

CLINICAL REVIEW

Strongyloides stercoralis infection

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Strongyloides stercoralis is an intestinal helminth that infects humans through contact with soil containing the larvae. Between 30 and 100 million people are infected worldwide.¹ In the United Kingdom, strongyloidiasis is seen predominantly in migrants and returning travellers from endemic areas in the tropics and subtropics. Strongyloidiasis may present with cutaneous or gastrointestinal symptoms but is asymptomatic in over 60% of cases and only indicated by a raised blood eosinophil count.² Diagnosis is important as the infection may persist for decades.³ Immunosuppressed patients with chronic strongyloidiasis are at high risk of developing strongyloides hyperinfection syndrome, a life threatening complication whereby larval proliferation leads to systemic sepsis and multiorgan failure. If strongyloidiasis is diagnosed early, however, it is easily treatable with oral antihelminthic drugs. In this article we review the epidemiology and common symptoms of strongyloidiasis and strongyloides hyperinfection syndrome, discuss the appropriate investigations, and summarise the evidence on treatment.

What is the lifecycle of strongyloides?

S stercoralis larvae are most likely to be present in rural areas with poor sanitation, resulting in faecal soil contamination. The infection starts when the host walks barefoot on contaminated soil and infectious filariform larvae penetrate the skin (figure 1). The larvae enter the venous circulation and migrate to the lungs from where they are expectorated to the pharynx and swallowed. In the small intestine the larvae develop into adult females, which reproduce asexually and release eggs into the gastrointestinal tract. The eggs then hatch into non-infectious rhabditiform larvae and are excreted in stool. Outside of the human host the free-living rhabditiform larvae either mature into male and female adult worms, which reproduce sexually, or transform directly into filariform larvae ready to invade another host.

S stercoralis can be distinguished from most other intestinal parasites by its ability to reinfect the host through the wall of the gastrointestinal tract. This phenomenon is called autoinfection and occurs when some of the rhabditiform larvae in the faeces transform into infectious filariform larvae in the

host's gastrointestinal tract. These larvae then penetrate the gut wall and re-enter the circulation back to the lungs to begin the cycle again. This is the key to the persistence of strongyloides infection and explains why it has been detected decades after initial exposure, up to 75 years later in one case report.³

Who gets strongyloidiasis?

Strongyloidiasis is most commonly encountered in sub-Saharan Africa, South America, and South East Asia, where prevalence may exceed 20%.⁴ The disease is also encountered in resident populations of the south eastern United States and in parts of southern Europe, in particular Spain and Italy.

In the United Kingdom, strongyloidiasis is primarily seen in immigrants or returning travellers from endemic areas. An estimated 499 780 non-European Union citizens arrived to live in the United Kingdom in the year to March 2013, representing a population at risk.⁵ Although no UK data on the prevalence of strongyloidiasis in these populations has been published, several studies from other countries have shown that the burden of disease in immigrants may be considerable. Studies from North America and Canada have shown the presence of serum antibodies to *S stercoralis* in 23-65% of immigrants from Africa and South East Asia.^{6 7}

Strongyloidiasis can also be transmitted sexually through oro-anal contact. This is most commonly seen in men who have sex with men.⁸ Case reports also exist of strongyloidiasis in recipients of solid organ transplants, derived from the donor organ.⁹ Infection with *S stercoralis* through the faecal-oral route may also be possible, as larvae have been identified in contaminated water used to wash vegetables in endemic areas.¹⁰

What are the symptoms of strongyloidiasis?

Infection with *S stercoralis* is often mild or asymptomatic. Two case series of 33 and 70 patients with strongyloidiasis found that 51% and 64%, respectively, had no symptoms.^{2 11} In such

Summary points

- Strongyloidiasis is endemic in the tropics and subtropics and anyone who has travelled to, or lived in, these areas is at risk
- Unlike most other intestinal parasite infections, strongyloidiasis may be life long
- The infection is often asymptomatic and may only be indicated by a peripheral blood eosinophilia
- Diagnosis is important as immunosuppression in patients with chronic infection can precipitate a life threatening hyperinfection syndrome
- Serology is the investigation of choice for diagnosis and follow-up, as stool microscopy has a low sensitivity
- Treatment is with 2×200 µg/kg doses of oral ivermectin given two weeks apart

Sources and selection criteria

We performed a search of PubMed using the search term "*Strongyloides stercoralis*", and included English language studies only. There is a paucity of randomised controlled trials investigating the treatment of strongyloides infection, and no Cochrane reviews have been published. Likewise there are no national or globally recognised guidelines for the investigation and management of this condition. We therefore relied on the studies from our literature search and clinical experience.

cases the only sign of infection is an increased peripheral blood eosinophil count.

