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REVIEW

Schistosomiasis in travellers and migrants

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Summary Schistosomiasis is a tropical parasitic disease caused by blood-dwelling fluke worms of the genus *Schistosoma* whose infective stages, the cercariae, are amplified through mollusks acting as intermediate hosts. People are infected when exposed to fresh water containing cercariae that penetrate the skin. There are however considerable differences in intensity of infection and morbidity, depending on the pattern of exposure and the infective species. In travellers, schistosomiasis differs substantially from infection in endemic populations in many aspects: geography, morbidity, treatment and prevention. In migrants, schistosomiasis manifests itself in a way more akin to what is seen in endemic populations. In this paper we will review the specific issues associated with schistosomiasis in travellers and migrants, with emphasis on the acute disease manifestations in non-immune persons, and on neuroschistosomiasis as a potential severe complication. We discuss new trends in diagnosis and treatment with respect to the specific disease stage, and summarize precautionary measures and novel ways to prevent *Schistosoma* infection in travellers.

Introduction

Schistosomiasis (or bilharziosis) is a tropical parasitic disease caused by blood-dwelling fluke worms of the genus *Schistosoma* (Phylum Platyhelminthes, Class Trematoda). The infection is amplified by fresh water mollusks acting as intermediate hosts, and acquired through infective cercariae penetrating the skin (Fig. 1). There are however considerable differences in intensity of infection and morbidity. Nowadays the bulk of schistosome morbidity, both gastrointestinal and urogenital, is found in Africa and the eastern part of South America, and to a lesser extent in Arabia, China and South East Asia.[1–4] In Africa and South America, human schistosomiasis is usually a stable disease but may evolve rapidly in newly infected populations.[5,6] Occupational as well as recreational contact play a major role in acquiring a significant parasite burden.[7,8]

The human schistosomes produce essentially hepatointestinal disease (*Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma intercalatum*, *Schistosoma mekongi*) and urogenital disease (*Schistosoma haematobium*).[9–14] *S. intercalatum* (pockets in West and Central Africa) and *S. mekongi* (downriver parts of the Mekong river basin in Laos and Cambodia) are only of local importance.[15,16]

Human schistosomiasis is mainly restricted to a human reservoir (*S. haematobium*, *S. intercalatum*) but animals

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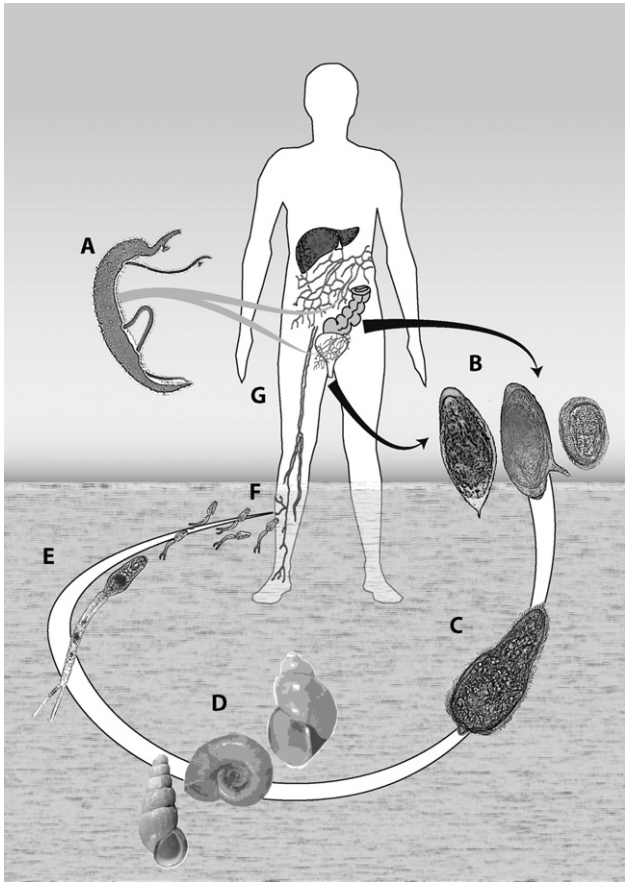

Figure 1 Life cycle of human schistosomiasis. A. Paired adult schistosomes. B. Excreted schistosome eggs (feces or urine). C. Miracidium larva in aquatic environment. D. Mollusks as intermediate hosts. E. Cercaria: infective larval stage. F. Penetration through skin. G. Developing stages in human host.

play a potentially important role as a transmission reservoir: rodents and primates for *S. mansoni*, and rodents, pigs and water buffaloes for *S. japonicum* and *S. mekongi*. In the latter two, the infection is in fact predominantly zoonotic.[17,18] Extensive treatment programmes have substantially reduced prevalence and disease manifestations in some heavily exposed populations, and may in the end reduce risk of infection as well.[19]

Schistosomiasis has been repeatedly reported in series of travellers and immigrants having undergone a post-travel examination. Prevalence ranges from 1% to 76% depending on the definitions used.[9,20–29] Travellers are almost exclusively infected while visiting Sub-Saharan Africa. Acute schistosomiasis is a significant cause of fever in travellers infected for the first time.[25,30–32] In travellers, chronic infection seldom results in major pathology.

Epidemiology

General epidemiology and transmission cycle

The completion of the parasite cycle requires contamination of these surface water by human excreta, either feces or urine, containing schistosome eggs, and regular contact with fresh water, harboring the infective cercaria. Notwithstanding these conditions, the epidemiology of schistosomiasis and the intensity of infection vary considerably between regions and localities. Fresh water mollusk populations, cercarial densities and human water contact show strong temporal and spatial variations, depending on local ecology.[3,4,7,33–37] The aquatic African vector snails *Biomphalaria* and particularly *Bulinus* can survive protracted droughts.[38]

Transmission of both species not only happens in rivers, ponds and lakes; irrigation systems play an important role in the local endemicity of schistosomiasis.[6]

The suitable intermediate snail host thrives only in a fresh water environment with a minimum temperature of 18 °C. Therefore the disease usually does not occur in African fresh water lakes above 2000 m altitude. *S. haematobium* mostly occurs in low lying plains of Africa, *S. mansoni* can be transmitted in a variety of ecotypes, from steaming valleys and savannah to rain forest and highlands.[2,36]

In East Asia, the parasitized *Oncomelania* snail survives long and cold winters, essential to complete the cycle of *S. japonicum*.[39] This species is endemic in the subtropical southern parts of China, along the Yang-tse river basin as well as in the mountains of Sichuan and the Central lake areas, where winters are severe but where warm summers allow intense seasonal transmission. It is also found in a few remote rural areas in the Philippines and in Indonesia.[40–42] *S. japonicum* causes the most severe form of hepato-intestinal disease, with early hepatofibrosis, portal hypertension and a febrile stage recurring at reinfection, the so called "Katayama fever".[43]

Epidemiology in travellers and expatriates

There is a considerable difference in exposure to schistosomiasis between travellers and indigenous people living in endemic areas. In the vast majority of western travellers and expatriates, exposure is occasional and short-lived, and is mainly recreational.

Travellers and expatriates contract schistosomiasis during a leisure activity (water sports like rafting, swimming or just taking a refreshing shower in a natural cataract), and are rarely occupational.[30–32,44–47] Travellers have been infected as well when taking a plunge in a swimming pool supplied with apparently clean water directly pumped from an infected small river.[48] Agronomes, surveyors of any kind and hobbyists of aquatic life may be at particular risk. In some series of expatriates being repeatedly infected, children constitute the majority of ova-excreting patients and often carry the highest parasitic burden.[49] It is not clear whether the intensity of exposure or immunological modulation is the main determinant here.

Only a handful of large studies on imported schistosomiasis exist to date, and there is no uniformity in defining the diagnosis, clinical presentation and the origin of infection.[23,50–54] Selection bias is therefore unavoidable (Table 1). In most reported series, diagnosis is predominantly made by antibody testing. The worm burden is mostly low, and often does not allow to determine the infecting schistosome species in feces or urine. Also the vast majority of the

Table 1 Imported schistosomiasis according to species and continent.

