individuals had eosinophilia.[2] For the purpose of these recommendations, eosinophilia is defined as a peripheral blood eosinophil count of $>0.45 \times 10^9$/L.

Helminth infection is the commonest identifiable cause of eosinophilia in the returning traveller or migrant, rates varying from 14%[2] to 64%.[3] However there are multiple causes, both infectious and non-infectious, of a peripheral blood eosinophilia and patients may present to a range of specialities other than infectious diseases. These recommendations are intended to guide infection specialists investigating and managing individuals returning from the tropics with eosinophilia, and do not attempt to cover non-infectious causes comprehensively.

Many of the infections discussed are seen rarely in the UK, and are rarely diagnosed outside tropical medicine units. Box 1 summarises contact details of tropical units in the UK offering 24 h clinical advice. All NHS microbiology laboratories offer concentrated stool microscopy for ova, cysts and parasites, and can access most other tests through a UK network of specialised laboratories (Box 1).

Helminth infections causing eosinophilia are usually self-limiting and benign, but some can cause long-term health problems. For example, *Strongyloides stercoralis* infection in the immunocompromised can result in a hyperinfestation syndrome with a high mortality, and may present over 50 years after exposure.[4–6] Schistosomiasis is occasionally associated with spinal cord compression[7] or bladder carcinoma.[8,9] Potentially serious helminth infections are diagnosed in 10–73% of returning travellers and migrants with eosinophilia.[2,3,10] Human immunodeficiency virus (HIV) infection may also present with eosinophilia, although helminth co-infection is still a more likely cause in this setting.[11]

Eosinophilia has numerous non-infectious causes. Common non-infectious causes include drugs (non-steroidal anti-inflammatory drugs, beta-lactam antibiotics, nitrofurantoin and others), atopy (asthma, eczema and hay fever) and allergy. These and uncommon but serious non-infectious causes such as haemopoietic malignancies and connective tissue disorders are not covered in these recommendations, but have been comprehensively reviewed elsewhere.[12–14] Long-standing moderate/high-grade eosinophilia ($>1.5 \times 10^9$/L) can itself result in significant end organ damage.[15]

2. General principles

2.1. Patient group

Clinical presentation may vary depending on the patient group. Migrants tend to have a higher burden of infection[1,2,16,17] while travellers are often newly infected and have a greater immune response with more pronounced eosinophilia.[18] Infection with multiple helminth species may occur in migrants, however, which is also associated with more pronounced eosinophilia.[2,3] Rare complications of chronic schistosomiasis such as bladder carcinoma or portal hypertension are more often seen in migrants, whereas Katayama syndrome and Loeffler's syndrome are more frequent in travellers.

2.2. Geographical area

The incidence of imported helminth infections depends on the geographical area visited: the geohelminths *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm sp, have a worldwide distribution. Others, especially those with a complex lifecycle involving an intermediate host or vector, or those associated with certain foods, have defined geographical limits. Table 1 lists commoner helminth infections by geographical area and summarises clinical presentations. A detailed travel history should include exact timings of possible exposures such as swimming in fresh water lakes in Africa, walking barefoot, drinking water and foods consumed (e.g. salads, raw fish).[19] See Box 1 for further resources available.

2.3. Timing

Eosinophilia may be transient in association with the tissue migration phase of infection, which occurs during the **prepatent period**, the period during which parasite eggs or larvae are not detectable. Samples sent for microscopy for ova or parasites may at this stage be negative. Eosinophilia often resolves when the infecting organism reaches the gut lumen and it is only at this stage that stool microscopy becomes positive. The **incubation period** is the time from infection to the development of symptoms.

2.4. Serology

Most serological tests do not become positive until 4–12 weeks after infection so may be negative when eosinophilia is first detected. Clinicians should be aware that many of the serological tests for helminths cross-react (Table 2), for example filarial serology may become positive in cases of strongyloidiasis; taking expert advice is recommended when interpreting serological tests. Table 2 outlines commoner helminths, diagnostic tests and their treatments.

3. Investigating asymptomatic eosinophilia

Eosinophilia is asymptomatic in 21–33% of returning travellers and migrants[3,10]; common causes of asymptomatic eosinophilia are intestinal helminths, schistosomiasis, strongyloidiasis and filariasis.[2,3,10,20] We propose a scheme

Box 1

Reference facilities

Laboratories in the UK offering specialist parasitological diagnostic tests, and specialist tropical disease units in the UK providing telephone advice on clinical management.

Hospital for Tropical Diseases, London, UK.
Capper Street, off Tottenham Court Road, London WC1E 6JB, UK
www.thehtd.org
Department of Clinical Parasitology (HPA Parasitology Reference Laboratory)
Tel.: 0207 387 4411x5413 (Serology)ext 5414 (Microscopy)
Fax: 020 7383 0041.
Clinical management
Tel.: +44 (0)845 155 5000 (24 h; ask for on call tropical/ID physician).
Fax: +44 (0)20 7388 7645.

Liverpool School of Tropical Medicine, Liverpool, UK.
Pembroke Place, Liverpool L3 5QA, UK
Diagnostic Parasitology Laboratory
Tel.: 0151 705 3220.
http://www.liv.ac.uk/lstm/travel_health_services/diagnos_lab.htm
Clinical management
Tel.: (0900–1700 h) +44 (0) 151 708 9393.
Tel.: +44 (0) 151 706 2000 (24 h; ask for tropical/ID physician on call).
Fax: +44 (0) 151 708 8733 or +44 (0) 151 705 3368.
http://www.liv.ac.uk/lstm/

Scottish Parasite Diagnostic Laboratory (SPDL)
House on the Hill, Stobhill Hospital, 133 Balornock Road, Glasgow G21 3UW, UK
Tel.: 0140 201 3029.
http://www.spdl.scot.nhs.uk

Mycology Reference Laboratory
Southwest HPA Laboratory, Myrtle Road, Kingsdown, Bristol BS2 8EL, UK
Tel.: 0117 9285028;
Fax: 0117 9226611.
http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1160994273112

Other sources of information

Health Protection Agency (HPA)
http://www.hpa.org.uk

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov

National Travel Health Network and Centre (NATHNAC)
http://www.nathnac.org/travel/index.htm

ProMed, International Society for Infectious Diseases (ISID)
http://www.promedmail.org/pls/otn/f?p=2400:1000:

Fever Travel
Provides comprehensive information on disease distribution by individual country.
http://www.fevertravel.ch/

Geosentinel
Worldwide and European surveillance data on imported infections.
http://www.istm.org/geosentinel/main.html

TropNet Europe
Worldwide and European surveillance data on imported infections.
http://www.tropnet.net/index_2.html

Table 1 Geographical distribution and clinical presentation of imported helminth infections.