Acute infection may give a characteristic cutaneous reaction as the larvae penetrate the skin, known as ground itch. The foot is the most commonly affected site and can result in serpiginous or urticarial tracts with severe pruritus lasting for several days. The rash may be difficult to distinguish from cutaneous larva migrans, a condition caused by animal species of hookworm that penetrate human skin but are unable to migrate further than the epidermis. In chronic infection *S stercoralis* larvae can also migrate intradermally, giving a different appearance from that of cutaneous larva migrans owing to the rapid speed of migration, progressing at around 5–15 cm per hour. This results in intensely itchy red tracts, usually on the perianal area and upper thighs, known as larva currens (literally "running larvae"), which are pathognomonic for strongyloidiasis.

As the larvae migrate through the lungs they can produce respiratory symptoms, such as a dry cough or wheeze. A Loeffler's-like syndrome, characterised by fever, dyspnoea, wheeze, pulmonary infiltrates on chest radiographs, and accompanying blood eosinophilia is rarely seen. Chronic strongyloidiasis can lead to recurrent pulmonary symptoms, such as repeated mild pneumonitis with fever or restrictive pulmonary disease.

Once the adult worms reach the small intestine they can stimulate vague gastrointestinal symptoms such as diarrhoea, anorexia, and vomiting, and epigastric pain worsened by eating. In one recent case series of 70 patients, gastrointestinal symptoms were present in 23%.²

How is strongyloidiasis diagnosed?

As strongyloidiasis is most commonly asymptomatic, or presents with vague symptoms, diagnostic investigations are key. Blood eosinophilia should always be investigated further, in the first instance by repeating the test to confirm the result. The commonest causes of eosinophilia are parasitic infections, atopy, and drugs (see box for other common causes). A careful history should therefore be taken, including the patient's travel record, the presence of allergic symptoms, and a drug review. The degree of eosinophilia with each of these conditions is highly variable and so cannot be reliably used for differentiation, although it is uncommon for atopy to give rise to an eosinophil count of $>2 \times 10^9/L$.¹²

Patients with a history of travel to an area where strongyloidiasis is endemic and either compatible symptoms or a blood eosinophilia should be investigated further, with three stool

samples for microscopy (collected on separate days) and a blood test for *S stercoralis* serology.

Standard stool microscopy for ova, cysts, and parasites is available at all National Health Service hospitals in the United Kingdom with a microbiology laboratory. Although it is a standard test for many intestinal protozoa and helminth infections, stool microscopy has low sensitivity for detecting *S stercoralis* (around 50%) because of intermittent larval excretion and low infectious burden.^{13 14} Certain stool concentration techniques performed in the laboratory, such as the Baermann technique and modified agar plate method, can be used to improve the sensitivity. Despite the low sensitivity, stool microscopy should still be routinely performed, as it is the gold standard for diagnosis. It can take 3–4 weeks for larvae to appear in the stool after dermal penetration.

Serological testing, which consists of an enzyme linked immunosorbent assay to detect IgG to a filariform larval antigen, is generally considered to be a superior investigation. Commercially available assays have a sensitivity between 83% and 89% and a specificity of 97.2%.¹⁵ In the presence of other helminth infections there is a risk of a false positive result owing to cross reactivity. This is particularly true for filariasis, where up to 60% of patients may have false positive *S stercoralis* serology.¹⁵ In the United Kingdom the serology test is only performed at large parasitology reference laboratories. All samples received by local hospitals are forwarded to these laboratories.

When should patients with strongyloidiasis be referred?

The diagnosis of strongyloidiasis can be made in primary care by stool microscopy and serology. In the event of a proved case, it is reasonable to refer the patient to an infectious diseases doctor, as commonly used treatments may be difficult to attain for many pharmacies outside of hospital.