Author	Harries	Whitty	Grobusch	Bierman	Meltzer	Nicolls
Year	1986	2000	2003	2005	2006	2008
N	173	1107	333	78	137	410
Ova detection (%)	100	45	68	22	26	48
S. mansoni (%)	78	29	57	40	30	52
S. haematobium (%)	17	68	41	60	39	44
Mixed Sm/Sh (%)	5	2	0	0	16	?
S. intercalatum (%)	0	1	2	0	0	0
Other (%)	0	0	0	0	1	3[a]
Africa (%)	99.4	97	93	94	99	83

[a] *S. japonicum*.

chronically infected travellers are asymptomatic, the more so when infected with *S. mansoni*.

In studies in travellers and expatriates where diagnosis is based on ova detection, there is a considerable variation in relative prevalence of either *S. mansoni* or *S. haematobium* depending on the travel destination and the country of origin. It may reflect differences in travel destination and risk profile. The overwhelming majority of travellers with either species are infected in Africa, and only very rarely so in South America. So far, the largest study published on schistosomiasis in travellers and expatriates has been retrospectively conducted between 1993 and 1997.[54] In total, 1107 patients with serological and/or parasitological evidence of schistosomiasis were included. Ova were detected in 493 (45%) in stools and/or urine, of whom 334 (68%) with *S. haematobium*, 145 (29%) *S. mansoni*, 10 (2%) mixed infection and 4 (1%) *S. intercalatum*. In this extensive series, *S. haematobium* largely predominated, and was the incriminating species in more than 80% of travellers returning from Malawi and Zimbabwe (Malawi lake), and in more than 60% of travellers having visited West Africa.

On the other hand, among patients being reported through the TropNetEurop and GeoSentinel surveillance networks, *S. mansoni* was by far the predominant species.[51,53]

In travellers, infection with *S. intercalatum is* exceptional due to the restricted or poorly frequented natural habitat of transmission.[51,54] This may also apply to *S. mekongi* and *S. japonicum* whose occurrence in travellers has only occasionally reported.[55,56] *S. mekongi* is endemic around the Mekong river rapids straddling the lao-cambodian border (Si Pan Don), an emerging travel destination.

Although schistosomiasis is widespread, travellers are most often infected in well-established foci in sub-Saharan Africa (Fig. 2). Frequent sources of infection include the natural Great Lakes of East Africa (lakes Malawi, Tanganyika, Kivu, Victoria), some of the partially man-made lakes (lake Kariba on the Zambesi at the Zambian—Zimbabwe border; Volta lake in Ghana; lake Nzilo in Katanga on the Lualaba river, a main tributary to the Congo river, DR Congo; lake Muhazi in Rwanda) and the river complexes of the Senegal, the Volta and the Niger in West Africa and the Zambesi in southern Africa. Small tributaries, such as the rivers transecting the Dogon country, Mali, have been repeatedly reported as an important source of infection in unsuspecting tourists.[30,32,44–47,57–62] The Omo river in south Ethiopia has been a source of infection in rafters.[31,63] Although schistosomiasis is endemic in the entire Nile river basin, the lower Nile does not constitute an important source of contamination in travellers. On the other hand there is more recent exposure to the upper Nile basin in Uganda, with substantial risk for infection.[64] Tourism flourishes as well around lake Malawi, and contributes significantly to new infections with both schistosome species.

In travellers, the absolute risk of schistosome infection has not been prospectively determined in large series. Among 3528 mostly asymptomatic travellers and immigrants attending the Tropical Diseases unit in Toronto, 48 (1.5%) were found infected with schistosomiasis.[21]

Incidence of acute infection reported in cluster series is much higher. It ranges from 32% in travellers having bathed in Malawi lake, to >90% in travellers who had taken a shower under a waterfall in Dogon country, Mali (Table 2).[32,57]

Epidemiology in immigrants

The epidemiological and clinical impact of schistosomiasis in immigrants from endemic regions differs considerably of what is seen in western travellers. Logically it would mimic exposure and subsequent pathological expression of the communities where immigrants originate from. The majority of infected immigrants are asymptomatic, and worm burden is rather low. In regions of endemicity the distribution of schistosomiasis is rural and focal, and this is not necessarily the environment where immigrants have been growing up. Immigrants present with chronic disease manifestations only, and then mainly signs and symptoms related to urinary schistosomiasis. Katayama syndrome is almost non-existent in immigrants.[24,26–29,54,65–73] There is not that much literature available that deals exclusively with large groups of immigrants from countries where schistosomiasis is endemic, but it reveals high exposure in specific ethnic groups who have been selected for mass immigration following political upheaval. Prevalence of schistosomiasis was particularly high among refugees ("lost boys and girls") from (southern) Sudan admitted in the USA.[29] Among 462 tested, 44% had serological evidence of schistosomiasis. Seroprevalence was even higher (73%) among a sample of 100 Somali Bantu, but *S. haematobium* ova were found in only 2% out of 390 Somali refugees screened, suggesting that worm burden is low.[74] In the early 80s, *S. mekongi* frequently was reported among

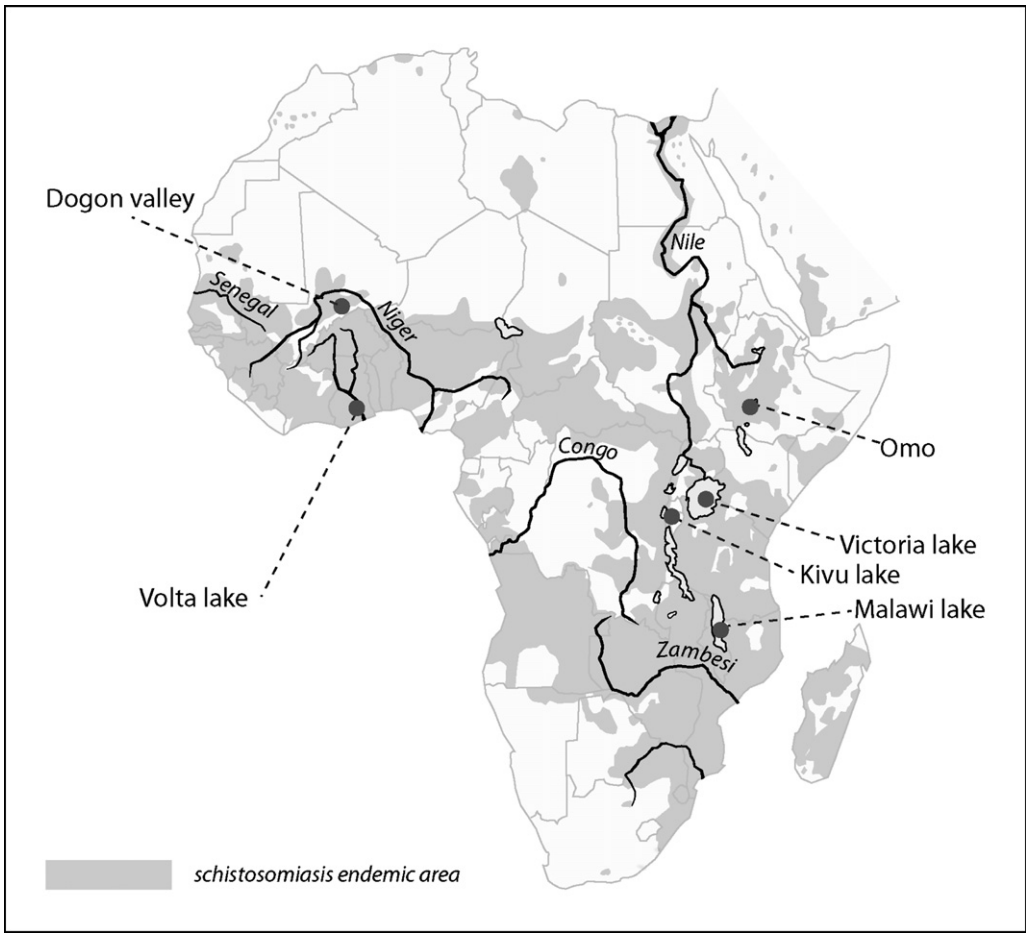

Figure 2 Schistosomiasis in travellers: main sources of infection.

