



## Review

## UK guidelines for the investigation and management of eosinophilia in returning travellers and migrants

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## SUMMARY

Eosinophilia is a common finding in returning travellers, migrants and other travelling groups. In this setting, it often indicates an underlying helminth infection. Infections associated with eosinophilia are frequently either asymptomatic or associated with non-specific symptoms but some can cause severe disease. Here the British Infection Association guidelines group has comprehensively reviewed and updated the UK recommendations for the investigation and management of eosinophilia in returning travellers, migrants and other relevant groups, first published in 2010.<sup>1</sup> Literature reviews have been undertaken to update the evidence on the prevalence and causes of eosinophilia in these groups and on the treatment of relevant pathogens and clinical conditions. Diagnostic tests available to UK-based clinicians are summarised.

Changes made to the guidelines include updates in the sections on the investigation and empirical treatment of asymptomatic eosinophilia and on the treatment of trichuriasis, lymphatic filariasis, onchocerciasis, hookworm, fascioliasis and taeniasis. Pathogens which are rarely encountered in UK practice have been removed from the guidelines and others added, including an expanded section on fungal infection. A section on off-license and rarely used drugs has been included.

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## 1. Introduction

Eosinophilia occurs commonly in returning travellers and migrants. Where endemic helminth infection rates are low, the reported prevalence is 2%–10%<sup>2–7</sup> in returning travellers, and 12–31% in migrants.<sup>8–13</sup> Here, we define eosinophilia as a peripheral blood eosinophil count of  $> 0.5 \times 10^9/L$ .<sup>14</sup>

While there are many causes, helminths (worms) are the commonest identifiable cause of eosinophilia in the returning traveller or migrant, with diagnosis rates varying from 19%–80%.<sup>2–5,10,11,12,15,16–21</sup> Helminth infections causing eosinophilia are usually self-limiting and benign, but some can cause long-term health problems and thus are important to recognise and treat. For example, *Strongyloides stercoralis* infection can persist lifelong and later present as hyperinfection syndrome, with a high mortality, in those who become immunocompromised.<sup>22,23</sup> *Schistosoma haematobium* is associated with squamous cell bladder carcinoma.<sup>24,25</sup>

This document guides the investigation and management of returning travellers and migrants of all ages with eosinophilia. Many people with helminth infection do not have eosinophilia, so testing for eosinophilia alone is not an adequate screening strategy for helminth infection.

Some of the infections discussed are rarely diagnosed in the UK outside of dedicated tropical medicine units. **Box 1** summarises contact details of specialist 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**).

There are multiple non-infectious causes of a peripheral blood eosinophilia (see **section 1.1**), so patients may present to a range of specialities. These recommendations are intended to guide infection specialists investigating and managing returning travellers/ migrants

with eosinophilia, and do not comprehensively cover non-infectious causes.

### 1.1. Non-infectious causes

See **Table 1**. In countries with low rates of endemic helminth infections, the commonest non-infectious causes of eosinophilia are allergy and atopy (asthma, eczema and hay fever), as well as drugs.<sup>26–28</sup> Rarer, but potentially serious, causes include systemic vasculitis as well as malignancy, such as lymphomas and myeloid neoplasms. Malignant causes have been comprehensively reviewed in the British Society for Haematology Guideline for the Investigation and Management of Eosinophilia.<sup>14</sup>

Regardless of the cause, persistent eosinophilia of any degree, and especially at very high levels, can cause significant end-organ damage, particularly affecting the heart, lungs, and central nervous system.<sup>14</sup> Any patient presenting with evidence of end-organ damage needs urgent medical assessment and consideration of emergency treatment. If patients have eosinophilia  $\geq 1.5 \times 10^9/L$  for more than 3 months but no evidence of end organ damage, consider referring them to a haematologist for further investigations once infectious causes have been excluded or treated. In some cases of persistent eosinophilia, no cause can be identified – a condition termed idiopathic hypereosinophilia (or idiopathic hyper-eosinophilic syndrome if there is evidence of end-organ damage).<sup>14</sup>

#### Box 1

Specialist Laboratory/Clinical Advice units.

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

##### Hospital for Tropical Diseases.

Department of Clinical Parasitology, 3rd Floor Mortimer Market, Capper Street, London, WC1E 6JB, UK.  
DX 6640701.

<https://uclh.nhs.uk/our-services/find-service/pathology-1/parasitology>

Laboratory telephone: + 44 (0)20 7307 9400 (ask for Parasitology Microscopy or Parasitology Serology as required).

Clinical management:

Email: [uclh.parasitologyspr@nhs.net](mailto:uclh.parasitologyspr@nhs.net).

Telephone: UCLH switchboard at + 44(0)2034567890 and ask for the Tropical SpR on call (24 h) or the Parasitology Registrar (weekdays 9am– 5pm).

##### Liverpool School of Tropical Medicine.

Clinical Diagnostic Parasitology Laboratory, Pembroke Place, Liverpool L3 5QA, UK.

Diagnostic Parasitology Laboratory DX 6966301.

Telephone: + 44(0)1517053220.

<https://www.lstmed.ac.uk/CDPL>.

Clinical management:

Email: [ahn-tr.liverpooltropicalclinics@nhs.net](mailto:ahn-tr.liverpooltropicalclinics@nhs.net).

Tel: + 44(0)1517062000 (24 h, ask for Tropical/ID physician on call).

##### Scottish Microbiology Reference Laboratories (SMiRL) Glasgow (Includes parasitology).

Level 5 New Lister Building, Glasgow Royal Infirmary, 10–16 Alexandra Parade, Glasgow, G31 2ER.

DX 6490200.

Telephone: +44(0)1412018663.

Email: [ggc.glasgowsmrl@nhs.scot](mailto:ggc.glasgowsmrl@nhs.scot).

<https://www.nhs.uk/scottish-microbiology-reference-laboratories>

##### UKHSA Mycology Reference Laboratory.

National Infection Services, UKHSA South West Laboratory.

Science Quarter, Southmead Hospital, Bristol BS10 5NB.

DX6120200.

Telephone: + 44(0)1174146222.

<https://www.gov.uk/government/collections/mycology-reference-laboratory-mrl>.

##### Other sources of information:

- UK Health Security Agency (UKHSA) <https://www.gov.uk/government/organisations/uk-health-security-agency>
- Centers for Disease Control and Prevention (CDC) <https://www.cdc.gov/>
- ProMed International Society for Infectious Diseases (ISID) <https://promedmail.org/>
- Fever Travel: Provides comprehensive information on disease distribution by country. <http://www.fevertravel.ch/>
- Geosentinel: Worldwide and European surveillance data on imported infection. <https://geosentinel.org/>
- TropNet Europe: <http://tropnet.eu/>

**Table 1**  
Non-infectious causes of eosinophilia.

Class of disorder	Examples	Suggestive features	Key tests & next steps
Respiratory and allergic disorders	Allergic rhinosinusitis Asthma Allergic bronchopulmonary aspergillosis (ABPA) Eosinophilic pneumonias (EP): <ul style="list-style-type: none"> <li>• Secondary to drugs</li> <li>• Secondary to dust inhalation</li> <li>• Secondary to EGPA</li> <li>• Idiopathic EP (acute &amp; chronic types)</li> <li>• Secondary to helminths (Loeffler's syndrome, see <a href="#">section 6.1.2</a>)</li> </ul>	Nasal blockage, discharge, facial pain, loss of smell Cough, wheeze, breathlessness	<ul style="list-style-type: none"> <li>• Nasal examination</li> <li>• Peak expiratory flow rate (PEFR) variability, spirometry + bronchodilator reversibility testing, exhaled nitric oxide (FeNO)</li> <li>• Serum total IgE and <i>Aspergillus fumigatus</i>-specific IgE</li> <li>• Chest X-ray/imaging</li> <li>• Consider bronchoalveolar lavage with differential cell count (to investigate EP), cytology/microscopy (including parasite/fungal) and microbiological cultures</li> </ul>
Vasculitis	Eosinophilic granulomatous polyangiitis (EGPA, formerly Churg Strauss syndrome)	Asthma/asthma like symptoms, ear nose and throat (ENT) disease, pulmonary infiltrates + /- extrapulmonary signs of vasculitis (e.g. renal, neurological, cardiac, skin)	<ul style="list-style-type: none"> <li>• Anti-neutrophil cytoplasmic antibodies (ANCA) screen, anti-nuclear antibody (ANA)</li> <li>• Chest CT scan</li> <li>• Consider referral for rheumatology/ respiratory opinion</li> <li>• Attempt tissue diagnosis for suspected EGPA</li> <li>• Full blood count</li> <li>• Blood film</li> <li>• Cross-sectional imaging</li> <li>• Haematology referral for bone marrow biopsy and gene mutation / fusion analysis</li> </ul>
Malignant disorders (mostly haematological)	Myeloid neoplasms <ul style="list-style-type: none"> <li>• Chronic eosinophilic leukaemia</li> <li>• Chronic myeloid leukaemia</li> <li>• Acute myeloid leukaemia</li> <li>• Myeloid neoplasms with eosinophilia and rearrangements of specific genes</li> <li>• Systemic mastocytosis</li> </ul> Lymphoproliferative neoplasms <ul style="list-style-type: none"> <li>• Hodgkin lymphoma</li> <li>• Non-Hodgkin lymphoma</li> </ul> Solid organ cancers – e.g. adenocarcinoma of lung, pancreas, thyroid	Weight loss, fevers, sweats, lymphadenopathy, hepatosplenomegaly, recurrent infections	<ul style="list-style-type: none"> <li>• Serology for coeliac disease: IgA tissue transglutaminase antibodies</li> <li>• Faecal calprotectin</li> <li>• Endoscopy</li> <li>• Detailed drug history- see<sup>27</sup></li> </ul>
Gastrointestinal disorders	Primary gastrointestinal eosinophilic disorders <ul style="list-style-type: none"> <li>• e.g. eosinophilic oesophagitis, colitis, gastritis</li> </ul>	Dysphagia, diarrhoea, nausea/vomiting, abdominal pain, weight loss, malabsorptive symptoms, stool changes	
Drugs	Anti-infective agents Anticonvulsants Non-steroidal anti-inflammatory drugs ACE inhibitors Proton pump inhibitors	Manifestations range from mild/self-limiting peripheral eosinophilia to potentially life-threatening reactions e.g. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome <sup>28</sup>	
Others	Rheumatological disorders <ul style="list-style-type: none"> <li>• e.g. Systemic lupus erythematosus, Rheumatoid arthritis</li> </ul> Sarcoidosis	Rash, arthralgia/ arthritis, renal dysfunction, fatigue, serositis, neurological symptoms  Fatigue, respiratory symptoms, skin rashes, uveitis	<ul style="list-style-type: none"> <li>• ANA, anti-double-stranded DNA, erythrocyte sedimentation rate (ESR), complement, rheumatoid factor, anti-CCP, antiphospholipid antibodies</li> <li>• Blood biochemistry (liver, kidney, calcium)</li> <li>• Serum Angiotensin Converting Enzyme (ACE)</li> <li>• Chest X-ray/imaging</li> <li>• Biopsy evidence of non-necrotising granulomas (exclude other causes of granulomatous diseases e.g. tuberculosis)</li> <li>• IgE &amp; IgM levels</li> <li>• Referral for specialist opinion if any suggestive features</li> <li>• Paired serum cortisol and plasma adrenocorticotrophic hormone (ACTH), Synacthen test</li> </ul>
	Immunodeficiencies <ul style="list-style-type: none"> <li>• e.g. Hyper IgE syndrome, Omenn syndrome</li> </ul> Addison's disease	History of recurrent infections  Unexplained collapse, hypotension, vomiting or diarrhoea, hyperpigmentation, electrolyte abnormality, co-existing autoimmune disease	
	Gleich syndrome	Episodic angioedema, fever, urticaria, weight gain	<ul style="list-style-type: none"> <li>• Immunoglobulins</li> </ul>
Unknown etiology	Idiopathic hypereosinophilia  <ul style="list-style-type: none"> <li>• In presence of end-organ damage, this is termed Idiopathic hypereosinophilic syndrome</li> </ul>		<ul style="list-style-type: none"> <li>• Refer to haematology if significant eosinophilia persists and no underlying cause is identified</li> </ul>

## 2. Summary of updates to guidance

- A comprehensive literature review has been undertaken to update the epidemiology of asymptomatic eosinophilia and its common causes. As a result:

- The algorithm for the first line investigation of asymptomatic eosinophilia has been updated: filarial investigations are now only recommended for those with a history of travel to/residence in West Africa. Serology is now suggested as the sole first line test, with day/ night bloods no longer recommended

in first line testing. This is due to changes in the global prevalence of filarial infections resulting in fewer cases being diagnosed in the UK.

- The treatment of asymptomatic eosinophilia in those aged > 24 months has been updated to recommend empirical albendazole (400 mg single dose) plus ivermectin (200 µg/kg single dose).
- The pathogens included have been updated in line with those commonly encountered in clinical practice e.g. within "Eosinophilia with gastrointestinal symptoms" a section on *Cystoisospora belli* has been added and *Angiostrongylus costaricensis* has been removed
- Updates have been made to reflect important changes in the epidemiology of infections causing eosinophilia (Table 2)
- Parasitological tests available at UK national laboratories and tests outside the UK available to UK clinicians have been reviewed and updated (Table 4)
- A comprehensive literature review of the treatment options for each pathogen has been conducted and, based on new evidence, significant updates made to the advice for several conditions including: trichuriasis, lymphatic filariasis, onchocerciasis, hookworm, fascioliasis and taeniasis.
- Where recommended drugs are not routinely used in UK practice, a new section has been added on their side effects, monitoring and use in pregnancy (Table 5).
- A section on diagnostic tests and treatment of fungal infections has been added (Table 6)

### 3. Methods

#### 3.1. Updating the evidence on the causes of eosinophilia in returning travellers/migrants

A comprehensive literature review was performed to update the evidence on prevalence of eosinophilia and its causes in returning travellers/migrants (Sections 1, 4.1, 5). This evidence was used to inform the recommendations for the investigation of asymptomatic eosinophilia (Section 5). A literature search to identify studies, set in countries with low endemic rates of helminth infection, examining "eosinophilia" in "returning travellers or migrants" was performed by an experienced information specialist (full details of search terms and strategy are available online<sup>57</sup>). 1208 articles were identified. Titles and abstracts were deduplicated and screened by one reviewer according to pre-specified inclusion and exclusion criteria (inclusion criteria: study with a primary aim to describe eosinophilia within study population; systematic reviews or observational cohorts; study population was returning tourists, returning non-tourist travellers (e.g. military, those who had visited friends and relatives), migrants, refugees or expatriates; the study was set in a one of a pre-specified list of countries deemed to have low rates of endemic helminth infection (see full search strategy<sup>57</sup> for list). Exclusion criteria: other article types (e.g. letters, editorials, case reports, narrative reviews); animal studies; non-English language papers). Full-text reviews were performed on shortlisted articles (n = 37) by one reviewer to identify relevant papers according to the same inclusion/exclusion criteria. Data was extracted from included papers (n = 23).

#### 3.2. Updating the evidence on the treatment of pathogens

A comprehensive literature review updating treatment recommendations for pathogens that can cause eosinophilia was performed. Literature searches to identify randomised controlled trials (RCTs) and systematic reviews (SRs) examining the treatment of relevant pathogens and clinical conditions were performed by an experienced information specialist (full details of search terms and

strategy available online<sup>57</sup>). The searches for RCTs identified 8730 possible articles and the searches for SRs identified 3082. Duplicates were removed and each article was screened (title and abstract) by one reviewer according to pre-specified inclusion and exclusion criteria (inclusion: study addresses the treatment of a pathogen of interest (see Appendix 1); study design: RCT or SR. Exclusion: other article types (e.g. letters, editorials, case reports, narrative reviews); animal studies; non-English language papers). Shortlisted articles (n = 663) were labelled according to the pathogen of interest and full texts sourced (where available). Each section author reviewed the full texts for the pathogens within their section and included the most relevant references favouring more recent papers and those with higher levels of evidence e.g. SRs.