Several other important parasitic infections may present with asymptomatic eosinophilia, particularly filariasis and schistosomiasis. As cross reactivity may occur between serological assays, this can complicate the diagnostic process. Therefore, if patients with unexplained eosinophilia have travelled to an area where strongyloidiasis, filariasis, and schistosomiasis are endemic, particularly sub-Saharan Africa, it is also advisable to refer them to a specialist.

Patients with a definite diagnosis of strongyloidiasis for whom immunosuppression is planned should also be referred, as the

Other common causes of eosinophilia

- Allergy
 - Asthma
 - Atopic dermatitis
 - Acute urticaria
- Parasitic infection
 - Schistosomiasis
 - Filariasis
 - Hookworm
 - Toxocara canis*
- Fungal infection
 - Allergic bronchopulmonary aspergillosis
 - Coccidioidomycosis
- HIV
- Churg-Strauss syndrome
- Haematological disorders
 - Eosinophilic leukaemia
 - Hypereosinophilic syndrome
- Adrenocortical insufficiency

risk of developing strongyloides hyperinfection syndrome must be assessed and appropriate counselling provided.

What is strongyloides hyperinfection syndrome?

Strongyloides hyperinfection syndrome occurs when patients chronically infected with *S stercoralis* become immunosuppressed, such as those receiving treatment for autoimmune disease or malignancy, or if immunosuppressed patients develop acute strongyloidiasis. This results in uncontrolled over-proliferation of larvae with dissemination to end organs, including the lungs, liver, and brain. Systemic sepsis is a common complication owing to translocation of enteric bacteria accompanying larval invasion of the gut wall.

The strongest risk factor seems to be administered corticosteroids. Case reports exist of strongyloides hyperinfection syndrome after courses of steroid as short as six days¹⁶ and with a dose of oral prednisolone as low as 20 mg per day.¹⁷ Individual cases linked with other steroid sparing immunosuppressants and chemotherapeutics have also been described,¹⁸ as well as strongyloides hyperinfection syndrome in both solid organ and bone marrow transplant recipients.^{19 20} Infection with human T cell leukaemia/lymphoma virus type I (HTLV-I) is also a major risk factor for strongyloides hyperinfection syndrome.²¹ Observational studies have reported treatment failure of chronic strongyloidiasis in patients infected with HTLV-I²² along with strongyloides hyperinfection syndrome in the absence of immunosuppression.²³ By contrast, HIV infection does not seem to predispose to strongyloides hyperinfection syndrome, although a greater prevalence of strongyloidiasis was seen in this group than in non-HIV infected people in one cross sectional study.²⁴

The initial symptoms of strongyloides hyperinfection syndrome may include fever, haemoptysis, and wheeze. A chest radiograph may reveal pulmonary infiltrates, which can represent a combination of oedema, haemorrhage, and pneumonitis. Gastrointestinal disturbance is common and may progress to paralytic ileus or frank bleeding. Hyponatraemia as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has also been reported but is less common.²⁵ Septicaemia and multiorgan failure secondary to translocated

gut flora may follow, along with Gram negative meningitis due to bacterial invasion of the cerebrospinal fluid.

Filariform larvae may be found in bodily fluids such as sputum or pleural or peritoneal fluid. Because of the effects of immunosuppression, eosinophilia is often absent.²⁵

How is strongyloidiasis treated?

Studies investigating the efficacy of drug treatment for *S stercoralis* have the drawback of being small open label clinical trials. None the less, ivermectin has consistently been shown to be the drug of choice to achieve parasitological cure (that is, the absence of larvae on stool examination) with few side effects.

Ivermectin is a semisynthetic antihelmintic drug derived from avermectin B₁. It has a different mechanism of action to the benzimidazoles, such as albendazole, which are also commonly prescribed for intestinal helminth infections. The drug works by binding to glutamate gated chloride ion channels, resulting in hyperpolarisation of neuronal cells and death of the parasite due to paralysis. This effect is not found in humans as ivermectin does not cross the blood-brain barrier.

Ivermectin is currently unlicensed for the treatment of strongyloidiasis in the United Kingdom and hence is only available from "special order" manufacturers and importing companies. The drug is most commonly administered as an oral preparation.

