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Acute schistosomiasis, a diagnostic and therapeutic challenge

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Abstract

In non-endemic countries, acute (invasive) schistosomiasis (AS) is typically seen in non-immune travellers, whereas chronic schistosomiasis is more frequently diagnosed in immigrants. Travellers with AS initially present with non-specific signs such as fever, cough, headache, and urticaria. Life-threatening cardiac and neurological complications may occur. The positive diagnosis of AS relies on seroconversion, which appears together with hypereosinophilia approximately 3 weeks after the onset of symptoms. When prescribed during AS, praziquantel usually does not prevent the chronic phase of the disease and is associated with exacerbation of signs and symptoms in approximately 50% of cases. According to the published literature, corticosteroids may be recommended alone or in association with praziquantel. When associated with corticosteroids, pharmacokinetic interactions may impair the efficacy of praziquantel. We suggest that corticosteroids should be restricted to use in patients with systemic complications of AS, whereas praziquantel should be initiated only when ova are detected in either stools or urine, depending on the culprit species.

Keywords: Acute schistosomiasis, eosinophilia, invasive schistosomiasis, Katayama fever, Katayama syndrome, praziquantel, review

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Acute schistosomiasis (also called Katayama fever or syndrome) is one of the clinical manifestations of infection with *Schistosoma* sp. [1]. It occurs several weeks after the penetration of schistosome cercariae through the skin, and is related to the migration of the larvae (schistosomulae) within the body. Oviposition, which defines the chronic phase of the disease, typically occurs weeks later. This symptomatic acute phase is mostly described in non-immune individuals (i.e. tourists) exposed to fresh water in endemic areas (Fig. 1) [1–3].

Acute schistosomiasis (AS) appears to be a more appropriate term than 'Katayama fever' for this disease. Katayama fever was described in 1847 in the Katayama district of Japan, and has been known to be caused by *Schistosoma japonicum* since 1904 [4,5]. It is of note that there is no longer schistosomiasis in the Katayama district as there is in the rest of Japan. In addition, all species of human schistosome can lead to AS in infected humans. There is thus no reason to use a name referring to *S. japonicum* or Japan in order to describe this disease. Finally, as fever is not always present in AS, the use of 'fever' in referring to the disease is not clinically relevant.

The recent report of a large series and clusters of AS in travellers with a single exposure allows us to better describe its natural history, pathophysiology, presentation, complications, diagnosis, and treatment.

Epidemiology

In Europe, the Geosentinel Surveillance network reported 401 cases of travel-associated schistosomiasis seen within 11 years (1997–2008) in 27 sites in 12 Western countries, without making a distinction between acute and chronic schistosomiasis [6]. In two European series of 257 and 1640 febrile travellers returning from abroad, AS was diagnosed in 1.6% and 1.7% of travellers, respectively [7,8]. In one of these series, AS was the third most common cause of febrile diseases imported from Africa, after malarial and rickettsial infections [8]. In France, a retrospective study conducted between 2000 and 2004 in 42 parasitology laboratories found that 77 patients were diagnosed with AS [9]. AS usually occurs sporadically or as small outbreaks [10,11].