Many parasitological causes of eosinophilia are neglected tropical diseases with a paucity of SR and RCT evidence available to guide treatment. Where this was the case, authors undertook additional independent literature searches to identify case series and cohorts to support treatment recommendations. Where evidence was particularly sparse or conflicting, consensus decision was made between authors. The wording of the recommendations reflects the level of evidence available:

- Recommend: SR or RCT evidence available
- Suggest: no SR or RCT evidence available but cases series/ cohorts available
- Expert opinion: an area with either very limited evidence or conflicting evidence where recommendation is based on a consensus decision among authors

#### 3.3. Diagnostics

To ensure the detail offered in this guideline is relevant to UK clinicians, the parasitological and fungal diagnostics section is tailored to the testing currently available to clinicians at national laboratories. For the parasitology diagnostics section, the full complement of investigations offered at the Hospital for Tropical Diseases, Liverpool School of Tropical Medicine, and Glasgow Diagnostic & Reference Parasitology Service specialist laboratories was collated, including specific detail on sensitivity and specificity of serological assays at the time of writing. We also list relevant tests that are not performed in the UK but may be sent by specialist parasitology laboratories to the Swiss Tropical and Public Health (STPH) Institute e.g. *Gnathostoma* spp. serology. The same approach was used for the fungal diagnostics section, primarily based upon the Bristol Mycology Reference Laboratory service.

### 4. General principles

#### 4.1. Patient group

Clinical presentation may vary depending on the patient group. Migrants have a higher prevalence of helminth infections<sup>4,20</sup> but exposure may be remote in time, while travellers are often newly infected and may have a more acute immune response, with more pronounced eosinophilia.<sup>58</sup> However, infection with multiple helminth species occurs predominantly in migrants, and can be associated with greater eosinophilia.<sup>5,12,18</sup> Rare complications of chronic schistosomiasis such as squamous cell carcinoma of the bladder or portal hypertension are more often seen in migrants, whereas syndromes of acute infection such as acute schistosomiasis and Loefler's syndrome are more frequent in travellers. It is important to recognise the limitations of serology in **immunocompromised patients** and the particular importance of test of cure in this group (e.g. following strongyloidiasis treatment).

**Table 2**  
The worldwide geographical distribution of imported pathogens causing eosinophilia.

Organism	Common name/ syndrome	Americas				Asia Pacific				Europe	Middle East	Africa	
		North America	South America	Central America	Caribbean	Central & South Asia	Eastern Asia	Southeastern Asia	Australia & Oceania			Northern Africa	Sub-Saharan Africa <sup>1</sup>
<i>Ancylostoma duodenale</i> / <i>Necator americanus</i>	Hookworm									Southern Europe			
<i>Ancylostoma</i> spp.	Zoonotic hookworm, cutaneous larva migrans									Mainly Southern Europe			
<i>Angiostrongylus cantonensis</i>	Eosinophilic meningitis, rat lung worm	Hawaii, rare in USA mainland					China		Pacific Islands, rare in Australia		Israel (sporadic cases only)		
<i>Anisakis</i> spp./ <i>Pseudoterranova</i> spp.*	Anisakiasis												
<i>Ascaris lumbricoides</i>	Roundworm, ascariasis	Very rare								Very rare			
<i>Blastomyces</i> spp.	Blastomycosis					India							
<i>Brugia malayi</i> / <i>B. timori</i>	Lymphatic filariasis, tropical pulmonary eosinophilia												
<i>Clonorchis sinensis</i> / <i>Opisthorchis</i> spp.	Clonorchiasis Opisthorchiasis					Opisthorchis spp.: central Asia				<i>Clonorchis</i> spp.: East Russia. <i>Opisthorchis</i> spp.: Germany, Italy, Russia, Eastern Europe			
<i>Coccidioides immitis</i>	Coccidioidomycosis, "valley fever"	Especially Arizona and Southern California											
<i>Cystoisospora belli</i>	Cystoisosporiasis												
<i>Echinococcus granulosus</i> **	Cystic echinococcosis, cystic hydatid												
<i>Echinococcus multilocularis</i> ***	Alveolar echinococcosis, alveolar hydatid						Especially China				Turkey		
<i>Enterobius vermicularis</i>	Pinworm, threadworm												
<i>Fasciola hepatica</i> / <i>F. gigantica</i>	Fascioliasis												
<i>Gnathostoma</i> spp.	Gnathostomiasis												
<i>Histoplasma capsulatum</i>	Histoplasmosis						China		Small area in Australia				
<i>Hymenolepis</i> spp.	Dwarf tapeworm, hymenolepiasis	****							****	****			
<i>Loa loa</i>	Eye worm, Calabar swelling, loiasis												Central /West Africa & South Sudan
<i>Onchocerca volvulus</i>	Onchocerciasis, river blindness		Yanomami area								Yemen		Mainly Central/ West Africa Limited distribution in East Africa and Southern Africa
<i>Paracoccidioides</i> spp.	Paracoccidioidomycosis												
<i>Paragonimus</i> spp.	Paragonimiasis					South Asia				Russia			
<i>Schistosoma haematobium</i>	Schistosomiasis, bilharzia, Katayama syndrome									Occasional cases linked to defined river systems			
<i>Schistosoma mansoni</i> / <i>S. japonicum</i> / <i>S. intercalatum</i> / <i>S. mekongi</i> / <i>S. guineensis</i>	Schistosomiasis, bilharzia, Katayama syndrome		Brazil, Venezuela, Suriname				China	Philippines, Indonesia, Mekong River basin					

(continued on next page)

Table 2 (continued)

<i>Schistosoma</i> spp.	Cercarial dermatitis, Swimmers' itch												
<i>Strongyloides</i> spp.	Strongyloidiasis									Southern & Eastern Europe			
<i>Taenia saginata</i>	Beef tapeworm									Especially Eastern Europe, Russia			Especially Eastern Africa
<i>Taenia solium</i>	Pork tapeworm, cysticercosis									Eastern Europe			
<i>Toxocara canis/T. cati</i>	Toxocariasis, Visceral larva migrans												
<i>Trichinella</i> spp.	Trichinellosis, trichinosis		Especially Argentina				Especially China			Especially Eastern Europe, Russia			
<i>Trichuris trichiura</i>	Whipworm									Very rare			
<i>Wuchereria bancrofti</i>	Lymphatic filariasis, tropical pulmonary eosinophilia				Haiti	India, Nepal			Some Pacific islands				Not South Africa, Botswana, Namibia or Somalia
	Present/endemic												
	Present but occurrence associated with limited access to adequate sanitation												
	Rare												
	Not endemic to region												

The presence of a pathogen in each geographical region is indicated by cell colour (see key). Where the pathogen has a limited distribution within a region, areas where it occurs are listed. If a pathogen is present throughout a region but particularly within a certain area this is noted as "Especially..."

\* Although found worldwide, transmission is only associated with the ingestion of raw fish

\*\* Although *Echinococcus granulosus* is distributed worldwide, cases in the UK most commonly originate from Eastern Europe, the Middle East and North Africa

\*\*\* Occurs in the Northern hemisphere only

\*\*\*\* Most often associated with children and those living in institutions

<sup>1</sup> "Sub-Saharan Africa" refers to countries comprising the UN regions of East Africa, West Africa, Central Africa and Southern Africa

## 4.2. Geographical area

The incidence of imported helminth infections depends on the geographical area visited. The geohelminths *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm species are distributed worldwide in areas with limited sanitation. Others, especially those with a complex lifecycle involving an intermediate host/vector, or those associated with certain foods, have defined geographical limits. Table 2 lists commoner helminth infections by geographical area and Table 3 summarises clinical presentations. A detailed travel history should include exact timings of possible exposures such as swimming in freshwater lakes in Africa, walking barefoot, drinking water and foods consumed (e.g. salads, raw fish). See Box 1 for further resources available.

## 4.3. Timing

Eosinophilia may be transient in association with the tissue migration phase of infection, which occurs during the **prepatent period**, when parasite eggs or larvae are not detectable. Samples sent for microscopy for ova or parasites may be negative at this stage. 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.

## 4.4. Serology

Cross-reactivity is commonly seen in helminth infection and common instances of this are outlined in Table 4 (e.g. low level positive filarial serology in strongyloidiasis). The decision to request specific serology should be based on clinical presentation and epidemiology. Beware requesting serological tests where the epidemiology does not support the diagnosis, as false positive results may

lead to unnecessary tests and treatment. Seek expert advice if you are struggling to interpret helminth serology, to avoid unnecessary treatment or investigation. Most serological tests will not become positive until 1–3 months after infection, so in the acute setting serology is often negative and convalescent serology required.

## 4.5. Treatment

Some of the drugs recommended in the guideline are unlicensed or hard to source within the UK. Table 5 gives information on adverse effects, monitoring and use in pregnancy for these drugs. Contact the Hospital for Tropical Diseases, UCLH, London, or the Liverpool School of Tropical Medicine for advice on drug procurement. Some tropical centers keep stocks of certain medicines-see Box 1 for contact details. Additional information on the treatment of parasitic infections in children has been recently published.<sup>33</sup>

## 5. Investigating asymptomatic eosinophilia

Eosinophilia is asymptomatic in 12–81% of returning travellers and migrants.<sup>2,4,5,10,12,13,18,20</sup> Common causes of eosinophilia are intestinal helminths, schistosomiasis, strongyloidiasis and filariasis,<sup>3–5,8,10,12,15,20,21,59</sup> although often no cause is found<sup>2,3,5,7,12,13,18,20,21</sup> or, conversely, multiple causes may be found (in up to 28% of patients in some studies).<sup>5,10,12,15,20,21,59</sup>

We propose an initial approach to investigating asymptomatic eosinophilia in returning travellers and migrants based on geographical area visited,<sup>5,20</sup> as illustrated in Fig. 1. Screening for helminths in the absence of both symptoms and eosinophilia is justifiable in some situations (e.g. a history of freshwater contact in Africa and in some refugee/ migrant populations), but this is beyond the remit of these recommendations.

All returning travellers/migrants with eosinophilia should be investigated with concentrated stool microscopy (or alternative tests

**Table 3**

The common symptomatic presentations of pathogens that cause eosinophilia.

Organism	Common name/syndrome	Respiratory	Gastrointestinal	Hepatobiliary	Neurological	Cutaneous/muscle	Other
<i>Ancylostoma duodenale</i> / <i>Necator americanus</i>	Hookworm	wheeze, dry cough (Loeffler's syndrome)	nausea, vomiting, diarrhoea, abdominal pain			urticarial rash (Loeffler's syndrome), transient itch / maculopapular rash	fever (Loeffler's syndrome) anaemia (children)
<i>Ancylostoma</i> spp.	Zoonotic hookworm, Cutaneous larva migrans					migratory serpiginous rash	
<i>Angiostrongylus cantonensis</i>	Eosinophilic meningitis, rat lung worm				severe headache, meningism, focal neurological signs		
<i>Anisakis</i> spp./ <i>Pseudoterranova</i> spp.	Anisakiasis		acute severe abdominal pain, nausea and vomiting				anaphylaxis
<i>Ascaris lumbricoides</i>	Roundworm, ascariasis	wheeze, dry cough (Loeffler's syndrome)	abdominal pain, diarrhoea intestinal obstruction (children)	biliary obstruction		urticarial rash (Loeffler's syndrome)	fever (Loeffler's syndrome)
<i>Blastomyces</i> spp.	Blastomycosis	acute: productive, cough, dyspnoea, chest pain chronic: cough, haemoptysis			brain abscesses or meningitis	verruccous lesions with irregular borders	bone and joint involvement - osteomyelitis chronic: fever, weight loss
<i>Brugia malayi</i> / <i>B. timori</i>	Lymphatic filariasis, tropical pulmonary eosinophilia	dry cough, wheeze, breathlessness (tropical pulmonary eosinophilia)				lymphadenitis, lymphoedema, hydrocele	fever (tropical pulmonary eosinophilia)
<i>Clonorchis sinensis</i> / <i>Opisthorchis</i> spp.	Clonorchiasis Opisthorchiasis		acute: abdominal pain	hepatomegaly, biliary obstruction chronic: cholangiocarcinoma		acute: urticarial skin rash	acute: fever
<i>Coccidioides immitis</i>	Coccidioidomycosis, "valley fever"	acute: cough, pleuritic chest pain chronic: cough			chronic: meningitis	acute: rash	acute: fever, headache chronic: night sweats, weight loss
<i>Cystoisospora belli</i>	Cystoisosporiasis		abdominal pain, diarrhoea, nausea				fever
<i>Echinococcus granulosus</i>	Cystic echinococcosis, cystic hydatid	cough, pleuritic pain, breathlessness, haemoptysis		asymptomatic, right upper quadrant pain, hepatomegaly biliary obstruction		bone involvement (rare)	fever, anaphylaxis, involvement of any organ
<i>Echinococcus multilocularis</i>	Alveolar echinococcosis, alveolar hydatid	cough, shortness of breath		asymptomatic, right upper quadrant pain, hepatomegaly, jaundice			disseminated infection to any organ late in infection
<i>Enterobius vermicularis</i>	Pinworm, threadworm		diarrhoea, abdominal pain, weight loss			pruritis ani	vaginal discharge
<i>Fasciola hepatica</i> / <i>F. gigantica</i>	Fascioliasis			acute: upper abdominal pain, nausea chronic: biliary obstruction and hepatic abscess		acute: rash	acute: fever
<i>Gnathostoma</i> spp.	Gnathostomiasis		abdominal pain		severe meningo- encephalitis and myelitis, focal neurology, intra-cranial haemorrhage	migratory subcutaneous nodules, pruritis, oedema	iritis/uveitis
<i>Histoplasma capsulatum</i>	Histoplasmosis	acute: cough, pleuritic chest pain chronic: cough	GI symptoms uncommon unless disseminated		stroke, focal CNS lesions, chronic meningitis, encephalitis	varied: papules, plaques, ulcers, vesicles, pustules, abscesses, nodules	acute: fever chronic: night sweats, weight loss
<i>Hymenolepis</i> spp.	Dwarf tapeworm, hymenolepiasis		diarrhoea, abdominal pain				
<i>Loa loa</i>	Eye worm, Calabar swelling, loiasis					Calabar swelling	conjunctival worm migration
<i>Onchocerca volvulus</i>	Onchocerciasis, river blindness					nodules, pruritic dermatitis, limb swelling	keratitis, anterior uveitis, chorioretinitis
<i>Paracoccidioides</i> spp.	Paracoccidioidomycosis	acute: cough, pleuritic chest pain chronic: cough			chronic: meningitis	ulcerative oral/ nasal/ cutaneous lesions	lymphadenopathy night sweats, weight loss, fever
<i>Paragonimus</i> spp.	Paragonimiasis	pleuritic chest pain, pleural effusion, cough, haemoptysis	acute: abdominal pain, diarrhoea		meningo-encephalitis, transverse myelitis, myelopathy	acute: urticarial rash	fever
<i>Schistosoma haematobium</i>	Schistosomiasis, bilharzia, Katayama syndrome	dry cough (Katayama syndrome)			paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever/ headache (Katayama syndrome) haematuria, proteinuria, dysuria, haemospermia, inter-menstrual bleeding

(continued on next page)

Table 3 (continued)

