

# Schistosomiasis

This is an ancient disease that may have had historical consequences for affected populations.

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Schistosomiasis is a blood fluke infection that has affected mankind for over four thousand years. A description of haematuria in agricultural communities of the Great River Valley found in the *Gynaecological Papyrus of Kahun* circa 1900BC is recognised as the first recorded description of the disease. Its geographical distribution continues to expand, a 5th human pathogenic schistosome, *Schistosoma mekongi*, having been described in Laos and Cambodia as recently as 1978. Five species of schistosomes are pathogenic in humans (Table I), four of which cause intestinal schistosomiasis, while *S. haematobium* causes urinary disease. This review will concentrate on the 3 main species affecting humans: *S. haematobium*, *S. mansoni* and *S. japonicum*. Schistosomiasis is a disease of poverty, related to poor sanitation and water supply. Africa bears the brunt of infections, with 85% of the estimated 193 million global cases. Children are disproportionately affected, with peak prevalence in the 10 - 14-year age group.

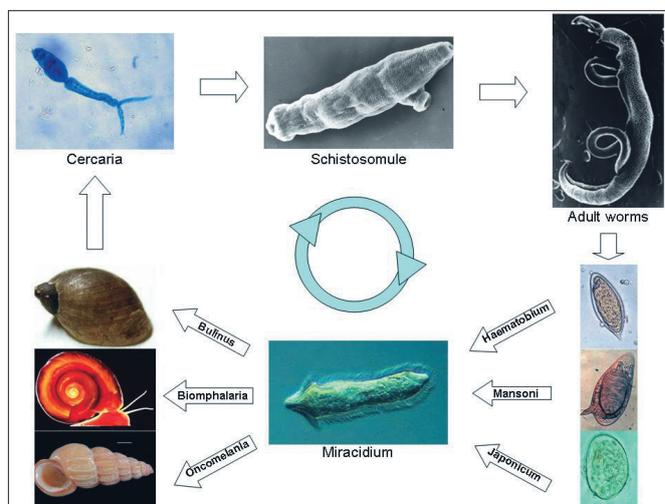


Fig. 1. Life cycle of schistosomiasis (see text for details).

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## The schistosome life cycle (Fig. 1)

The *Schistosoma* species that cause disease in man share a common life cycle, differing only in the nature of the intermediate snail host and the morphology of the schistosome eggs. Eggs are excreted from the adult fluke either via stool or urine, depending on the respective schistosome species. Once the egg encounters fresh water, the developing larva hatches, releasing a single miracidium. Miracidia are motile and remain infective for 8 - 12 hours, locating the intermediate snail host by chemotactic stimuli. A process of asexual multiplication of single-sexed cercariae occurs

Table I. Schistosomes causing human disease					
Schistosoma species	Geographical area	Intermediate snail host	Egg characteristics	Egg production (number/day)	Location of adult worms
<i>Haematobium</i>	Africa, Madagascar, Zanzibar, Pemba, Middle East	Bulinus	Terminal spine	20 - 200	Pericolonic plexus
<i>Intercalatum</i>	Central and West Africa	Bulinus	Terminal spine	Unknown	
<i>Mansoni</i>	Africa, Madagascar, Gulf of Arabia, Brazil, Venezuela, Suriname, Caribbean Islands	Biomphalaria	Lateral spine	100 - 300	
<i>Japonicum</i>	China, Philippines mainland, Indonesia	Oncomelania	No spine	500 - 3 500	
<i>Mekongi</i>	Laos, Cambodia	Tricula	No spine	Unknown	

in the snail (Table I and Fig. 1). Each snail produces thousands of cercariae, which are released upon stimulation by sunlight and temperature to coincide with the daytime activities of humans in water. Once released, cercariae survive 36 - 48 hours and penetrate human skin aided by secretion of lytic chemicals. Once in subcutaneous tissues, the cercaria loses its tail to become a schistosomule and penetrates peripheral vessels allowing migration to the heart and then the lungs. Development continues within the lungs, from where the fluke travels intravascularly to splanchnic organs. Penetration through splanchnic capillaries allows access to the hepatic portal system, at which stage motility decreases and feeding begins. Pairing of male and female flukes occurs, the female secure within the gynaecophoric canal of the male. Migration to the terminal venules of the genitourinary system/pelvic plexus (*S. haematobium*) or to the pericolonic venules (*S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum*) completes migration and signals the start of egg release (oviposition). Approximately half of the eggs released will traverse tissues with the aid of a spine (*S. haematobium*, *S. intercalatum* and *S. mansoni*) and cytolytic secretions, resulting in expulsion of the egg into urine or faeces.

