INVITED ARTICLE

Tropical Infections in Returning Travelers

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Abstract

In the modern era, the relative ease and faster speed of travel have made the world a global village. An increasing number of people are traveling to distant and sometimes exotic locations for vacation/leisure or at times for business purposes. Along with the experiences of far-fetched lands, sometimes they bring bugs/organisms that are not native to their motherland. This makes the diagnosis and management of illnesses in a traveler challenging. In this review, we have tried to outline a management protocol for travelers returning with fever, with specific emphasis on trypanosomiasis and schistosomiasis.

Keywords: Diagnosis, Fever in traveler, Management, Traveler, Tropical infection.

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Introduction

Unexplained fever in any patient is a challenge for the treating physician, more so in a traveler returning from other countries makes it more difficult as it can have a varied etiology. Etiological diagnosis of fever in a returning traveler depends on many variables. The important ones are the travel geography itinerary, diseases endemic in traveled areas, recent outbreaks, vaccinations received in the past, pretravel vaccination/chemoprophylaxis, nature/time frame of potential exposures, and the incubation period(s) of the prevalent infections in the traveled countries. Common differential diagnoses are shown in Table 1.

A significant number of patients remain with unknown diagnosis even after extensive investigations; coinfections with two different organisms have also been reported in travelers

In view of these, a treating physician should try to collect as much information as possible not only regarding the clinical presentation of the patient, but also the nature of possible exposures, the activities carried out during the stay, treatment received if any, and sources of the food or water consumed. One should always keep in mind the possibility of any preexisting infection (before travel) flaring-up or becoming manifest after a short trip abroad.

- **History and examination:** A detailed clinical history should be obtained in every traveler returning with fever. It is very important to obtain a timeline, especially if the patient has visited many countries and continents or even has had a short stopover at any airport in an endemic area. Any symptoms/clinical signs present before embarking on the journey or present in the preceding 12 months prior to the presentation should also be considered. The important points that need to be noted include:
- A near-exact time of the onset of signs and symptoms: Understanding the clinical timeline is essential for establishing the likely incubation period, which is helpful in narrowing.
- The timeline and the details of the itinerary of travel are to be taken into consideration as well (details of geographic areas visited, travel dates, type and nature of transportation/accommodations, and days or hours spent in a location).
- Exposure history is very important (note the type and duration). Exposure to food, nature of the food (raw/cooked/hot/cold); exposure to water (bottled/potable, river/stream/well/handpump); exposure to animals (domestic pets/wild animals, type of exposure, and bites/scratches); exposure to insects (especially sleeping habits and use of nets); and sexual contact (type, duration, frequency, number of partners, protection used, and accidents).
- Pretravel medical precautions if taken: It is important to obtain vaccination history (type of vaccine, boosters, and last dose) and chemoprophylaxis, if any.
- Treatment history: It is also important to record any specific/indigenous treatment instituted for any symptoms while in a foreign country.
- Physical findings: Detailed physical findings should be recorded. It should specifically include evaluation for skin/eyes/oral/genital lesions, lymphadenopathy, organomegaly (especially enlargement of liver/spleen), neurologic findings, cardiac evaluation, and respiratory distress. Careful evaluation of the scalp for lesions/nits/tics, fingers/toes (including nails and web space), skin over back/breast/natal cleft, etc., is essential as many clues may be missed if the patient is not disrobed and examined thoroughly.
- **Investigations:** The initial laboratory evaluation for febrile travelers should include complete and differential blood counts with a detailed peripheral blood film examination, liver and kidney function tests, blood cultures, and/or rapid diagnostic tests (RDTs) for malaria/leptospirosis/scrub typhus/dengue fever.