<i>Schistosoma mansoni</i> / <i>S. japonicum</i> / <i>S. intercalatum</i> / <i>S. mekongi</i> / <i>S. guineensis</i>	Schistosomiasis, bilharzia, Katayama syndrome	dry cough (Katayama syndrome)	abdominal pain, diarrhoea intestinal obstruction, intestinal bleeding	hepatosplenomegaly, portal hypertension	paraplegia, spinal cord syndromes	urticarial rash (Katayama syndrome)	fever/ headache (Katayama syndrome)
<i>Schistosoma</i> spp.	Cercarial dermatitis, Swimmers' itch					pruritic maculopapular rash	
<i>Strongyloides</i> spp.	Strongyloidiasis	wheeze, dry cough (Loeffler's syndrome)	diarrhoea, abdominal pain, bloating paralytic ileus (in hyperinfection)		meningitis (in hyperinfection)	itchy urticarial rash (larva currens)	fever (Loeffler's syndrome) gram negative bacteraemia (in hyperinfection)
<i>Taenia saginata</i>	Beef tapeworm		abdominal pain, diarrhoea, segments expelled per rectum				
<i>Taenia solium</i>	Pork tapeworm, cysticercosis		abdominal pain, diarrhoea, segments expelled per rectum		seizures, headache (usually space-occupying lesion(s) without eosinophilia) obstructive hydrocephalus, rarely eosinophilic meningo-encephalitis		
<i>Toxocara canis</i> / <i>T. cati</i>	Toxocariasis, Visceral larva migrans	wheeze, cough, dyspnoea	abdominal pain	hepatosplenomegaly	meningo-encephalitis, myelitis	urticarial rash	fever ocular larva migrans (eosinophilia usually absent)
<i>Trichinella</i> spp.	Trichinellosis, trichinosis		upper abdominal pain, vomiting, diarrhoea dysphagia		meningo-encephalitis	periorbital oedema, urticaria, myalgia, muscle weakness	myocarditis, cardiac conduction disturbances fever
<i>Trichuris trichiura</i>	Whipworm		diarrhoea dysentery, rectal prolapse				
<i>Wuchereria bancrofti</i>	Lymphatic filariasis, tropical pulmonary eosinophilia	dry cough, wheeze, breathlessness (tropical pulmonary eosinophilia)				lymphadenitis, lymphoedema, hydrocele	fever (tropical pulmonary eosinophilia)
	usual symptomatic presentation						
	uncommon symptomatic presentation						

Note, while this table summarises symptomatic presentations, helminth infection is frequently asymptomatic. See main text for detailed information on the clinical presentation of each pathogen

e.g. PCR) and strongyloides serology. Both have good diagnostic yield across all regions of travel worldwide.<sup>5,13,20</sup> Vigilance for strongyloidiasis is important, as a high prevalence of strongyloidiasis has been found in some migrant populations with asymptomatic eosinophilia<sup>60</sup> and while concentrated stool microscopy identifies most common soil-transmitted helminths it has a lower sensitivity for *Strongyloides* spp..<sup>61–63</sup> We also suggest testing for human immunodeficiency virus (HIV) where recommended by British HIV Association (BHIVA) guidelines.<sup>64</sup> HIV infection has been associated with eosinophilia, although helminth co-infection is a more likely cause in the setting of the returned traveller living with HIV.<sup>65</sup>

Other initial screening investigations are region-specific. For those returning from Africa, perform concentrated stool and terminal urine microscopy (for schistosoma ova) and serology for schistosomiasis and strongyloidiasis. Almost all schistosomiasis cases diagnosed in the UK are following travel to Africa.<sup>5,20</sup>

Filarial serology is indicated for patients from West/Central Africa where the filarial infections *Loa loa*, *Onchocerca volvulus* and *Wuchereria bancrofti* are still prevalent. While filarial infections are endemic in areas outside of West/Central Africa (Table 2), the yield of filarial serology in those without travel to this region is too low to warrant wider first line testing in asymptomatic patients, particularly as serological specificity is reduced by cross reactions.<sup>12,20</sup>

### 5.1. Empirical treatment of asymptomatic eosinophilia

Based on expert opinion, consider empirical treatment with a single dose of albendazole 400 mg plus a single dose of ivermectin 200 µg/kg (microgram/kg) to treat possible prepatent or undetected geohelminth infection (e.g. ascariasis/hookworm/strongyloidiasis) as the cause of eosinophilia with negative stool microscopy in those aged > 24 months.<sup>3,18,21,59,66</sup> In children aged 12–24 months,

consider albendazole 200 mg single dose (expert opinion). In infants < 12 months, discuss with an expert. Exclude *Loa loa* in people who have travelled to endemic regions BEFORE treating with ivermectin.

## 6. Eosinophilia associated with specific symptoms

### 6.1. Eosinophilia with respiratory symptoms

#### 6.1.1. Acute schistosomiasis (Katayama syndrome) (*Schistosoma* spp.) (Also see section 6.2.2; section 6.3.4; section 6.4.1; section 6.5.4).

This occurs in early schistosomiasis infection, during the migration and initiation of egg-laying phases. It is probably immunologically mediated and is almost exclusively reported in newly exposed travellers.

**Incubation period:** 2–8 weeks.<sup>67</sup>

**Distribution:** See section 6.2.2; section 6.4.1.

**Mode of transmission:** See section 6.2.2.

**Clinical presentation:** Symptoms include fever, cough, urticarial rash, diarrhoea, and headache.<sup>68–70</sup> Marked eosinophilia is typical, sometimes higher than  $5 \times 10^9/L$ , but it can occasionally be absent. Nodules and infiltrates may be seen on chest radiograph.<sup>71</sup>

**Investigations:** The combination of eosinophilia with fever and rash 2–8 weeks after freshwater swimming in Africa makes the diagnosis likely and justifies empirical treatment. Serology and stool or terminal urine microscopy may be negative at this stage of infection but are useful if positive (see Table 4).

**Treatment:** Praziquantel 40 mg/kg as a single dose is recommended except following travel to the Asia-Pacific region in which case praziquantel 60 mg/kg in two divided doses is recommended.<sup>72–74</sup> Eggs and immature schistosomulae are relatively resistant to treatment; repeat treatment at 8 weeks (expert opinion) to treat any residual worms once they have developed into adults.

**Table 4**  
Diagnosis and treatment of parasitological pathogens associated with eosinophilia.  
Diagnostic tests and treatments are those available in UK practice.

Infection	Diagnostic Tests	Sensitivity	Specificity	Possible serological cross reaction	Treatment (adult dosing) <sup>f</sup> See relevant section for detailed treatment advice and Table 5 for additional information on pregnancy/lactation
Angiostrongylosis ( <i>Angiostrongylus</i> spp.)	Serology <sup>c</sup>  Laboratory identification of larvae	STPH >99% (in convalescent phase)- lower in acute phase	STPH 80-92%	31 kDa antigen: <i>Gnathostoma</i> , <i>Toxocara</i> , <i>Echinococcus</i> and <i>Strongyloides</i> . <sup>30</sup>	Corticosteroids, possibly plus albendazole. Seek expert advice
Anisakiasis ( <i>Anisakis</i> spp., <i>Pseudoterranova</i> spp.)	Serology <sup>c</sup> Laboratory identification of larva	STPH 92%	STPH 80-91%	<i>Toxocara</i> , <i>Ascaris</i> , <i>Contracaecum osculatum</i>	Seek expert advice: if worm not removed, consider albendazole PO 400mg twice daily 21 days
Ascariasis ( <i>Ascaris lumbricoides</i> )	Concentrated stool microscopy Faecal PCR Laboratory identification of adult worm	98%	96%		Albendazole PO 400mg or mebendazole PO 500mg or ivermectin PO 200µg/kg <sup>a,e</sup>
Clonorchiasis/ Opisthorchiasis ( <i>Clonorchis sinensis</i> , <i>Opisthorchtis</i> spp.)	Concentrated stool microscopy Faecal PCR				Praziquantel PO 25mg/kg 3 times daily for 2–3 consecutive days
Cystoisosporiasis ( <i>Cystoisospora</i> spp.)	Concentrated stool microscopy Faecal PCR				Co-trimoxazole PO 960mg twice daily for 7 days. Antibiotics usually not needed. Seek expert advice for immunocompromised patients
Echinococcosis/ Hydatid disease ( <i>Echinococcus granulosus</i> , <i>E. multilocularis</i> )	Serology <sup>b</sup> ELISA, then Western blot for confirmation and species determination  Histology of tissue samples and microscopy of cyst contents	<b>Cystic:</b> 80-93% (liver) 60% (lung), <b>Alveolar:</b> 85%	89-97%	Cysticercosis: filariasis; <i>Trichinella</i> , <i>Anisakis</i> , <i>Ascaris</i>	Seek specialist advice. Echinococcosis should be managed in or under the guidance of specialist centres.
Threadworm ( <i>Enterobius vermicularis</i> )	Perianal swab or perianal adhesive tape test preferred to faecal concentrate. Faecal PCR Laboratory identification of adult worm				Albendazole PO 400mg <sup>a</sup> OR mebendazole PO 100mg <sup>a</sup> . Repeat in 2 weeks.
Fascioliasis ( <i>Fasciola hepatica</i> , <i>F. gigantica</i> )	Concentrated stool microscopy Faecal PCR Serology <sup>b</sup> Laboratory identification of adult fluke	77-97%	97%	<i>Schistosoma</i> spp. <i>Echinococcus granulosus</i>	Triclabendazole PO 10mg/kg once daily for 2 days (NB increasing triclabendazole resistance)
Gnathostomiasis ( <i>Gnathostoma</i> spp.: <i>G. spinigerum</i> in Asia; <i>G. binucleatum</i> in the Americas)	Serology <sup>c</sup> (Geographical travel history essential for test selection) Laboratory identification of larva or immature adult worm	STPH 99%	STPH 80-94%	<i>Anisakis</i> , <i>Angiostrongylus</i> , <i>Strongyloides</i> , <i>Toxocara</i> .	<b>Cutaneous/MSK:</b> Ivermectin PO 200µg/kg once daily for 2 days or albendazole PO 400 mg twice daily for 21 days <b>Neurological:</b> seek specialist advice
Hookworm ( <i>Ancylostoma duodenale</i> , <i>Necator americanus</i> )	Concentrated stool microscopy Faecal PCR Laboratory identification of adult worm	87%	98%		Albendazole PO 400 mg once daily for 3 days
Hymenolepiasis ( <i>Hymenolepis</i> spp.)	Concentrated stool microscopy; visualization of segments passed in stool Faecal PCR				Praziquantel PO 25 mg/kg <sup>a</sup> OR niclosamide PO 2g once daily for 7 days  (continued on next page)

Table 4 (continued)

Infection	Diagnostic Tests	Sensitivity	Specificity	Possible serological cross reaction	Treatment (adult dosing) <sup>f</sup> See relevant section for detailed treatment advice and Table 5 for additional information on pregnancy/lactation
Loiasis ( <i>Loa Loa</i> )	Day blood microscopy between 10:00 and 14:00 Serology <sup>b</sup>  Laboratory identification of adult worm	90–99% (pan filarial antibody ELISA)	80%	<i>Strongyloides</i> , lymphatic filariasis, <i>Mansonella perstans</i> , onchocerciasis, hookworm	Seek specialist advice. First exclude co-existing onchocerciasis. See Box 2 and Section 6.6.5 for details and cautions. Drug regimen depends on the level of microflaraemia
Lymphatic filariasis ( <i>Wuchereria bancrofti</i> , <i>Brugia</i> spp.)	Night blood microscopy (22:00–02:00) Serology <sup>b</sup>  Skin snips Serology <sup>b,d</sup> Slit lamp examination Laboratory identification of adult worm	Up to 90%	90%	<i>Strongyloides</i> , onchocerciasis, loiasis, and other filaria	Seek specialist advice. First exclude co-existing onchocerciasis. See Box 2 and Section 6.6.4 for details and cautions.
Onchocerciasis ( <i>Onchocerca volvulus</i> )	Skin snips Serology <sup>b,d</sup> Slit lamp examination Laboratory identification of adult worm	90%	80%	Lymphatic filariasis, loiasis, <i>Strongyloides</i>	Seek specialist advice. See Box 2 and Section 6.6.2 for details and cautions. First exclude co-existing loiasis. See text for treatment recommendation.
Paragonimiasis ( <i>Paragonimus</i> spp.)	Serology <sup>f</sup> Microscopy sputum/tissue/stool/CSF Laboratory identification of adult worm	STPH 95%	STPH 95%	<i>Strongyloides</i>	Seek specialist advice. Praziquantel PO 25mg/kg 3 times daily for 2 days OR triclabendazole PO 10mg/kg/day 2 doses, 12 hours apart.
Schistosomiasis <i>Schistosoma haematobium</i>	Microscopy of nitrocellulose- filtered terminal urine Serology <sup>b</sup>	92%	98%	<i>Fasciola</i> and other flukes	Praziquantel PO 40mg/kg <sup>a</sup> (For treatment of neurological disease see Section 6.5.4)
<i>Schistosoma mansoni</i> , <i>S. intercalatum</i> , <i>S. guineensis</i>	Concentrated stool microscopy Serology <sup>b</sup> Faecal PCR	96%	98%	<i>Fasciola</i> and other flukes	Praziquantel PO 40mg/kg <sup>a</sup> (For treatment of neurological disease see Section 6.5.4)
<i>Schistosoma japonicum</i> , <i>S. mekongi</i>	Concentrated stool microscopy Serology <sup>b</sup> Faecal PCR			<i>Fasciola</i> and other flukes	Praziquantel PO 60mg/kg in two divided doses. (For treatment of neurological disease see Section 6.5.4)
Strongyloidiasis ( <i>Strongyloides stercoralis</i> )	Concentrated stool microscopy Stool culture (agar plate or charcoal method) Serology <sup>b</sup>  Faecal PCR	73% in travellers; 98% in migrants  90%	94% (non-endemic area); 77% (patients with other parasitoses)	Lymphatic filariasis, onchocerciasis, loiasis, hookworm	Ivermectin PO 200µg/kg single dose if normal immunity. If immunocompromised: Ivermectin PO 200µg/kg on day 1, 2, 15 and 16  If concerned re: hyperinfection send stool and sputum microscopy as serology may be negative. Prolonged treatment required in hyperinfection- seek specialist advice
Tapeworm ( <i>Taenia solium</i> , <i>T. saginata</i> )	Concentrated stool microscopy; visualization of segments passed in stool. Faecal PCR Serology and antigen detection are not helpful for detection of intestinal taeniasis <sup>b</sup>	Not indicated for intestinal taeniasis		Not applicable	Identify the species. If not possible, treat with niclosamide PO 2g <sup>a</sup> . If <i>T. saginata</i> or intestinal <i>T. solium</i> (with neurocysticercosis excluded) Praziquantel PO 10mg/kg <sup>a</sup>
Neurocysticercosis ( <i>Taenia solium</i> )	Serology Antibody Western blot  Antigen detection ELISA	Antibody: 94% (2 or more cysts) 28% (single lesions) <sup>31</sup>  99% but much lower if single 50 kDa band only <sup>32</sup>	99%	<i>Echinococcus</i>	Expert advice essential. Parenchymal disease >2 cysts: combination albendazole plus praziquantel plus steroid. Parenchymal disease 1–2 cysts: Albendazole plus steroids. For co-existing intestinal <i>T. solium</i> infection: niclosamide PO 2g <sup>a</sup> (does not exacerbate neurocysticercosis).