### Pathology

The remaining 50% of eggs become trapped in tissues such as the bladder or intestinal wall. The host immune response to trapped eggs drives the pathological process of schistosomiasis, the hallmark feature being the schistosomal granuloma. Granulomas are composed of a central egg surrounded by closely adherent activated macrophages, eosinophils, lymphocytes, polymorphs, plasma cells and fibroblasts (Fig. 2). The delayed hypersensitivity response that results in granuloma formation is driven by soluble egg antigens (SEA) that diffuse out of the egg's shell. Pathology correlates with egg load and is completed by fibroblastic proliferation and abnormal collagen deposition. Genetic factors such as HLA haplotype may play a role in pathogenesis, but the severity of the pathological process depends predominantly on egg burden.

*S. haematobium* infection mainly affects the bladder and urinary tract, although eggs are found in intestinal mucosa, genital tract and ectopic locations such as the skin. The characteristic features of bladder pathology

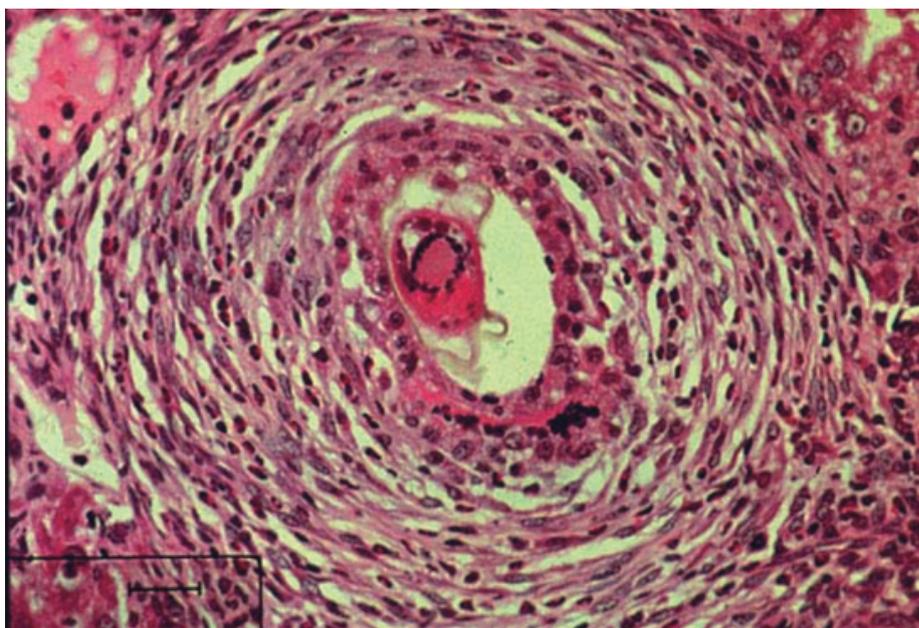


Fig. 2. Schistosome egg granuloma in human liver.

are sandy patches containing eggs and fibrous material, which sit on a background of hyperaemic mucosa. Involvement of the trigone and ureteric orifices is typical, the latter giving rise to ureteric obstruction and obstructive uropathy. Polyps and nodules may also be present. Squamous cell (as opposed to the more common transitional cell) bladder cancer is a long-term complication of urinary schistosomiasis.

Infection with *S. mansoni* or *S. japonicum* causes intestinal schistosomiasis and periportal hepatic fibrosis. Eggs of both species may spread as a result of portocaval shunting to ectopic sites, resulting in pulmonary hypertension, brain and spinal cord involvement. Adult *S. mansoni* reside within the inferior mesenteric veins, seeding the recto-sigmoid colon and causing intestinal disease with colonic polyps. Anaemia and protein-losing enteropathy result from blood and protein loss from these lesions. Periportal fibrosis of pre-sinusoidal vessels resulting from schistosomal granulomas deposited in and around the portal tracts leads to portal hypertension and its long-term sequelae. Hepatic function is usually spared by the formation of new capillaries originating from enlarged hepatic arteries at the portal tracts, ensuring continued vascular supply to hepatocytes. Hypersplenism as a result of portal hypertension may render those infected pancytopenic, and schistosomal cor pulmonale may result from pulmonary arteritis. This is a more common feature of *S. mansoni* than *S. japonicum* infection.