Geographical area	Helminth	Common name, syndrome	Respiratory	Gastrointestinal	Right upper quadrant pain, jaundice	Neurological	Cutaneous, muscle	Other
Worldwide	*Ancylostoma duodenale*	Hookworm	wheeze, dry cough (Loeffler's syndrome)	nausea, vomiting, diarrhoea, abdominal pain			transient itch, maculopapular rash	fever (Loeffler's syndrome)
	Ascaris lumbricoides	Roundworm	wheeze, dry cough (Loeffler's syndrome)	abdominal pain, diarrhoea	biliary obstruction		urticarial rash (Loeffler's syndrome)	fever (Loeffler's syndrome)
	Echinococcus granulosus	Cystic hydatid	cough, pleuritic pain, breathlessness		asymptomatic, right upper quadrant pain			anaphylaxis
	Enterobius vermicularis	Pinworm, threadworm		diarrhoea, abdominal pain, weight loss			prurutis ani	vaginal discharge
	Fasciola hepatica	Fascioliasis			upper abdominal pain (acute), biliary obstruction and hepatic abscesses (chronic)			fever
	Necator americanus	Hookworm	wheeze, dry cough (Loeffler's syndrome)	nausea, vomiting, diarrhoea, abdominal pain			transient itch, maculopapular rash	fever (Loeffler's syndrome)
	Schistosoma spp.	Cercarial dermatitis					itchy maculopapular rash	
	Strongyloides stercoralis	Strongyloidiasis	wheeze, dry cough (Loeffler's syndrome), hyperinfestation syndrome	diarrhoea, abdominal pain, bloating, hyperinfestation syndrome			itchy urticarial rash (larva currens[a])	fever (Loeffler's syndrome)
	Taenia saginata	Beef tapeworm		abdominal pain, diarrhoea, segments expelled PR				
	Toxocara canis, cati	Visceral larva migrans	wheeze, cough	abdominal pain	hepatosplenomegaly	meningo-encephalitis		
	Trichuris trichiura	Whipworm		diarrhoea dysentry				
	Trichinella spiralis	Trichinellosis, trichinosis		upper abdominal pain, fever, vomiting, diarrhoea dysphagia		meningo-encephalitis	periorbital oedema, urticaria, myalgia, muscle weakness	myocarditis, cardiac conduction disturbances
Worldwide, tropical only	*Ancylostoma spp.*	Cutaneous larva migrans					serpiginous rash[b]	
	Hymenolepis nana	Dwarf tapeworm		diarrhoea, abdominal pain				
	Taenia solium	Pork tapeworm, cysticercosis		abdominal pain, diarrhoea, segments expelled *per rectum*		usually space-occupying lesions without eosinophilia rarely eosinophilic meningo-encephalitis.		
	Wuchereria bancrofti	Lymphatic filariasis, tropical pulmonary eosinophilia	dry cough, wheeze, breathlessness (tropical pulmonary eosinophilia)				lymphadenitis, lymphoedema	fever (tropical pulmonary eosinophilia)
Africa (all)	*Schistosoma haematobium*	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)			paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever (Katayama syndrome), haematuria, proteinuria, dysuria, haematospermia
	Schistosoma mansoni	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)	abdominal pain, diarrhoea	hepatosplenomegaly, portal hypertension	paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever (Katayama syndrome)
Africa (Central and West predominantly[c])	*Loa loa*	Eye worm, Calabar swelling					Calabar swelling	conjunctival worm migration
	Onchocerca volvulus	Onchocerciasis, river blindness					nodules, pruritic dermatitis, limb swelling	keratitis, anterior uveitis, choroidoretinitis
	Paragonimus spp.	Paragonimiasis	pleuritic chest pain, pleural effusion, cough, haemoptysis	abdominal pain, diarrhoea		meningo-encephalitis, transverse myelitis, myelopathy	subcutaneous migratory nodules	
South Asia	*Brugia malayi*	Lymphatic filariasis	dry cough, wheeze, breathlessness (tropical pulmonary eosinophilia)				lymphadenitis, lymphoedema	fever (tropical pulmonary eosinophilia)
Southeast Asia	*Angiostrongylus cantonensis*	Eosinophilic meningitis, rat lung worm				severe headache, meningism, focal neurological signs		
	Anisakis spp.	Fish tapeworm		severe abdominal pain, nausea and vomiting				anaphylaxis
	Brugia malayi	Lymphatic filariasis	dry cough, wheeze, breathlessness (tropical pulmonary eosinophilia)				lymphadenitis, lymphoedema	fever (tropical pulmonary eosinophilia)
	Clonorchis sinensis	Clonorchiasis			hepatomegaly, biliary obstruction, (acute) abdominal pain (acute), cholangiocarcinoma (chronic)		urticarial skin rash	fever
	Echinococcus multilocularis	Alveolar hydatid			asymptomatic, right upper quadrant pain			disseminated infection to any organ late in infection
	Gnathostoma spinigerum	Gnathostomiasis		abdominal pain		severe meningo-encephalitis and myelitis, focal neurology, sub-arachnoid and intra-cerebral haemorrhage	intermittent subcutaneous swelling, pruritis, oedema	
	Opisthorchis spp.	Opisthorchiasis			hepatomegaly, biliary obstruction, (acute) abdominal pain (acute), cholangiocarcinoma (chronic)		urticarial skin rash	fever
	Paragonimus westermani	Paragonimiasis	pleuritic chest pain, pleural effusion, cough, haemoptysis	abdominal pain, diarrhoea		meningo-encephalitis, transverse myelitis, myelopathy	subcutaneous migratory nodules	
	Schistosoma japonicum	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)	abdominal pain, diarrhoea	hepatosplenomegaly, portal hypertension	focal neurological signs, seizures	urticarial rash (Katayama syndrome)	fever (Katayama syndrome)
	Pseudoterranova decipiens	Fish tapeworm		severe abdominal pain, nausea and vomiting				

for investigating asymptomatic eosinophilia in returning travellers and migrants based on geographical area visited.[3] Initial investigations with a high yield are suggested, to be followed if necessary by further investigations. Screening for helminths in the absence of both symptoms and eosinophilia is justifiable in some situations (e.g. a history of fresh water contact in Africa), but this is beyond the remit of these recommendations.

All patients returning from the tropics with eosinophilia should be investigated with concentrated stool microscopy[21]

Table 1 (*continued*).

Geographical area	Helminth	Common name, syndrome	Respiratory	Gastrointestinal	Right upper quadrant pain, jaundice	Neurological	Cutaneous, muscle	Other
Oceania	*Angiostrongylus cantonensis*	Eosinophilic meningitis, rat lung worm				severe headache, meningism, focal neurological signs		
	Brugia malayi	Lymphatic filariasis	dry cough, wheeze, breathlessness (tropical pulmonary eosinophilia)				lymphadenitis, lymphoedema	fever (tropical pulmonary eosinophilia)
Middle East, Central Asia	*Echinococcus granulosus*	Cystic hydatid	cough, pleuritic pain, breathlessness		asymptomatic, right upper quadrant pain			anaphylaxis
	Echinococcus multilocularis	Alveolar hydatid			asymptomatic, right upper quadrant pain			disseminated infection to any organ late in infection
	Onchocerca volvulus	Onchocerciasis, river blindness					nodules, pruritic dermatitis, limb swelling	keratitis, anterior uveitis, choroidoretinitis
	Schistosoma haematobium	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)			paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever (Katayama syndrome) haematuria, proteinuria, dysuria, haematospermia
	Schistosoma mansoni	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)	abdominal pain, diarrhoea	hepatosplenomegaly, portal hypertension	paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever (Katayama syndrome)
South America	*Angiostrongylus costaricensis*			severe abdominal pain, diarrhoea, constipation				
	Anisakis spp.	Fish tapeworm		severe abdominal pain, nausea and vomiting				anaphylaxis
	Coccidioides immitis	Coccidioidomycosis	fever, cough, pleuritic chest pain			chronic meningitis	rash	
	Gnathostoma spinigerum	Gnathostomiasis		abdominal pain		severe meningo-encephalitis and myelitis, focal neurology, sub-arachnoid and intra-cerebral haemorrhage	intermittent subcutaneous swelling, pruritis, oedema	
	Onchocerca volvulus	Onchocerciasis, river blindness					nodules, pruritic dermatitis, limb swelling	keratitis, anterior uveitis, choroidoretinitis
	Paracoccidioides brasiliensis	Paracoccidioidomycosis	cough, night sweats, weight loss, malaise			chronic meningitis	ulcerative oral, nasal, cutaneous lesions	
	Paragonimus spp.	Paragonimiasis	pleuritic chest pain, pleural effusion, cough, haemoptysis	abdominal pain, diarrhoea		meningo-encephalitis, transverse myelitis, myelopathy	subcutaneous migratory nodules	
	Pseudoterranova decipiens	Fish tapeworm		severe abdominal pain, nausea and vomiting				
	Schistosoma mansoni	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)	abdominal pain, diarrhoea	hepatosplenomegaly, portal hypertension	paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever (Katayama syndrome)
Central America	*Coccidioides immitis*	Coccidioidomycosis	fever, cough, pleuritic chest pain			chronic meningitis	rash	
	Gnathostoma spinigerum	Gnathostomiasis		abdominal pain		severe meningo-encephalitis and myelitis, focal neurology, sub-arachnoid and intra-cerebral haemorrhage	intermittent subcutaneous swelling, pruritis, oedema	
	Onchocerca volvulus	Onchocerciasis, river blindness					nodules, pruritic dermatitis, limb swelling	keratitis, anterior uveitis, choroidoretinitis
	Paracoccidioides brasiliensis	Paracoccidioidomycosis	cough, night sweats, weight loss, malaise			chronic meningitis	ulcerative oral, nasal, cutaneous lesions	
	Paragonimus spp.	Paragonimiasis	pleuritic chest pain, pleural effusion, cough, haemoptysis	abdominal pain, diarrhoea		meningo-encephalitis, transverse myelitis, myelopathy	subcutaneous migratory nodules	
Caribbean	*Angiostrongylus cantonensis*	Eosinophilic meningitis, rat lung worm				severe headache, meningism, focal neurological signs		
	Angiostrongylus costaricensis			severe abdominal pain, diarrhoea, constipation				
	Gnathostoma spinigerum	Gnathostomiasis		abdominal pain		severe meningo-encephalitis and myelitis, focal neurology, sub-arachnoid and intra-cerebral haemorrhage	intermittent subcutaneous swelling, pruritis, oedema	
	Schistosoma mansoni	Bilharzia, Katayama syndrome	dry cough (Katayama syndrome)	abdominal pain, diarrhoea	hepatosplenomegaly, portal hypertension	paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever (Katayama syndrome)
North America	*Coccidioides immitis*	Coccidioidomycosis	fever, cough, pleuritic chest pain			chronic meningitis	rash	
	Paracoccidioides brasiliensis	Paracoccidioidomycosis	cough, night sweats, weight loss, malaise			chronic meningitis	ulcerative oral, nasal, cutaneous lesions	
Europe	*Anisakis spp.*	Fish tapeworm		severe abdominal pain, nausea and vomiting				anaphylaxis
	Echinococcus multilocularis	Alveolar hydatid			asymptomatic, right upper quadrant pain			disseminated infection to any organ late in infection
	Opisthorchis spp.	Opisthorchiasis (Siberia)			hepatomegaly, biliary obstruction, (acute) abdominal pain (acute), cholangiocarcinoma (chronic)		urticarial skin rash	fever
	Pseudoterranova decipiens	Fish tapeworm		severe abdominal pain, nausea and vomiting				

more commonly imported condition

usual presentation

uncommon presentation

[a] see fig. 3

[b] see fig. 2

[c] West/ central African countries: Benin, Congo, Gabon, Ghana, Guinea, Guinea Bissau, Cote d'Ivoire, Nigeria, Togo, Burkina Faso, Gambia, Liberia, Mali, Mauritania, Equatorial Guinea, Senegal, Sierra Leone, Central African Republic, Cameroon, Niger, Chad.