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Table 4 (continued)

Infection	Diagnostic Tests	Sensitivity	Specificity	Possible serological cross reaction	Treatment (adult dosing) <sup>f</sup> See relevant section for detailed treatment advice and Table 5 for additional information on pregnancy/lactation
Toxocarasis ( <i>Toxocara canis</i> , <i>T. cati</i> )	Serology <sup>b</sup> ELISA plus Western blot Laboratory identification of adult worm	91%	86%	<i>Strongyloides</i> , trichinosis, and <i>Fasciola</i>	Seek specialist advice VLM: Albendazole PO 400mg twice daily for 5 days Ocular disease: requires joint care with ophthalmology
Trichinellosis ( <i>Trichinella</i> spp.)	Serology <sup>b</sup> - IFAT Muscle biopsy (histopathology)	90% after two weeks		Filariasis, <i>Paragonimus</i> , <i>S. mansoni</i> , Auto-immune disease	Seek specialist advice. Albendazole PO 400mg twice daily for 3 days (mild disease) to 14 days (severe disease). Prednisolone PO 40 - 60mg once daily in severe disease
Whipworm ( <i>Trichuris trichiura</i> )	Concentrated stool microscopy Faecal PCR Laboratory identification of adult worm	90%	96%		Mebendazole PO 100mg twice daily for 3 days plus ivermectin PO 200µg/kg once daily for 3 days

<sup>a</sup> Where duration of treatment is not mentioned, treatment consists of a single dose only

<sup>b</sup> Will generally be sent to specialist laboratories

<sup>c</sup> Investigations not performed by UK laboratories so the Hospital for Tropical Diseases sends samples away to STPH (Swiss Tropical and Public Health) Institute

<sup>d</sup> Filarial serology is non-specific as the *Onchocerca* specific recombinant ELISA is not commercially available.

<sup>e</sup> Ivermectin is not licensed for use in the UK

<sup>f</sup> For children, also see published guidance<sup>43</sup>

Steroids may reduce the duration of symptoms;<sup>75,76</sup> 30 mg prednisolone daily for 5 days (expert opinion). Dexamethasone may result in reduced praziquantel levels due to increased metabolism.<sup>77</sup> Combination therapy with artemisinin derivatives<sup>78</sup> has been proposed as they have a greater impact on immature schistosomulae; but there is no clinical trial evidence to support this.<sup>79,80</sup>

#### 6.1.2. Loeffler's syndrome

Loeffler's (Löffler's) syndrome results from larval migration through the lungs following acute helminth infection, most often involving the nematodes *Ascaris*, hookworm and *Strongyloides* spp..

**Incubation period:** 1–2 weeks, depending on the species.

**Distribution:** Worldwide; see individual species.

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

**Investigations:** The diagnosis is clinical as symptoms occur during the prepatent period. Migratory pulmonary infiltrates may be seen on chest radiograph (see Fig. 2). Larvae may be seen in sputum (rare) or bronchoalveolar lavage.

**Treatment:** See Table 4 for individual species. Where no organism is identified, consider empirical treatment with single dose ivermectin 200 µg/kg and albendazole 400 mg (expert opinion).<sup>81</sup> Consider retreatment 1 month after the resolution of pulmonary symptoms to ensure adult worms treated (expert opinion). Caution using steroids, which may cause hyperinfection in strongyloidiasis.

#### 6.1.3. Strongyloidiasis (*Strongyloides* spp.)

Hyperinfection can present with respiratory symptoms including cough and breathlessness. Urgent diagnosis and treatment are imperative; see section 6.2.1.

#### 6.1.4. Visceral larva migrans/acute toxocariasis (*Toxocara canis* and *T. cati*)

Visceral larva migrans (VLM) occurs when larvae from ingested *Toxocara* eggs penetrate the gut mucosa and enter the portal and then systemic circulation. Ocular larva migrans is a distinct syndrome without eosinophilia (see section 6.5.5).

**Incubation period:** Uncertain.

**Distribution:** Worldwide, including temperate areas.<sup>82</sup>

**Mode of transmission:** Ingestion of soil containing eggs of *T. canis* or *T. cati* (as a result of dog or cat fouling) or through eating raw meat, particularly liver.<sup>83</sup>

**Clinical presentation:** VLM is usually seen in children < 5 years old, although it occurs in adults through raw meat consumption. Infection is usually asymptomatic; symptomatic presentation is with fever, eosinophilia, dyspnoea or wheeze and cough.<sup>84</sup> Abdominal pain, hepatosplenomegaly and urticarial rash may also occur.<sup>85</sup> Respiratory symptoms may rarely be due to cardiac disease.<sup>86</sup> It can cause an eosinophilic meningitis or encephalitis (see section 6.5.5). Chest radiograph may be normal, with CT showing pulmonary ground-glass abnormalities or nodules.<sup>87</sup>

**Investigations:** Serology.

**Treatment:** Some cases are mild and self-limiting. Where anti-parasitic treatment is considered necessary, use 5 days albendazole (expert opinion).<sup>88,89</sup> Steroids and antihistamines have been used (expert opinion) for hypersensitivity reactions.

#### 6.1.5. Tropical pulmonary eosinophilia (*Wuchereria bancrofti*, *Brugia* spp.)

This is a rare presentation of filariasis triggered by a hypersensitivity reaction to lymphatic filarial worms (*W. bancrofti*, *B. malayi* and *B. timori*) in the lung.<sup>90</sup>

**Incubation period:** up to one year.

**Distribution:** See section 6.6.4.

**Clinical presentation:** Fever, dry cough, wheeze and dyspnoea; often misdiagnosed as asthma. Gradual onset with paroxysms,

**Table 5**  
Pharmacological considerations for drugs included in these guidelines that are not routinely encountered in UK practice.

Drug	Side effects	Monitoring/precautions	Pregnancy	Lactation
Albendazole*	Nausea, abdominal pain, alopecia (reversible), raised liver enzymes, leucopaenia, rash	FBC/LFTs every two weeks for 3 months, then monthly if remain within range.	Ideally avoid pregnancy until 1 month after finishing course. If required, avoiding the first trimester should be considered <sup>53</sup> Discuss with expert in pregnancy, avoid DEC in pregnancy	Very low levels are excreted into breastmilk so likely to be compatible with breastfeeding.
DEC (diethylcarbamazine)*	Dizziness, nausea, fever, headache or pain in muscles or joints. Mazzotti reaction if unsuspected <i>Onchocerca volvulus</i> microfilariae in the skin	Exclude co-existing onchocerciasis before use (see Box 2) Use with care if <i>Loa loa</i> infection possible (see Box 2). Prednisolone usually given alongside when DEC is used for <i>Loa loa</i> treatment when microfilaraemic (see section 6.6.5) Warm patients alcohol is reported to worsen side effects. Take without food, but with water. High fat food increases bioavailability by 2.5 times Azithromycin can significantly increase serum ivermectin concentration		No data available
Ivermectin*	Mild: fever, pruritus, rash In onchocerciasis: tender lymphadenopathy, headache, bone/joint pain. Mazzotti reaction due to microfilarial death is possible- fever/urticaria/asthma/GI upset		No teratogenicity or toxicity attributable to ivermectin has been observed in limited human pregnancy experience <sup>53</sup>	Compatible with breastfeeding
Mebendazole	Rare: Abdominal pain, nausea, diarrhoea.		WHO suggests can be used in second/third trimesters.	Limited human data, probably compatible
Niclosamide*	Anorexia, nausea, vomiting, GI upset, dizziness, pruritus		Not systemically absorbed, so likely to be low risk	Lack of maternal systemic absorption means transfer to breastmilk unlikely, and even if transferred to infant, would not be absorbed
Praziquantel*	Dizziness, drowsiness, vomiting, rash, fever Warn not to drive due to dizziness and drowsiness.	Caution in reduced hepatic function <sup>54</sup> Take with or after food Metabolism induced by anticonvulsants and steroids.	No evidence of harm when used in second or third trimester <sup>53</sup> WHO considers safe in pregnancy due to experience with single dose mass drug administration programmes.	Low concentration excretion in breast milk so amounts ingested by the infant are likely to be small. <sup>55</sup> Limited data but lactation not viewed as a contraindication to use.
Triclabendazole*	Minimal side effects: Diarrhoea, headache, epigastric pain. QT prolongation (in dogs): avoid in patients taking drugs which cause QT prolongation	Obstruction of biliary ducts by dying flukes may cause biliary colic or ascending cholangitis. Pre-treatment ECG recommended. Take with food, administer with hyoscine butylbromide. Use with caution in G6PD deficiency and if liver impairment.	No human data, animal data suggests low risk <sup>53</sup>	No data available, but as drug is highly protein bound (96–99%) exposure of the breastfed infant is likely to be low <sup>56</sup>

FBC- full blood count, LFT- liver function tests, FDA- Food and Drugs Administration (USA), MHRA- Medicines and Healthcare products Regulatory Agency, WHO-World Health Organisation

#### Drugs in Pregnancy

Prescribing in pregnancy may be more complex due to a lack of data about medication safety. However, it is often appropriate to use medications in pregnancy when the risks to mother and baby of inadequate treatment outweigh the risks of harm related to the treatment. Careful risk-benefit discussion with the patient is advised.

#### Unlicensed Drugs (\* above)

Many of these drugs are unlicensed but are the best treatment option. Discuss drug side-effects with the patient.

**Table 6**  
Diagnosis and treatment of fungal pathogens associated with eosinophilia.

Infection	Culture*	Serology	Antigens	Treatment <i>Refer to a specialist center</i>
Histoplasmosis ( <i>Histoplasma capsulatum</i> )	20 – 75% sensitivity <sup>34</sup> Can take 21 days	Specific Methods <sup>b</sup> : EIA 95% sensitivity CFT 95% sensitivity in pulmonary infection Greatly reduced sensitivity in immune compromise <sup>35</sup> Most sensitive in chronic pulmonary infection. Beta D Glucan: 87% sensitive, 68% specific <sup>36</sup> Galactomannan: 69% sensitive <sup>37</sup> Specific Methods <sup>b</sup> : EIA cell wall antigen: 93% sensitivity, 79% specificity <sup>42</sup> No role for CFT or IDT due to cross reactivity with other endemic mycoses <sup>42</sup> Beta D Glucan: <i>negative</i> in blastomycosis	Urinary antigen: MiraVista EIA <sup>cd</sup> 82 – 91% sensitivity, 78% specificity <sup>38</sup> Most sensitive in disseminated infection. Lateral flow assay now available. Sensitivity 78.8% and specificity 99.3% <sup>39</sup>	Mild infection may not require treatment <sup>40</sup> Moderate disease: itraconazole PO 200 mg 3 times daily for 3 days followed by twice daily for 6 weeks (discuss duration with a specialist) <sup>40</sup> Severe disease/ immunocompromised patient: IV liposomal amphotericin B 3 mg/kg/day for 1–2 weeks followed by itraconazole PO 200 mg 3 times daily for 3 days, then 200 mg twice daily for at least 12 weeks <sup>40</sup>
Blastomycosis ( <i>Blastomyces</i> spp.)	Culture Can take up to 28 days. Microscopy 8–15 µm yeasts with broad based buds are distinctive, 40% sensitivity <sup>41</sup>	Galactomannan: 69% sensitive <sup>37</sup> Specific Methods <sup>b</sup> : EIA cell wall antigen: 93% sensitivity, 79% specificity <sup>42</sup> No role for CFT or IDT due to cross reactivity with other endemic mycoses <sup>42</sup> Beta D Glucan: <i>negative</i> in blastomycosis	Cross reacts with histoplasma	Mild infection in the immunocompetent may not require treatment Mild to moderate pulmonary blastomycosis: itraconazole PO 200 mg 3 times per day for 3 days followed by twice daily for 6–12 months <sup>43</sup> Moderate to severe infection or infection in the immune compromised: IV liposomal amphotericin B for 1–2 weeks followed by itraconazole PO 200 mg 3 times daily for 3 days, then 200 mg twice daily for 6–12 months. <sup>43</sup>
Coccidioidomycosis ( <i>Coccidioides</i> spp.)	Culture takes 5–7 days	Galactomannan: may be positive Specific methods <sup>b</sup> : EIA 86% sensitivity CFT 56% sensitivity IDT 71% sensitivity Lower sensitivity in immune compromise <sup>44</sup> Beta D Glucan: Sensitivity 43.9%, Specificity 91.1% <sup>45</sup> Galactomannan: up to 90% sensitivity <sup>46</sup>	Sensitivity 70% <sup>b,47</sup>	Mild or limited disease in the immunocompetent: often no treatment required Pulmonary disease can be treated with fluconazole PO 400–800 mg once daily for 6–12 weeks. <sup>48</sup> In severe disease, IV liposomal amphotericin B 3–5 mg/kg/day then switch to fluconazole PO when clinically stabilized. <sup>48</sup>
Paracoccidioidomycosis ( <i>Paracoccidioides</i> spp.)	Culture can take up to 30 days	Specific methods <sup>b</sup> : Quantitative immunodiffusion: Sensitivity 97%, specificity 100% <sup>49</sup> Beta D Glucan: usually positive <sup>50</sup> Galactomannan: 50% sensitivity <sup>51</sup>	Not commercially available	Mild/moderate disease: itraconazole PO 200 mg per day for 6–12 months. <sup>52</sup> IV Liposomal amphotericin B 3–5 mg/kg/day may be needed for severe disease until clinically stable, then itraconazole PO. <sup>52</sup> Trimethoprim/sulfamethoxazole PO 960 mg twice daily is an alternative. Treatment duration usually 6–12 months <sup>52</sup>

#### Key

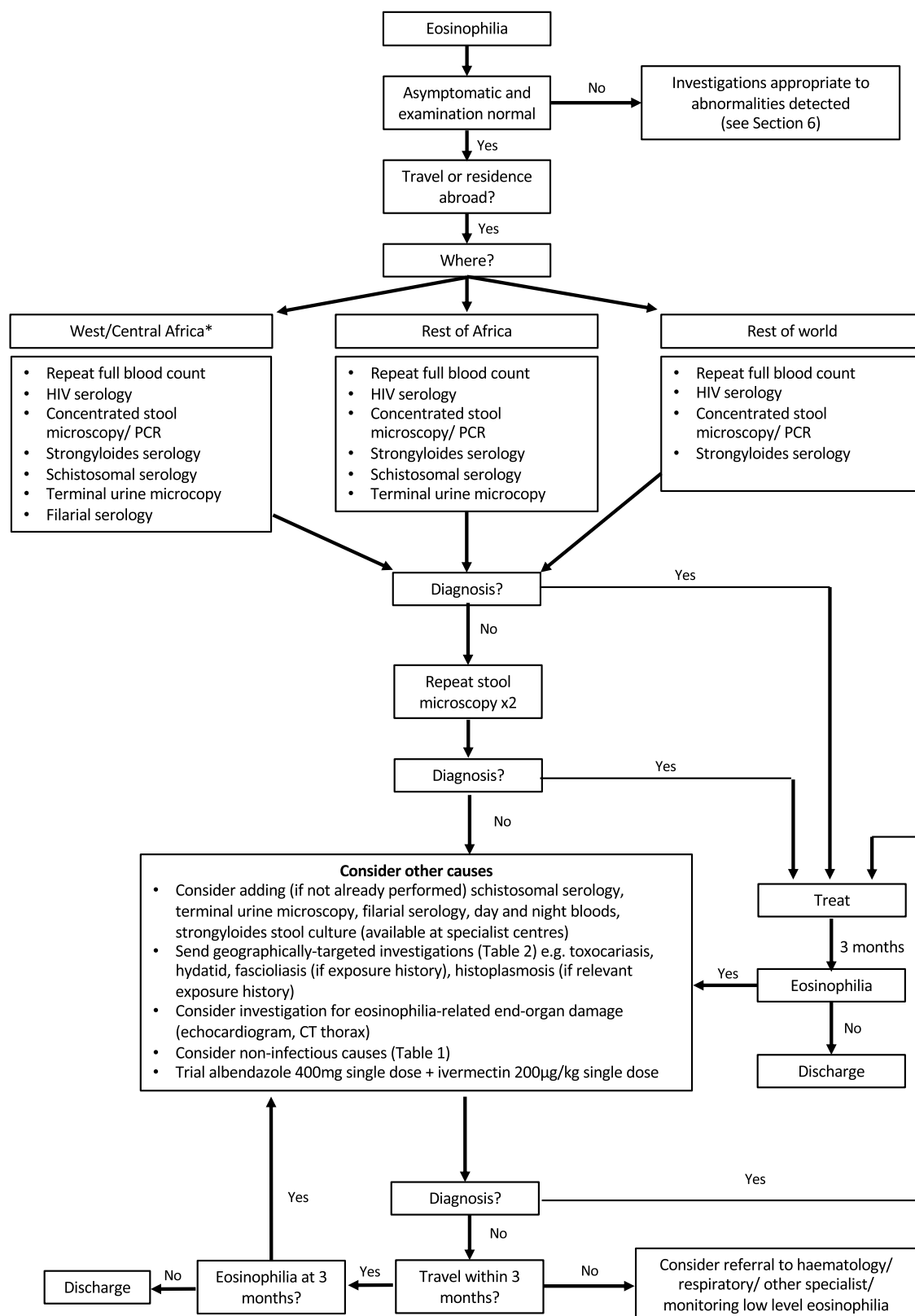
\*Requires containment level 3 facilities

<sup>b</sup>Generally sent to specialist laboratories

<sup>c</sup>Not performed in UK

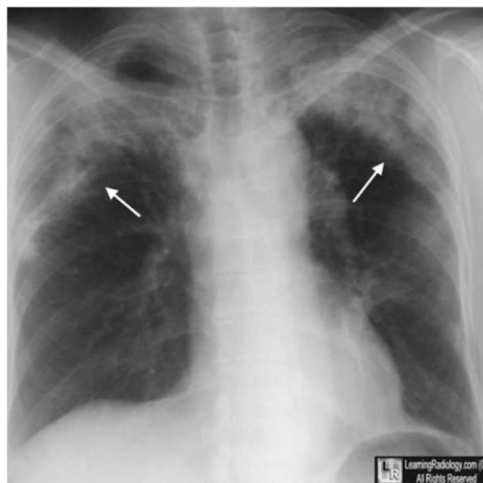
<sup>d</sup>MiraVista Laboratories

Abbreviations: EIA- enzyme immunoassay, CFT- Complement fixation test, IDT- immunodiffusion test  
Please note that *Talaromyces marneffei* infection is not considered to be associated with eosinophilia.