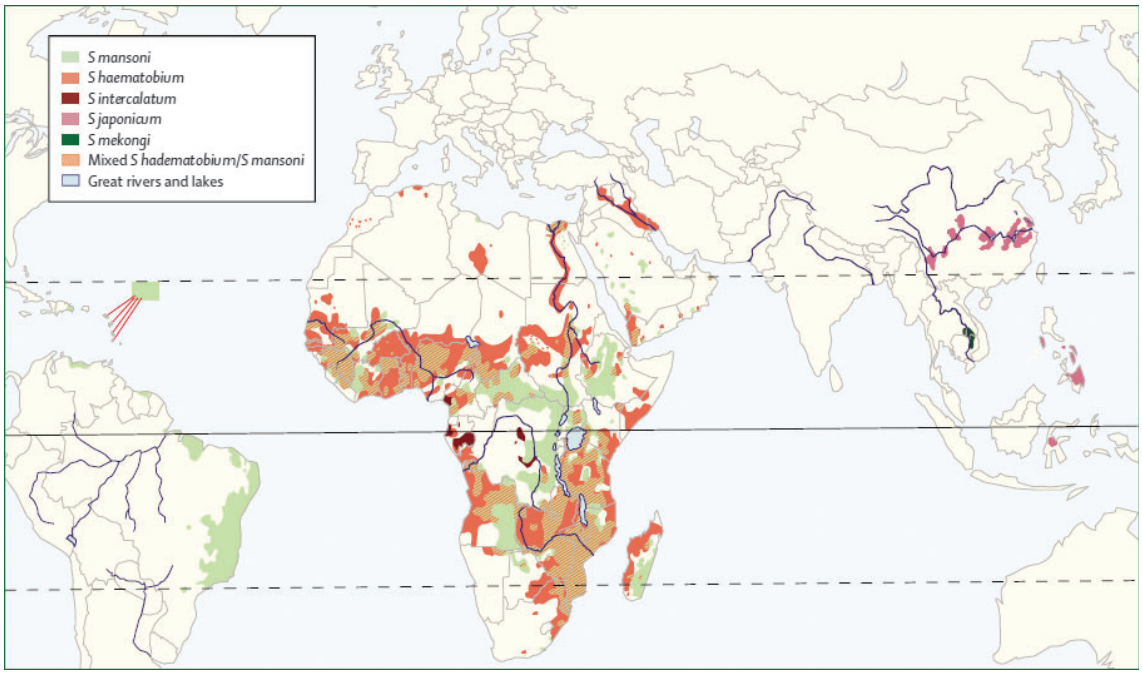

FIG. 1. Global distribution of schistosomiasis, adapted from Gryseels and Doumenge [2].

Most cases of imported AS are described in travellers returning from West and East African countries such as Mali (Dogon country), Burkina Faso (Banfora falls), Ethiopia (National Park of Omo), Malawi Lake, and Zambia (Zambese Falls), from Brazil, and also from Laos [8,11–22]. Attack rates during outbreaks in tourists exposed while swimming in contaminated water vary from 39% [23] to 100%, but are usually above 65% [3,12,19].

One study showed relationships between the number of exposures, the duration of exposure and the risk of infection [24]. Overall, infection is symptomatic in 54–100% of the non-immune infected travellers (Table 1). During the last two decades, AS has been more often reported in travellers infected with *Schistosoma mansoni* or *Schistosoma haematobium* than in those infected with *S. japonicum* or *S. mekongi* [6,9].

Pathophysiology

Acute schistosomiasis is considered to be a toxaemic and allergic reaction to the migrating and maturing larvae of *Schistosoma* [1,25]. The severity of the clinical presentation varies according to the cercarial burden and the immune response to the released parasite antigens [26]. Dry cough and angio-oedema, together with high counts of eosinophils, point to a type I hypersensitivity reaction.

TABLE 1. Summary of reports of outbreaks of acute schistosomiasis (involving at least ten patients) among travellers

Reference	[13]	[33]	[15]	[14]	[12]	[16]	[17]	[17]	[18]	[21]	[11]	[24]
Year	1995	1995	1996	1996	1998	1998	2001	2001	2002	2003	2003	2008
Exposed persons	29	13	12	16	10	29	13	13	31	18	18	27
Attack rate (%)	96	62	92	100	100	69	92	100	100	94	100	81
Country of infection	Mali	Mali	Burkina Faso	Malawi Mozambique	Ghana	Burkina Faso	Brazil	Brazil	Brazil	Brazil	Mali	Tanzania
Culprit species	*Sh*, *Sm*, *Si*	*Sm*	*Sm*	*Sh*	*Sm*	*Sm*	*Sm*	*Sm*	*Sm*	*Sm*	*Sh*	*Sm*
History of CD (%)	36	62.5	NA	13	20	5	100	NA	NA	100	94	13.6
Incubation period	2–10 weeks	NA	3–6 weeks	36 days	2–5 weeks	27 days	2–4 weeks	20 days	3–4 weeks	32 days	19 days	3–13 weeks
Acute schistosomiasis (%)	54	54	54	100	80	70	91	92	100	100	77	86

CD, cercarial dermatitis (swimmer's itch); NA, not available; *Sm*, *Schistosoma mansoni*; *Sh*, *Schistosoma haematobium*; *Si*, *Schistosoma intercalatum*.

Circulating immune complexes are found in *c.* 55–93% of patients with AS, and their presence is correlated with the intensity and severity of symptoms [27,28]. Moreover, direct toxicity of eosinophils seems also to play an important role [29]. High counts of eosinophils are found during severe forms of AS. Major basic protein and eosinophil cationic protein, found in the eosinophil granules, are released during cell activation and could contribute to the severity of the disease by their direct toxicity, affecting vessels of the heart and brain [29,30]. A particular cytokine pattern, with high levels of pro-inflammatory cytokines (interleukin (IL)-1, IL-6, and tumour necrosis factor-α) and a poor Th2-type response (IL-4 and IL-5), has been described during AS. This cytokine pattern could explain the altered general status seen during AS [18].