and strongyloides serology.[22] Concentrated stool microscopy identifies most common soil-transmitted helminths (*A. lumbricoides*, *T. trichiura*, hookworm sp.) but has a low sensitivity in detecting strongyloides.[22,23] Other screening investigations are region-specific. Terminal urine microscopy (for ova) and serology for schistosomiasis should be performed in those returning from Africa.[24] Patients from West Africa have a significant prevalence of the filarial

Table 2 Diagnosis and treatment of common helminths presenting in travellers and migrants.

Infection	Diagnostic tests	Sensitivity of serology	Specificity of serology	Possible serological cross-reaction	Treatment
Ascariasis (*Ascaris lumbricoides*)	Concentrated stool microscopy				Albendazole 400 mg[a] (mebendazole 500 mg)
Pinworm (*Enterobius vermicularis*)	Perianal sellotape test				Albendazole 400 mg/mebendazole 100 mg, repeat in 2 weeks
Fascioliasis (*Fasciola hepatica*)	Concentrated stool microscopy, serology[b]	Up to 97%	99%	*Schistosoma* sp.	Triclabendazole 10 mg/kg
Hookworm (*Ancylostoma duodenale*/ *Necator americanus*)	Concentrated stool microscopy				Albendazole 400 mg
Hydatid (*Echinococcus granulosus*/ *Echinococcus multilocularis*)	Serology[b]	Cystic: 80—90% (liver), 60% (lung)[105] Alveolar: 85%	89%	Cysticercosis; filariasis	Seek specialist advice. Combination of praziquantel 20 mg/kg bd 14 days pre and post procedure, prolonged course of albendazole 400 mg bd, PAIR[c], surgery
Loaisis (*Loa loa*)	Day blood microscopy[b], serology[b]	Up to 90%	80%	Lymphatic filariasis, onchocerciasis, strongyloides	Seek specialist advice (Box 2). First exclude co-existing onchocerciasis. Diethylcarbamazine 50 mg day 1 increasing by day 4 to 200 mg tds for 3 weeks, pre-treat with prednisolone if microfilariae seen on blood film.
Neurocysticercosis (*Taenia solium*)	Serology[b]	94% (2 or more cysts), 28% (single lesions)[164]	99% but much lower if single 50 kDa band only[165]	Hydatid	Albendazole 400 mg bd for 14 days + dexamethasone 4—12 mg qds, reducing after 7 days
Onchocerciasis (*Onchocerca volvulus*)	Skin snips[b], filarial serology[b], slit lamp examination	93% (recombinant antigen)[166]	93% (recombinant antigen)	Lymphatic filariasis, loaisis, strongyloides	Ivermectin 200 μg/kg monthly doses for 3 months, repeat every 3—6 months usually for several years, seek ophthalmological advice, observe first dose.
Schistosomiasis (*Schistosoma haematobium*)	Microscopy of nitrocellulose—filtered terminal urine, serology[b]	92%[73]	98%	*Fasciola*	Praziquantel 40 mg/kg
Schistosomiasis (*Schistosoma mansoni*)	Concentrated stool microscopy, serology[b]	96%[73]	98%	*Fasciola*	Praziquantel 40 mg/kg
Strongyloidiasis (*Strongyloides stercoralis*)	Concentrated stool microscopy, serology[b], stool culture[b] (agar plate or charcoal method)	73% in travellers; 98% in migrants[22]	94% (non-endemic area), 77% (patients with other parasitosis)	Lymphatic filariasis, onchocerciasis, loaisis, hookworm	Ivermectin 200 μg/kg (prolonged course in hyperinfestation- seek specialist advice)(Albendazole 400 mg od/bd 3 days)

(*continued on next page*)

Table 2 (*continued*)

Infection	Diagnostic tests	Sensitivity of serology	Specificity of serology	Possible serological cross-reaction	Treatment
Tapeworm (*Taenia solium*/ *Taenia saginatum*)	Concentrated stool microscopy (low sensitivity)				Praziquantel 10 mg/kg (except *Hymenolepis nana*, 25 mg/kg) Identify the species and exclude co-existing cysticercosis in cases of *Taenia solium* before treating
Whipworm (*Trichuris trichiura*)	Concentrated stool microscopy				Mebendazole 100 mg bd 3 days/Albendazole 400—800 mg bd 3 days -low cure rate in heavy infection.
Lymphatic filariasis (*Wuchereria bancrofti*/*Brugia malayi*)	Night blood microscopy, serology[b]	Up to 90%	80%	Onchocerciasis, loaisis, strongyloides	Seek specialist advice (Box 2). First exclude co-existing onchocerciasis. DEC 50 mg day 1 increasing by day 4 to 200 mg tds for 3 weeks

[a] where duration of treatment is not mentioned, treatment consists of a single dose only.
[b] Will generally need to be sent to specialist laboratories.
[c] PAIR: puncture, aspiration, injection and re-aspiration.

infections *Loa loa*, *Onchocerca volvulus* and *Wuchereria bancrofti* so filarial serology is additionally indicated. Fig. 1 illustrates a flow chart for the initial investigation of asymptomatic eosinophilia.

Empiric albendazole (400 mg bd 3 days) is recommended by some experts to cover the possibility of prepatent geohelminth infection (e.g. *Ascaris*/hookworm) as the cause of a transient eosinophilia with negative stool microscopy.[25,26]

4. Eosinophilia associated with specific symptoms

The remainder of the recommendations is divided into the clinical syndromes associated with eosinophilia that may be encountered in returning travellers and migrants. Each section is organised with the more frequently seen syndromes or conditions in this population listed first.

4.1. Eosinophilia with fever and/or respiratory symptoms

4.1.1. Katayama syndrome — *Schistosoma* sp.

(See 4.2.2, 4.6.1.)

This occurs early in schistosomiasis infection, during the migration and initiation of egg-laying phases. It is probably immunologically mediated, and is rare in chronically exposed individuals.

Incubation period: 2—9 weeks.[27]

Distribution: Africa (occasionally SE Asia, South America and the Arabian peninsula).

Mode of transmission: Fresh water exposure (usually swimming in lakes or rivers) allows cercariae released from snails to penetrate skin.

Clinical presentation[28,29]: Eosinophilia, which may be high grade ($>5 \times 10^9$/L), fever, dry cough and urticarial rash. Abdominal pain, diarrhoea and pulmonary infiltrates on chest radiograph may occur, and occasionally neurological features (4.4.4).

Investigations: The combination of eosinophilia with fever and rash 2—9 weeks after fresh water swimming in Africa makes the diagnosis likely, and justifies empirical treatment. Serology and stool and terminal urine microscopy have a low sensitivity at this stage.

Treatment: Praziquantel 40 mg/kg as a single dose (*Schistosoma japonicum*: 60 mg/kg in 3 divided doses)[30—32] should be repeated at 6—8 weeks as eggs and immature schistosomules are relatively resistant. Evidence from case series suggests that steroids reduce the duration of symptoms.[33] Standard practice at the Hospital for Tropical Diseases, London is to give a 5-day course of oral prednisolone at 20 mg/day. Artemesinins may be useful as they have a greater impact on immature schistosomula, but trial evidence for their use in Katayama syndrome is absent.[34]

4.1.2. Loeffler's syndrome

Loeffler's syndrome results from larval migration through the lungs during acute infection, most often involving the nematode worms *Ascaris*, hookworm and *Strongyloides*.

Incubation period: 1—2 weeks, depending on species.

Distribution: Worldwide; see individual species.