Cambodian and Laotian refugees fleeing to Thailand and subsequently resettled in the USA.[75–77] Among immigrants and refugees from South East Asia, *S. japonicum* infection is an exceptional finding.[78] Immigrants infected with *S. intercalatum* have been occasionally reported.[79]

Pathology

General pathology in an endemic setting

Schistosomiasis is essentially a chronic parasitic infection, in which through a longstanding evolutionary process, the parasite has adapted itself very well to the human host. It developed an ability to fend off host related immune defence mechanisms, and its way to survival and reproduction causes only limited morbidity in the majority of infected individuals.

Schistosomiasis is an end-stage infection in humans and its parasite burden increases over time only by means of repeated contact with cercariae infested water, but this is not a linear process.[80,81] Parasite burden builds up during childhood, and it increases well until adolescence and early adulthood, when a gradually evolving host related self-regulating immune mechanism steps in to limit parasite burden and pathology ever further.[13,82]

In established infections, most pathology is not caused by the worms themselves but by the ova produced in great numbers. These are trapped in the gut and urinary tract tissues during their transmural (vesical or intestinal) migration, and may be embolized in the liver and the lungs when carried away by the venous splanchnic system. Ova manage to bypass the pulmonary circulation in some cases, and may then be entrapped in the smaller vessels of the cerebrospinal system or in other less critical organs. This remains often asymptomatic when only a few eggs manage to enter the main circulation. From autopsy cases and imaging studies, it has been amply demonstrated that this is not an exceptional phenomenon.[83] The ova secrete proteolytic enzymes that provoke a typical inflammatory and granulomatous reaction with predominantly eosinophilic infiltration, which are progressively replaced by fibrotic depositions as infection persists.[84,85]

As a result, in schistosomiasis, the severity of the symptoms depends on the intensity of infection, the individual immune responses, and the duration of active disease.

Chronic disease manifestations are basically modulated by a gradually shifting immune process, and are age dependent.[81,84] In its initial stage, a largely reversible granulomatous inflammatory reaction surrounding the ova deposited in various tissues predominates, and evolves over time into a more persisting pathology where perilesional

Table 2 Acute schistosomiasis in clusters of travellers and/or expatriates.

Author	Visser	Cetron	Loutan	Elcuaz	Schwartz	Clerinx[c]
Year	1994	1996	1996	1998	2005	2010
Region	Dogon, Mali	Malawi lake	Burkina Faso	Burkina Faso	Omo, Ethiopia	Muhazi, Rwanda
Type patient	Traveller	Expatriate	Traveller	Traveller	Traveller	Traveller
N exposed	29	440	11	29	37	9
N infected	28 (97%)	141 (32%)	11 (100%)	20 (69%)	28 (76%)	9 (100%)
N symptomatic	15 (54%)	?	8? (82%)	14 (70%)	16 (57%)	7 (76%)
S. mansoni (%)	68[a]	0	?	100[a]	100[a]	100[a]
S. haematobium (%)	32[a]	96[b]	?	0	0	0

[a] Among ova-excreting patients.
[b] *S. haematobium* serum antigen pos.
[c] Submitted for publication.

fibrosis takes the upper hand. Both non-fibrotic and early fibrotic lesions are largely reversible when removing the stimulus that causes them.[86,87] In early chronic schistosomiasis eradicating the egg-laying adult worm pairs usually brings about complete remission of urinary and intestinal lesions.

Late chronic schistosomiasis is mainly a disease of poor rural populations living in regions where schistosomiasis is hyperendemic. Severe manifestations are seen in individuals with high parasite loads, and this may be aggravated by immunogenetic factors.[84]

In the industrialized world, only mild forms of late chronic schistosomiasis are occasionally seen in immigrants and long-term expatriates, often after years or decades of occult infection.[21,52,68,69,71,73]

Clinical aspects in travellers

First stage following cercarial penetration

Cercarial penetration through the skin may take upto 72 h to be completed. Particularly in non-immune persons, such as tourists and first-time expatriates, this may provoke a transient itchy papular rash soon after infection, which sometimes persists for days as papulopruriginous lesions, known as swimmers' itch. Usually the rash is discreet, and rarely requires medical attention. Swimmers' itch has been reported in 10—36% in series of travellers diagnosed with schistosomiasis.[32,88] A similar and more intense "swimmers' itch" is also frequently caused by cercariae of avian or mammalian schistosomiasis in temperate and tropical climate zones.[89—91]

Acute hypersensitivity reaction in non-immune travellers: "Katayama fever"

Acute schistosomiasis is a systemic hypersensitivity reaction directed against the maturing schistosomulae. In the beginning of last century, schistosomiasis due to *S. japonicum* was identified as the cause of this syndrome among the population from the Katayama district, prefecture of Hiroshima, Japan, hence the name of "Katayama fever".[43]

In persons infected for the first time with schistosomiasis, symptoms occur from three weeks to three months after infection with one of the human schistosome species, and include low to medium grade fever, a non-productive cough sometimes with dyspnea, abdominal pain and/or diarrhoea.[44,92—96] An urticarial rash and/or angio-oedema may precede fever.[93,97] Not all patients present with fever. Katayama syndrome may be a more appropriate description of signs and symptoms associated with acute schistosomiasis. Katayama fever is thought to follow maturation of schistosomules in the liver, where schistosomules have migrated to, after having accomplished one or several lung passages. Some patients develop only fever and abdominal pain.[94] This probably coincides with the positioning of the mature worms in the perirectocolic (and perivesical) venous plexus, and with the onset of oviposition. Most patients recover spontaneously after 2—10 weeks, and only exceptionally require hospitalization. Both the pulmonary and the early abdominal symptoms coincide with hypereosinophilia.[46,93] Additional symptoms, such as malaise, myalgia, nausea and fatigue may appear, but are nonspecific and therefore not very helpful to suspect the disease.[93]

The risk of developing Katayama fever after exposure is only mildly correlated with the intensity of infection, and probably depends on host related immune reactions.[98]

Katayama fever due to *S. japonicum* is however not restricted to primary infection alone. Its clinical picture is outspoken with persistent fever, hepatosplenomegaly and cachexia, and evolves soon into severe hepatic fibrosis and portal hypertension.[14,98,99]

Katayama fever is a frequent diagnosis in travellers and expatriates from nonendemic countries recently exposed to cercariae in fresh water. In that population, it is almost exclusively associated with *S. mansoni* and *S. haematobium* infection, and only exceptionally with other species (Table 2). Among travellers presenting with fever after returning from the tropics, Katayama fever takes up 2—4% of the final diagnoses.[22] Travellers contract Katayama fever almost exclusively in sub-Saharan Africa, often in families or group clusters (Fig. 2). The infective water contact is largely recreational, ranging from bathing and swimming to scuba diving, water skiing, sailing and rafting.[31,32,46,47,56,58,61,63,93] After exposure the schistosomiasis infection rate may reach nearly 100% in non-immune travellers and the risk of developing Katayama fever after primary infection may exceed 50%.[32,46,57,58,93]

On the other hand, Katayama fever due *S. mansoni* and *S. haematobium* is rarely reported within chronically exposed populations from where immigrants emerge; this has been explained by in utero sensitisation, but probably endemic cases are not recognized as such.[100]

In travellers having recently been exposed to fresh water in a known endemic area, the diagnosis has to be strongly

suspected when a high-grade eosinophilia, often exceeding 1000 eosinophils/μl, is found during the workup for a protracted fever of unclear origin.[101,102] In fact, suspicion may be extended to patients presenting only with cough or abdominal pain in association with hypereosinophilia.