These symptoms are typically seen before oviposition, egg-laying, and the appearance of granulomatous reactions around eggs, which defines the chronic phase of the disease. However, the two phases of the cycle may overlap, because an individual schistosomula may make several circuits in the pulmonary and systemic circulation before finding its way to the hepatic portal system [31]. This explains why the delay between skin penetration of the cercariae and egg-laying may vary from one study to another. This is also illustrated by some studies that found eggs in stool or urine although some symptoms of AS were still present [8].

Clinical Presentation

The most common signs of AS are fever, dry cough, weakness, headache, abdominal symptoms, and urticaria or angio-oedema (Fig. 2).

A history of exposure to contaminated water in endemic areas is essential. The disease is usually acquired while people are bathing in fresh water and, to a lesser extent, when they are crossing rivers or showering with contaminated water [9]. Contact as brief as 1–5 min may be enough to allow transcutaneous penetration by cercariae [32,33]. A diffuse maculopapular pruritic skin eruption, named cercarial dermatitis, appears within 24 h after exposure. Pruritus alone may be the only sign [13]. The eruption lasts for a few hours before disappearing spontaneously [1,34]. Therefore, a history of such an eruption can be found upon questioning, but it is rarely noticeable on the skin of returning travellers [25].

Reports of outbreaks in travellers with a single exposure have contributed to a better description of the natural history of schistosomiasis (Table 1). Cercarial dermatitis is reported in 5–100% of exposed travellers. The first symptoms of AS usually occur 2–6 weeks after exposure [11,14,25]. However, incubation periods from 1 to 12 weeks have been reported [8,13,35]. The main signs and symptoms are fever, cough, headaches and urticaria, but these may vary according to the infecting *Schistosoma* species (Table 2). Fever is frequent but usually mild. Fever above 39°C is seen in approximately one-third of cases [8], and appears approximately 19 days after exposure [11].

Nonetheless, this phase of schistosomiasis may be unapparent. Among 137 cases of schistosomiasis acquired during travel, clinical findings compatible with AS were found in 75 patients (66%). Thus, more than one-third of infected patients may have no signs of AS [36]. As a consequence, individuals exposed to contaminated water should be investigated for schistosomiasis even in the absence of symptoms.

Life-threatening Complications

Neurological, pulmonary and cardiac complications can occur during AS, and some may be life-threatening. Neurological manifestations have been observed in *c.* 2% of cases of AS in the largest series conducted so far, during the Philippines

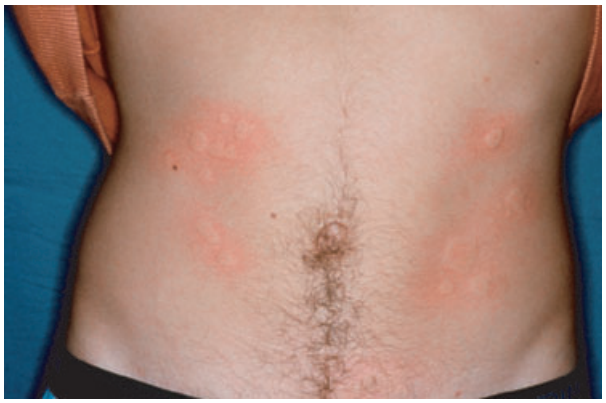

FIG. 2. Acute urticaria during acute (invasive) schistosomiasis.

TABLE 2. Major signs and symptoms observed during acute schistosomiasis according to the culprit species of *Schistosoma*

Signs and symptoms (%)	*Schistosoma mansoni* 95 patients [12,15–18]	*Schistosoma haematobium* 34 patients [11,14]
Fever	54–100	93–94
Abdominal pain	33–93	0
Dry cough	17–91	44–86
Headache	33–87	31–93
Diarrhoea	25–81	14
Liver enlargement	17–75	0–25
Myalgias	50–74	14–69
Neck pain	64	71
Urticaria	8–17	13–57

campaign of 1944–1945 during World War II [37]. Of the 1200 US soldiers infected with *S. japonicum*, 27 presented with neurological involvement during AS. Headache, disturbances of sensorium and weakness were all present, and *c.* 84% of the patients were febrile at one time or another; 44% presented with transient hemiplegia or tetraplegia; 60% complained of visual impairment; and 50% complained of incontinence, speech impairment, or ataxia. Neurological manifestations have also been described in travellers with AS caused by *S. mansoni* or *S. haematobium* infection [29,38]. The brain involvement during AS may be perceived as headache, confusion, seizures, loss of consciousness, focal deficiencies, visual impairment, ataxia, urinary incontinence, or motor paralysis [29,37,39–43]. In one of these cases, magnetic resonance imaging showed border-zone infarcts suggestive of cerebral vasculitis [29].