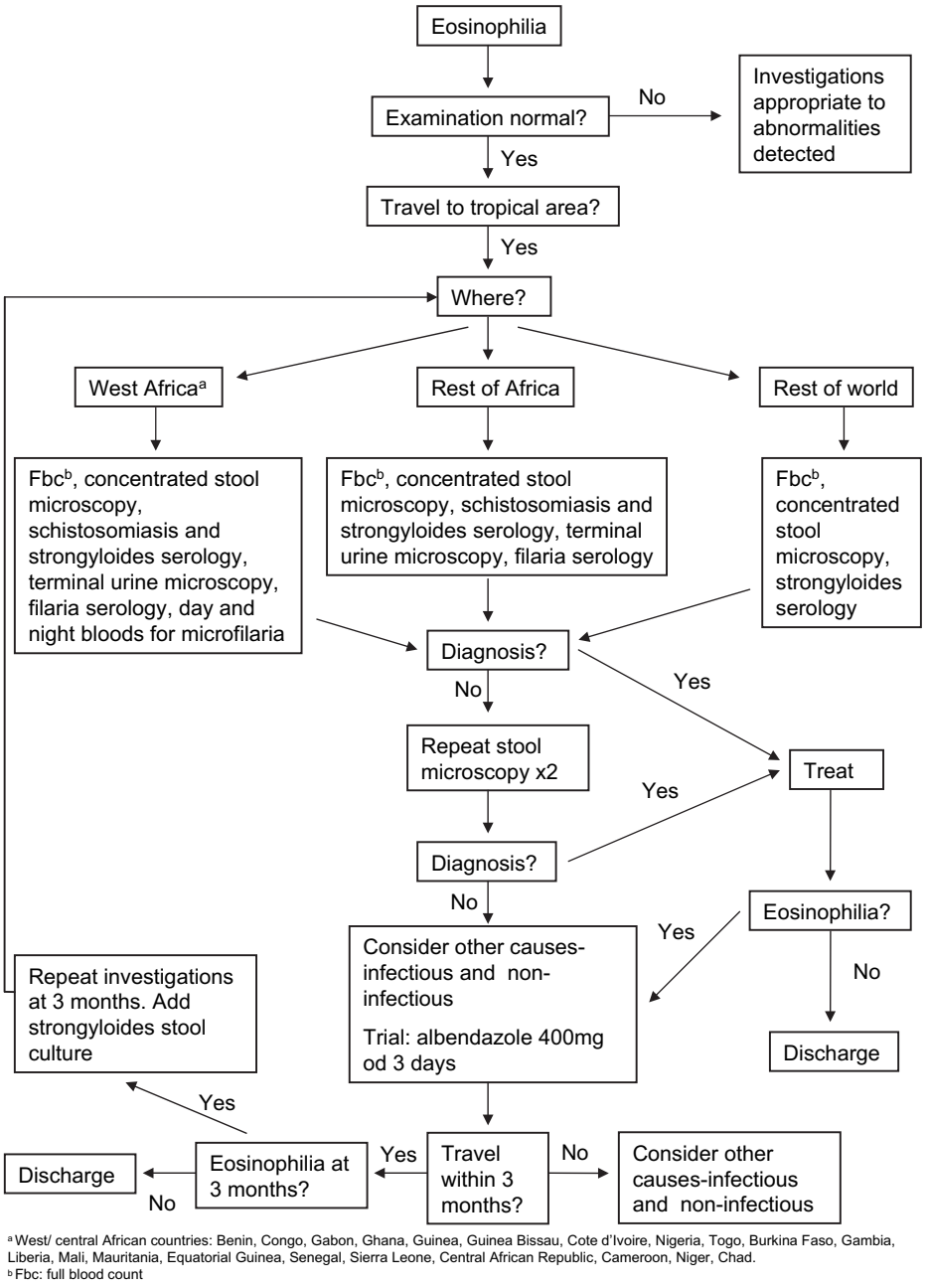

Figure 1 Investigation of asymptomatic eosinophilia based on geographical exposure.

Clinical presentation: Fever, urticaria, wheeze, dry cough, rarely haemoptysis.

Investigations: Diagnosis is clinical as symptoms occur during the prepatent period. In addition to eosinophilia, migratory pulmonary infiltrates may be seen on chest radiograph.

Treatment: See Table 2 for individual species. Empirical treatment is recommended with albendazole 400 mg bd 3 days when investigations are negative.

4.1.3. Visceral larva migrans/acute toxocariasis — *Toxocara canis* and *T. catis*

Visceral larva migrans occurs when larvae from ingested toxocara eggs penetrate the gut mucosa and enter the portal and then the systemic circulation. Occular larva migrans is a distinct syndrome without eosinophilia, and is not discussed.

Incubation period: Uncertain.

Distribution: Worldwide, including temperate areas.[35]

Mode of transmission: Ingestion of soil containing eggs of *T. canis* or *T. catis* (as a result of dog or cat fouling),[36] or through eating raw meat, particularly liver.[37]

Clinical presentation: Usually seen in children <5 years old, although occurs in adults through raw meat consumption. Infection is usually asymptomatic; symptomatic presentation is with fever, eosinophilia, wheeze and cough. Abdominal pain, hepatosplenomegaly and urticarial rash may also occur.[38] It can cause an eosinophilic meningo-encephalitis (4.4.5).

Investigations: Serology.

Treatment: Some cases are mild and self-limiting. For others, albendazole 400 mg bd 5 days.[39] Steroids and antihistamines may be necessary for hypersensitivity reactions.

4.1.4. Tropical pulmonary eosinophilia — *Wuchereria bancrofti* and *Brugia malayi*

This rare condition is a hypersensitivity reaction to the lymphatic filarial worms *W. bancrofti* and *B. malayi*[40] (4.5.3). It is more often seen in visitors to than long-term inhabitants of endemic regions.[41,42]

Distribution: See 4.5.3

Clinical presentation: Fever, dry cough, wheeze and breathlessness; patients are often initially misdiagnosed as having asthma.[42,43] It rarely progresses to lymphatic damage.

Investigations: Chest radiograph (normal in 20% cases) may show interstitial shadowing, reticulonodular or military infiltrates, and pulmonary function tests may reveal either an obstructive (early) or a restrictive (late) deficit. Eosinophil count is typically greater than 3×10^9/L, and IgE levels are elevated. Filaria serology is strongly positive and microfilariae are not detected on blood film microscopy.

Treatment: Symptoms typically resolve rapidly following treatment with diethylcarbamazine[44]; see Box 2 for details and **cautions**. Steroids may be used for the treatment of ongoing alveolitis and pulmonary fibrosis[41] (exclude strongyloidiasis).

Clinical management issues: If treatment is delayed or incomplete, pulmonary fibrosis may result. Relapses occur in 20% of cases necessitating re-treatment.

4.1.5. Pulmonary hydatid disease (*Echinococcus granulosus* and *E. multilocularis*)

This most commonly affects the liver (4.3.1), but cysts occur in the lungs in 20% cases.[45] Lung cysts may be asymptomatic for some time before presenting with cough, pleuritic pain and breathlessness with mass lesions seen on chest radiograph. Occasionally intrabronchial rupture may occur, with expectoration of cyst contents. Pulmonary hydatid disease requires management in specialist centres. Treatment is surgical, with complete excision, conserving as much lung tissue as is feasible. Praziquantel is given pre- and post-operatively, and albendazole post-operatively for a prolonged course, unless cyst excision is complete (4.3.1).[46]

4.1.6. Paragonimiasis (*Paragonimus* sp.)

Prepatent period: 65—90 days.[47]

Incubation period: Days—3 weeks.

Distribution: SE Asia accounts for 90% cases (predominantly *Paragonimus westermani*), West Africa, India, Central and South America (other *Paragonimus* sp).

Mode of transmission: Ingestion of intermediate stage metacercariae in raw fresh water crab and crayfish meat.

Clinical presentation: Abdominal pain, diarrhoea and urticaria followed by pleuritic chest pain, eosinophilic pleural effusions and cough, which becomes chronic.[48,49] About 6 months after infection haemoptysis may develop, mimicking tuberculosis. CNS infection is seen in 1% of patients, and migratory subcutaneous nodules can occur[50] (4.4.7).

Investigations: Diagnosis is usually based on clinical features and may be confirmed by sputum microscopy. Serology is available at McGill University, Montreal, Quebec, Canada (quoted sensitivity of 90—96%, specificity 99%[51]). Eosinophilia and elevated serum IgE levels are present in more than 80% patients. Chest radiograph may show pleural effusion, consolidation or cavitation.

Treatment: Praziquantel 25 mg/kg tds 2 days.[52] Triclabendazole 10 mg/kg/day 3 days is an alternative.

4.1.7. Coccidioidomycosis and paracoccidioidomycosis — *Coccidioides immitis, Paracoccidioides braziliensis*

Incubation period: Coccidioidomycosis: 7—21 days (reactivation following immunosuppression: many years).

Paracoccidioidomycosis: 1 month to many years.

Distribution: Coccidioidomycosis: Widely distributed through arid parts of the Americas.[53,54]

Box 2

Diethylcarbamazine (DEC) and lymphatic filariasis and loaisis

DEC is the treatment of choice for lymphatic filariasis and loaisis but can cause severe reactions including blindness in individuals co-infected with onchocerciasis. Onchocerciasis should be excluded by taking skin snips and by giving a test dose of 50 mg DEC. If onchocerciasis is present, this test dose will precipitate a mild Mazzotti reaction, consisting of pruritis and erythema. Treating with full dose DEC when onchocerciasis is present results in a severe reaction with pruritis, erythema, hypotension and blindness. Alternatively, presumptive pre-treatment of onchocerciasis with ivermectin may be undertaken before treating filariasis (see Table 2).