\*West/ Central Africa countries: Angola, Benin, Burkina Faso, Cameroon, Cape Verde ,Central African Republic, Chad ,DR Congo, Gabon, Gambia, Ghana, Guinea, Guinea Bissau, Equatorial Guinea, Côte D'Ivoire, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Senegal, Sierra Leone, Togo

**Figure 1.** Investigation of asymptomatic eosinophilia based on geographical exposure.



**Figure 2.** Chest radiograph in Loeffler's Syndrome. There are bilateral peripheral infiltrates in the upper lung fields. This has been called the reverse pulmonary oedema sign. Published with permission from *LearningRadiology.com*.

especially at night. Lymphadenopathy may be present; lymphatic damage is rare. Diagnosis is often delayed; the illness may last for years and is eventually self-limiting. Thought to be less common in those who have acquired a degree of immunotolerance (e.g. residents of endemic areas).

**Investigations:** Chest radiograph: increased broncho-alveolar markings, reticulonodular or miliary infiltrates (normal in 20% cases). Eosinophil count is often  $> 3 \times 10^9/L$ .<sup>91</sup> IgE level usually high and filarial serology strongly positive (see Table 4). Microfilariae are rarely detected on blood film microscopy.

**Treatment:** Seek expert advice with regards to use of doxycycline and diethylcarbamazine (theoretical benefit); see Box 2 for details and cautions;<sup>92</sup> relapses may occur.<sup>90</sup> Corticosteroids<sup>90,93</sup> have been used (expert opinion) with the aim of preventing the establishment of pulmonary fibrosis and ongoing management by a respiratory physician may be helpful. Dyspnoea may be responsive to bronchodilators (expert opinion).

#### 6.1.6. Pulmonary echinococcosis/Hydatid disease (*Echinococcus granulosus* and *E. multilocularis*)

For an overview of hydatid infection see section 6.3.1.

**Pulmonary cystic echinococcosis (CE).** CE most commonly affects the liver (section 6.3.1), but around 20% of affected individuals have cysts in the lungs.<sup>94,95</sup>

**Clinical presentation:** Lung cysts may be asymptomatic or present with cough (sometimes haemoptysis), pleuritic pain and breathlessness, with mass lesions seen on chest radiography. Intrabronchial rupture may occur, with expectoration of cyst contents, or retention as a nidus for bacterial infection. Significant eosinophilia ( $> 1 \times 10^9/L$ ) is uncommon except following cyst rupture.

**Treatment:** Pulmonary CE requires management in specialist centers, following guidance from the World Health Organisation (WHO) Informal Working Group on echinococcosis (IWGE)- summarised below for reference. Treatment for most is primarily surgical, with complete excision, conserving as much lung tissue as is feasible. Praziquantel is given pre- and post-operatively, and albendazole<sup>96-98</sup> (more effective than mebendazole<sup>98,99</sup>) post-operatively, the length of the post-operative course being determined by whether or not the excised material was assessed as viable. Percutaneous aspiration, injection of chemical scolecidal agents and re-aspiration (PAIR), or aspiration alone, are contraindicated for lung cysts. Some small lung cysts ( $< 5$  cm) may respond to medical treatment, although cyst rupture is a risk of medical treatment of pulmonary

CE.<sup>100</sup> Albendazole may be given for inoperable lung cysts; where used, albendazole should be given as a continuous treatment course.<sup>101</sup> In patients with both lung and liver CE, management of the lung cysts should be prioritized over the liver cysts.

Cases should be discussed at a specialist hydatid MDT where parasitology, infectious diseases and surgical specialist input is available. At the time of writing these are available at The Hospital for Tropical Diseases (HTD), UCLH, London, and Liverpool; hub and spoke management is supported. Contact the Parasitology Registrar on [uclh.parasitologyspr@nhs.net](mailto:uclh.parasitologyspr@nhs.net) (HTD) or [idsecretaries@liverpoolft.nhs.uk](mailto:idsecretaries@liverpoolft.nhs.uk) (Liverpool).

**Pulmonary alveolar echinococcosis (AE).** AE is found almost exclusively in the liver and is rarely found as a primary lesion outside the liver.<sup>102</sup> (see section 6.3.1). The lung may become involved by direct local spread from the liver or by metastasis. Given the disseminated nature at this stage, pulmonary AE is not amenable to curative surgery.

Indefinite treatment with albendazole is suggested for pulmonary AE, along with management of the concomitant hepatic lesion in a specialist center.<sup>101</sup>

Cases should be managed by regional infectious diseases centers with discussion in the Hospital for Tropical Diseases Echinococcosis MDT meeting where hub and spoke management is supported. Contact the Parasitology Registrar on [uclh.parasitologyspr@nhs.net](mailto:uclh.parasitologyspr@nhs.net).

#### 6.1.7. Paragonimiasis (*Paragonimus* spp.)

**Prepatent period:** 65–90 days<sup>103</sup>.

**Incubation period:** Days–3 weeks.

**Distribution:** predominantly *P. westermani* in Asia;<sup>104</sup> other *Paragonimus* spp. predominate in Africa and across the Americas.

**Mode of transmission:** Normally transmitted through ingestion of intermediate stage metacercariae in raw freshwater crab and crayfish meat; also ingestion of uncooked meat of a paratenic host e.g. wild boar.

**Clinical presentation:** Epigastric or abdominal pain, diarrhoea and urticaria may occur in weeks 1–2 as parasites migrate. Week 2 onwards, cough with sputum and pleuritic chest pain. Fever is rare. Foul smelling “chocolate” haemoptysis may subsequently occur. CNS and skin manifestations are rare. May mimic tuberculosis (TB) or lung cancer.<sup>105</sup>

**Investigations:** Eosinophilia is seen in around half of cases,<sup>105</sup> elevated serum IgE is common. Can be confirmed by sputum/bronchoalveolar lavage microscopy. Serology can be performed at the Swiss Tropical and Public Health Institute (STPH)- see Table 4. Chest radiograph changes include pleural nodules and effusions, pneumothorax, linear opacities, cysts, parenchymal masses and cavities.

**Treatment:** Seek specialist advice. Praziquantel 25 mg/kg three times a day for 2 days is recommended.<sup>106</sup> As an alternative, we suggest triclabendazole 10 mg/kg/day 2 doses, 12 h apart (in patients  $> 6$  years old).<sup>107</sup>

#### 6.1.8. Coccidioidomycosis and paracoccidioidomycosis (*Coccidioides immitis*, *Coccidioides posadasii* and *Paracoccidioides* spp.)

**Incubation period:** Coccidioidomycosis: acute (7–21 days) or chronic (months–years) Paracoccidioidomycosis: acute (months) or chronic (years).

**Distribution:** Coccidioidomycosis: Widely distributed through arid parts of the Americas. Paracoccidioidomycosis: South and Central America.<sup>108</sup>

**Mode of transmission:** Respiratory exposure to airborne fungal conidia (paracoccidioidomycosis) or arthroconidia (coccidioidomycosis) found in soil.

**Clinical presentation:** Often asymptomatic. Acute illness: fever, cough, pleuritic chest pain, headache, and rash. Chronic disease (months–years): cough, night sweats, weight loss and malaise, and

**Box 2**

WARNING: Diethylcarbamazine (DEC) in Lymphatic Filariasis (LF) and *Loa loa* treatment.

**Seek specialist parasitology or tropical medicine input before treating patients for filarial infection.**

**Diethylcarbamazine (DEC).**

DEC is the treatment of choice for lymphatic filariasis and loiasis, but in individuals co-infected with onchocerciasis it can cause severe reactions including blindness, hypotension, pruritus and erythema. Therefore, skin snips and a slit lamp exam to look for onchocerciasis are indicated before using DEC in patients who have travelled to co-endemic regions. If these preliminary investigations are negative, then a test dose of 50 mg DEC can be trialed. If onchocerciasis is present, then the test dose will precipitate a mild Mazzotti reaction (pruritus and erythema). **We strongly advise discussion with a specialist tropical medicine or parasitology team prior to treating patients with onchocerciasis.**

**Loa loa:**

Is your patient with *Loa loa* microfilaraemic? This is important to know before starting treatment with DEC as it may cause encephalopathy with a high mortality rate. Individuals with high levels of blood microfilaraemia (> 1000/ml) are at greatest risk of complications. If microfilariae are seen in the blood, corticosteroids should be used with albendazole to reduce the microfilaria load in these patients, before definitively treating with DEC when the microfilaria count is < 1000/ml. **We strongly advise discussion with a specialist tropical medicine or parasitology team prior to treating patients with *Loa loa*.**

cutaneous, ulcerative oral or nasal lesions (in paracoccidioidomycosis). Severe disease (disseminated/chronic meningitis) occurs more commonly in the immunocompromised.

**Investigations:** Serology (see Table 6), or microscopy and culture of respiratory samples. Culture is slow and requires a containment level 3 (CL3) laboratory. Eosinophilia is more common in coccidioidomycosis and juvenile paracoccidioidomycosis. Beta-d-glucan may be raised. Chest radiograph: consolidation, cavitation, pleural effusion (coccidioidomycosis). In paracoccidioidomycosis symptomatic diffuse pulmonary infiltrates, hilar lymphadenopathy and, rarely, adrenal failure may be seen.<sup>109</sup>

**Treatment and clinical management issues:** See Table 6 and published guidance<sup>109,52,48</sup> for further details. Mild disease in immunocompetent individuals often resolves spontaneously. In moderate disease we suggest oral (PO) itraconazole 200 mg once daily (paracoccidioidomycosis) or fluconazole 400–800 mg once daily (coccidioidomycosis).<sup>110</sup> In severe disease initial treatment with IV liposomal amphotericin B (3 mg/kg once daily) for 1–2 weeks is suggested followed by long-term PO azole. Immunocompromised individuals require prolonged treatment followed by long-term azole prophylaxis. Relapse in paracoccidioidomycosis is common.

**6.1.9. Histoplasmosis and blastomycosis (*Histoplasma capsulatum* and *Blastomyces* spp. including *B. dermatitidis*)**

**Incubation period:** Histoplasmosis: acute (7–21 days) or chronic (months-years). Blastomycosis: 1–3 months.

**Distribution:** Histoplasmosis: Wide distribution across the Americas, Africa, South and Southeast Asia.<sup>108</sup> Blastomycosis: Eastern/Central United States and Canada, likely distributed across most of Africa although data is limited.<sup>108</sup>

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

**Clinical presentation:**

Histoplasmosis: May be asymptomatic. Acute illness (7–21 days): fever, myalgia, cough, pleuritic chest pain. Often mistaken for community acquired pneumonia. Chronic disease (months-years): cough, night sweats, weight loss and malaise. Disseminated disease may occur in the immunocompromised and can affect any body system including the CNS.

Blastomycosis: Acute: Cough (usually productive of sputum), chest pain, dyspnoea, haemoptysis. Chronic: Fever, cough, haemoptysis, weight loss. Can mimic TB or malignancy. Skin involvement is common (see section 6.6.9).

**Investigations:** Serology (see Table 6), or microscopy and culture of respiratory samples (culture is slow and requires a CL3 laboratory). PCR is available at the UKHSA Bristol Mycology Reference Laboratory. Blastomyces serology is highly cross reactive with

histoplasmosis. In disseminated disease, urinary or serum histoplasma antigen is more useful to diagnose blastomycosis than blastomycosis serology. Blastomyces antigen for CSF and serum is available but cross reacts with histoplasmosis.<sup>111</sup> Beta-d-glucan may be raised in histoplasmosis but not in blastomycosis. Galactomannan may be raised in either. Chest radiograph can demonstrate consolidation, cavitation, pleural effusion, hilar lymphadenopathy or a miliary picture in disseminated infection.

**Treatment and clinical management issues:** See Table 6. Detailed guidance has been published by the Infectious Diseases Society of America (IDSA).<sup>40,43</sup> Mild disease (immunocompetent individuals) may require no treatment and often resolves spontaneously. Suggested treatment for moderate disease is PO itraconazole and for severe disease is IV liposomal amphotericin B (3 mg/kg once daily) for 1–2 weeks followed by PO itraconazole. Discuss duration of therapy with an experienced infection specialist.

**6.1.10. Other causes**

There are multiple non-infectious causes of eosinophilia with respiratory symptoms (Table 1).<sup>112,113</sup> Take a detailed drug history as drug-induced eosinophilia is often accompanied by pulmonary involvement.<sup>114</sup> Investigate for asthma, presence of pulmonary eosinophilia and other system/organ involvement.<sup>115</sup>

**6.2. Eosinophilia with gastrointestinal symptoms**

**6.2.1. Strongyloidiasis (*Strongyloides* spp.)**

Strongyloidiasis is most often caused by *S. stercoralis* but other species e.g. *S. fuelleborni* may rarely be encountered.

**Incubation period:** Days to weeks for larva currens (Fig. 3, section 6.6.3) and Loeffler's syndrome (section 6.1.2), 2 weeks onwards for gastrointestinal symptoms.<sup>116</sup> Very long latent periods (up to several decades after infection) can occur due to autoinfection cycles.<sup>23</sup>

**Prepatent period:** 4 weeks.

**Distribution:** Worldwide distribution with predominance in regions with reduced access to sanitation.<sup>117</sup> In Europe, endemic cases have been reported from Spain,<sup>118,119</sup> Italy<sup>120</sup> and Eastern Europe.<sup>121</sup>

**Mode of transmission:** Larvae penetrate the skin of humans walking barefoot on affected soil or sand.<sup>116</sup>

**Clinical presentation:** Most patients are asymptomatic. Larva currens is the commonest presentation (Fig. 3, section 6.6.3) but a range of non-specific gastrointestinal symptoms (up to 60% of symptomatic patients), including diarrhoea and upper abdominal symptoms, may occur.<sup>122–124</sup> Infection may also present as Loeffler's syndrome (section 6.1.2). Hyperinfection syndrome results from cycles of autoinfection and unchecked parasite replication in



**Figure 3.** The migratory, urticarial rash of larva currents. Copyright to Prof David Moore, Hospital for Tropical Diseases, UCLH, London, UK.

immunocompromised individuals, often associated with chemotherapy, malignancy, steroid treatment or HTLV-1 infection. It may manifest sub-acutely, with malaise and worsening of gastrointestinal symptoms, or acutely with Gram-negative sepsis and/or meningitis (due to translocation of gut bacteria across the bowel wall), paralytic ileus, intestinal ulceration or protein losing enteropathy, and has a high mortality.<sup>125</sup> Pulmonary involvement commonly occurs. Onset may occur many years after return from endemic areas.<sup>123</sup>

**Investigations:** *Infection:* serology (specialist laboratories). Concentrated stool microscopy has very low sensitivity. Faecal PCR and strongyloides stool culture (specialist laboratories) are more sensitive.