Cardiac injuries such as myocarditis, pericarditis or asymptomatic myocardial ischaemia have also been described during AS [29,44,45]. As was the case for neurological complications, the first description of cardiac complications was made during the Leyte campaign [46]. An analysis of 315 electrocardiograms revealed various repolarization abnormalities: anomalies of T-waves (99%) or ST segments (52%). In addition, cardiac involvement has been described during an outbreak in Brazil [18]. Among the 31 patients infected with *S. mansoni*, 12 (38.7%) had chest pain and six (19%) had a positive ultrasound diagnosis of pericarditis.

Pulmonary complications of AS are better described [47,48]. In a series of ten patients with AS, systematic chest computed tomography scan showed pulmonary nodules ranging in size from 2 to 15 mm, even in the absence of associated respiratory symptoms in as many as four patients [47]. When patients have respiratory symptoms, chest X-rays show ill-defined pulmonary nodules. Pulmonary symptoms and radiographic abnormalities point to interstitial pneumonitis, similar to what is seen in tropical pulmonary eosinophilia. It is noteworthy that these severe forms can occur either during spontaneous evolution of the disease or after treatment with praziquantel [11,29,45,49].

Diagnosis

Eosinophilia

The eosinophil count is usually above normal limits during AS. The onset of eosinophilia is delayed as compared with the onset of symptoms. Among 13 patients with AS, the mean delay between onset of fever and occurrence of hypereosinophilia was 21 days, whereas the delay between contaminating bathing and occurrence of hypereosinophilia was 47 days (range: 25–119 days) [11]. In another series of 42 cases of AS, the eosinophil count was within normal limits in 27% [36]. Therefore, the absence of eosinophilia does not rule out the diagnosis of AS.

Stool and urine analysis

Ova production begins at the end of adult maturation and migration to the vesical plexus or mesenteric veins, depending on the *Schistosoma* species, with at least 30–50 days from skin penetration to egg-laying [31]. In the early stages of AS, a search for ova in stools or urine is typically negative, and will remain so until the end of the entire life cycle. Nonetheless, ova may still be detected in the urine or stools of patients complaining of symptoms compatible with AS. For example, among 23 patients with signs of AS, a search for ova in stools or urine at first investigation was positive in five (22%), laboratory examination being performed within 3 weeks of onset of fever [8]. Overall, the period of egg detection varies from 5 to 10 weeks after exposure. Moreover, early treatment with praziquantel can delay egg-laying, as suggested by one study in which the mean delay between exposure and detection of ova was 196 days (range: 124–330 days) [11].

Serodiagnosis

The diagnosis of AS relies on serological testing. Nonetheless, there are three things to keep in mind. First, serological findings are usually negative at the onset of clinical signs, and serological investigations must be repeated to identify seroconversion, which may appear up to 3 weeks (mean interval: 26 days) after the onset of symptoms, and *c.* 6 weeks (range: 27–100 days) after contact with contaminated water [11,25]. Therefore, upon primary investigation by a physician, serological findings are positive in no more than 65% of the cases [8,11].

Second, the sensitivity and specificity of serological tests vary with the antigens used; the tests are not uniform throughout the world; and most of the tests can be performed only in research laboratories. ELISA usually makes use of egg antigens (Schistosoma Egg Antigen/ELISA). It is indicated for the detection of schistosomiasis; however, sensitivity is no more than 50% [1,50]. Enzyme-linked immunotransfer blot is used for confirmation in the case of a positive ELISA result. This test is considered to be 100% specific, and results are usually available 4–6 weeks after exposure [51]. When worm antigens are used, as in indirect haemagglutination tests, sensitivity reaches 70–90% for the diagnosis of AS according to the cut-off titre defining positivity [50]. A combination of both ELISA and indirect haemagglutination gives 90% sensitivity and 92.9% specificity [50].

Moreover, infecting species identification cannot be performed with serological testing. For example, in one series of 22 patients infected with *S. mansoni*, serological cross-reactivity to *S. haematobium* was found in three patients, whereas only one patient was formally diagnosed as having *S. mansoni* by identification of ova in stool [24]. According to outbreak reports, seroconversion and ova production may appear up to 6 months and 330 days after exposure, respectively [11,14].

ALAT rate is increased in *c.* 40–50% of cases, but to no more than five times above the normal upper limit [11,17]. Thrombocytopenia is seen in *c.* 10% of cases.

Treatment

Corticosteroid treatment better than praziquantel treatment?