In patients with cough and/or dyspnea, patchy nodular infiltrates are occasionally seen on chest X-ray, but pulmonary lesions may sometimes more extensive and show a diffuse interstitial infiltrate.[45,95,96] Exceptionally more severe complications such as myocarditis and ischemic colitis are seen during the disease course.[103,104]

Diagnosing correctly Katayama fever in an early stage requires a fair knowledge of the sequence of clinical events and of the evolution of the crucial diagnostic test results (Fig. 3).[93,105] At the start of the feverish episode, a raised eosinophilia may not yet be marked and may be overlooked. It will however increase rapidly in the course of the following days to levels rarely seen in other parasitic diseases, with hypereosinophilia rising up to and above 50% of the total white blood cell count. At that moment it is still difficult to confirm the diagnosis, while it takes more time for antibody tests (based on adult worm antigen or egg antigen) to become positive or for eggs to appear in feces or urine. Early infection with *S. haematobium* is closely associated with microscopic hematuria and/or pyuria. Antibody production against (adult) worm antigens starts only after maturing of the schistosomules in the liver has been completed, thus 4—12 weeks after cercarial penetration, and ova deposition only happens shortly after, at earliest from the 6th week (35 days) after infection.[93] Species-specific diagnosis depends on egg identification. In order to be detected in feces or in urine, ova have to migrate first from the perivesical *(S. haematobium*) and perirectal (*S. mansoni*) venous plexus through the mucosa to reach the bladder or the rectosigmoid and this process takes another few days to weeks. At that stage direct microscopy of small rectal biopsies ("rectal snips") might show ova embedded in the mucosa more readily.[106,107] As a consequence, in many cases the clinical syndrome is already subsiding or has completely resolved before the final diagnosis is confirmed.

From large series in imported pathology, it has been observed that a possible or proven contact with fresh water in sub-Saharan Africa a few weeks prior to the onset of fever, combined with a raised eosinophilia is already specific enough to strongly suspect the diagnosis and to initiate appropriate treatment.[28,108] In practice, the syndrome is seldom recognized by primary health care providers not familiar with tropical pathology. By the time patients are referred to a travel clinic, evidence of schistosomiasis is found in the majority, mainly by serum antibody detection.[50]

Chronic pathology in travellers and immigrants

Urinary schistosomiasis

Even when parasite burden is relatively low, urinary schistosomiasis is often symptomatic. In early chronic infection, the eggs of *S. haematobium* provoke a granulomatous inflammation, ulcerations and pseudopolyposis in the vesical and ureteral walls.[109,110] Common early symptoms include dysuria, pollakisuria, and particularly (microscopic and/or macroscopic) hematuria. Macroscopic hematuria often presents as terminal hematuria, and is the most common clinical manifestation in travellers inciting a diagnostic workup. At that stage it is usually possible to confirm the diagnosis, when ova of *S. haematobium* are seen by microscopy of a concentrated urine sample. On cystoscopy, small exulcerations with patchy thickening of the bladder wall and/or pseudopolyps are frequently observed, and often interpreted as (pre)malignant growths when schistosomiasis is not suspected.[111,112] Travellers are repeatedly referred to a tropical diseases consultant only when schistosome ova are accidentally found in biopsies taken from these suspicious bladder lesions. Occasionally epididymitis with hematospermia and cystitis may be on the foreground.[113,114] In early chronic disease, ultrasound examination may reveal a hydrourether and (unilateral) hydronephrosis when granulomatous inflammation engulfs the uretherovesical junction.[115,116]

In immigrants who grew up in an endemic setting the picture may be somewhat different.

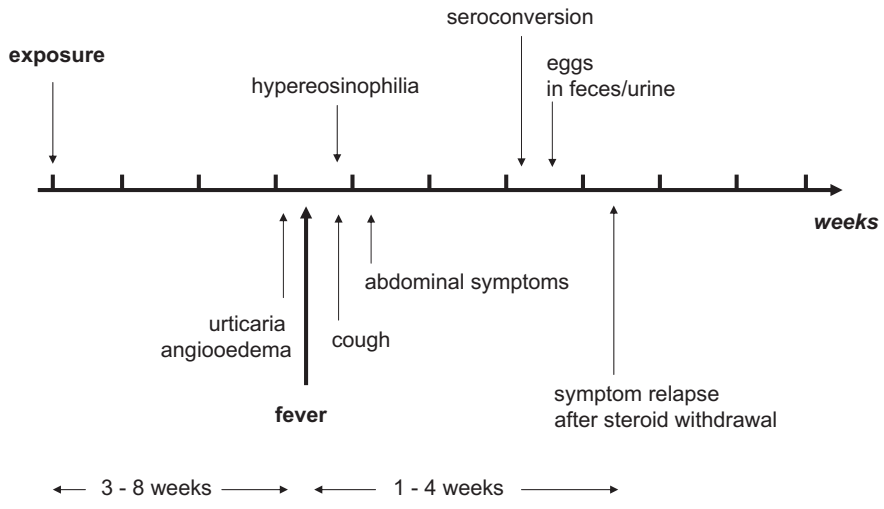

Figure 3 Katayama syndrome: timeframe of disease events.

Gross hematuria is mainly seen in children between 5 and 12 years old, and therefore sometimes considered as the menarche in girls, and even in boys.[2] In non-treated populations exposed to *S. haematobium*, microhaematuria can be found in 40–100% of the infected children, gross hematuria in 10–40%.[117] These symptoms mostly wane during adolescence. Over time chronic lesions may evolve to fibrosis and calcification of the bladder and lower ureters, with irreversible hydrourether and hydronephrosis as a consequence.[118] Bladder calcifications are occasionally seen in immigrants as a sign or a sequel of late chronic disease.

Bladder pathology can be detected by ultrasound or radiology in a majority of infected people, and upper urinary tract lesions in the range of 5–20%.[118] Many cases with serious morphological lesions show a surprising lack of apparent functional disease.

After eliminating the ova producing adult helminths, early lesions readily resolve.[119]

Intestinal schistosomiasis

In hepato-intestinal schistosomiasis, ova deposited in the perirectal venous plexus and further up in the splanchnic veins are mostly retained locally, and migrate through the intestinal wall where they provoke a granulomatous inflammation that may extend into the rectosigmoidal mucosa and higher up into the colon. When parasite burden is high, this leads to pseudopolyposis, micro-ulcerations and superficial bleeding of the (distal) large intestine.[120] These lesions are nonspecific and may be confused with chronic inflammatory bowel diasease.[121]

The most common clinical symptoms associated with intestinal schistosomiasis are chronic or intermittent abdominal pain and discomfort, loss of appetite and diarrhoea with or without blood. Occult blood loss is a frequent feature in *S. japonicum* and *S. mansoni* infections.[15] The reported frequency of intestinal disease in patients living in an endemic region for *S. mansoni* or *S. japonicum* is usually in the range of 10–50%, with attributable fractions around 30% for diarrhoea and 60% for bloody diarrhoea.[10] Even in regions where schistosomiasis is hyperendemic, most infected individuals remain asymptomatic.

Travellers and immigrants chronically infected with *S. mansoni* rarely develop symptoms specific enough to guide, or even to suspect a diagnosis.[53,54] Nevertheless in a Brazilian study on early intestinal schistosomiasis, the vast majority of patients presented with at least one abdominal symptom (pain, diarrhoea or hepatomegaly). Interestingly there was no association of any of these symptoms with the parasite burden, except for fecal blood loss.[98] In travellers, this translates occasionally into a nonspecific colitis at colonoscopy but remains largely unreported.

Hepatic schistosomiasis

Hepatic schistosomiasis is associated with *S. mansoni*, *S. japonicum* and *S. mekongi*. *S. intercalatum* only causes mild intestinal disease.[122]

To better understand its clinical presentation in travellers and in immigrants it is essential to discern two different stages in hepatic disease following infection: an early granulomatous hepatic involvement with diffuse hepatosplenomegaly on one hand, and a late fibrotic hepatic disease with periportal hepatofibrosis and secondary portal hypertension on the other. These manifestations should be considered as the two extreme expressions of a pathological process that evolves over many years. This process is further modulated both by a changing immunological reaction and by a shifting parasite burden.[123]

The first stage of hepatic schistosomiasis is the result of an early immune reaction to ova that are embolized and trapped in the presinusoidal periportal spaces of the liver, producing a local granulomatous inflammation.[123,124] This inflammatory process is the main cause of schistosomal hepatomegaly in children and adolescents living in endemic areas, often associated with splenomegaly and strongly correlated with the intensity of infection and causes widening of the periportal spaces.[125] At that stage there is no portal hypertension. There is also a striking lack of hepatic dysfunction.[126] The organomegaly apparently resolves with age, probably due to downregulation of perioval inflammation but is also reversed after successful treatment.[127]