### Clinical presentation

As with many tropical infections, immunity acquired from repeated infection during childhood and adolescence often determines the type of clinical manifestation experienced following infection. Acute schistosomiasis, for example, is far commoner in non-immune travellers, whereas in general this group do not acquire a high enough intensity of infection to manifest chronic disease. Chronic disease in travellers is also prevented by a heightened awareness of the risks of acquiring schistosomiasis, leading to asymptomatic travellers seeking worm eradication with praziquantel.

**Cercarial dermatitis** (swimmer's itch) is a pruritic eruption resulting from cercarial penetration of skin or mucous membranes, common to all infecting schistosomes. Schistosomal dermatitis may also be acquired by penetration of avian schistosomes in non-human schistosomiasis endemic areas.

**Acute schistosomiasis (Katayama fever)** is most frequently a result of *S. japonicum* and *S. mansoni* infection, but may occur with *S. haematobium*. It is most often seen in non-immune, returning travellers or persons living in endemic areas with heavy re-infections. It results from a systemic hypersensitivity reaction predominantly as a result of initial egg laying or migration of schistosomulae. The incubation period varies between species, but most presentations occur 14 - 87 days after acquisition of infection. Occasionally, shorter incubation periods occur with symptoms reported as soon as 1 week after infection. Fever ( $\pm$  sweats and rigors) and eosinophilia are the hallmarks of acute schistosomiasis. Dry cough, diarrhoea, malaise and headaches may occur. Urticaria and wheeze may be present on examination, as well as tender hepatosplenomegaly due

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to deposition of granulomas, cell proliferation, reticuloendothelial hyperplasia and an inflammatory infiltrate.

### Chronic schistosomiasis

The clinical manifestations of chronic schistosomiasis depend on the infecting species. The hallmark of *S. haematobium* infection in chronic urinary schistosomiasis is haematuria, which may be associated with other urinary symptoms such as dysuria and frequency and, less commonly, haemospermia. Chronic obstructive uropathy and squamous cell bladder cancer are long-term sequelae of chronic infection. Co-existent bacteriuria may accompany chronic disease, requiring antibiotic therapy.

Chronic infection with *S. mansoni* and *S. japonicum* results in intestinal schistosomiasis, although in the majority of individuals infection is asymptomatic. Bloody diarrhoea is common in heavy persistent infections with or without constitutional symptoms of anorexia, weight loss and fevers. Chronic dysentery may result from polyp formation. Hepatosplenomegaly develops secondary to periportal hepatic fibrosis, but unless co-existent hepatic viral infections or other liver pathology is present, classic signs of chronic liver disease other than organomegaly are usually absent.

*S. japonicum* infection is associated with cerebral schistosomiasis, most commonly presenting with meningoencephalitis. Other neurological complications of schistosomiasis include transverse myelitis and other myelopathies.

Recurrent *Salmonella typhi* bacteraemia is associated with schistosomiasis due to binding of salmonellae to the adult worm. Treatment of schistosomiasis in this instance is mandatory to prevent further episodes of salmonella bacteraemia.

### Differential diagnosis

The list of differential diagnoses for schistosomiasis is long, and depends on the stage of disease, regional variation in endemic diseases and exposure risks of the patient. In returning travellers presenting with fever, a detailed exposure history during travel is vital to making a correct diagnosis. In the case of schistosomiasis, a history of immersion in inland waterways is key. A cross-sectional study of expatriates and tourists living near Lake Malawi identified a 1-day absolute risk of acquiring schistosomiasis of 52 - 74%.<sup>1</sup> In a further study of 29 travellers who acquired schistosomiasis in the Dogon area of Mali, West Africa, 28 had swum in the freshwater pools.<sup>2</sup>

## The clinical manifestations of chronic schistosomiasis depend on the infecting species.

### Laboratory investigations

The diagnosis of schistosomiasis relies either on direct tests, i.e. visualisation of eggs in urine, stool or tissue specimens, indirect tests such as identification of circulating antibody or antigen, or clinical suspicion when a patient presents with clinical features suggestive of eosinophilia from an endemic area.

The characteristic eggs of *S. haematobium* with their terminal spine (Fig. 1) are best visualised by microscopy of sedimented or centrifuged urine that has been taken between 10h00 and 14h00, when egg shedding is maximal. Similarly, stool samples sent for qualitative analysis for *S. mansoni* or *S. japonicum* require a concentration technique to increase the sensitivity of the test, particularly in light infections. Three stool and urine samples should be requested to increase yield, as egg shedding may be variable. It is vital to alert the laboratory that the specimens you are sending are for direct visualisation of schistosome eggs. Only then will the correct technical procedures be applied. Eggs may also be visualised in rectal biopsies (snips), which are commonly employed in the diagnosis of schistosomiasis.