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Table 1: Infectious etiology of fever in a returning traveler[1]

Area traveled	*Common tropical infections*	*Other miscellaneous infections*
South/Central America	Dengue fever, malaria (*Plasmodium vivax*), Zika, and schistosomiasis	Enteric fever, leptospirosis, histoplasmosis, leishmaniasis, and bartonellosis
South/Central Asia	Enteric fever, malaria (*non-falciparum*), rickettsial disease—scrub typhus	Chikungunya, traveler's diarrhea (cholera and typhoid), hepatitis A, and hepatitis E
Southeast Asia	Dengue, malaria (*non-falciparum*), rickettsial disease—scrub typhus, HIV/STD, hepatitis B, and hepatitis C	Chikungunya, leptospirosis, traveler's diarrhea (cholera and typhoid), hepatitis A, and hepatitis E
South/East/West/Central Africa	Malaria (*Plasmodium falciparum*), yellow fever, dengue, African trypanosomiasis, enteric fever, onchocerciasis, HIV/STD, hepatitis B, and hepatitis C	Rickettsioses, viral hemorrhagic fevers (Ebola virus, Rift Valley fever, Lassa fever, and Crimean–Congo hemorrhagic fever), traveler's diarrhea (cholera and typhoid), hepatitis A, hepatitis E, schistosomiasis, dracunculiasis, echinococcosis, rabies, tuberculosis, plague, and meningococcal meningitis
North Africa	Leishmaniasis, rickettsioses, HIV/STD, hepatitis B, hepatitis C, and enteric fever	Traveler's diarrhea (cholera and typhoid), hepatitis A, hepatitis E, schistosomiasis, echinococcosis, rabies, tuberculosis, and plague
Middle East	MERS-CoV infection, traveler's diarrhea (cholera and typhoid), hepatitis A, hepatitis E, HIV/STD, hepatitis B, and hepatitis C	Egypt and Yemen (nematode infections, filarial infections, schistosomiasis, fascioliasis, leprosy, and trachoma), Syria, Iran, Libya, and Morocco (leishmaniasis)

Mlarial parasites may be sequestered in the deep vasculature in patients with falciparum malaria, so only a few parasites may be visible on a peripheral smear even in severe infections. Therefore, it is advised that even if the initial smear is negative, additional smears should be evaluated over the subsequent 24–72 hours. Whereever possible, RDTs may be preformed, but one should be aware of the endemicity of a particular strain of organism suspected in the geographic area where the travel has been undertaken.

- Syndromic approach in diagnosing possible infectious etiology of fever in a traveler

  The clinical approach to the evaluation of fever in a returned traveler requires integration of the patient's clinical history and physical examination with relevant exposures. A suggested approach based on the presenting syndrome is given in Table 4.

- Empirical treatment with ceftriaxone and either doxycycline or azithromycin and artemether-based combination therapy (if malaria is strongly suspected) covers most of the tropical fevers. This can be instituted wisely after the most likely organism(s) are established. Once a definite diagnosis is made, empiric therapy may be de-escalated or a specific therapy may be instituted.

Trypanosomiasis

Human African trypanosomiasis (HAT) or sleeping sickness occurs in an acute form, occurring mainly in East and Southern Africa and caused by Trypanosoma brucei rhodesiense, and a chronic form, occurring mainly in West and Central Africa, caused by Trypanosoma brucei gambiense. Both T. brucei parasite subspecies are transmitted by tsetse flies (Glossina). These two forms differ in epidemiology, clinical presentation, and management. HAT mainly affects poor communities in rural Africa who are exposed to tsetse flies via their day-to-day activities on rivers, fields, or livestock.[4]

Life Cycle

Gambiense HAT is endemic to a region affecting primarily humans, whereas rhodesiense HAT is a zoonosis with humans affected only occasionally with wild animals and cattle being the main reservoir.

During a blood meal, an infected tsetse fly injects trypomastigotes into the host skin tissue. A painful chancre (local inflammatory reaction) develops at the site of inoculation. Thereafter, the parasites disseminate in the bloodstream via lymphatics. The metacyclic trypomastigotes differentiate into long, slender forms, measuring 15–35 microns that one can see on blood smear examination. On smears, these are characterized by a flagellum and a kinetoplast. Trypomastigotes pass into the connective tissues and enter the brain (CSF).

The tsetse fly during a blood meal ingests the trypomastigotes that move to the midgut, where they transform into procyclic trypomastigotes and undergo replication. Then, these procyclic trypomastigotes migrate into the salivary gland, where they transform into epimastigotes, and finally, 3–4 weeks after the initial infection of the fly, they develop into new metacyclic trypomastigotes, ready to be transmitted to another host.