Treatment of AS is a real challenge, given that the efficacy of drugs varies according to the age of the schistosomulae [52–54]. Usually, the recommended dosage of praziquantel for chronic infection with *S. mansoni* or *S. haematobium* is 40 mg/kg once daily. Nonetheless, praziquantel is not effective during AS, and is sometimes associated with severe reactions [29,33,38,55]. It is ineffective on schistosomulae above 7 days of age [52,53], and does not prevent the chronic phase of the disease [11,36]. Indeed, in a series of 18 travellers, treatment with praziquantel during the incubation and acute phase of schistosomiasis was unable to prevent egg-laying and progression to a chronic stage [11]. Furthermore, early treatment can worsen the symptoms of AS by inducing an allergic type of response to parasitic destruction [11,13,56]. This paradoxical reaction occurs in approximately 50% of patients treated for AS with praziquantel [8,11,56]. In some cases, this worsening of symptoms can be life-threatening by causing encephalitis related to vasculitis [29], myocarditis [45], or pulmonary events [49].

Considering that the pathophysiological mechanisms of AS result more from the immunological response to larvae migration than to the parasitic location, more and more authors recommend the use of corticosteroids [11,13,14,18,25,42,57]. According to them, praziquantel is used either in combination with corticosteroids [14,15,57] or following corticosteroid treatment [17,58]. Others, including ourselves, wait for egg-laying before using praziquantel [13,18]. It is of note that the use of corticosteroids decreases plasma levels of praziquantel by 50% [59]. Praziquantel needs a good host-specific response against *Schistosoma* to be efficient [26,53]. During the early stage of AS, the weakness of the specific immune response might explain why praziquantel is not effective at this stage [52]. Overall, the use of corticosteroids is discussed on a case-by-case basis after ruling out bacterial infection and strongyloïdosis [8,60].

Relapses of AS have also been described [8,61]. Relapsing forms, which occur after a median time period of 15 days after the end of the primary symptomatically similar episode, are treated with praziquantel and/or corticosteroids in an unknown proportion of patients [8,61].

Oxamniquine, arthemeter, and combined treatment

Oxamniquine (50 mg/kg once) could be indicated at the early phase of schistosomiasis, because it is more efficient against schistosomulae than praziquantel. Nonetheless, it is efficient only in the case of *S. mansoni* infection. When prescribed during the early stage (first week) of the infection or during AS, it prevents the occurrence of chronic *S. mansoni* infection and egg-laying [26,62,63].

Arthemeter, an artemisin derivative, is also efficient against schistosomulae aged 7–21 days [52]. In one comparative trial performed in the Côte d'Ivoire, arthemeter reduced the incidence of *S. mansoni* infection by 50% in exposed children [64]. Moreover, a 60–100% protective effect has been suggested in a Chinese population exposed to *S. japonicum* [65]. A double-blind study comparing oral arthemeter and placebo in 322 exposed children in the Côte d'Ivoire showed a decrease in the incidence rate of *S. haematobium* by 65% as compared with 49% in the placebo group [66].

Combined therapy should also be considered [53]. A combination of arthemeter and praziquantel showed a 99% reduction in egg burden, as compared with a 94% reduction with the use of praziquantel alone, in 88 and 89 children, respectively, treated in Gabon [67]. Other antimalarial drugs, such as mefloquine, seem to have an antischistosomidae effect on mice [26,68].

Prevention

Obviously, the best way to prevent AS is to avoid exposure to contaminated water in endemic areas. Otherwise, many topical ointments have been evaluated to protect swimmers from cercarial dermatitis. With the exception of *N,N*-diethyl-m-toluamide 50% ointment, none have given promising results; the use of sunscreens, copper salt, niclosamide, dimethyl phthalate-based or butylacetylaminopropionate-based ointments did not protect against *Schistosoma* infection [69]. The use of petroleum jelly and vigorous drying with towels, with application of ethanol to exposed skin, has been proposed as an effective means of reducing cercarial penetration, but no study has demonstrated the effectiveness of this procedure

[25,61]. In contrast, the use of *N,N*-diethyl-m-toluamide 50% ointment in 15 travellers at Lake Malawi was associated with the absence of infection during a 3-month follow-up period [70]. Prior to being used for personal cleaning, contaminated water should be heated to 50°C for 5 min or treated with iodine or chlorine. Water can also be filtered with paper filters or left standing for 3 days before use [61].

Conclusion

The diagnosis and treatment of AS remains a challenge. Diagnosis relies mainly on positive serological testing. Treatment is based on corticosteroids in severe forms, and praziquantel should be initiated only when ova are detected in stools or urine, depending on the culprit species. Early treatment with oxamniquine (in the case of *S. mansoni* infection) or artemether shows promise and should now be evaluated in exposed travellers.

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Transparency Declaration

The authors declare no conflict of interest.