Fibrotic or chronic hepatic schistosomiasis develops years later in the course of hepatic infection, and only in a small fraction of those infected.[117] Both a longstanding high parasite burden and a cellular immune response that fails to downregulate the intense granulomatous inflammatory reaction are its main causes. During this process, collagen is gradually deposited around the ova embedded in the periportal spaces. This produces after many years the pathognomic periportal or "Symmer's pipestem" fibrosis with progressive occlusion of the portal veins that is characteristic of established late hepatic schistosomiasis.[120] This results in portal hypertension, splenomegaly, collateral venous circulation, portovocal shunting and gastrointestinal varices. In contrast to cirrhosis the parenchymal functions and biological parameters remain largely unaffected. In *S. mansoni* infections the process takes at least 5–15 years, by which time the infection is often not present or detectable anymore. In *S. japonicum* this process may evolve more rapidly, with little or no interval between acute and chronic diseases. Bleeding from gastro-oesophageal varices is the most serious and often fatal complication. Before the advent of praziquantel, advanced liver fibrosis due to schistosomiasis was a frequent and serious health problem in large parts of Egypt, Brazil, China, the Philippines and many other countries. Chemotherapy and reduced exposure have led to a dramatic reduction of such morbidity world-wide.[2,128]

In travellers and expatriates the hepatosplenomegaly is absent or at most mild and seen mainly in children as a consequence of a relatively low parasitic burden.[25,49,69,80] The burden of infection is too low and the duration of active disease is usually too short-lived to ever develop late stage disease.

Late stage hepatic schistosomiasis is also exceptionally seen among immigrants. Whether this is the result of a low parasite burden or of occasional treatment is unclear.

Mortality associated with advanced disease is difficult to determine even in endemic populations. In a heavily exposed population in Sudan, the annual mortality rate was estimated at only 0.05% and the annual case fatality rate for oesophageal bleeding at 1.1%.[129] Mortality associated with schistosomiasis was non-existent in a large published series of infected travellers and immigrants.[54]

Neuroschistosomiasis

Neurologic complications of schistosomiasis follows (accidental) ectopic migration and embolization of adult schistosome pairs in the small vessels of the brain and/or the spinal chord, where these continue to produce ova in situ, that elicit a locally destructive eosinophilic granulomatous immune response.[130–132] The resulting lesions may evolve into irreversible fibrotic scars if left untreated.[133]

This is a potentially serious complication, and a major source of concern for schistosomiasis in travellers and expatriates. It may occur early as well as late in the course of infection. Almost in all reported cases both *S. mansoni* and *S. haematobium* infections have been implicated. *S. mekongi* and *S. japonicum* are exceptionally the causative agents.[55]

The absolute risk of developing neuroschistosomiasis after infection is difficult to calculate, and most of the reports are anecdotal. Although there is a considerable selection bias in schistosomiasis reported from centers conducting post-travel screening, this is probably the most reliable approach to estimate its prevalence in persons found to be infected. Among 1061 cases with a positive serological test for schistosomiasis detected at the outpatient department of the ITMA from 2000 to 2004, only one single case of neuroschistosomiasis has been diagnosed.[134]

The clinical and diagnostic aspects of neuroschistosomiasis have been studied extensively from series of infected patients in Brazil.[135–137] Myelopathy is more frequent than cerebral disease in symptomatic patients.[136] Schistosomiasis accounts for 1–4% of spinal cord lesions in sub-Saharan Africa.[132] Spinal cord schistosomiasis usually affects the conus medullaris and the cauda equina.[133] The clinical picture includes flaccid paraparesis, sometimes with paresthesia, urinary retention and even paraplegia. Lumbar pain may herald the onset of disease.

CSF analysis may reveal a raised protein level and a pleiocytosis often with eosinophilia, but these findings lack sensitivity.[138,139] The diagnostic value of a CSF IFAT and ELISA antibody test is currently investigated.[139,140] Imaging of the spine by NMR may reveal extradural or intramyelitic lesions. However the appearance of lesions is varied, and include increased volume of medullar cone, a linear radicular thickening or a nodular, often pseudotumoral appearance. These findings are not pathognomonic for schistosomal myelopathy.[141–144] In the absence of indirect confirmation of diagnosis by serology or by finding *Schistosoma* eggs elsewhere (rectum of bladder), definite diagnosis sometimes requires biopsy.[145] As it may develop years after exposure the link with schistosomiasis may escape attention, and this delays considerably appropriate treatment in its early course.[146] A high degree of suspicion is therefore essential.

Brain localization is often multiple, and presents itself with a wide variety of symptoms, including localized or generalized seizures, motor or sensory impairment, and a cerebellar syndrome depending on the involved brain structure.[147] Pathology studies indicate that brain involvement may be more frequent than clinically suspected.[83] MRI and CT-scan images of the brain mainly reveal nonspecific contrast enhancing infiltrates suggesting brain tumors, but a rather characteristic arborisation pattern has been occasionally described.[141–144] In cerebral schistosomiasis definite diagnosis also requires the demonstration of active schistosomiasis, by indirect or direct means. Finding schistosome eggs in feces, in urine or in rectal biopsy is strongly suggestive, but sometimes a biopsy specimen of the CNS lesions is required to demonstrate the characteristic granuloma surrounding ova embedded the affected tissue.[142] A positive serum antibody test provides a probable diagnosis only, and a negative antibody test does not rule out this diagnosis. Antibody tests on the cerebrospinal fluid have been reported as a more reliable alternative.[139,148]

To prevent irreversible damage in neuroschistosomiasis, especially in myelitis, anthelmintic treatment with praziquantel must be initiated as early as possible. Adjuvant treatment with corticosteroids is essential to prevent further tissue damage resulting from the immune reaction against the decomposing embolized worms and the in situ produced eggs (see below).[149]

Other ectopic sites of schistosomiasis

Genital schistosomiasis, due to eggs of *S. haematobium* and sometimes *S. mansoni* migrating through the reproductive organs, is a quite frequent but mostly occult disease in some endemic populations, and a regular finding in travellers.[113,150–152] Symptoms in women include hypertrophic and ulcerative lesions of the vulva, vagina and cervix, which may eventually facilitate the transmission of sexually transmitted infections. Lesions of the ovaries and the Fallopian tubes can lead to infertility. In men, the epididymis, testicles, spermatic chord and prostate may be affected; haemospermia is a common symptom.

Diagnosis

Diagnosis of schistosomiasis depends on its infection stage and intensity. A large variety of tests are available for clinical practice, each with its limitations in specificity and sensitivity (Table 3).

To this day, the parasitological examination of either urine or feces remains the gold standard for the diagnosis of active schistosomiasis in travellers and immigrants.[153] Identification of the parasite species is easy by simple microscopy, and the parasite burden can be derived from the egg counts in calibrated samples (Fig. 4).[154]

When the worm load is low, as is often the case in travellers, eggs often escape detection even in concentrated fecal or urine samples.[25,54,73] On the other hand, significant clinical infection in its chronic stage is associated with detectable egg excretion, both in intestinal and urinary schistosomiasis.[155] Egg excretion in feces and urine fluctuates greatly over time. Quantitative egg counts correlate well with worm burden, but may be determined as well by worm fecundity, tissue retention and immune reactions against eggs.[156] Prophylactic antimalarial treatment with mefloquine may reduce egg production and subsequent detection.[157]

Thus, concentration methods of feces and urine fail to detect (very) light infection which is common in travellers. This can be offset partially by repeating the procedure, or to resort to more invasive techniques such as detecting ova by direct microscopy in small rectal biopsies ("rectal snips") or bladder biopsies. These techniques have a much higher sensitivity than fecal microscopy, even for *S. haematobium* infection whose ova can be found embedded in the rectum as well.[107,158]

Table 3 Currently available diagnostic procedures for schistosomiasis in travellers and immigrants.

	Sm[a]	Sh[a]	Parasite load	Sensitivity	Specificity	Cost
Schistosome polyclonal antibody tests	+	+	−	Moderate	High[b]	Low
Schistosome antigen detection (CAA)	+	+	+	Low	High[b]	High
Ova detection urine	−	+	+	Moderate	High[c]	Low
Ova detection feces	+	(+)	+	Low	High[c]	Low
Ova rectal snips	+	(+)	+	High	High[c]	Low
PCR schistosome DNA in feces or urine	+	+	?	High	High	Moderate

[a] Sm: *Schistosoma mansoni*; Sh: *Schistosoma haematobium*.
[b] For *Schistosoma* sp.
[c] For *S. mansoni* and *S. haematobium* specifically.