*Suspected hyperinfection:* urgent stool and sputum microscopy to look for larvae is essential. Isolation of larvae from sputum or broncho-alveolar lavage is highly suggestive of hyperinfection. Serology may be negative and eosinophils within the normal range.

**Treatment:** We recommend ivermectin 200 µg/kg single dose as first line; it has a higher cure rate than albendazole (400 mg twice daily for 3 days).<sup>126</sup> More than one dose of ivermectin does not confer additional benefit in immunocompetent individuals.<sup>127</sup> In immunocompromised patients, treat with ivermectin 200 µg/kg PO on days 1, 2, 15, 16 with stool culture test of cure following treatment (expert opinion).

**Empirical treatment** for strongyloidiasis should be considered in patients from high prevalence settings or high-risk occupations (e.g. military) who are critically ill or require urgent immunosuppression, to minimise the risk of hyperinfection syndrome (expert opinion).

**Hyperinfection treatment:** Treat with broad spectrum antibiotics and seek specialist input regarding dose and duration of ivermectin (expert opinion). Unlicensed sub-cutaneous veterinary preparations of ivermectin may be required (in stock at the Hospital for Tropical Diseases, UCLH, London).<sup>128</sup> Patients should be managed with contact precautions due to risk of transmission of infection.

**Clinical management issues:** All migrants from endemic regions (including in the absence of eosinophilia) should be screened for strongyloidiasis before commencing treatment with immunosuppressive drugs, including steroids (expert opinion).<sup>129–132</sup>

#### 6.2.2. Schistosomiasis/bilharzia (*Schistosoma mansoni*, *S. japonicum*, *S. intercalatum*, *S. guineensis* and *S. mekongi*)

**Incubation period:** 2–8 weeks.<sup>67</sup>

**Distribution:** Africa, Arabian Peninsula, South America (*S. mansoni*); China, the Philippines, Indonesia (*S. japonicum*). *S. intercalatum* and *S. guineensis* (Central and West Africa and Madagascar) and *S. mekongi* (Mekong River Basin) are less extensively distributed. Most cases diagnosed in the UK are acquired in Africa.

**Mode of transmission:** Fresh water exposure, usually in lakes or slow-moving rivers, allows cercariae released from snails to penetrate skin. The patient may not recall a specific exposure.

**Clinical presentation:** Most infections are asymptomatic, although acute schistosomiasis ('Katayama syndrome') may occur (section 6.1.1). Intestinal schistosomiasis symptoms include chronic or intermittent abdominal pain, weight loss and diarrhoea. Very heavy infection can manifest as dysenteric illness or obstruction, and chronic colonic ulceration may cause intestinal bleeding and iron deficiency anemia.<sup>133</sup> Hepatosplenic schistosomiasis (HSS) can result in hepatosplenomegaly, hepatic 'pipestem' fibrosis and portal hypertension with oesophageal varices.<sup>134</sup> Chronic *S. japonicum* infection has been tentatively linked to liver and colon cancers.<sup>135</sup>

**Investigations:** Serology (positive at 4–8 weeks but may be later)<sup>136,137</sup> and microscopy of concentrated stool samples (low sensitivity); abdominal ultrasound and upper gastrointestinal endoscopy if portal hypertension is suspected. May be diagnosed histologically following colonoscopy and biopsy. Serology may remain positive for many years,<sup>138,139</sup> so cannot be used to assess success of treatment.

**Treatment and clinical management:** We recommend praziquantel PO 40 mg/kg as a single dose for *S. mansoni*, *S. intercalatum* and *S. guineensis* infections, and 60 mg/kg in two divided doses for *S. japonicum* and *S. mekongi* infections. Where the diagnosis has been made on the basis of serology alone, schistosomiasis from the Asia-Pacific region should be treated with 60 mg/kg praziquantel in two divided doses.<sup>140–145</sup>

#### 6.2.3. Ascariasis (*Ascaris lumbricoides*)

**Prepatent period:** 2–3 months.<sup>146</sup>

**Distribution:** Worldwide; commonest in rural settings in Africa, Asia and South America; rare or absent in Europe, North America and Australasia.<sup>146</sup>

**Mode of transmission:** Faeco-oral route.

**Clinical presentation:** Usually asymptomatic; abdominal pain, diarrhoea and occasionally gastrointestinal obstruction in children and biliary obstruction in adults.<sup>146</sup> Earthworm-sized, pink or white adult worms may be passed in stools or occasionally regurgitated/sneezed out. May present acutely as Loeffler's syndrome (section 6.1.2).

**Investigations:** Concentrated stool microscopy or faecal PCR.

**Treatment:** We recommend either albendazole PO 400 mg or mebendazole PO 500 mg or ivermectin PO 200 µg/kg, as a single dose.<sup>147,148</sup>

#### 6.2.4. Tapeworm (*Taenia saginata* and *T. solium*)

Is not usually associated with eosinophilia, but taeniasis is seen regularly in returning travellers and migrants.

**Prepatent period:** 2–3 months.<sup>149</sup>

**Distribution:** Worldwide. *T. saginata* is most commonly seen in Eastern Europe, Russia, Horn of Africa and Latin America; *T. solium* is typically seen in Central & South America, Eastern Europe, Africa south of the Sahara, India and Asia; *T. asiatica* limited to Asia (mostly eastern).<sup>149</sup>

**Mode of transmission:** Consumption of undercooked or raw beef (*T. saginata*) or pork (*T. solium*/*T. asiatica*).<sup>150</sup>

**Clinical presentation:** Usually asymptomatic but may be associated with minor abdominal symptoms. Segments may be passed in stool or may actively expel themselves per rectum.<sup>149</sup> *T. solium* can also cause cysticercosis (section 6.5.3).

**Investigations:** Concentrated stool microscopy (eggs) or visualization of segments passed in stool. Eggs (identical between species) are shed intermittently; send repeat specimens to increase diagnostic yield. Faecal PCR is also available. Serology and antigen detection are not helpful for detection of intestinal taeniasis. Screen household members in cases of *T. solium*.

**Treatment:** *T. solium*: We suggest a single dose of niclosamide PO 2 g to clear the intestinal infection (this only kills adult worms).<sup>151</sup> Praziquantel (PO 10 mg/kg single dose) should not be used for *T. solium* unless concomitant neurocysticercosis has been excluded (expert opinion).

*T. saginata*: We suggest praziquantel PO 10 mg/kg as a single dose.<sup>152</sup> Alternatives include a single dose of niclosamide PO 2 g.<sup>153</sup>

Causative *Taenia* species uncertain: Use a single dose of niclosamide PO 2 g (expert opinion).

#### 6.2.5. Hymenolepiasis (*Hymenolepis nana* and *H. diminuta*)

**Distribution:** Worldwide: in Europe, North America, and Australasia most common in children and people living in institutions.<sup>154</sup>

**Mode of transmission:** Faecal-oral route, including auto-infection (*H. nana* only)<sup>154</sup> or arthropod (intermediate host) ingestion (*H. nana* and *H. diminuta*).<sup>154</sup>

**Clinical presentation:** Usually asymptomatic; heavy infections may present with diarrhoea and abdominal pain.<sup>154</sup>

**Investigations:** Concentrated stool microscopy or faecal PCR.

**Treatment:** We recommend praziquantel PO 25 mg/kg as a single dose.<sup>155-157</sup> Niclosamide PO 2 g once daily for 7 days is an alternative.<sup>158-160</sup>

#### 6.2.6. Hookworm (*Ancylostoma duodenale* and *Necator americanus*)

**Prepatent period:** 5–9 weeks.<sup>161</sup>

**Distribution:** Worldwide.<sup>162</sup> Most common in areas with limited access to adequate sanitation.

**Mode of transmission:** Larvae penetrate the skin of humans walking barefoot or lying on affected soil or sand. Some species can also be acquired orally.<sup>163</sup>

**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 anemia, particularly in young children.<sup>163</sup>

**Investigations:** Concentrated stool microscopy or faecal PCR.

**Treatment:** We recommend albendazole PO 400 mg daily<sup>148,164</sup> for 3 days.<sup>165,166</sup>

#### 6.2.7. Whipworm (*Trichuris trichiura*)

**Prepatent period:** 60–70 days.<sup>167</sup>

**Distribution:** Worldwide; most common in areas with limited access to adequate sanitation.<sup>167</sup>

**Mode of transmission:** Faeco-oral route.<sup>167</sup>

**Clinical presentation:** Usually asymptomatic, but heavy infections can cause significant morbidity in children, including anemia, dysentery, rectal prolapse and impaired growth and cognitive development.<sup>167</sup>

**Investigations:** Concentrated stool microscopy or faecal PCR.

**Treatment:** We recommend mebendazole PO 100 mg twice daily<sup>148,168,169</sup> in combination with ivermectin PO 200 µg/kg once daily for 3 days. Low cure rates are seen in heavy infection; combination treatment improves cure rates.<sup>169-171</sup>

#### 6.2.8. Threadworm (*Enterobius vermicularis*)

**Prepatent period:** 2–6 weeks.<sup>172</sup>

**Distribution:** Worldwide, particularly affecting children.<sup>173</sup>

**Mode of transmission:** Ingestion of eggs from self-infection (common),<sup>173</sup> from oral-anal contact or from contaminated surfaces/fomites.

**Clinical presentation:** Frequently asymptomatic; most common symptom is pruritus ani. Worms may enter the female genital tract, causing vulvovaginitis.<sup>173</sup> Sometimes weight loss, irritability, diarrhoea, abdominal pain and, occasionally, colitis with eosinophilia.<sup>174,175</sup>

**Investigations:** Perianal swab or adhesive tape test; faecal PCR also available.

**Treatment:** We recommend either mebendazole PO 100 mg<sup>176</sup> or albendazole PO 400 mg<sup>177</sup> as a single dose.<sup>178</sup> Repeat dose at 2 weeks to prevent re-infection by newly hatched adult worms (eggs may not be affected by the initial treatment, and can survive in the environment for at least 2 weeks).<sup>178</sup> Good hygiene measures (particularly washing hands and scrubbing under fingernails, and washing/disinfecting potentially contaminated surfaces and fomites) are important to prevent reinfection.<sup>178</sup>

#### 6.2.9. Trichinellosis (*Trichinella* spp.)

This is caused by *Trichinella* spp. 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.<sup>179</sup>

**Incubation period:** 7–30 days (enteral phase), 2–6 weeks (parenteral phase).<sup>179</sup> Time to seroconversion: 3–5 weeks.

**Distribution:** Worldwide, particularly Argentina, central and Eastern Europe, Russia and China.<sup>180</sup> Can occur 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 (section 6.6.7). Presentation may be severe, causing meningo-encephalitis, myocarditis and cardiac conduction disturbances, with approximately 5% mortality.<sup>179</sup>

**Investigations:** Serology (specialist centers, including the Hospital of Tropical Diseases, UCLH, London). Muscle biopsy is helpful. An elevated blood creatinine kinase level is frequently seen, and eosinophil count > 3 × 10<sup>9</sup>/L.<sup>180</sup>

**Treatment:** We suggest albendazole PO 400 mg twice daily for 3 days (mild disease) to 14 days (severe disease).<sup>181-183</sup> Early treatment is associated with successful outcome; encysted larvae can survive treatment.<sup>180</sup> Prednisolone PO 40–60 mg once daily is suggested in severe disease.<sup>184</sup> Seek specialist advice; management in an intensive care setting may be needed.

#### 6.2.10. Anisakiasis (*Anisakis* spp. and *Pseudoterranova* spp.)

**Incubation period:** 2–5 h for gastric disease and up to 5 days for intestinal disease.<sup>185</sup>

**Distribution:** Worldwide.<sup>186,187</sup>

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

**Clinical presentation:** Severe acute abdominal pain, nausea and vomiting. Rarely, anaphylaxis following sensitisation.<sup>188</sup> A tingling sensation in the mouth or throat immediately after eating may indicate a moving worm; occasionally it may be successfully removed or coughed out.<sup>186</sup>

**Investigations:** Diagnosis is usually made following visualisation of the worm at endoscopy or laparotomy. Serology is available (sent away abroad at the time of writing- see Table 4).

**Treatment:** Surgical or endoscopic removal. Failing this, albendazole PO 400 mg twice daily for 21 days with monitoring of liver function and full blood count (expert opinion).<sup>189-191</sup>

#### 6.2.11. Cystoisosporiasis (*Cystoisospora belli*, formerly *Isospora belli*)

**Prepatent period:** 10 days.<sup>192</sup>

**Distribution:** Worldwide, with predominance in regions with reduced access to sanitation.<sup>193,194</sup>

**Mode of transmission:** Faecal-oral route. Excreted immature oocysts mature and sporulate in the environment over a few days before becoming infectious; person to person spread rare.<sup>192</sup>

**Clinical presentation:** Sudden onset watery non-bloody diarrhoea, abdominal cramps, nausea, and occasional fever. Usually self-limiting. In immunocompromised patients, *Cystoisospora* can cause a prolonged or relapsing illness.<sup>195,196</sup> Secretory diarrhoea can lead to hypokalaemia and bicarbonate wasting, and chronic cholecystitis has been described.<sup>197</sup> Some persons living with HIV appear to have a relapsing course even after immune reconstitution.<sup>198</sup>

**Investigations:** Concentrated stool microscopy and/or faecal PCR.

**Treatment:** Supportive care to manage electrolyte abnormalities, dehydration and nutrition. No additional treatment is needed in immunocompetent individuals where symptoms resolve within 5 days. For prolonged symptoms, or in immunocompromised patients, we suggest trimethoprim-sulfamethoxazole PO 960 mg twice daily for 7 days.<sup>199</sup> Dose and duration of treatment may need to be increased in immunocompromised patients, and long-term maintenance therapy is needed in some patients.<sup>200</sup> Ciprofloxacin is a second line alternative (PO 500 mg twice daily for 7 days) but is less effective than trimethoprim-sulfamethoxazole.<sup>199</sup> We suggest pyrimethamine plus folinic acid or nitazoxanide can be considered in refractory cases.<sup>201–203</sup>

### 6.2.12. Other causes of eosinophilia and GI symptoms

The protozoa *Dientamoeba fragilis* (rarely considered pathogenic)<sup>204</sup> and *Toxoplasma gondii* may present with eosinophilia. Visceral larva migrans can present with abdominal pain and hepatosplenomegaly, although usually also in the presence of respiratory symptoms (section 6.1.4). Paragonimiasis commonly presents with abdominal pain and diarrhoea, followed later by the development of characteristic respiratory symptoms (section 6.1.7). *Angiostrongylus costaricensis* is rarely seen in UK practice.