References

1. Ross AG, Vickers D, Olds GR, Shah SM, McManus DP. Katayama syndrome. *Lancet Infect Dis* 2007; 7: 218–224.
2. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. *Lancet* 2006; 368: 1106–1118.
3. Jaureguiberry S, Perez L, Paris L, Bricaire F, Danis M, Caumes E. Invasive schistosomiases. *Presse Med* 2005; 34: 1641–1645.
4. Tanaka H, Tsuji M. From discovery to eradication of schistosomiasis in Japan: 1847–1996. *Int J Parasitol* 1997; 27: 1465–1480.
5. Ishii A, Tsuji M, Tada I. History of Katayama disease: schistosomiasis japonica in Katayama district, Hiroshima, Japan. *Parasitol Int* 2003; 52: 313–319.
6. Nicolls DJ, Weld LH, Schwartz E *et al.* Characteristics of schistosomiasis in travellers reported to the GeoSentinel Surveillance Network 1997–2008. *Am J Trop Med Hyg* 2008; 79: 729–734.
7. Ansart S, Perez L, Vergely O, Danis M, Bricaire F, Caumes E. Illnesses in travellers returning from the tropics: a prospective study of 622 patients. *J Travel Med* 2005; 12: 312–318.
8. Bottieau E, Clerinx J, de Vega MR *et al.* Imported Katayama fever: clinical and biological features at presentation and during treatment. *J Infect* 2006; 52: 339–345.
9. Agbessi CA, Bourvis N, Fromentin M *et al.* Acute schistosomiasis in French travellers. *Rev Med Interne* 2006; 27: 595–599.
10. Haus-Cheymol R, Burlation G, Berger F *et al.* Clustered cases of urinary and intestinal bilharziasis in French military personnel. *Med Trop* 2007; 67: 98–99.
11. Grandiere-Perez L, Ansart S, Paris L *et al.* Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travellers. *Am J Trop Med Hyg* 2006; 74: 814–818.
12. Chapman PJ, Wilkinson PR, Davidson RN. Acute schistosomiasis (Katayama fever) among British air crew. *BMJ* 1988; 297: 1101.
13. Visser LG, Polderman AM, Stuiver PC. Outbreak of schistosomiasis among travellers returning from Mali, West Africa. *Clin Infect Dis* 1995; 20: 280–285.
14. Doherty JF, Moody AH, Wright SG. Katayama fever: an acute manifestation of schistosomiasis. *BMJ* 1996; 313: 1071–1072.
15. Loutan L, Farinelli T, Robert CF. Acute schistosomiasis or Katayama syndrome: apropos of 2 mini-epidemics. *Schweiz Med Wochenschr* 1996; 126: 1482–1486.
16. Elcuaz R, Armas M, Ramirez M *et al.* Outbreak of schistosomiasis in a group of travellers returning from Burkina Faso. *Enferm Infecc Microbiol Clin* 1998; 16: 367–369.
17. Barbosa CS, Montenegro SM, Abath FG, Domingues AL. Specific situations related to acute schistosomiasis in Pernambuco, Brazil. *Mem Inst Oswaldo Cruz* 2001; 96 (suppl): 169–172.
18. De Jesus AR, Silva A, Santana LB *et al.* Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. *J Infect Dis* 2002; 185: 98–105.
19. Schwartz E, Kozarsky P, Wilson M, Cetron M. Schistosome infection among river rafters on Omo River, Ethiopia. *J Travel Med* 2005; 12: 3–8.
20. Enk MJ, Caldeira RL, Carvalho OS, Schall VT. Rural tourism as risk factor for the transmission of schistosomiasis in Minas Gerais, Brazil. *Mem Inst Oswaldo Cruz* 2004; 99: 105–108.
21. Enk MJ, Amorim A, Schall VT. Acute schistosomiasis outbreak in the metropolitan area of Belo Horizonte, Minas Gerais: alert about the risk of unnoticed transmission increased by growing rural tourism. *Mem Inst Oswaldo Cruz* 2003; 98: 745–750.
22. Leshem E, Meltzer E, Marva E, Schwartz E. Travel related schistosomiasis acquired in Laos. *Emerg Infect Dis* 2009; 15: 1823–1826.
23. Centers for Disease Control. Schistosomiasis among river rafters—Ethiopia. *MMWR* 1983; 32: 585–586.
24. Leshem E, Maor Y, Meltzer E, Assous M, Schwartz E. Acute schistosomiasis outbreak: clinical features and economic impact. *Clin Infect Dis* 2008; 47: 1499–1506.
25. Corachan M. Schistosomiasis and international travel. *Clin Infect Dis* 2002; 35: 446–450.
26. Coelho PM, Enk MJ, Katz N. Treatment of clinical schistosomiasis at the prepatent phase: an option? *Trends Parasitol* 2009; 25: 299–300.
27. Hiatt RA, Ottesen EA, Sotomayor ZR, Lawley TJ. Serial observations of circulating immune complexes in patients with acute schistosomiasis. *J Infect Dis* 1980; 142: 665–670.
28. Hiatt RA, Sotomayor ZR, Sanchez G, Zambrana M, Knight WB. Factors in the pathogenesis of acute schistosomiasis mansoni. *J Infect Dis* 1979; 139: 659–666.
29. Jaureguiberry S, Ansart S, Perez L, Danis M, Bricaire F, Caumes E. Acute neuroschistosomiasis: two cases associated with cerebral vasculitis. *Am J Trop Med Hyg* 2007; 76: 964–966.
30. Leiferman KM, Gleich GJ. Hypereosinophilic syndrome: case presentation and update. *J Allergy Clin Immunol* 2004; 113: 50–58.
31. Southgate VR, Bray RA. Medical helminthology. In: Cook GC, Zumla A, eds. *Manson's tropical diseases*. London: Saunders Elsevier, 2003; 1649–1716.
32. Whitfield PJ, Bartlett A, Brown MB, Marriott C. Invasion by schistosome cercariae: studies with human skin explants. *Trends Parasitol* 2003; 19: 339–340.