In most travellers and migrants, schistosomiasis infection is predominantly asymptomatic and with a low parasite burden. In published series, most travellers have only mild (<100 epg) to moderate (<400 epg) infection, with no or negligible symptoms.[49,51,159] In urinary schistosomiasis, measurable ova excretion is much more likely to induce urinary tract lesions important enough to be symptomatic or to be detected by ultrasound or cystoscopy.[32,111]

A recent or ongoing low-level infection is determined primarily by antibody testing.[59,158,160] Serological antibody assays are a more sensitive method to confirm infection, but cannot distinguish active infection from past exposure, and do not provide reliable information on parasite burden.[161,162] Serological assays are thus important for diagnosis in travellers, migrants and other occasionally exposed people. Most routine techniques detect IgG, IgM or IgE against Soluble Worm Antigen (SWA) or Soluble Egg Antigen (SEA) by ELISA, IHA or immunofluorescence. A cercarial antigen ELISA has been tested recently and proved promising in a nonendemic setting.[163] Seroconversion happens within 4–8 weeks after infection, but may take longer. Most assays remain positive for at least two years after effective treatment, and often much longer.[164] Sensitivity of individual serological tests in egg-excreting travellers is satisfactory but not absolute. Combining the results of IHA and ELISA outcomes significantly improves sensitivity beyond 90%, both in recent and in established infection, while retaining specificity at over 97%.[164,165] Occasionally, in egg-excreting immigrants with longstanding infection, serum antibody tests may be negative.

A Western blot antibody test has been developed and proved promising, but costs are probably high.[166] The schistosome antigens used in the current serum antibody tests are not species-specific and therefore not useful to identify the infective schistosome species.

Diagnostic tests using species-specific monoclonal antibodies have been developed, but never found their way in clinical practice upto now.[167] Detection and quantitation of the circulating schistosome antigen levels in serum and in urine by ELISA with labeled monoclonal antibodies is another interesting method to confirm active infection. Both the Circulating Anodic Antigen (CAA) and Circulating Cathodic Antigens (CCA) are used for this purpose.[168,169] A semiquantitative serum CAA assay is probably a more direct and stable method to estimate the parasite burden than a fecal egg count, but it lacks sensitivity in light infections and is currently too expensive and cumbersome to be used as a diagnostic routine tool.[170,171] As a consequence, this method does not offer tangible advantages compared with ova detection in a post-travel clinic setting.[172] Recently, an improved CAA detection technique has been tested in exposed travellers with promising results.[173] CAA is detectable early after infection.[174]

The latest addition in the diagnostic arsenal is the development of polymerase chain reaction (PCR) based assays to detect parasite DNA both in excreta and in serum.[175] Some of these assays are able to identify a given species.[176] Whether these assays may be more sensitive and specific than the current methods in early disease and in a nonendemic setting requires further testing.[177]

In urinary schistosomiasis, an excess of red blood cells in the urine is very closely associated with active disease.[178] Therefore reagent strips for microhaematuria and urine sediment microscopy are reliable screening methods to detect active infection in exposed travellers with a positive schistosome serological test.

Indirect diagnostic predictors of schistosomiasis such as eosinophilia and a raised IgE level lack both sensitivity and specificity to be useful as a marker of active infection, but can be used to raise suspicion.[28,65,66,72,108,179] The only exception here is Katayama fever, where hypereosinophilia is the hallmark test to raise suspicion.[50,101]

In most series dealing with parasitic diseases in immigrants, the prevalence of schistosomiasis is low.[20,21] Therefore serological screening for schistosomiasis, however imperfect, can be helpful in immigrants to ascertain exposure, and these patients may be singled out for further workup to estimate the parasite burden.

Ultrasonography is the preferential diagnostic tool in the workup of pathology associated with schistosomiasis in travellers and migrants, and early chronic disease as well as in late disease.[180] Bladder wall thickening, pyelectasia and hydronephrosis due to ureteral (sub)obstruction are frequently seen in urinary schistosomiasis.[115] Hepatosplenomegaly is the echographic hallmark of acute intestinal schistosomiasis. Broadening of the periportal spaces is seen in late acute and chronic diseases but its extent may underestimate disease severity.[181,182]

Invasive endoscopy (either cystoscopy or rectosigmoidoscopy) is useful only in situations where schistosomiasis has not been suspected in the first place or to ascertain active infection in patients not excreting eggs. Urinary schistosomiasis has been repeatedly found in biopsies from a variety of bladder lesions, ranging from reddened mucosa to (pseudo)

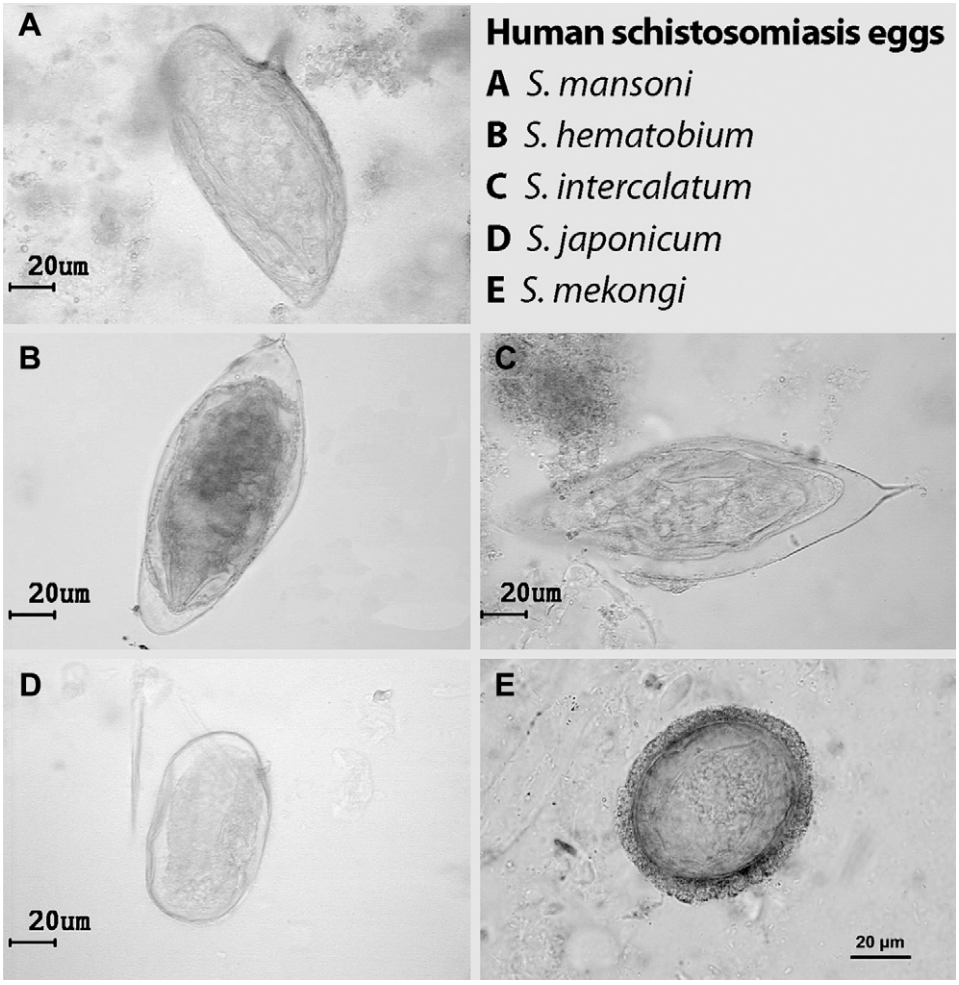

Figure 4 Egg morphology of human schistosomiasis.

polyps mimicking neoplasia. Histology shows eosinophilic granulomas surrounding ova embedded in the submucosa.[110—112] Classic radiology (intravenous pyelography, retrograde uretherography) allows to visualise renal, ureteral and bladder pathology quite easily, but it is complementary to ultrasound for diagnosis of nonfunctioning kidney and hydrourether.[115]

In patients with high parasite burden of intestinal schistosomiasis, pseudopolyps as well as diffuse mucosal inflammation has been seen on endoscopy.[121] However in imported schistosomiasis, advanced hepatic schistosomiasis is only exceptionally seen. Both laparoscopy and liver biopsy may be needed to discern periportal liver fibrosis from cirrhosis.[181]

In neuroschistosomiasis, magnetic resonance imaging is the preferential diagnostic imaging technique.[183,184]

Treatment

General comments

Treating schistosomiasis serves three main objectives: reversing acute or early chronic disease, preventing common complications associated with chronic established infection, and preventing less common complications with potentially severe morbidity, i.e. neuroschistosomiasis.