The dose of DEC is 50 mg day 1 increasing by day 4—200 mg tds for 3 weeks (regimen based on expert opinion only).

A combination of ivermectin and albendazole may be used instead of DEC in areas of onchocerciasis endemnicity[167].

***Loa loa*: additional points**

It is important to establish if an individual infected with *Loa loa* is microfilaraemic before commencing treatment, as **encephalopathy**, with a high mortality rate, may develop after treatment with DEC, particularly in individuals with high levels of blood microfilaraemia (>8000/ml). If microfilariae are seen on blood film, corticosteroids should be used in conjunction with DEC (expert opinion[149]). Albendazole and ivermectin have been used to reduce microfilarial load in these patients, before treating definitively with DEC.

Paracoccidioidomycosis: South and Central America.

Mode of transmission: Respiratory: exposure to airborne fungal spores.

Clinical presentation: Coccidioidomycosis: Fever, cough, pleuritic chest pain, headache and rash.[55]

Paracoccidioidomycosis: Usually insidious, with cough, night sweats, weight loss and malaise, or ulcerative oral, nasal and cutaneous lesions. Severe infection (disseminated/chronic meningitis (4.4.6)) may occur in the immunosuppressed.

Investigations: Diagnosis is by serology, or microscopy and culture of respiratory samples (high laboratory risk). Chest radiograph demonstrates consolidation and cavitation, plus pleural effusion (coccidioidomycosis) or hilar lymphadenopathy (paracoccidioidomycosis). Eosinophilia is common.

Treatment and clinical management issues: Mild cases in immunocompenent individuals often resolve spontaneously. Oral itraconazole 200–400 mg od (limited evidence in paracoccidioidomycosis[56]) or fluconazole 400–800 mg od (coccidioidomycosis), for 3–6 months for mild/moderate disease; intravenous liposomal amphotericin B (3 mg/kg od) for 1–2 weeks followed by long-term oral fluconazole for severe infection. Immunocompromised individuals require prolonged treatment followed by long-term azole prophylaxis. See Infectious Diseases Society of America guidelines.[55] Relapse in paracoccidioidomycosis is common.

4.1.8. Other causes of peripheral eosinophilia and pulmonary infiltrates

There are multiple non-infective causes of eosinophilia with pulmonary infiltrates, which have been comprehensively reviewed elsewhere.[12] A detailed drug history should be established as drug-induced eosinophilia is often accompanied by pulmonary involvement.[57] Other causes include atopy including asthma, allergic bronchopulmonary aspergillosis,[58] connective tissue disorders such as Churg Strauss syndrome and Wegener's granulomatosis, haemopoietic and other malignancies, and hypereosinophilic syndrome.[59] Tuberculosis is a rare cause of peripheral and pulmonary eosinophilia.[60]

4.2. Eosinophilia with gastrointestinal symptoms

4.2.1. Strongyloidiasis – *Strongyloides stercoralis*

Incubation period: Days to weeks for larva currens, 4.5.2 and Loeffler's syndrome, 4.1.2, 2 weeks onwards for gastrointestinal symptoms.[61]

Prepatent period: 4 weeks.

Distribution: Widely distributed throughout the tropics, small foci in temperate regions.[62,63]

Mode of transmission: Larvae penetrate the skin of humans walking barefoot on affected soil or sand.

Clinical presentation: Larva currens is the commonest presentation (4.5.2) but a range of non-specific gastrointestinal symptoms, including diarrhoea and abdominal bloating, may occur.[64] The infection may also present as Loeffler's syndrome (4.1.2). ***Hyperinfestation syndrome*** results from cycles of autoinfection and unchecked replication in individuals with defective granulocyte function often associated with chemotherapy, malignancy, steroid treatment or HTLV-1 infection. It manifests as paralytic ileus and gram-negative sepsis following translocation of bacteria across the bowel wall, and has a high mortality. Pulmonary involvement commonly occurs, with abundant larvae present in sputum as well as stool samples. It may present many years after return from the tropics.[4–6]

Investigations: Serology is the most sensitive test. Concentrated stool microscopy has very low sensitivity except in hyperinfestation syndrome when eosinophilia is often absent and serology may be negative, but stool samples contain abundant larvae. Stool culture methods such as the agar plate and charcoal methods (available in specialist parasitology laboratories, Box 1),[65,66] may be useful when other tests are negative. Isolation of S*trongyloides* larvae from the sputum is highly suggestive of hyperinfestation. Check HTLV-1 serology in hyperinfestation.

Treatment: Ivermectin 200 μg/kg single dose is more effective than the alternative of albendazole 400 mg bd 3 days.[67,68] Hyperinfestation should be treated with broad-spectrum antibiotics and a prolonged course of ivermectin, which should be administered parenterally in the case of paralytic ileus[69,70]; seek specialist advice.

Clinical management issues: Migrants from all tropical regions (even in the absence of eosinophilia) should be screened for strongyloides before commencing treatment with immunosuppressive drugs, including steroids.

4.2.2. Schistosomiasis/bilharzia with gastrointestinal symptoms – *Schistosoma mansoni* and *S. japonicum*

Incubation period: 5–12 weeks (Katayama syndrome from 2 weeks onwards).

Distribution: Africa, the Arabian peninsula and South America (*S. mansoni*); China, the Philippines and Indonesia (*S. japonicum*). *S. intercalatum* and *S.mekongi* are of local importance only.

Mode of transmission: See 4.1.1.

Clinical presentation: Infection is often asymptomatic, although in early infection acute schistosomiasis, or 'Katayama syndrome' may occur (4.1.1), and later on abdominal pain, diarrhoea or, in very heavy acute infections, dysentery.[71] Chronic infection results in hepatosplenomegaly, hepatosplenic fibrosis and portal hypertension with oesophageal varices.[72]

Investigations: Serology (positive at 4–8 weeks or sometimes later)[73,74] and microscopy of concentrated stool samples (low sensitivity); abdominal ultrasound and upper gastrointestinal endoscopy if portal hypertension is suspected.

Treatment and clinical management: Praziquantel 40 mg/kg as a single dose (*S. japonicum* 60 mg/kg in 3 doses). Portal hypertension is treated conventionally. *S. japonicum* has been tentatively linked with hepatic and colon cancers.[75,78] Serology may remain positive for many years,[76,77] so cannot be used to assess success of treatment.

4.2.3. Ascariasis–*Ascaris lumbricoides*

Prepatent period: 2–3 months.[13]

Distribution: Worldwide.

Mode of transmission: Faeco-oral route.

Clinical presentation: Usually asymptomatic; abdominal pain, diarrhoea and occasionally gastrointestinal obstruction in children and biliary obstruction in adults.[78]

Earthworm-sized, white adult worms may be passed in stools or occasionally regurgitated. May present acutely as Loeffler's syndrome (4.1.2).

Investigations: Concentrated stool microscopy.

Treatment: Albendazole 400 mg as a single dose[78] (mebendazole 500 mg).

4.2.4. Tapeworm — *Taenia saginata/T. solium*

It is unclear how often this is associated with eosinophilia, but it is a very commonly diagnosed helminth infection in returning travellers and migrants.

Incubation period: 8—14 weeks.

Distribution: Worldwide, but the horn of Africa and southern Africa have a particularly high prevalence of beef tapeworm (*T. saginata*), and central and South America and south Asia of pork tapeworm (*T. solium)*.[79]

Mode of transmission: Consumption of undercooked or raw beef (*T.saginata*) or pork (*T. solium*).

Clinical presentation: Usually asymptomatic, but may be associated with minor abdominal symptoms, and segments may be passed in stool or may actively expel themselves *per rectum*.

Investigations: Concentrated stool microscopy for ova or worm segment (proglottid). Eggs are only eliminated intermittently and repeat specimens should be examined to increase diagnostic yield. Cysticercosis serology (see below).

Treatment: Praziquantel 10 mg/kg as a single dose.

Clinical management issues: The species of infecting tapeworm should be established where possible by microscopy of the worm segment as very occasionally intestinal stages of *T. solium* may coexist with neurocysticercosis (4.4.3), which should be treated with steroids and albendazole. Consider cysticercosis serology if the infecting species is *T. solium*, or if the species has not been identified.

4.2.5. Dwarf tapeworm — *Hymenolepis nana*

H. nana is seen commonly in the Americas, Africa and the Indian subcontinent, but is imported into the UK and Europe less often than *Taenia sp*. It is seen mainly in children, and transmission is associated with poor hygiene. It is usually asymptomatic, although it may present with diarrhoea and abdominal cramps.[80] Diagnosis is by concentrated stool microscopy, and treatment requires a higher dose of praziquantel (25 mg/kg as a single dose).[81,82]

4.2.6. Hookworm — *Ancylostoma duodenale/Necator americanus*

Prepatent period: 5—12 weeks.