Transmission

HAT is transmitted to humans via the bite of a tsetse fly (*Glossina* spp.). Tsetse flies are found commonly in warm, shaded areas and have a lifespan of about 2–6 months.[5] Once trypanosomes have colonized the salivary glands of the tsetse fly, the fly remains infective for life. Tsetse flies are restricted to the African continent, between 14° north and 19° south of the equator, which defines the geographic range for the transmission of HAT. Humans are exposed to bites during daily activities, including bathing/swimming/washing in small rivers or pools of water in rural areas. Asymptomatic individuals may carry skin-dwelling trypanosomes and act as parasite reservoirs (Fig. 1).

Table 2: Incubation periods of common tropical infections, fever, in a returning traveler[1]

Anthrax	1–7 days (can be >2 weeks)
Bartonellosis (cat scratch, trench fever, and Carrion's disease)	1–3 weeks
Brucellosis*	2–4 weeks
Chikungunya	2–14 days
Dengue	4–14 days
Diphtheria	2–10 days
Encephalitis, arboviral (Japanese encephalitis, West Nile virus, and others)	Japanese encephalitis: 5–15 days West Nile virus: 2–14 days
Enteric fever (typhoid and paratyphoid fevers)	7–45 days
Hantavirus infections (e.g., hemorrhagic fever with renal syndrome (HFRS), hantavirus pulmonary syndrome (HPS), and others)	HFRS: 2–4 weeks HPS: 2 weeks
Lassa, Ebola, and other viruses causing hemorrhagic fevers	7–21 days
Influenza	1–4 days
Leptospirosis	2–21 days
Malaria, *P. falciparum*	10–12 days
Malaria, *Plasmodium vivax*	14 days
Melioidosis	2 days–3 weeks
Meningococcal infections	3–10 days
Plague	2–14 days
Scrub typhus (*Orientia* spp.)	8–12 days
Trypanosomiasis, African	1–3 weeks
Yellow fever	1–614 days
Zika virus	2–14 days
Hepatitis A	28–50 days
Hepatitis B	60–150 days
Hepatitis C	2 weeks–6 months
Hepatitis E	2–9 weeks
Leishmaniasis, visceral	10 days to >1 year
Schistosomiasis (Katayama syndrome)	14–90 days
Fascioliasis	6–12 weeks

Table 3: Lab investigations for the etiology of fever in a returning traveler[2,3]

Malaria	Peripheral blood smears x 3 (examined by Giemsa staining method) or rapid immunochromatographic test for malarial antigen [based on the detection of histidine-rich protein 2 (HRP-2) and parasite-specific lactate dehydrogenase (pLDH)]. A combined test is preferred.
Scrub typhus	Scrub typhus IgM ELISA or Scrub typhus PCR from blood/eschar
Enteric fever	Blood culture for *Salmonella typhi* or *S. paratyphi* A or B (two 10 mL culture bottles sent for BACTEC blood culture system) Widal test, nonspecific, should not be relied upon
Dengue fever	NS1 antigen assay positive or dengue IgM positive (depending on the day of presentation) Dengue IgG may also provide important information if a secondary infection is suspected
Leptospirosis	Leptospira IgM

Table 4: Tropicodromes in a returning traveler

Tropicodromes	*Possible etiology*
Fever with renal failure	Scrub typhus, leptospirosis, melioidosis, dengue fever (DHSS), acute viral hepatitis (hepatitis A/B/E and others), and yellow fever
Fever with liver failure	Acute viral hepatitis (hepatitis A/B/E and others), scrub typhus, leptospirosis, dengue fever, and yellow fever
Fever with altered sensorium	Tubercular meningitis, encephalitis (HSV/JE/other prevalent viruses), scrub typhus, and leptospirosis
Fever with rash	Scrub typhus, leptospirosis, dengue fever (DHSS), and viral exanthems
Fever with ARDS	SARS-CoV2, influenza, H1N1 influenza, scrub typhus, leptospirosis, and dengue fever (DHSS)

Clinical Presentation

The clinical presentation of HAT is dependent on the parasite subspecies, the disease stage, and host factors (endemic vs nonendemic population). The incubation period of rhodesiense HAT is usually less than 3 weeks.[6] The incubation period of gambiense HAT is variable. There are two stages of infection. Often it is impossible to clearly differentiate between the two stages.