33. Colebunders R, Verstraeten T, Van Gompel A *et al.* Acute schistosomiasis in travellers returning from Mali. *J Travel Med* 1995; 2: 235–238.
34. Bouree P, Caumes E. Cercarial dermatitis. *Presse Med* 2004; 33: 490–493.
35. Ross AG, Bartley PB, Sleigh AC *et al.* Schistosomiasis. *N Engl J Med* 2002; 346: 1212–1220.
36. Meltzer E, Artom G, Marva E, Assous MV, Rahav G, Schwartzt E. Schistosomiasis among travelers: new aspects of an old disease. *Emerg Infect Dis* 2006; 12: 1696–1700.
37. Kane C, Most H. Schistosomiasis of the central nervous system. *Arch Neurol Psychiatry* 1948; 59: 141–183.
38. Jaureguiberry S, Caumes E. Neurological involvement during Katayama syndrome. *Lancet Infect Dis* 2008; 8: 9–10.
39. Pittella JE. Neuroschistosomiasis. *Brain Pathol* 1997; 7: 649–662.
40. Vachon F, Jebrak G, Boulu P, Coulaud JP. Manifestations précoces sévères d'une bilharziose à *S. mansoni*. A propos d'un cas avec échec du traitement précoce par le Praziquentel*. *Med Mal Infect* 1984; 14: 102–106.
41. Kirchhoff LV, Nash TE. A case of schistosomiasis japonica: resolution of CAT-scan detected cerebral abnormalities without specific therapy. *Am J Trop Med Hyg* 1984; 33: 1155–1158.
42. Granier H, Potard M, Diraison P, Nicolas X, Laborde JP, Talarmin F. Acute encephalitis concurrent with primary infection by *Schistosoma mansoni*. *Med Trop* 2003; 63: 60–63.
43. Pittella JE. The relation between involvement of the central nervous system in schistosomiasis mansoni and the clinical forms of the parasitosis. A review. *J Trop Med Hyg* 1991; 94: 15–21.
44. Sarazin M, Caumes E, Cohen A, Amarenco P. Multiple microembolic borderzone brain infarctions and endomyocardial fibrosis in idiopathic hypereosinophilic syndrome and in *Schistosoma mansoni* infestation. *J Neurol Neurosurg Psychiatry* 2004; 75: 305–307.
45. Epelboin L, Jaureguiberry S, Esteve J *et al.* Myocarditis during acute schistosomiasis in 2 travelers. *Am J Trop Med Hyg* 2010. in press.
46. Most H, Kane CA, Lavietes PH *et al.* Schistosomiasis japonica in American military personnel; clinical studies of 600 cases during the first year after infection. *Am J Trop Med Hyg* 1950; 30: 239–299.
47. Nguyen LQ, Estrella J, Jett EA, Grunvald EL, Nicholson L, Levin DL. Acute schistosomiasis in nonimmune travelers: chest CT findings in 10 patients. *AJR Am J Roentgenol* 2006; 186: 1300–1303.
48. Schwartz E. Pulmonary schistosomiasis. *Clin Chest Med* 2002; 23: 433–443.
49. Schwartz E, Rozenman J, Perelman M. Pulmonary manifestations of early schistosome infection among nonimmune travelers. *Am J Med* 2000; 109: 718–722.
50. Van Gool T, Vetter H, Vervoort T, Doenhoff MJ, Wetsteyn J, Overbosch D. Serodiagnosis of imported schistosomiasis by a combination of a commercial indirect hemagglutination test with *Schistosoma mansoni* adult worm antigens and an enzyme-linked immunosorbent assay with *S. mansoni* egg antigens. *J Clin Microbiol* 2002; 40: 3432–3437.
51. Cetron MS, Chitsulo L, Sullivan JJ *et al.* Schistosomiasis in Lake Malawi. *Lancet* 1996; 348: 1274–1278.
52. Sabah AA, Fletcher C, Webbe G, Doenhoff MJ. *Schistosoma mansoni*: chemotherapy of infections of different ages. *Exp Parasitol* 1986; 61: 294–303.