## 6.3. Eosinophilia and right upper quadrant pain/jaundice

### 6.3.1. Hydatid disease (echinococcosis) in the liver (*Echinococcus granulosus* and *E. multilocularis*)

The main echinococcal (hydatid) species infecting humans are *Echinococcus granulosus*, responsible for cystic echinococcosis (CE), and *E. multilocularis*, the cause of alveolar echinococcosis (AE). Radiographic appearance, diagnostics and treatment differ significantly between the two species, and it is essential to distinguish the two infections from the outset. *E. granulosus* presents more commonly in the UK. Patients should be managed through a multidisciplinary team involving surgeons, radiologists, and infectious disease physicians.<sup>101</sup>

**Cystic echinococcosis of the liver (*Echinococcus granulosus*).** Eosinophilia is usually associated with leaking cysts; most asymptomatic cases do not have eosinophilia.

**Incubation period:** Months to (usually) years.<sup>205</sup>

**Distribution:** Worldwide. In the UK, most commonly presents in migrants from Eastern Europe,<sup>206</sup> Middle East<sup>207</sup> and North Africa.

**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%<sup>94,95</sup> (see section 6.1.6) and other sites including CNS, bone (especially spine), eye, skeletal and heart muscle in 10%.<sup>208</sup> Multi-site disease is seen in 20–40% of individuals. Asymptomatic cysts (sometimes more than a litre) 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 and obstructive jaundice. Cysts may rupture into the peritoneal space, causing anaphylaxis or secondary cyst formation.

**Investigations:** Serology (not invariably positive) and compatible ultrasound (US) and MRI appearances. Cyst type is defined by US.<sup>101</sup>

MRI correlates with US better than CT does.<sup>209</sup> Eosinophilia may indicate cyst leakage.

**Treatment and clinical management issues:** Treatment should only be performed in specialist centers due to risk of anaphylaxis and cyst dissemination following surgical or percutaneous interventions. The WHO IWGE has developed a classification of US appearances of hepatic CE and suggests a stage-specific approach to the management (according to cyst size, location, and stage); for the UK, the regimen under “optimal” resource setting applies.<sup>101</sup>

Cases should be discussed at a specialist hydatid MDT where parasitology, infectious diseases and surgical specialist input is available. At the time of writing these are available at The Hospital for Tropical Diseases (UCLH, London) and Liverpool; hub and spoke management is supported. Contact the Parasitology Registrar on [uclh.parasitologyspr@nhs.net](mailto:uclh.parasitologyspr@nhs.net) (UCLH) or [idsecretaries@liverpoolft.nhs.uk](mailto:idsecretaries@liverpoolft.nhs.uk) (Liverpool).

**Alveolar echinococcosis of the liver (*Echinococcus multilocularis*).** The primary lesion of AE is found almost exclusively in the liver. Whilst primary lesions in other locations are extremely rare, liver lesions may invade local structures and metastasize to other locations, principally lung and brain. It does not produce cysts like CE but may appear as a mixture of hyper and hypoechoic areas in an irregular pseudotumour with scattered calcification. There may be central necrosis, but it is not a true cyst. It is commonly mistaken for a tumour or TB by those unfamiliar with its characteristic radiological appearance. AE is usually fatal if untreated, so prompt recognition and referral for specialist care are crucial.

**Incubation period:** 5 to 15 years.

**Distribution:** Found only in the Northern Hemisphere, mainly in China. Also found in Europe, north and central Asia and some parts of North America. In recent years, *E. multilocularis* has expanded its geographical range in Europe from France, Germany, and Switzerland to include most countries in Central and Eastern Europe. It is not endemic in the UK.<sup>210</sup>

**Mode of transmission:** Ingestion of eggs passed in the faeces of the red fox which is the definitive host. Domestic cats and dogs can also be definitive hosts.

**Clinical presentation:** One third are found on imaging for hepatomegaly, fatigue, or weight loss. One third present with abdominal pain and one third with cholestatic jaundice.<sup>101</sup>

**Investigations:** Serology, imaging US, CT, MRI, PET. Biopsy and review of histopathology.<sup>211</sup>

**Treatment and clinical management issues:** Stage AE cases from the outset to determine the management strategy- a staging system and treatment recommendations are detailed in the WHO IWGE consensus statement (for the UK, the regimen under “optimal” resource setting applies).<sup>101</sup> Albendazole is suggested for first line treatment and is preferable to mebendazole. Praziquantel has no activity against AE, so is not used. Duration of treatment depends on staging and whether or not curative resection can be performed. Lifelong albendazole may be required. Unlike CE, AE lesions can progress rapidly in immunocompromised patients. Liver transplantation is an option in advanced, inoperable disease or liver failure.

Given the rarity and seriousness of AE, we strongly suggest it is managed in a tertiary care setting with full access to hepatobiliary surgeons with experience of this condition and transplantation. Cases should be discussed in the Hospital for Tropical Diseases Echinococcosis MDT meeting where hub and spoke management is supported. Contact the Parasitology Registrar on [uclh.parasitologyspr@nhs.net](mailto:uclh.parasitologyspr@nhs.net).

### 6.3.2. Fascioliasis (*Fasciola hepatica* and *F. gigantica*)

**Incubation period:** 3–12 weeks.

**Prepatent period:** 3–4 months.

**Distribution:** Worldwide, but high prevalence in Bolivia, Peru, Egypt and Iran.<sup>212</sup> *Fasciola* is endemic in sheep and cattle in the UK, with seroprevalence of up to 84% in dairy herds in Wales.<sup>213</sup>

**Mode of transmission:** Ingestion of intermediate stage metacercariae when eating contaminated water-based vegetation or chewing contaminated “Khat”. Transmission has occurred in the UK after eating wild watercress.<sup>214</sup>

**Clinical presentation:** Acute phase (months 1–3): fever, nausea, rash, hepatomegaly causing abdominal pain and eosinophilia. Chronic phase (3–6 months onwards, lasting up to 10 years): biliary obstruction with elevation of liver enzymes, cholecystitis and liver abscesses (50% cases are asymptomatic).<sup>215,216</sup> Occasionally diagnosed after unusual biliary imaging findings on MRI or ultrasound (e.g. serpiginous or tubular lesions).<sup>214</sup>

**Investigations:** Acute phase: diagnosis is clinical, with confirmatory serology later. 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: concentrated stool microscopy (low sensitivity) or serology in specialist laboratories. Ultrasound may show biliary obstruction. CT may show hepatic calcification or liver abscesses. Occasionally, *Fasciola* are seen on ERCP.

**Treatment:** We recommend triclabendazole PO 10 mg/kg/day for 2 days; response is rapid.<sup>217–220</sup> Triclabendazole resistance is widespread in livestock, but rare in humans. Nitazoxanide has been used in cases of triclabendazole failure.<sup>221,222</sup> Manual extraction from bile duct via ERCP has been described.<sup>223</sup> Antispasmodics may reduce the risk of biliary obstruction with treatment (expert opinion).

#### 6.3.3. Liver flukes (*Clonorchis sinensis* and *Opisthorchis* spp.)

**Prepatent period:** 4 weeks.<sup>224</sup>

**Incubation period:** 4 weeks but can present up to 25 years after infection.<sup>225</sup>

**Distribution:** *C. sinensis* is endemic in East Asia and eastern Russia;<sup>224,225</sup> *O. viverrini* in SE Asia; and *O. felinus* in Russia, Eastern Europe, Germany and Italy.<sup>226</sup>

**Mode of transmission:** Ingestion of raw/ undercooked freshwater fish (including lightly pickled, salted or smoked fish).

**Clinical presentation:** Acute infection (particularly in the case of *Opisthorchis* spp.) may result in fever, abdominal pain, urticarial skin rash and eosinophilia.<sup>227</sup> Chronic infection is more often seen, with asymptomatic hepatomegaly or biliary obstruction. There is an increased risk of cholangiocarcinoma and pyogenic cholangitis.<sup>228</sup> 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:** We recommend praziquantel 25 mg/kg three times a day for 2–3 consecutive days.<sup>229,230</sup>

#### 6.3.4. Schistosomiasis (*Schistosoma* spp.)

See section 6.2.2.

### 6.4. Eosinophilia with genitourinary symptoms

#### 6.4.1. Schistosomiasis/bilharzia (*Schistosoma haematobium*)

**Prepatent period:** 5–12 weeks.

**Distribution:** In travellers returning to the UK, the great lakes of East and southern Africa are the commonest sources.<sup>231–233</sup> Occasional outbreaks have been reported in southern Europe.<sup>234,235</sup>

**Mode of transmission:** section 6.2.2.

**Clinical Presentation:** Often asymptomatic. Haematuria may be micro or macroscopic; dysuria, proteinuria and superadded bacterial

infection may also feature. Polyps and eventually fibrosis may cause obstructive uropathy (e.g. hydronephrosis, bladder neck obstruction); polyps may also mimic tumours radiologically.<sup>236</sup> Individuals with heavy egg burdens of *S. haematobium* are at increased risk of bladder malignancy.

Genital involvement manifests with a wide range of symptoms: haematospermia and rarely hydrocoele in males, and stress incontinence, infertility, vulval lesion (sandy patches), inter-menstrual bleeding and increased risk of foetal loss in females.<sup>133,237–239</sup>

May present with acute schistosomiasis (‘Katayama syndrome’) (section 6.1.1).

**Investigations:** Serology and microscopy of nitrocellulose membrane– filtered terminal urine. Midday collection of urine for microscopy increases sensitivity, but sensitivity remains too low for microscopy to be used in isolation.<sup>240</sup> Urine dipstick for microscopic haematuria and proteinuria has low sensitivity and should not be relied on.<sup>241</sup> Seroconversion usually occurs between 4 and 8 weeks (up to 22 weeks). Urinary tract ultrasound may identify bladder wall changes in severe or chronic infection. Hypertrophic or ulcerative lesions of the vulva, vagina and cervix may be seen on colposcopy in women.<sup>237</sup>

**Treatment and clinical management:** We recommend treatment with praziquantel PO 40 mg/kg<sup>242</sup> as a single dose.<sup>144,145</sup>

Patients with long-standing infection or persistent symptoms including microscopic haematuria warrant further investigation such as radiological imaging and consideration of cystoscopy to exclude underlying malignancy.<sup>241</sup> Management of genital manifestations of schistosomiasis beyond drug treatment requires expert advice. Serology may remain positive for many years, so should not be used to assess success of treatment.<sup>136,139</sup> Serum Circulating Cathodic Antigen (CAA) can be used to monitor treatment response but is currently only performed at Leiden University Medical Center, Netherlands. Some specialist centers in the UK offer a send away service for this.

### 6.5. Eosinophilia with neurological symptoms

There are a small number of parasites which invade the central nervous system and cause eosinophilic meningitis, encephalitis or myelitis. There are few randomized controlled trials to guide therapy. Peripheral eosinophilia is common but not invariable, and the laboratory must be asked to look specifically for eosinophils in the cerebrospinal fluid (CSF), which are usually present at > 10% of the differential CSF leucocyte count in eosinophilic meningitis. Cytospin and manual cell count should be requested.

There is no role for ivermectin in the treatment of CNS infections as it does not reach sufficient concentrations in CSF.<sup>243,244</sup>

Treatment of many conditions discussed here requires prolonged/ high dose courses of steroid. **Concurrent strongyloidiasis infection should be excluded** where this is the case.

#### 6.5.1. *Angiostrongylus cantonensis* (rat lung worm)

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

**Distribution:** Endemic in Southeast Asia, China, Pacific islands and Hawaii, with sporadic cases reported from Caribbean, mainland USA, Australia, Israel.<sup>245</sup>

**Mode of transmission:** Ingestion of raw/undercooked molluscs (snails, slugs) containing *Angiostrongylus* larvae.<sup>245</sup> Humans are dead-end hosts.

**Clinical presentation:** *A. cantonensis* is the most common infectious cause of eosinophilic meningitis: headache +/- meningism, fever, vomiting, cranial nerve palsies, visual disturbances.<sup>246–249</sup>

**Investigations:** Discuss with a parasitology laboratory. Serology can be investigated (currently sent away to the Swiss Tropical and Public Health Institute (STPH)).

**Treatment:** Discuss with a specialist parasitology center. We recommend corticosteroids (60 mg prednisolone once daily for 14 days then wean according to local guidance) +/- albendazole PO 15 mg/kg/day for 14 days to reduce severity and duration of headache.<sup>250-253</sup>

#### 6.5.2. *Gnathostomiasis* (*Gnathostoma* spp.)

**Incubation period:** > 30 days.

**Distribution:** Endemic in Southeast Asia (most commonly *G. spinigerum*), with sporadic cases in South and Central America (*G. binucleatum*).<sup>254</sup>

**Mode of transmission:** Ingestion of larvae in raw/undercooked freshwater fish, eels, reptiles. Humans are dead end hosts.

**Clinical presentation:** Neuro-gnathostomiasis may be severe or fatal; it presents as eosinophilic meningo-encephalitis or myelitis. Radiculo-myelitis may cause severe nerve root pain and paralysis. Intra-cranial haemorrhage has also been reported.<sup>255</sup> Ocular presentations also occur.

**Investigations:** Discuss with parasitology laboratory. Serology can be performed (currently sent away to the Swiss Tropical and Public Health Institute (STPH)).

**Treatment:** Seek specialist advice, including parasitology and neurosurgery. The risks and benefits of treatment should be carefully considered; if pursued, treatment may include corticosteroid with albendazole (expert opinion).<sup>256-259</sup> Repeat anthelmintic therapy may be required.<sup>260</sup> Ophthalmic surgical removal is suggested as the first line treatment for ocular gnathostomiasis.<sup>261</sup>

#### 6.5.3. *Neurocysticercosis* (*Taenia solium*)

Ingestion of the eggs of the pork tapeworm *Taenia solium* (section 6.2.4) may result in the development of encysted larvae throughout the body (cysticercosis).

**Incubation period:** Cysticerci develop over a period of 3 to 8 weeks after ingestion of ova, but the incubation period prior to development of symptoms is on average 3.5 years and may be greater than 10 years.<sup>262</sup>

**Distribution:** See section 6.2.4. In some endemic villages 10–20% of individuals have evidence of neurocysticercosis (NCC) on CT scans.<sup>263,264</sup>

**Mode of transmission:** Faecal-oral route by ingestion of *T. solium* ova or proglottids.

**Clinical presentation:** Parenchymal NCC typically presents with seizures or headache. Ventricular NCC most often presents with obstructive hydrocephalus. Subarachnoid NCC can present with communicating hydrocephalus, meningitis, stroke, or focal neurological findings. Mixed forms are common. Patients may also present with nausea and vomiting. Fever is typically absent.

**Diagnosis:** Serology<sup>31,265</sup> and MRI brain with contrast.<sup>266</sup> Stool microscopy (including all household contacts)<sup>267</sup> is recommended to investigate for concomitant intestinal infection, along with fundoscopy to evaluate for ocular cysticercosis. Thigh radiographs may be used to investigate for disseminated infection. Cystic lesions with scolex visible on neuroimaging and retinal cysticercosis are diagnostic.

**Treatment:** Treatment should be individualized according to disease stage and severity;<sup>268</sup> always discuss in a neuro-infection or neuro-parasitology multidisciplinary team: email uclh.parasitologyspr@nhs.net (Hospital for Tropical Diseases, UCLH, London) or ahn-tr.neuroid.liv@nhs.net (Liverpool University Hospitals, Liverpool).

Management (expert opinion) may include anti-inflammatories (corticosteroids), anthelmintic treatment, anti-epileptic medication and surgical interventions. The priority is for symptom control, including control of seizures and raised intra-cranial pressure.

Corticosteroids are recommended if there is significant perilesional oedema; they must always be used when anthelmintic

treatment is given. Accepted regimens are prednisolone 1 mg/kg/day or dexamethasone 0.1 mg/kg/day whilst anthelmintic medication is given, followed by a slow wean.<sup>269-272</sup> Monitor blood glucose and consider bone and stomach protection measures (e.g. protein pump inhibitors). Exclude strongyloidiasis prior to steroid use.