. First stage: The trypanosomes penetrate the skin and circulate in the blood and lymphatics.
. CNS stage: There is CNS involvement.

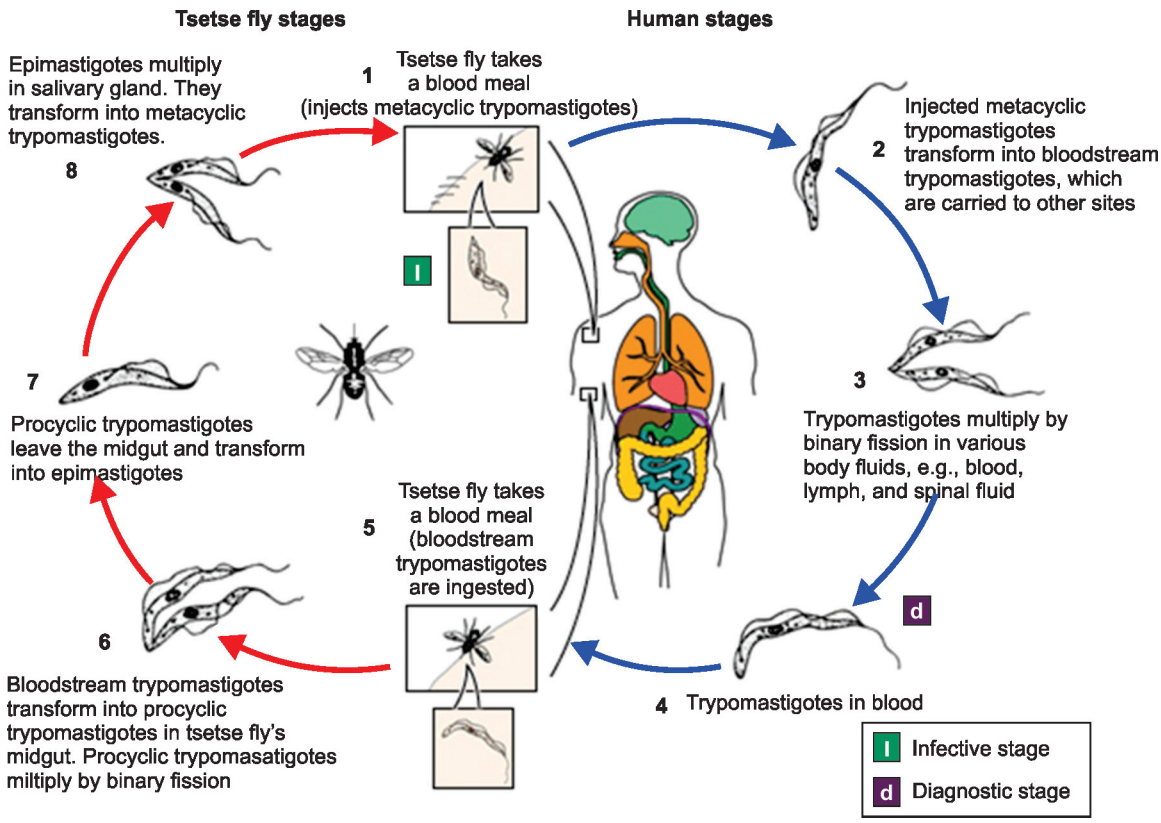

Fig. 1: Life cycle of African trypanosomiasis (Reproduced from: Centers for Disease Control and Prevention. DPDx: Trypanosomiasis, African. Available at: http://www.cdc.gov/dpdx/trypanosomiasisAfrican/index.html.)