As a consequence, the treatment approach depends to a large extent on the target population. It ranges from parasite load reduction through intermittent treatment in populations chronically exposed to schistosome infection, to eliminate the parasite altogether in accidentally infected travellers. In asymptomatic but exposed travellers and expatriates, preventing neuroschistosomiasis is in fact the main underlying and pressing reason to detect and treat schistosomiasis in a post-travel workup.[46]

Early antischistosomal compounds, including antimonials and arsenic compounds, but also Niridazole and hycanthone had potentially severe and even lethal side effects that limited severely its role as an acceptable treatment in persons with asymptomatic infection. The latter became only an option during the 1970s, when effective, safe and simple antischistosomal drugs were put into practice: metrifonate, oxamniquine and praziquantel.[185] Oxamniquine (Vansil®) acts only on *S. mansoni* and is nowadays mainly used in Brazil. It is however less effective as praziquantel and may provoke more pronounced side effects, most notably drowsiness, sleep induction and in some cases epileptic seizures.[186] Its cost price is currently at par with

that of praziquantel, which diminishes further its attractiveness as a treatment option.

Current treatment in travellers and migrants

At present, praziquantel is by far the most cost-effective and most widely used antischistosomal compound, both in treatment and in morbidity control.[187,188] Praziquantel is an acylated quinoline—pyrazine which is active against all schistosome species and (human) cestodes.[128] It is mostly marketed as 600 mg tablets, with a recommended standard regimen of 40 mg/kg in a single dose. The drug acts within an hour after ingestion by inducing a sustained muscular contraction, effectively paralyzing the schistosomes and damaging their tegument. Praziquantel is subject to a first pass liver clearance, and most (80%) of its inactive metabolites are excreted mainly in the urine within 24 h after ingestion. It is strongly bound to serum proteins. Praziquantel induces an almost immediate hepatic relocation of the affected adult schistosomes from the mesenteric veins ("hepatic shift"). Side effects may result in part from parasite disintegration, but are usually mild. These include nausea, vomiting, malaise and abdominal pain. In Katayama fever and in heavy infections, pulmonary and abdominal symptoms may be temporarily exacerbated due to massive antigen release.[189] It is safe to use during pregnancy and in small children.[190]

For established schistosomiasis, praziquantel has become the treatment of choice, ever since generic production reduced the treatment costs to around 0.3 $ per single dose. Praziquantel has one minor drawback: it does not act on immature worms (schistosomulae) and it does not kill the miracidium inside the ova. As a result ova already migrating through the tissues may continue to be excreted in stools and/or urine for several weeks after successful treatment, while recently acquired schistosomulae may continue to become productive, and start producing ova. This is of particular importance for acute schistosomiasis, and in recently (re)infected travellers (see below).

Efficacy data in humans are measured in terms of parasite load reduction and in eradication of infection.[188] The latter is however not easy to ascertain because in light infections ova excretion and circulating antigen production is often too low to be picked up by the commonly used test procedures, and the antibody response usually persists for quite some time after successful treatment.[162] Nevertheless, both parameters continue to be used to evaluate treatment efficacy.

A single dose of 40 mg/kg of praziquantel is well tolerated and manages to reduce the parasite load by over 90%, as measured by egg counts or circulating antigen levels. Cure rates are achieved in 70—95% of patients living in endemic areas, but these depend largely on the timing after initial infection, on the pretreatment parasite load and the intensity of reinfection. Signs of established gastrointestinal and urinary disease are to a great extent reversible, and more so in children.[191] The standard dose of 40 mg/kg is thus often sub-curative, but parasite load can still be reduced further by repeating the treatment. Higher dosages are not always well tolerated, and therefore not a suitable standard treatment option.

In nearly all travellers and expatriates with low to medium parasite burden, a single treatment with praziquantel at 40 mg/kg will suffice to reduce infection to negligible levels.[188,192] An exception must be made for patients in the incubation phase of schistosomiasis whether symptomatic or not. Early treatment with praziquantel does not prevent persistence of infection and a second treatment has to be given after schistosomules have fully matured.[193] The optimal retreatment interval has not been firmly established but a second dose given 4—6 weeks after initial treatment seems adequate to prevent relapse (see below).

Most schistosome-induced acute or early chronic pathology resolves quite well after praziquantel treatment and usually no other therapeutic interventions are required. Clinical, radiological and sonographic studies have demonstrated the regression over weeks to months of intestinal and vesical lesions, reactive hepatomegaly, and even severe upper urinary tract lesions and liver fibrosis.[86]

Some expatriates do not shy away from repeated exposure, mostly through water sport activities, despite being aware of the risk of reinfection.[49] They may benefit from repeated treatment to keep the parasite burden low. The ideal frequency of praziquantel treatment in this particular population has not been firmly established. From observations in endemic populations, it can be assumed that a yearly treatment with a single dose of praziquantel may be adequate to prevent significant morbidity, both in *S. haematobium* and *S. mansoni* infection.[119,188]

Treatment in special situations

In Katayama fever, corticosteroids are given to suppress the hypersensitivity reaction to schistosomal antigen and praziquantel is given concomitantly to kill off the already matured schistosomes.[32,92] The optimal treatment duration has not been investigated in a controlled trial, but corticosteroid treatment in decreasing dosage for 2 weeks produced good results in small clusters. When corticosteroids have been withdrawn early, some patients develop a relapse of Katayama fever, with this time mainly abdominal symptoms on the foreground.[101] In acute schistosomiasis, praziquantel treatment has produced symptom worsening when corticosteroids were not concomitantly used. Even when the worm burden is low, a second dose of praziquantel must be given 4—8 weeks later to eliminate the schistosomes matured meanwhile.[193] When praziquantel is given to patients whose Katayama symptoms have recently abated, it may cause fever in upto 50% of cases.

Treatment of neuroschistosomiasis requires specialized care, with corticosteroids and anticonvulsants as essential adjuvants to praziquantel, particularly when concomitant neurocysticercosis cannot be excluded.[149,194] A single dose of praziquantel at 40 mg/kg may suffice to eliminate the adult schistosomes and halt egg production, but it does not inactivate the already embedded eggs.[195] This might explain why in transverse myelitis, early administration of corticosteroids reduces clinical progression markedly, and speeds up recovery.[130,137] It should not be withheld until absolute proof of diagnosis is obtained, which may be difficult in developing countries. Corticosteroid treatment

duration depends on the clinical evolution but should be maintained for several weeks to months. Even in a well established transverse myelitis, prolonged (>2 months) treatment with corticosteroids was associated with a more favorable outcome.[196] For brain involvement, adjuvant corticosteroid therapy has been found equally useful.