Recent advances in direct diagnosis have been made in the detection of species-specific circulating antigens (circulating anodic antigen and circulating cathodic antigen). However, these tests are expensive, and are mainly used as a research tool at present.

Indirect tests for schistosomiasis rely on detection of circulating antibodies to egg, cercarial or adult schistosomes. Most antibodies remain present lifelong, making interpretation difficult in patients living in endemic areas. Antibody tests are most useful in the asymptomatic returning traveller who attends your practice concerned about having acquired infection or in those with suspected Katayama fever, when antibodies may already be present. Antibody production can be delayed up to 3 months, so the test should be repeated if it returns negative before this time.

### Treatment

Praziquantel is the treatment of choice for schistosomiasis. It is active against adult

worms, causing the worm to detach from the vein wall and die. It is not active against migrating schistosomulae. *S. haematobium* and *S. mansoni* infections are treated with 40 mg/kg for 1 day given in 2 divided doses, whereas *S. japonicum* requires a dose of 60 mg/kg in three divided doses. In patients presenting with Katayama fever, a second course of praziquantel should be given after 1 month to ensure eradication of any adult worms that may have been developing at the time of initial treatment. Ideally this second dose should be given 3 months after the last risk exposure to ensure any migrating schistosome have developed into adult worms.

Praziquantel is well tolerated, with cure rates of 60 - 90%. Stool or urine should be re-examined 4 weeks after treatment and any residual infections should be re-treated with a second dose of praziquantel. Follow-up of antibody titres as a means of interpreting treatment efficacy is not recommended. Efficacy of praziquantel is unaltered in patients co-infected with HIV. Cases of resistance or tolerance to praziquantel due to alteration of the tegument of the adult worm have been reported, especially from high-burden areas such as Egypt, where some patients have required multiple courses of the drug.

Alternatives to praziquantel include oxamniquine for *S. mansoni* infection (contraindicated in pregnancy) and metrifonate as an alternative for *S.*

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*haematobium*, although both have limited availability. In addition, the efficacy and safety of praziquantel makes it the drug of choice. Interestingly, the antimalarial drug artemether is active against migrating schistosomulae in humans, and studies suggest a synergistic activity with praziquantel against adult worms. However, the global importance of reserving artemesinins for malaria treatment means that artemether is unlikely to be used as a strategy for schistosomiasis prophylaxis due to the risk of selecting for resistant strains. Praziquantel is not used as chemoprophylaxis against schistosomiasis due to its inability to kill migrating schistosomulae and its very short half-life.

There are no randomised controlled trials studying the role of steroids in the treatment of Katayama fever. However, most practitioners give prednisone prior to praziquantel to limit exacerbating the

hypersensitivity reaction as the adult worm dies. Steroids are also indicated in cerebral schistosomiasis, when surrounding oedema is present on neuroimaging.<sup>3</sup>

### Prevention

Prevention strategies depend largely on community education programmes, large-scale population-based chemotherapy, modification of snail habitats and development of an effective vaccine. Most vaccine candidates target schistosomula antigens, and promising results in animal models have been obtained. A global effort is currently underway to develop a vaccine for human use, and candidate vaccines show much promise.

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### In a nutshell

- Schistosomiasis is an ancient disease, the majority of infections occurring in Africa.
- Infection is acquired via immersion in inland waterways. A thorough exposure risk history should be taken from all returning travellers.
- Clinical presentation differs depending on previous exposure history.
- Acute schistosomiasis (Katayama fever) manifesting as fever and eosinophilia is most commonly seen in non-immune returning travellers.
- Chronic urinary schistosomiasis (*S. haematobium*) causes haematuria and is associated with obstructive uropathy and squamous cell bladder cancer.
- Chronic intestinal schistosomiasis (*S. mansoni* and *S. japonicum*) causes dysentery and periportal hepatic fibrosis, leading to portal hypertension and varices.
- Direct visualisation of schistosoma eggs in urine and/or stool is key to diagnosis. Always inform the laboratory on the request form that you are looking for schistosome ova.
- Three specimens should be sent to optimise diagnostic yield. Optimal timing of urine collection is between 10h00 and 14h00.
- In asymptomatic travellers returning from an endemic area, antibody tests for schistosomiasis are best taken 3 months after acquisition of infection.
- Praziquantel is the treatment of choice, is safe and highly efficacious.