Rhodesiense HAT is usually acute in onset and progresses rapidly. Patients usually present with a critical severe acute febrile illness with multiorgan failure. On the other hand, gambiense HAT is a slow, progressive disease, developing over months to years. Patients usually present with PUO, neurologic manifestations (headache, behavioral change, and sleeping disorder), weight loss, and lymphadenopathy (posterior cervical). Painless enlargement of the soft, mobile posterior cervical nodes is classically referred to as "Winterbottom's sign." The first sign of HAT infection is usually a trypanosomal chancre at the site of the tsetse bite.[7] A rash may also be observed over the trunk. CNS symptoms include headache, difficulty in concentrating, personality changes, and psychosis. Alteration of the circadian sleep/wake cycle leads to daytime somnolence. The patient gradually deteriorates to a stuporous or comatose state.

Nonendemic Population/Travelers/Expatriates

Among travelers, rhodesiense HAT is observed more frequently than gambiense HAT. Among travelers, sleep disorders and neuropsychiatric signs are observed less frequently.

Diagnosis

A definitive diagnosis of HAT requires demonstration of trypanosomes in body fluids (blood and/or CSF) or tissues (lymph node or chancre aspirate) via microscopy.[8]

- Serologic tests
- Gambiense HAT: RDTs for diagnosis include the card agglutination test for trypanosomiasis (CATT) and rapid lateral flow tests for detection of antibodies against purified variant surface glycoproteins. The sensitivity of CATT is generally 94–98%; the specificity depends, in part, upon whether whole blood (97% specificity) or plasma/serum dilutions are used (further increasing specificity). The sensitivity and specificity of the rapid lateral flow tests are 90–100% and 95%, respectively. Enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody test (IFAT), and the trypanolysis test require laboratory facilities and have varying sensitivities and specificities.
- Rhodesiense HAT: No rapid tests are available. ELISA or IFAT using whole parasites or crude trypanosome extracts are the mainstay for the diagnosis.
- Parasite detection: Trypanosomes can be visualized in tissues (lymph node or chancre aspirate), body fluids (blood or CSF), direct thin blood smear preparations, or Giemsa-stained thin or thick smears. Gambiense HAT is generally associated with a lower level of parasitemia (often below the detection limit of 5,000 parasites/mL for thick smears); specimen concentration increases the likelihood of diagnosis. For diagnosis of rhodesiense HAT, trypanosomes are usually readily detected in stained thin or thick films or wet preparations of blood.
- *Cerebrospinal fluid:* In the diagnosis of gambiense HAT, CSF examination is warranted to differentiate between first-stage (defined by ≤5 white blood cell (WBC)/μL of CSF and no trypanosomes in CSF) and second-stage disease (>5 WBC/μL of CSF or trypanosomes in CSF). For rhodesiense HAT, CSF examination is also needed to differentiate between first-stage (≤5 WBC/μL of CSF and no trypanosomes in CSF) and second-stage disease (>5 WBC/μL of CSF or trypanosomes in CSF).

- CNS imaging: T2-weighted MRI scans may show hyperintense signals in the frontal cortical and periventricular white matter, together with the involvement of the basal ganglia and cerebellum. These findings are nonspecific and may just support the diagnosis.
- Molecular detection: Polymerase chain reaction and loop-mediated isothermal amplification are research tools mainly. The sensitivity and specificity of these tests vary. One needs to have access to specialized laboratory facilities to perform these tests.

Special Situations

- Relapse
- If a patient relapses after initial treatment with fexinidazole, NECT should be given.
- If a patient relapses after treatment with NECT, a long duration of NECT (in which eflornithine is administered for 14 days rather than 7 days) or eflornithine monotherapy is given. Melarsoprol may be tried as a last resort.
- Pregnant women: Data on the safety of antitrypanosomal drugs in pregnancy are limited. Nifurtimox, eflornithine alone or NECT should be avoided during pregnancy. Newborns should be examined clinically, undergo blood concentration methods to evaluate for the presence of circulating trypanosomes, and should be followed clinically.
- Rhodesiense HAT
- Start empirical first test dose of suramin prior to lumbar puncture
- Pentamidine is also effective against first-stage rhodesiense HAT
- For refractory disease—melarsoprol
- Second-stage disease
- Melarsoprol is an arsenical compound. It should always be started along with oral prednisolone for 10 days. Never stop steroids abruptly, instead taper every third day by 25% of the original dose. The use of prednisone reduces the likelihood of developing melarsoprol-induced encephalopathy.
- Pregnant women: There are sparse data on the safety of antitrypanosomal drugs in pregnancy. Newborns should be examined clinically, undergo blood concentration methods to evaluate for the presence of circulating trypanosomes, and should be followed clinically.