Distribution: Worldwide, tropical and sub-tropical.

Mode of transmission: Larvae penetrate the skin of humans walking barefoot or lying on affected soil or sand.

Clinical presentation: Usually asymptomatic. A transient itch ('ground itch') and sometimes a maculopapular rash are followed weeks later by nausea, vomiting, diarrhoea and abdominal pain. Heavy infections may result in anaemia, particularly in young children.

Investigations: Concentrated stool microscopy.

Treatment: Albendazole 400 mg as a single dose.

4.2.7. Whipworm — *Trichuris trichiura*

Prepatent period: 4—12 weeks.

Distribution: Worldwide.

Mode of transmission: Faeco-oral route.

Clinical presentation: Usually asymptomatic, but heavy infections can cause significant morbidity in children, including anaemia, dysentery and rectal prolapse.

Investigations: Concentrated stool microscopy.

Treatment: Mebendazole 100 mg bd 3 days/albendazole 400—800 mg bd 3 days[78] (low cure rate in heavy infection).

4.2.8. Pin worm — *Enterobius vermicularis*

Prepatent period: 2—4 weeks.

Distribution: Worldwide, particularly affecting children.

Mode of transmission: Faeco-oral route.

Clinical presentation: Intense *pruritis ani*. Sometimes weight loss, irritability, diarrhoea, abdominal pain, and occasionally colitis with eosinophilia.[83,84] It may colonise the female genital tract, causing vaginal discharge.

Investigations: Diagnosis is by the 'sellotape test' — performed by placing the sticky side of sellotape on the perianal skin then examining it under the microscope for ova.

Treatment: Albendazole 400 mg or mebendazole 100 mg, both as a single dose.

4.2.9. Trichinellosis — *Trichinella* sp.

This is caused by *Trichinella* sp.[85] larvae encysting in muscle tissue. An 'enteral phase' as the ingested larvae mature to adulthood and produce larvae in the intestinal tract is followed by a 'parenteral phase' as the larvae migrate from intestine to muscle, where they encyst.[86]

Incubation period: 7—30 days (enteral phase), 2—6 weeks (parenteral phase).

Time to seroconversion: 3—5 weeks.

Distribution: Worldwide, particularly Eastern Europe, Russia, Argentina and China.[87] Typically occurs in outbreaks.

Mode of transmission: Consumption of raw or undercooked meat, usually pork.

Clinical presentation: Upper abdominal pain, fever, vomiting and diarrhoea, followed by severe myalgia, muscle weakness and consequent respiratory failure, periorbital and facial oedema, conjunctivitis, dysphagia and urticarial rash (4.5.6). Presentation may be severe, requiring intensive care. Meningo-encephalitis, myocarditis and cardiac conduction disturbances may occur.

Investigations: Serology or muscle biopsy. An elevated blood creatinine kinase level is frequently seen, and eosinophil count $>3 \times 10^9$/L.

Treatment: Albendazole 400 mg od 3 days (mild disease) to 14 days (severe disease).[88,89] Prednisolone 40—60 mg od in severe disease.[87,90]

4.2.10. Anisakiasis — *Anisakis* spp. and *Pseudoterranova decipiens*

Incubation period: 2—5 h.[91]

Distribution: Most commonly reported from SE Asia; occurs worldwide wherever the consumption of raw or pickled seafood occurs (Pacific coast of South America, Scandinavia, the Netherlands).

Mode of transmission: Infective larvae present in raw or pickled fish penetrate the gastric and intestinal mucosa.

Clinical presentation: Severe, acute abdominal pain, nausea and vomiting. Rarely, anaphylaxis may occur following sensitisation.

Investigations: Diagnosis is usually made following visualisation of the worm at endoscopy or at laparotomy.[92] Serology is available at the Scottish Parasite Diagnostic Laboratory (Box 1).

Treatment: Surgical or endoscopic removal of the worm; albendazole 400 mg has been used.[93,94]

4.2.11. *Angiostrongylus costaricensis*

Incubation period: Unknown.

Distribution: Endemic in Central America and the Caribbean.

Mode of transmission: Via the ingestion of snails or vegetable matter contaminated by snail slime.[95]

Clinical presentation: Severe abdominal pain, diarrhoea or constipation, fever and eosinophilia.

Investigations: Usually diagnosed at laparotomy (diagnostic serology is available in endemic areas).

Treatment: Supportive.

4.2.12. Other causes of eosinophilia and GI symptoms

The protozoa *Isospora belli*,[96,97] *Dientamoeba fragilis*,[98] and toxoplasmosis may rarely present with eosinophilia. Visceral larva migrans may present with abdominal pain and hepatosplenomegaly, although usually also in the presence of respiratory symptoms (4.1.3). Paragonimus commonly presents with abdominal pain and diarrhoea, followed later by the development of characteristic respiratory symptoms (4.1.6).

4.3. Eosinophilia and right upper quadrant pain/ jaundice

4.3.1. Hydatid disease in the liver − *Echinococcosis granulosus* and *E. multilocularis*

E. granulosus, 'cystic hydatid', is the commonest cause of hydatid disease in UK practice. Eosinophilia is usually associated with leaking cysts; most asymptomatic cases do not have eosinophilia.

Incubation period: Months to (more commonly) years.[99]

Distribution: Most common in individuals returning to the UK from the Middle East[100] and, more recently, Eastern Europe,[101] although also endemic in north and east Africa and Asia (in particular central Asia[102]).

Mode of transmission: Ingestion of eggs from canine faeces, sometimes via contaminated vegetable matter.

Clinical presentation: The liver is affected in 70% cases of *E. granulosus*, with the lungs being the primary site in 20% (4.1.5) and other sites including CNS, spine, eye, skeletal and heart muscle and bone marrow in 10%.[103] Asymptomatic cysts (up to several litres) are typically identified on routine abdominal imaging. Occasionally liver cysts leak or become infected and present with right upper quadrant pain and fever. Other presentations include hepatomegaly, cholestasis, biliary cirrhosis, portal hypertension and ascites. Cysts may rupture into the peritoneal space, causing anaphylaxis or secondary cyst formation.

Investigations: Serology (not invariably positive) and compatible ultrasound and CT appearances. Eosinophilia may indicate cyst leakage.

Treatment and clinical management issues: The risks of anaphylaxis and cyst dissemination following surgical or percutaneous interventions are significant and it is recommended that treatment only be carried out in specialist centres. The WHO Informal Working Group on echinococcosis has developed a classification of ultrasound appearances of cysts, on which treatment according to cyst size, location and stage may be based.[45] Puncture, aspiration, injection and re-aspiration (PAIR) together with drug therapy is recommended for simple liver cysts (stage 1) $\geq$5 cm in diameter. Albendazole alone is recommended for cysts $<$5 cm in size. Medical treatment is with albendazole (400 mg bd), duration determined by cyst type, with the addition of praziquantel (20 mg/kg bd) for 2 weeks pre and post aspiration or surgery.[104] Surgery may be indicated for larger, extrahepatic or multiple cysts. Late stage cysts (WHO type 4 or 5) may be treated by careful observation with sequential ultrasound scans.

The more serious *E. multilocularis* is rare in UK practice. A series of small, interconnected cysts infiltrates the infected organ and metastasises to distant organs.[105] The absence of a surrounding membrane makes cyst enucleation at surgery difficult, so radical resection is necessary. Long, often life-long courses of albendazole are required, and recurrence is common.

4.3.2. *Fasciola hepatica/F. giganta*

Incubation period: 3−12 weeks.

Prepatent period: 3−4 months.

Distribution: Worldwide but commonest in individuals returning from the Middle East. Also common in SE Asia, Eastern Europe, Africa and Central America. Fasciola is endemic in sheep and cattle in the UK, with prevalences of up to 86% in dairy herds in Wales.[106]

Mode of transmission: Consumption of vegetation contaminated with encysted intermediate stage metacercariae, or occasionally from chewing Khat (a plant with stimulant properties). Transmission has occurred in the UK after eating wild watercress.

Clinical presentation:

Acute phase (months 3−5): prolonged fever, hepatomegaly causing abdominal pain and eosinophilia.

Chronic phase (6 months onwards): biliary obstruction with elevation of liver enzymes, cholecystitis and liver abscesses (although 50% cases are asymptomatic at this stage).[107,108]

Investigations:

Acute phase: diagnosis is clinical, based on an appropriate travel history and clinical features, with confirmatory serology later.[109] CT in the acute phase may show lesions characteristic of migration of flukes through the liver, or multiple lesions with the appearance of metastases.

Chronic phase: stool microscopy (low sensitivity), serology. Ultrasound may show biliary obstruction. CT may show hepatic calcification or liver abscesses. Occasionally fasciola is seen on ERCP.

Treatment: Triclabendazole 10 mg/kg as a single dose,[110] response is rapid.