Recommended anthelmintic regimens include single agent albendazole 15 mg/kg per day in 2 divided doses up to 1200 mg with food (for 1 or 2 viable cysts) or in combination with praziquantel at 50 mg/kg/day in 3 divided doses (where there are more than 2 cysts), for 10–14 days; discuss with an expert.<sup>269,270,272,273-275</sup>

Cysticercotic encephalitis is a contraindication for anthelmintic therapy due to risk of diffuse cerebral oedema and potential brain herniation (expert opinion). Most cases are treated with corticosteroids alone e.g. dexamethasone 0.2 to 0.4 mg/kg/day and the duration tailored according to clinical and radiographic resolution of oedema.<sup>271,272</sup>

#### 6.5.4. *Schistosomiasis* and CNS symptoms (*Schistosoma* spp.)

See section 6.2.2 and section 6.4.1. Schistosomiasis is a rare cause of myelopathy and CNS space occupying lesions and has been reported in returning travellers.<sup>276,277</sup>

**Clinical:** Acute myelopathy is the commonest presentation (*S. mansoni* or *S. haematobium*). A rapidly progressive transverse myelitis affecting the conus medullaris and cauda equina presents with lower limb pain, lower motor dysfunction, bladder paralysis and bowel dysfunction. Cerebral disease (*S. japonicum* infection),<sup>278</sup> presents with seizures, motor or sensory impairment or a cerebellar syndrome. Rarely, encephalopathy may mimic acute vasculitis.<sup>279,280</sup>

**Diagnosis:** Serology on serum and CSF (more sensitive)<sup>281</sup>, terminal urine microscopy and concentrated stool microscopy. Peripheral eosinophilia is usually absent; cerebrospinal fluid (CSF) eosinophils are seen in 40 to 90% of cases.<sup>282</sup> CSF serology is positive in 80 to 90% of cases.<sup>281</sup> MRI imaging shows nonspecific contrast enhancing intracerebral, spinal extra-dural or spinal intramedullary lesions. Biopsy may be performed if malignancy is suspected; histology shows granulomatous inflammation with eosinophilic infiltration, and schistosome ova may be identified.<sup>283</sup>

**Treatment:** Expert opinion advises prompt corticosteroid therapy with dexamethasone 4 mg four times a day starting one day before praziquantel and reducing after 7 days, longer courses (weeks to months) if marked oedema on imaging or deterioration in clinical status following anthelmintic treatment.<sup>282,284,285</sup> Expert opinion advises praziquantel PO 40 mg/kg daily for 3 days (*S. haematobium*, *S. mansoni*, *S. intercalatum* and *S. guineensis*), 60 mg/kg daily (2 divided doses) for 3 days (*S. japonicum* and *S. mekongi*).<sup>281</sup> Monitor blood glucose and consider bone and stomach protection measures (e.g. protein pump inhibitors) if course of corticosteroids is likely to be long.

#### 6.5.5. *Toxocariasis* (*Toxocara canis* and *T. cati*)

See section 6.1.4.

Neurotoxocariasis can present with myelitis, encephalitis +/- meningitis. Seek specialist advice; treatment may include albendazole for 3–4 weeks +/- corticosteroids (expert opinion). Repeat anthelmintic therapy may be required.<sup>286-288</sup> Ocular toxocariasis may occur as part of a more generalised visceral larva migrans syndrome, or as the only involved organ; in the latter case eosinophilia is less common. It most commonly presents with visual change and fundoscopic appearances of retinal granuloma or uveitis.<sup>289</sup> Formal ophthalmological examination is essential. Treatment (expert opinion) may include surgery, topical or systemic corticosteroids plus albendazole for 2 weeks.<sup>290,291</sup>

#### 6.5.6. *Coccidioidomycosis* (*Coccidioides* spp.)

The most frequent fungal cause of eosinophilic meningitis is *Coccidioides* (section 6.1.8), which presents with insidious

onset, progressive headache +/- altered mental state or hydrocephalus. See Table 6 for guidance on diagnosis.<sup>292,293</sup> Seek specialist advice for treatment.

#### 6.5.7. Other causes

*Baylisascaris procyonis* is a nematode infection acquired by ingestion of eggs in animal faeces (particularly racoons), that can present as eosinophilic meningitis or with ocular symptoms. Discuss with specialists regarding diagnosis and treatment.<sup>294</sup> Cerebral paragonimiasis (section 6.1.7) is rare, but may present with meningitis, encephalitis, myelitis, intracranial haemorrhage or seizures.<sup>295-297</sup>

#### 6.6. Eosinophilia with skin/musculoskeletal symptoms

Helminth infections frequently cause skin and soft tissue manifestations such as pruritus and urticarial rash. Common examples include *Ascaris lumbricoides* (section 6.2.3), hookworm (section 6.2.6), *Strongyloides stercoralis* (section 6.2.1), visceral larva migrans (section 6.1.4), *Schistosoma* spp. (section 6.2.2) and *Paragonimus westermani* (section 6.1.7). Sparganosis is rare but increasing in prevalence.<sup>298</sup> Ectoparasites such as scabies may be associated with eosinophilia.<sup>299,300</sup> Dimorphic fungi including *Blastomyces* spp.<sup>301</sup> (section 6.1.9), *Coccidioides immitis*<sup>302</sup> (section 6.1.8), *Histoplasma capsulatum*<sup>303</sup> (section 6.1.9) and *Paracoccidioides* spp.<sup>304</sup> (section 6.1.8) present with a wide variety of cutaneous manifestations particularly in disseminated infection or in the immunocompromised (See Table 6).

##### 6.6.1. Cutaneous larva migrans (*Ancylostoma braziliense* and *A. caninum*)

**Distribution:** Worldwide distribution with predominance in warmer regions.<sup>305</sup>

**Mode of transmission:** Penetration of skin by dog/cat hookworm larvae.

**Clinical presentation:** Characteristic self-limiting itchy, serpiginous rash migrating at 1–2 cm per day (Fig. 4), may be associated with eosinophilia. In contrast, ground itch is a blister-like eruption at the point of entry of human hookworm larvae (section 6.2.6).

**Investigations:** Clinical diagnosis.

**Treatment:** We suggest Ivermectin PO 200 µg/kg single dose or albendazole PO 400 mg once daily for 3 days.<sup>306</sup>

##### 6.6.2. Onchocerciasis (*Onchocerca volvulus*)

**Incubation period:** 8–20 months.

**Distribution:** Close to fast flowing rivers in Africa south of the Sahara, Yemen and the Yanomami area of Brazil, Venezuela and Bolivian Republic.<sup>307</sup>

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

**Clinical presentation:** Diffuse dermatitis; severe pruritus and excoriation results in skin hypo or hyper pigmentation, lichenification and ultimately depigmentation.<sup>308,309</sup> Nodules (onchocercoma) may appear on bony prominences, head and trunk. Ocular manifestations include keratitis, uveitis and choroidoretinitis, with eventual blindness ('river blindness'). Travellers usually present with mild to intense pruritus and limb swelling only.<sup>308,309</sup>

**Investigation:** Microscopic visualisation of microfilariae following incubation of skin snips in normal saline (low sensitivity, especially in recent infection) or on slit lamp examination (rarely positive in travellers), serology.<sup>310</sup>

**Treatment:** Specialist input advised. Seek urgent ophthalmology assessment. Exclude loiasis prior to treatment and seek expert advice in loiasis co-infection. We suggest treating with doxycycline PO 200 mg once daily for 6 weeks to target symbiotic *Wolbachia*.<sup>311</sup> Starting on day one of the doxycycline course, we suggest ivermectin PO 200 µg/kg monthly for 3 months to target microfilariae and to

reduce microfilarodermia.<sup>312</sup> Repeat ivermectin every 3–6 months until asymptomatic then annually, if necessary, for several years.<sup>313,314</sup>

##### 6.6.3. Larva currens (*Strongyloides stercoralis*)

This is an itchy, linear, urticarial rash associated with subcutaneous larval migration in *S. stercoralis* infection (section 6.2.1). It typically moves 5 to 10 cm per hour and occurs most commonly around the trunk, upper legs, and buttocks (Fig. 3).

##### 6.6.4. Lymphatic filariasis (*Wuchereria bancrofti* and *Brugia* spp.)

**Prepatent period (time to appearance of microfilariae):** *W. bancrofti* 7–8 months, *B. malayi* 2 months.

**Incubation period (time to appearance of clinical symptoms and signs):** Very variable, 4 weeks to 16 months.

**Distribution:** *W. bancrofti*: previously high prevalence throughout equatorial areas but now much reduced. Endemic in parts of Africa, West Pacific, and Caribbean. Sporadic cases in South America, India, and SE Asia.<sup>315</sup> *B. malayi*, *B. timori*: mainly SE Asia.<sup>315,316</sup>

**Mode of transmission:** Bite of mosquitoes, including *Aedes* spp., *Anopheles* spp. and *Culex*.

**Clinical presentation:** Most infections are initially asymptomatic, but cause lymphatic damage nevertheless. Acute fever and localised skin inflammation with lymphadenitis and lymphangitis is followed by chronic lymphoedema (previously referred to as elephantiasis) and scrotal oedema/ hydrocoele. Non-immune travellers from endemic regions may present with fever and respiratory symptoms (tropical pulmonary eosinophilia, section 6.1.5).<sup>317,318</sup>

**Investigations:** Serology and nocturnal blood microscopy (10 pm to 2 am in 4x citrated blood bottles 20 ml total volume, not to be refrigerated).

**Treatment:** Specialist input advised. Exclude onchocerciasis and loiasis if the patient has travelled to co-endemic areas- see Box 2. We recommend diethylcarbamazine (DEC) PO 6 mg/kg in 3 divided doses for 14 days<sup>319</sup> plus doxycycline PO 200 mg daily for 6 weeks.<sup>320-322</sup> In cases of onchocerciasis or loiasis co-infection, seek expert advice.

##### 6.6.5. Loiasis (*Loa loa*)

**Prepatent period (time to appearance of microfilariae):** Up to 18 months.<sup>323</sup>

**Incubation period (time to appearance of clinical symptoms and signs):** 6 months to 6 years.

**Distribution:** Central/West Africa (particularly Gabon, The Democratic Republic of Congo and Cameroon) and South Sudan.<sup>324,325</sup>

**Mode of transmission:** Bite of the *Chrysops* fly.

**Clinical Presentation:** Raised subcutaneous 'Calabar' swellings lasting up to a week (commonest in visitors to endemic areas) or conjunctival redness and swelling (commonest in migrants from endemic areas) with occasional direct visualisation of a sub-conjunctival 'eye worm' due to migration of adult worms (see Fig. 5).<sup>326</sup>

**Investigations:** Serology and day blood microscopy (10 am to 2 pm in 4x citrated blood bottles 20 ml total volume, not to be refrigerated).

**Treatment:** Seek specialist advice. Exclude onchocerciasis if the patient has travelled to onchocerciasis co-endemic areas: see Box 2. Diethylcarbamazine is the definitive treatment for *Loa loa*. First determine the microfilarial load. If high, DEC or ivermectin may precipitate encephalopathy with high mortality- see Box 2.<sup>327,328</sup> According to expert opinion:

- If microfilariae < 1000 mf/ml: use DEC and prednisolone (30 mg once daily for 7 days, starting the day before DEC).



**Figure 4.** The serpiginous rash of cutaneous larva migrans. Copyright to Dr Steve Walker, Hospital for Tropical Diseases, UCLH, London, UK.

- If microfilariae > 1000 mf/ml: treat with prednisolone (first screen for strongyloidiasis) and 21 days of albendazole PO 200 mg twice daily.<sup>329,330</sup> Check day blood microscopy at day 28, repeat the albendazole course as needed until a level of < 1000 mf/ml is achieved. Then treat with DEC with prednisolone cover.
- If peripheral blood is negative for microfilariae: DEC can be given without steroid cover.

The DEC regimen is PO: 50 mg single dose on day 1, 50 mg three times a day on day 2, 100 mg three times a day on day 3, 200 mg three times a day on day 4, then continue 200 mg three times a day for 21 days. Repeat day bloods at 6 and 12 months after the last negative sample to monitor for relapse (expert opinion).

#### 6.6.6. *Gnathostomiasis* (*Gnathostoma* spp.)

**Incubation period:** 7 days.<sup>331</sup>

**Distribution:** see section 6.5.2

**Mode of transmission:** see section 6.5.2

**Clinical presentation:** Recurrent pruritic or painful, ill-defined migratory subcutaneous nodules. Rarely presents with meningitis, encephalitis, myelitis (section 6.5.2), iritis, uveitis or intra-ocular haemorrhage. Abdominal or retroperitoneal pain or haematuria may rarely occur.<sup>331</sup>

**Investigation:** Diagnosis is usually clinical; serology is not available in the UK but can be sent to the Swiss Tropical and Public Health Institute (STPH), see Table 4.

**Treatment:** Seek expert advice. We recommend ivermectin PO 200 µg/kg daily for 2 days with monitoring for relapse (alternatively albendazole PO 400 mg twice daily for 21 days). Treatment may need to be repeated.<sup>256,257,260,332,333</sup>

#### 6.6.7. *Trichinellosis* (*Trichinella* spp.)

Trichinellosis consists of 2 phases; an initial 'enteral' phase of diarrhoea and gastrointestinal symptoms followed by a 'parenteral phase', as the larvae migrate from intestine to muscle, consisting of facial and periorbital oedema, urticarial rash, severe myalgia, and myositis (section 6.2.9).

#### 6.6.8. *Swimmers' itch/cercarial dermatitis* (*Schistosoma* spp.)

**Incubation period:** Hours.

**Distribution:** Worldwide and often in outbreaks.<sup>334</sup>

**Mode of transmission:** Penetration of human skin by cercariae in fresh or salt water during recreational activities, especially swimming.<sup>335</sup>

**Clinical presentation:** Pruritic maculopapular rash. Repeated exposure can result in sensitisation and papulovesicular rash.

**Treatment:** Usually resolves spontaneously within days to weeks; topical corticosteroids or systemic antihistamines may be used in severe cases.<sup>336</sup>

#### 6.6.9. *Histoplasmosis and blastomycosis* (*Histoplasma capsulatum* and *Blastomyces* spp. including *B. dermatitidis*)

**Incubation period:** see section 6.1.9

**Distribution:** see section 6.1.9

**Mode of transmission:** see section 6.1.9

**Clinical presentation:** Skin manifestations of histoplasmosis can be seen in disseminated infection, particularly in the immunocompromised. These are numerous and can include ulcers, vesicles, nodules or plaques. Note that disease caused by *Histoplasma capsulatum* var *duboisii* (aka African histoplasmosis) primarily affects the skin and often occurs in apparently immunocompetent individuals.

Skin is the second commonest site of infection (after pulmonary) in blastomycosis. The classic finding is an irregularly edged verrucous lesion.

**Investigations:** In addition to serology, microscopy, culture and antigen tests (see section 6.1.9), skin lesions can be biopsied – organisms and/ or granulomata may be seen on histopathological examination or detected by PCR.

**Treatment and clinical management issues:** see section 6.1.9

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#### Appendix A

**External review group:** As part of the writing process the guidelines were reviewed by an external panel: Dr Mike Brown<sup>ab</sup>, Dr Jonathan Cohen<sup>cd</sup>, Dr Charlotte Frise<sup>e</sup>, Prof David Mabey<sup>b</sup>, Mrs June Minton<sup>f</sup>, Dr William Newsholme<sup>g</sup>, Prof Andrew Ustianowski<sup>h</sup>, Dr Steve Walker<sup>ab</sup>, Prof Christopher Whitty<sup>a</sup>.

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**Figure 5.** Subconjunctival migration of adult *Loa loa*. Copyright to Dr Tara Moshiri, Nottingham University Hospitals NHS Trust, Nottingham, UK.

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## Appendix B. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106328.

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