Four studies have compared the efficacy of a single oral dose of 200 µg/kg of ivermectin with two oral doses of 200 µg/kg given either on consecutive days or two weeks apart.²⁶⁻²⁹ Only one study showed a greater efficacy of two doses over a single dose (100% v 77% cure, respectively²⁸) whereas the other three showed comparative efficacy (>93%) for both regimens.^{26 27 29} However, as an autoinfection cycle takes 3-4 weeks to complete²⁷ and the activity of ivermectin on the extraintestinal stages of the parasite remains uncertain, our local practise is to give two doses two weeks apart.

From our experience, ivermectin is generally well tolerated with few side effects. Two studies have noted a transient increase in alanine aminotransferase levels with ivermectin treatment in a small number of patients,^{26 30} while abdominal distension and chest tightness have also been reported.³¹

Ivermectin also has activity against parasites other than *S stercoralis*, which may result in unintended harmful treatment effects. This is particularly important for *Loa loa*, an insect-borne filarial infection characterised by migration of large adult worms through subcutaneous tissues of the body. This manifests as transient localised subcutaneous swellings (Calabar swellings) and occasional visible passage of worms beneath the conjunctiva. Epidemiological evidence shows that patients coinfecting with *L loa* show an increased incidence of encephalopathy in association with ivermectin treatment.³² It is therefore advisable that patients who have travelled to west and central Africa, where both conditions are endemic, are screened for *L loa* microfilaraemia with a blood film before treatment with ivermectin. We recommend referral of such patients to an infectious diseases doctor.

In patients who are unable to tolerate ivermectin, albendazole is a reasonable alternative, although cure rates in clinical trials were inferior.^{26 30 31 33} In one recent study a course of 400 mg twice daily for seven days produced a cure rate of 63.3%.²⁶

How is strongyloides hyperinfection syndrome treated?

Strongyloides hyperinfection syndrome is a difficult condition to treat and is associated with a high mortality. Management involves a combination of antibiotic treatment for systemic Gram negative bacterial sepsis, antihelminthic treatment of *S stercoralis* itself, multiple organ support during the critical phase of the illness, and reduction of immunosuppression where possible.^{18 34} Ivermectin is still considered the drug of choice,¹⁸ although this is based only on case report evidence. Due to the high burden of larvae in strongyloides hyperinfection syndrome compared with chronic strongyloidiasis, stool microscopy is used to determine treatment efficacy. Daily dosing with ivermectin should therefore continue until two weeks after the last positive stool sample to cover a complete autoinfection cycle.³⁴ Parenteral ivermectin has been shown to be effective in cases complicated by paralytic ileus or gastrointestinal bleeding where the oral route is not suitable.^{35 36} It should be noted, however, that parenteral ivermectin is currently only available as a veterinary preparation and therefore is not licensed for use in humans. We recommend that expert advice should be sought in such cases.

How is treatment efficacy assessed?

As strongyloidiasis is often asymptomatic, resolution of symptoms is a poor indicator of treatment efficacy. Stool microscopy is also inadequate owing to low sensitivity. Repeat serological testing after treatment seems to be the best way to test for cure. If the antibody titre has decreased at 6-12 months after treatment this is indicative of eradication of the parasite.³⁷ It has been suggested that a post-treatment to pre-treatment titre ratio of <0.6 is a good indicator of treatment success,³⁸ and this has been observed in 65-90% of patients at six months after treatment.^{37 39} Monitoring of blood eosinophil count may also be an effective tool, as a significant decrease in count was seen at an average of 96 days after treatment in one retrospective study.⁴⁰ Patients who fail to clear the parasite after two doses of ivermectin should be tested for HTLV-I infection.²² A concerted effort to look for other causes of eosinophilia is recommended if it persists after three months despite a serological response to ivermectin treatment.

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Additional educational resources

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Experience of treating strongyloides infection in the tropics

In Thailand the prevalence of strongyloidiasis is estimated to be between 15.9% and 20.6% in certain rural areas. Furthermore, the Foreign and Commonwealth Office states that over 800 000 British nationals visit Thailand every year,⁴¹ so UK based clinicians should be vigilant.

Although the incidence of strongyloides hyperinfection syndrome is low, around 12-24 cases per year are seen at the Hospital for Tropical Diseases in Bangkok. The diagnosis of strongyloidiasis in this environment can be challenging, although clinicians have a low threshold for routine stool examination. Serological testing is also available but is used less often.