After successful treatment, recovery is the rule, but may be slow and incomplete. Clinical cure rates are higher in cerebral schistosomiasis.[130]

Resistance to antischistosomals and combination therapy

Current treatment of schistosomiasis relies on a single, yet very potent and safe drug, praziquantel. The potential emergence of schistosomes resistant to praziquantel is of major concern.[197,198] Resistance to praziquantel can be induced under sustained drug pressure in animals. On the other hand tolerance to the usual doses of praziquantel has been suspected in a Senegalese focus where low cure rates were observed.[199] Tolerance to praziquantel may also have been the mechanism in the few instances where insufficient cure has been reported in infected travellers.[200–203] Once again, distinction between failure to eradicate infection and worm burden reduction has not always been clearly stated in these reports. Whether failure was a consequence of drug tolerance, acquired resistance or of suboptimal treatment is not determined.[204]

High parasite burden and intense transmission with rapid reinfection may lead to insufficient cure rates.[205] Reportedly resistant strains in Egypt do not seem to spread in spite of intense drug pressure.[206]

Using combinations of antischistosomals may forestall resistance. However, combining praziquantel and oxamniquine has not led to better results than either of the compounds used alone.[207] Combinations of artemisinin and praziquantel look more promising, not in the least because these compounds act on different development stages of the parasite.[208]

New developments in the treatment of schistosomiasis

Artemisinin derivatives (artemether and artesunate) have recently been introduced on a large scale to treat malaria, but also exhibit activity mainly against the immature schistosomules of *S. japonicum*, *S. mansoni*, and possibly those of *S. haematobium*.[209] The penetrating cercariae and adult schistosomes are however a lot less susceptible. This has potentially interesting implications in early post-exposure prophylaxis for (acute) schistosomiasis in non-immune travellers.

In a mouse model, artemether has been able to reduce the worm burden by upto 80% when given at a dose of 200 mg/kg 14–21 days after infection with *S. mansoni*.[210] Dosages superior than 200 mg/kg did not improve the parasite reduction rate any further. These are in fact very high dosages when extrapolated to humans.[208] Artemisinin is rapidly but incompletely absorbed by oral route and quickly transformed in the liver into active metabolites such as dihydro-artemisinin. Brain stem neurotoxicity has been demonstrated in animal models, and is the main limiting factor for dosage and treatment duration of artemisinin.

In schistosomiasis, artemisinin derivatives interfere probably with the glucose metabolism in the immature schistosomes. It is enhanced in the presence of hemin, and affects adversely the integrity of the parasite tegument. Hepatic shift occurs more slowly than with praziquantel. In humans, artemether has been tested in the prevention of the three main schistosomiasis species, in doses of 6 mg/kg given every 2–4 weeks for upto 6 months without evidence of neurotoxicity.[211] Although the protective efficiency was limited (25%) this treatment approach significantly reduced the parasite burden.[212] Similar results were obtained in urinary schistosomiasis.[213]

Several trials with artesunate were conducted in China to prevent *S. japonicum* infection after exposure. Artesunate given at weekly or fortnightly doses of 6 mg/kg for 4–26 weeks produced protective rates in excess of 85%.[214] In established schistosomiasis however, combining artemether with praziquantel may not be superior to praziquantel alone.[215]

Recently, the combination of mefloquine and artesunate has been able to substantially reduce the worm burden in children with *S. haematobium*.[216] A single treatment with mefloquine at 25 mg/kg alone reduced parasite burden by >50%. It would be interesting to assess whether malaria prevention with mefloquine would prevent travellers to acquire a significant parasite burden.

Prevention of schistosomiasis in (non-immune) travellers

Schistosomiasis is not acquired by unavoidable exposure, but by willfully entering cercariae infected fresh water. Unlike other vector-borne diseases, schistosomiasis can thus be prevented by behavioural changes and by providing a safe water supply for bathing. The risk of transmission is not evenly distributed. In places frequently visited by tourists such as Lake Malawi and the Dogon country in Mali, putting up warning posts to indicate which places are suitable for swimming and bathing and which areas are at high risk could be successful to spread awareness and avoid infection.

Over the last few decades, strategies of schistosomiasis control have fundamentally shifted from transmission and vector control towards morbidity control through population-based chemotherapy, with excellent results in reducing endemicity in some countries such as Brazil and Egypt.[128] In travellers to Africa, the risk of acquiring the infection has not decreased sizeably. For non-immune travellers and expatriates repeatedly exposed, different options need to be considered: prevention of established infection on one hand, and prevention of morbidity on the other.

Primary prevention consists of avoiding cercaria to successfully penetrate the skin, a process that takes usually a little while. Therefore, vigorously rubbing down the skin with a towel after swimming has been effective to prevent infection to a large extent.[217]

DEET (N,N-diethyl-m-toluamide) has been proven an effective substance that inactivates penetrating cercariae in a mouse model, even at modest concentration.[218] Applying a 50% DEET solution to the skin immediately after exposure has

prevented infection in non-immune travellers bathing in lake Malawi.[219]

In non-immune travellers post-exposure treatment to prevent symptoms is a more commonly considered option. To be effective, a post-exposure prophylactic treatment should be able to eradicate the schistosomules before they sensitize the host immune defences, thus before maturing and oviposition happens. Preliminary studies in populations endemically exposed indicate that artemisinin derivatives given intermittently for a prolonged period may slow down the newly acquired parasite burden.[220] In non-immune travellers however, its main objective would be to ward off Katayama syndrome, and treatment should therefore be taken before maturation has begun and when immature schistosomes are sufficiently susceptible to artemisinin, thus 2—3 weeks after exposure. Because artemisinin derivatives have not yet been tested for this particular purpose, it is still unclear which dosage scheme (total dose and frequency) is needed to achieve parasite eradication in its preclinical stage.

Praziquantel has been tried as a prophylactic in a small group of recently exposed non-immune travellers. When given 4—6 weeks after exposure to *S. haematobium* in Mali, Katayama fever did not occur, but travellers were found to be infected later on. However treatment at a shorter interval could not prevent Katayama fever.[193]

Probably a single dose of artemisinin at 6 mg/kg body weight at 3 weeks after exposure, followed by a single dose of praziquantel at 40 mg/kg at 6—8 weeks post-exposure may be an appropriate preventive treatment scheme in non-immune travellers with limited exposure.[210] This strategy requires validation.

Vaccination against schistosomiasis is currently under evaluation as an additional tool to praziquantel treatment to limit morbidity in populations endemically exposed.[221] The most advanced vaccine (Bilhvax®) uses the glutathione S-transferase (GST28) schistosomal antigen as a target, and has been tested in human Phase I and II clinical trials in *S. haematobium* infection, with tangible results on parasite burden. There is at present no established role for vaccination as a means of prevention of schistosomiasis infection in travellers, but it may be useful to test it as a tool to prevent Katayama syndrome in non-immune travellers, once development has progressed.

Future developments in imported schistosomiasis

Nowadays a well-informed physician has all the means at hand to suspect, diagnose and successfully treat schistosomiasis in travel clinics, as well as in health services from endemic regions. Severe pathology is becoming infrequent in most endemic countries, and can in most cases be adequately managed. Exposure to schistosomiasis by global travellers is on the increase, and it may be assumed that disease manifestations of imported schistosomiasis may follow this trend. There are useful tools to provide pre-travel information about the sites that carry the highest risk for infection. Detailed virtual maps such as offered by Google Earth may help in this process.

The main challenges for applied research are the further improvement of diagnostic methods in sub-clinical infection or in the early stages of infection.

There is still a need for more sensitive indirect tools to confirm diagnosis when neuroschistosomiasis is suspected.

Schistosome ELISA antibody tests of CSF are promising but require validation.[140] Development of schistosome DNA detection by means of polymerase chain reaction (PCR)-based technology may provide a better tool. It has proven its superiority to other tests, at least for the qualitative diagnosis of infection.

Selecting specific schistosome DNA probes will make the identification of the infective species possible as well.[222] Semiquantitative real-time PCR technology is a promising measuring tool to estimate the parasite burden and to monitor treatment results as an alternative to microscopy. PCR based techniques can be used to identify schistosome DNA in stool, urine, blood and tissue samples. The latter could be used to confirm neuroschistosomiasis.

Semiquantitative determination of schistosome DNA in serum does not seem to be a good marker for early monitoring of treatment success.[177] In contrast, PCR assays on stool samples show a marked decrease of schistosome DNA soon after treatment of intestinal schistosomiasis.[223] The reason for this discrepancy is unclear. Furthermore it has not yet been established whether semiquantitative determination of schistosome DNA in serum is a good marker of parasite burden.

The essential tools to prevent infection after exposure are now available but not yet fully tested in non-immune travellers. The ideal sequencing and performance of a combined post-exposure prophylaxis remains to be established in clinical trials. There may be a role for vaccination, both in preventing Katayama syndrome as in reducing the parasite burden. These are a few of the challenges that could be taken up by travel clinics in a collaborative effort.

Conflict of interest

None declared.

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