Schistosomiasis

Schistosomiasis or "bilharziasis" is caused by infection with parasitic blood flukes. The prevalence of schistosomiasis is highest in sub-Saharan Africa. Schistosoma mansoni (Africa and South America), S. japonicum (East Asia), and S. haematobium (Africa and Middle East) are the three main schistosomal species causing the disease. S. mansoni and S. japonicum cause intestinal tract disease, while S. haematobium targets primarily the genitourinary tract disease.[10,11]

Humans, especially children, acquire the infection by bathing in freshwater ponds, lakes, and rivers contaminated with cercarial larvae. Slowly the worm becomes endemic to the population and by adolescence, most individuals in that area have a mild-to-moderate parasite load. This infection can be acquired by travelers following a single exposure. Each human schistosome species requires a specific snail (mollusk) species: *S. mansoni—Biomphalaria* spp., *S. haematobium* and *S. intercalatum—Bulinus* spp., *S. japonicum—Oncomelania* spp., and *S. mekongi—Tricula* spp.

Life Cycle

The life cycle (Fig. 2) of schistosomiasis requires both intermediate and definitive hosts. Seeding of eggs from infected humans or animal reservoirs in freshwater occurs via feces (S. mansoni and S. japonicum) or urine (S. haematobium). These eggs hatch and release miracidia. These miracidia can remain viable for up to 7 days and penetrate the intermediate hosts, i.e., the snail. In snail, there is formation of sporocysts followed by cercariae, which are subsequently into the water after 4 to 6 weeks. Cercariae can survive up to 2 days in water but are maximally infectious to humans during the first few hours after release from the snail. Cercariae penetrate human skin, shed their tails, and become schistosomulae and then migrate through the bloodstream to reach the liver where they mature into adults over the next 2 to 4 weeks. The adult worms migrate via the portal blood flow to the mesenteric venules of the small and large intestines (S. japonicum and S. mekongi), the mesenteric venules of the colon (S. mansoni and S. intercalatum), or the vesical venous plexus (S. haematobium). The male schistosome forms a groove in which the female resides. After 1–3 months, the female worms (7–20 mm) deposit eggs in the small venules of the mesenteric or perivesical systems. These eggs move toward the lumen of the intestine (S. mansoni and S. japonicum) or bladder and ureters (S. haematobium) and are eliminated in feces or urine, respectively.

Clinical Manifestations

Manifestations of acute schistosomiasis syndrome (Katayama fever) are usually observed among travelers returning from endemic areas. Most individuals living in the endemic zones with schistosomiasis infection are asymptomatic and usually have a low parasite burden.

- Acute infection:
- Swimmer's itch: Skin penetration by cercariae most commonly is asymptomatic. Some individuals develop an itchy rash ("swimmer's itch") at the site of the larval entry after swimming in freshwater. The rash is a hypersensitivity reaction that occurs only with repeat exposure.
- Acute schistosomiasis syndrome[12] (aka Katayama fever): It is a systemic hypersensitivity reaction to schistosome antigens and circulating immune complexes. It usually occurs 3–8 weeks after infection. Acute schistosomiasis occurs with the initial infection with *S. haematobium*, *S. mansoni*, *S. intercalatum*, and *S. mekongi* but can also reappear after reinfection with *S. japonicum*. The syndrome occurs most frequently among nonimmune individuals, such as travelers, who take bathing/scuba diving, water skiing, and rafting in a freshwater reservoir. Clinical manifestations are fever, urticaria/angioedema, chills, myalgias, arthralgias, dry cough, diarrhea, and abdominal pain.
- Chronic infection:[13] Chronic schistosomal infection is most common among individuals living in endemic areas who have continuous exposure.
- Intestinal schistosomiasis: Intestinal schistosomiasis is caused by infection due to *S. mansoni*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*, *and*, rarely *S. haematobium*. Abdominal pain, decreased appetite, and diarrhea are the common symptoms observed. Intestinal bleeding may occur—the etiology is multifactorial, intestinal polyps/dysplasia due to granulomatous inflammation surrounding eggs deposited in the bowel wall, and ulcers.