In Thailand the first line treatment for adults and children remains albendazole. Ivermectin is not available in all centres so is considered second line treatment despite superior efficacy. Cases of strongyloides hyperinfection syndrome are treated with monthly cycles of albendazole (once daily for five days) followed by ivermectin (single dose) every month for as long as *Strongyloides stercoralis* larvae are detectable in stool.

Patients with intestinal infection alone (that is, non-strongyloides hyperinfection syndrome) have a stool microscopy follow-up a week, one month, and two months after treatment. Serology follow-up occurs in some cases 3-6 months after treatment, at the clinician's discretion. Ongoing serial follow-up occurs if the patient remains positive.

Tips for non-specialists*Patients who should be investigated for strongyloidiasis*

- People who travel to, or migrate from, an endemic area and develop the following within 3-4 weeks of travel:
 - Persistent unexplained eosinophilia
 - Gastrointestinal symptoms: nausea, vomiting, abdominal pain, bloating
 - Pulmonary symptoms: fever, wheeze, persistent cough
 - Cutaneous symptoms: larva currens, hives, or pustules

Patients in whom strongyloides hyperinfection should be suspected

- Risk factors for strongyloides as above plus:
 - Immunosuppressive drug therapy (particularly with steroids)
 - Bone marrow allograft
 - Solid organ transplantation
 - HTLV-I infection

Questions for future research

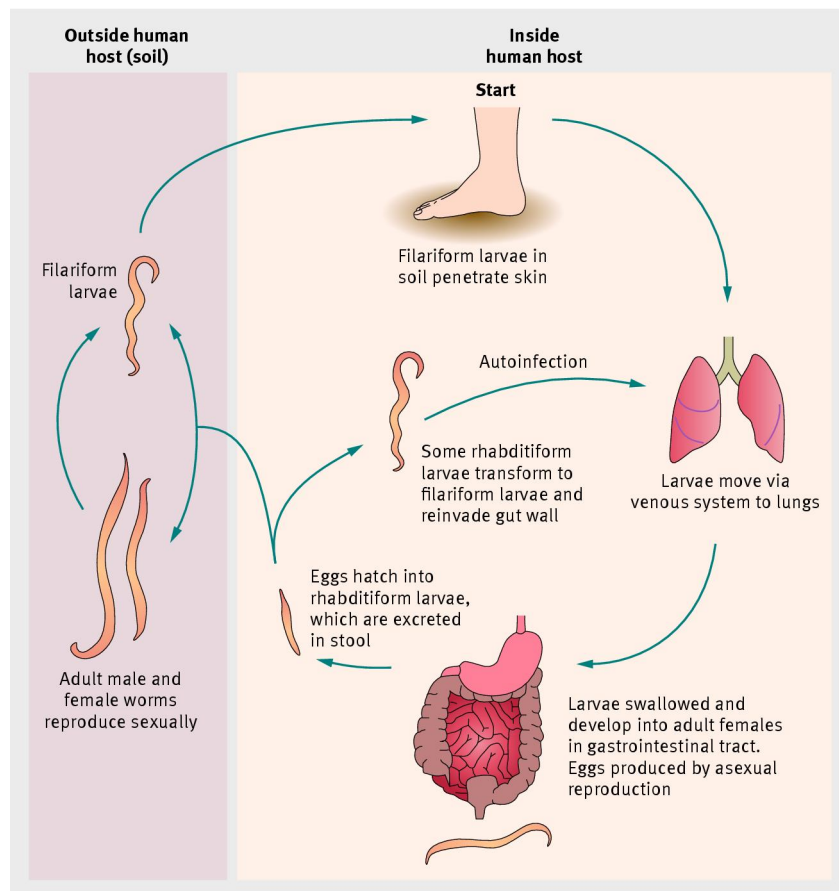
- What is the UK prevalence of strongyloidiasis among immigrant populations from endemic areas?
- Is ivermectin the best drug for treatment of strongyloidiasis and what is the optimal dosing regimen?
- What is the optimum treatment regime for strongyloides hyperinfection syndrome?
- Can serological testing be improved to allow more accurate post-treatment evaluation of the likelihood of cure?

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Figure



Life cycle of *Strongyloides stercoralis*