4.3.3. Liver flukes: *Clonorchis sinensis* and *Opisthorchis* sp.

Prepatent period: 4 weeks (Clonorchis[111])

Incubation period: 2−4 weeks[112]

Distribution: C. sinensis and *Opisthorchis* sp. are endemic in SE Asia. Opisthorchiasis is endemic in Siberia.

Mode of transmission: Ingestion of intermediate stage metacercariae in raw fish.

Clinical presentation: Acute infection (particularly in the case of *Opisthorchis* infection) may result in fever, abdominal pain, urticarial skin rash and eosinophilia.[113] Chronic infection is more often seen, with asymptomatic hepatomegaly or biliary obstruction. There is an increased risk of cholangiocarcimona and pyogenic cholangitis.[112] Adult flukes live for 20–25 years, so the diagnosis should be considered in those who have not lived in an endemic country for many years.

Investigations: Diagnosis is by concentrated stool microscopy (eggs of each species are indistinguishable). 10–40% individuals have eosinophilia.

Treatment/clinical management issues: Praziquantal 20–25 mg/kg tds for 2 days.

4.3.4. Schistosomiasis – *S. mansoni* and *S. japonicum*

See 4.2.2.

4.4. Eosinophilia with neurological symptoms

There are a small number of parasites which invade the central nervous system (CNS) and cause an eosinophilic meningitis, encephalitis, or myelitis.[114] Peripheral eosinophilia is common but not invariable, so the laboratory must be asked to look specifically for eosinophils within the CSF, which are usually greater than 10%. Inexperienced laboratory technicians may identify eosinophils- with bilobed nuclei- as neutrophils and the diagnosis will be missed. There are few controlled trials to guide therapy.[115,116] The commonest neurological presentation of helminth infection is neurocysticercosis causing seizures, but this seldom causes eosinophilia.

4.4.1. *Angiostrongylus cantonensis* – rat lung worm

Incubation period: 1–3 weeks (range 1 day-3 months).

Distribution: This is a common cause of eosinophilic meningitis in SE Asia, and is well-documented in travellers to this region.[117,118] It has also been reported from the Caribbean[119] and Hawaii.[120]

Mode of transmission: Ingestion of larvae in undercooked snails, prawns, crabs, or frogs.

Clinical presentation: Severe acute headache, meningism, visual disturbance, parasthesiae and cranial nerve palsies.[121]

Investigations: Serology, available via the Hospital for Tropical Diseases, London. Peripheral eosinophilia is marked. CT and MRI of the brain are often normal.[114]

Treatment: Corticosteroids are the mainstay of treatment (prednisolone 60 mg od 14 days), reducing the severity and duration of headache.[115] Albendazole (15 mg/kg/day 14 days)[116] probably has a similar effect. Therapeutic lumbar punctures may be necessary.

4.4.2. Gnathostomiasis – *Gnathostoma spinigerum*

Incubation period: >30 days.

Distribution and mode of transmission: See 4.5.5.

Clinical presentation: Severe and sometimes fatal acute meningo-encephalitis and myelitis. Focal neurology is common, in particular radiculo-myelitis, which presents with excruciating nerve root pain[114]; other complications include sub-arachnoid haemorrhage and intra-cerebral haemorrhage.[122]

Diagnosis: Often clinical; CSF is often xanthochromic or frankly bloody, serology is available via the Hospital for Tropical Diseases, London. Brain imaging may show oedema, haemorrhage and occasionally worm migration.[114,123]

Treatment: Albendazole 400 mg bd 21 days[124] and prednisolone 60 mg/day 14 days.[115]

4.4.3. Neurocysticercosis causing meningitis – *T. solium*

Ingestion of eggs of the pork tapeworm *T. solium* (4.2.4) may result in the development of encysted larvae throughout the body (cysticercosis). Dissemination to the CNS (neurocysticercosis) predominantly causes cerebral space occupying lesions which are rarely associated with an eosinophilia. Subarachnoid cysts, however, can manifest as acute or chronic eosinophilic meningitis.[125,126] Here we focus on this more unusual presentation of neurocysticercosis, which may present with eosinophilia and eosinophilic meningitis.

Incubation period: >1 year.

Distribution: South and SE Asia, Central and South America, probably Africa although data are scarce.[127]

Mode of transmission: Faeco-oral route.

Clinical presentation (of cysticercal meningitis): Severe headache, meningism, altered consciousness, and focal neurological signs resulting from infarction secondary to angiitis.[128] Hydrocephalus is common.

Investigations: Diagnosis is by serology and brain imaging. CSF usually shows lymphocytosis, with CSF eosinophilia in 20% cases and positive CSF serology.[129]

Treatment: The management of classical neurocysticercosis has been well reviewed.[130] For cysticercal meningitis, most authorities suggest albendazole (400 mg bd 14 days) and dexamethasone (4–12 mg/day, reducing after 7 days), with ventricular shunting for hydrocephalus.[125] Repeated courses of treatment may be required. Prognosis is poor in cysticercal meningitis, particularly in the presence of acute hydrocephalus.

4.4.4. Schistosomiasis/bilharzia and CNS symptoms – *Schistosoma haematobium*, *S. mansoni*, *S. japonicum* (4.2.2)

Clinical presentation: Occasionally schistosomiasis in the CNS results in myelitis[131] or, more rarely, meningo-encephalitis. Inflammatory lesions cause cerebral or spinal cord infarction, or mass effect secondary to space-occupying lesions. Involvement of the cord, commonly resulting in paraplegia, is most widely reported in Africa with *S. mansoni* and *S. haematobium* infections, and should always be considered as a cause of gradual onset paraplegia. Cerebral involvement with focal neurological signs or seizures is commonest with *S. japonicum* infection, prevalent in SE Asia. Acute schistosomiasis or Katayama syndrome may present with encephalitis or cerebral vasculitis,[132] with altered consciousness, headache, seizures and focal neurological signs.

Diagnosis: Serology (4.2.2), stool and terminal urine microscopy are often negative, and peripheral eosinophilia may not be present. MRI typically shows enlargement of the affected region of spinal cord in the acute phase, and contract enhancement. MRI brain shows enhancing areas of cerebral, cerebellar or brain stem inflammation, or mass lesions. There is CSF eosinophilia in <50% cases.[131]

Treatment: Praziquantel 40 mg/kg bd 5 days; and dexamethasone 4 mg qds, reducing after 7 days, over a total of 2–6 weeks (expert opinion only).[131] Serology is not invariably positive, so a trial of treatment may be worthwhile in patients with a compatible clinical picture. Acute neuroschistosomiasis (Katayama syndrome accompanied by neurological symptoms) should be initially treated with corticosteroids alone to avoid neurological complications (4.1.1).

4.4.5. Toxocariasis – *T. canis, T. catis* (4.1.3)

T. canis can cause an eosinophilic meningo-encephalitis.[133] Treatment is with corticosteroids,[134] in addition to albendazole.

4.4.6. Coccidioidomycosis and paracoccidioidomycosis – *C. immitis, P. braziliensis* (4.1.7)

Eosinophilic meningitis resulting from infection with these organisms is most commonly seen in the immunocompromised. Presentation is with chronic meningitis,[135,136] usually occurring weeks to months after primary infection.[137] Diagnosis is by CSF serology. CSF shows lymphocytosis and elevated protein. Treatment is with life-long fluconazole 400 mg od.[138,139]

4.4.7. Other causes

CSF eosinophilic pleocytosis is occasionally seen in syphilis, tuberculosis, cerebral vasculitis, and lymphoma. In 1% of cases, paragonimus infection results in meningo-encephalitis, transverse myelitis or myelopathy[140,141] (4.1.6).

4.5. Eosinophilia with skin/musculokeletal symptoms

Helminth infection is frequently associated with skin symptoms, most commonly itch and urticaria. Strongyloidiasis, schistosomiasis, paragonimiasis, trichinosis, ascariasis and hookworm infections all do this in the migratory stage of infection; symptoms may be prolonged in schistosomiasis and strongyloidiasis. Visceral larva migrans may be associated with urticarial rash (4.1.3). ***Cutaneous larva migrans*** can be associated with eosinophilia, but almost always presents with the characteristic migratory rash[142,143] (Fig. 2). Treatment of this infection is with ivermectin (200 μg/kg as a single dose) or albendazole (400 mg od 3 days).[143] Paragonimus occasionally presents with migratory cutaneous nodules (4.1.6). *E. vermicularis* may present with perianal skin rash and intense itch (4.2.8). Ectoparasites such as scabies and, less commonly, myiasis,[144,145] may also present with eosinophilia. Rarely, lepromatous leprosy may cause eosinophilia.

4.5.1. Onchocerciasis – *Onchocerca volvulus*

Incubation period: 8–20 months.

Distribution: Close to fast flowing rivers predominantly in Africa (also parts of Central and South America and the Arabian peninsula).

Mode of transmission: The bite of the Simulium black fly.