53. Utzinger J, Keiser J, Shuhua X, Tanner M, Singer BH. Combination chemotherapy of schistosomiasis in laboratory studies and clinical trials. *Antimicrob Agents Chemother* 2003; 47: 1487–1495.
54. Silva LM, Menezes RM, de Oliveira SA, Andrade ZA. Chemotherapeutic effects on larval stages of *Schistosoma mansoni* during infection and re-infection of mice. *Rev Soc Bras Med Trop* 2003; 36: 335–341.
55. Nash TE, Cheever AW, Ottesen EA, Cook JA. Schistosome infections in humans: perspectives and recent findings. NIH conference. *Ann Intern Med* 1982; 97: 740–754.
56. Harries AD, Cook GC. Acute schistosomiasis (Katayama fever): clinical deterioration after chemotherapy. *J Infect* 1987; 14: 159–161.
57. Roca C, Balanzo X, Gascon J *et al.* Comparative, clinico-epidemiologic study of *Schistosoma mansoni* infections in travellers and immigrants in Spain. *Eur J Clin Microbiol Infect Dis* 2002; 21: 219–223.
58. Farid Z, Mansour N, Kamal K, Girgis N, Woody J, Kamal M. The diagnosis and treatment of acute toxaemic schistosomiasis in children. *Trans R Soc Trop Med Hyg* 1987; 81: 959.
59. Vazquez ML, Jung H, Sotelo J. Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. *Neurology* 1987; 37: 1561–1562.
60. Gendrel D. Salmonella–Schistosoma interactions. *Rev Prat* 1993; 43: 450–452.
61. Centers for Disease Control. Acute schistosomiasis in US travellers returning from Africa. *MMWR* 1990; 39: 141–142.
62. Enk MJ, Katz N, Zech Coelho PM. A case of *Schistosoma mansoni* infection treated during the prepatent period. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5: 112–115.
63. Garcia Goyco C, Nazario-Lopez H, Ruiz-Tiben E, Vazquez G, Borges T, Nash TE. The efficacy of oxamniquine in acute schistosomiasis: a clinical analysis of 28 treated patients. *Bol Asoc Med P R* 1997; 89: 63–69.
64. Utzinger J, N'Goran EK, N'Dri A, Lengeler C, Xiao S, Tanner M. Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. *Lancet* 2000; 355: 1320–1325.
65. Xiao SH, Booth M, Tanner M. The prophylactic effects of artemether against *Schistosoma japonicum* infections. *Parasitol Today* 2000; 16: 122–126.
66. N'Goran EK, Utzinger J, Gnaka HN *et al.* Randomized, double-blind, placebo-controlled trial of oral artemether for the prevention of patent Schistosoma haematobium infections. *Am J Trop Med Hyg* 2003; 68: 24–32.
67. Borrmann S, Szlezak N, Faucher JF *et al.* Artesunate and praziquantel for the treatment of *Schistosoma haematobium* infections: a double-blind, randomized, placebo-controlled study. *J Infect Dis* 2001; 184: 1363–1366.
68. Keiser J, Chollet J, Xiao SH *et al.* Mefloquine—an aminoalcohol with promising antischistosomal properties in mice. *PLoS Negl Trop Dis* 2009; 3: e350.
69. Caumes E, Felder-Moinet S, Couzigou C, Darras-Joly C, Latour P, Leger N. Failure of an ointment based on IR3535 (ethyl butylacetylaminopropionate) to prevent an outbreak of cercarial dermatitis during swimming races across Lake Annecy, France. *Ann Trop Med Parasitol* 2003; 97: 157–163.
70. Jackson F, Doherty JF, Behrens RH. Schistosomiasis prophylaxis in vivo using *N,N*-diethyl-m-toluamide (DEET). *Trans R Soc Trop Med Hyg* 2003; 97: 449–450.