Clinical presentation: Diffuse, pruritic dermatitis usually over the legs and buttocks.[146,147] In chronic cases this may develop into a 'leopard skin' pattern of hypo-pigmented patches. Nodules or onchocercoma occur. Migration of microfilaria within the anterior chamber of the eye results in keratitis, anterior uveitis and choroidoretinitis,

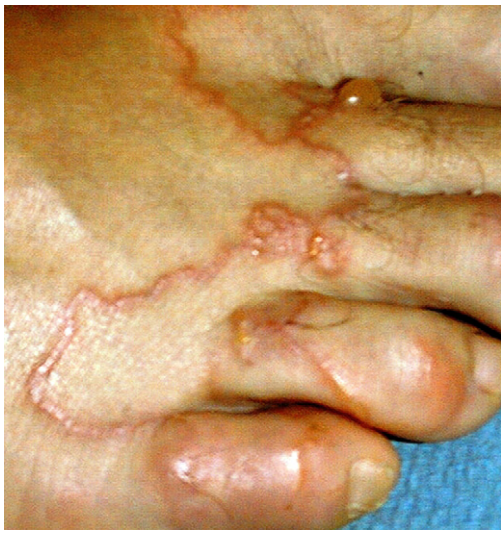

Figure 2 Cutaneous larva migrans. Copyright to Dr. Ron Behrens, Hospital for Tropical Diseases, London, UK.

with pain and redness and eventual blindness (river blindness). Dermatitis and limb swelling are often the only manifestation in travellers.[147,148]

Investigations: Microscopic visualisation of microfilariae following incubation of skin snips in normal saline (low sensitivity, particularly in recent infection[149]). Microfilariae seen on slit lamp examination (very rarely in travellers). Positive filarial serology supports the diagnosis.

Treatment: Ivermectin 200 μg/kg monthly for 3 months, repeated every 3–6 months usually for several years. Seek opthalmological advice and observe the first dose.

4.5.2. Larva currens – *S. stercoralis*

This is an itchy, linear, urticarial rash associated with strongyloides infection (Fig. 3). It typically moves several millimetres per second, and is the result of subcutaneous larval migration. It occurs most commonly around the trunk, upper legs and buttocks (4.2.1).

4.5.3. Lymphatic filariasis – *W. bancrofti, B. malayi*

Incubation period: 4 weeks to 16 months.

Prepatent period: W. bancrofti: 7–8 months, *B. malayi:* 2 months.

Distribution: W. bancrofti: worldwide tropical distribution,[150] *B. malayi:* mainly Asia.

Mode of transmission: Mosquito-borne, requires months of exposure in an endemic area.

Clinical presentation: Fever, lymphadenitis, lymphangitis, lymphoedema and scrotal oedema. Non-immune travellers may present acutely, with fever and respiratory symptoms (4.1.4).

Investigations: Microscopy of blood taken within 2 h of midnight and serology.

Treatment: Treatment is with diethylcarbamazine; **see warning**, Box 2. Seek specialist advice. When lymphatic damage is established, ongoing care is directed towards limb care (elevation, bandaging) and prompt recognition and treatment of acute inflammatory episodes.[150]

Other filariases such as *Mansonella perstans* can cause eosinophilia, may be associated with pruritus and other

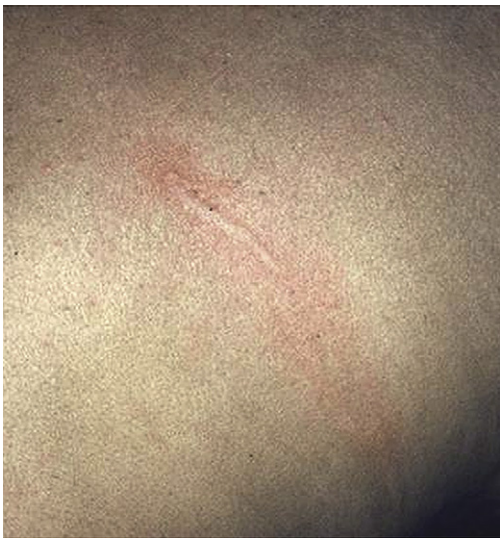

Figure 3 Migratory, urticarial rash of *larva currens* (strongyloides infection). Copyright to Dr. Alison Grant, Hospital for Tropical Diseases, London, UK.

non-specific symptoms in travellers and expatriates and may be diagnosed by filarial serology, blood microscopy or skin snips. They are rarely associated with long-term serious pathology and only merit therapy if eosinophilia does not resolve spontaneously.

4.5.4. Loiasis — *Loa loa*

Loiasis is caused by the filarial parasite *Loa loa*.

Incubation period: 6 months—6 years.

Prepatent period: ≥17 months.[151]

Distribution: Areas of central and West Africa only.

Mode of transmission: Chrysops fly.

Clinical presentation: Migratory soft tissue 'Calabar' swellings, usually on the limbs, usually lasting for several days. In 10—20% of cases[18] the adult worm is seen migrating across the conjunctiva.

Investigations: Diagnosis is by microscopic visualisation of microfilariae in a 'day blood' sample taken within 2 h of midday or is clinical if conjunctival migration is seen. Positive filarial serology supports the diagnosis.

Treatment and clinical management issues: diethylcarbamazine: **see warning**, Box 2. Adverse events such as fever, headache, itching and oedema may occur, in proportion to the microfilarial load.

4.5.5. Gnathostomiasis — *Gnathostoma spinigerum*

Incubation period: 3—7 days.

Distribution: Endemic in SE Asia, reports from South and Central America.[152] Often occurs in outbreaks.[153,154]

Mode of transmission: Ingestion of a larval stage of *G. spinigerum*, usually found in under-cooked fish, frog, snake or chicken.

Clinical presentation: Intermittent subcutaneous swelling associated with pruritis and oedema, occasionally eosinophilic meningo-encephalitis or myelitis (4.4.2).

Investigations: Diagnosis is based on classical clinical picture of intermittent swelling and marked eosinophilia. Serology is available via the Hospital for Tropical Diseases, London.

Treatment: Albendazole 400 mg bd for 21 days.[155] Repeat treatment may be required; ivermectin 200 μg/kg od 2 days is an alternative.[156,157]

4.5.6. Trichinellosis — *Trichinella spiralis*

Trichinellosis consists of 2 phases; an initial 'enteral' phase of diarrhoea and gastrointestinal symptoms, which is followed by a parenteral phase consisting of facial and periorbital oedema, urticarial rash, severe myalgia and muscle weakness. See Section 4.2.9.

4.5.7. Swimmers' itch/cercarial dermatitis — *Schistosoma* sp.

This occurs as a result of a localised subcutaneous infection by species of schistosome which usually infect birds.[158]

Incubation period: Hours.

Distribution: Worldwide, often occurring in outbreaks.[159]

Mode of transmission: Fresh and salt water exposure, usually through swimming, allows cercariae released from snails to penetrate skin.

Clinical presentation: Itchy maculopapular rash.

Investigations: Diagnosis is clinical.

Treatment/clinical management: There are no serious sequelae; the rash resolves spontaneously over days to weeks, and may respond to topical corticosteroids.

4.6. Eosinophilia and urinary symptoms

4.6.1. Schistosomiasis/bilharzia — *Schistosoma haematobium* (4.2.2)

This is increasingly commonly imported into Europe.[160,161]

Prepatent period: 5—12 weeks.

Distribution: In travellers returning to the UK the great lakes of East and southern Africa (Lakes Malawi, Victoria and the Okavango delta) are the commonest sources.

Clinical Presentation: Often asymptomatic or microscopic haematuria only; symptoms include macroscopic haematuria, proteinuria, dysuria, haematospermia.[71,72,162] May present acutely with acute schistosomiasis, or 'Katayama syndrome' (4.1.1).

Mode of transmission: See 4.1.1.

Investigations: Serology and microscopy of nitrocellulose — filtered terminal urine; midday collection of urine for microscopy increases sensitivity, but the sensitivity remains too low for microscopy to be used in isolation.[3,24] Urine dipstick for microscopic haematuria and proteinuria has low sensitivity, and should not be relied on.[163] Seroconversion usually occurs between 4 and 8 weeks (up to 22 weeks).

Treatment and clinical management: Light infections in travellers require treatment with praziquantel 40 mg/kg[31] as a single dose. *S. haematobium* infection has been linked to squamous cell carcinoma of the bladder,[163] and potentially heavy infections associated with haematuria warrant further investigation. Other complications include obstructive uropathy, bladder stones and bacterial superinfection. Serology may remain positive for many years, so should not be used to assess success of treatment.[74,77]

5. Conclusion

Eosinophilia is common in returning travellers and migrants, and often indicates an underlying helminth infection. Concentrated stool microscopy and strongyloides serology should be performed on all patients regardless of geographic exposure. Recommended additional investigations depend on the region visited and the presence of suggestive signs and symptoms. In the absence of a specific diagnosis empiric treatment with an antihelminthic agent such as albendazole may be considered. Non-infective causes should be considered, particularly if the eosinophilia is persistent.

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