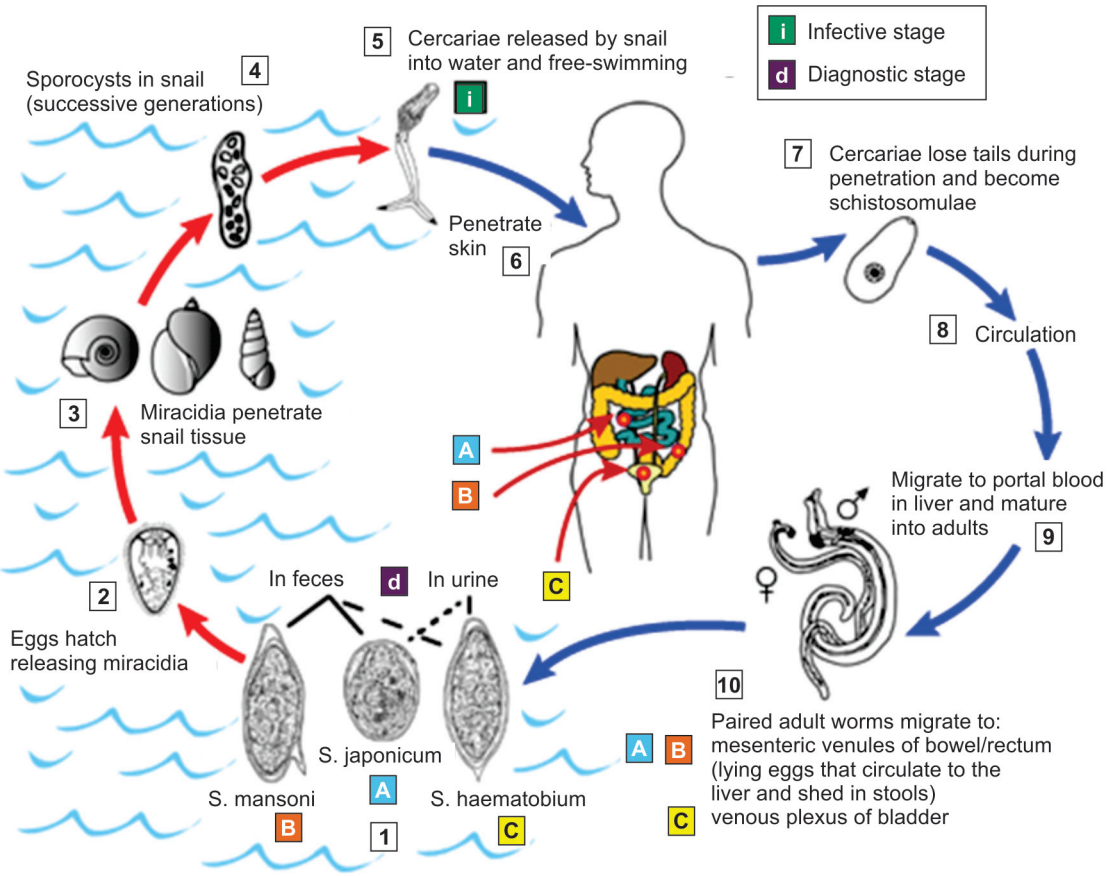

Fig. 2: Life cycle of schistosomiasis (Reproduced from: Centers for Disease Control and Prevention. DPDx: Schistosomiasis. Available at: http://www.cdc.gov/dpdx/schistosomiasis/.)

- Hepatosplenic schistosomiasis: Hepatosplenic schistosomiasis is caused by infection due to *S. mansoni*, *S. japonicum*, *S. intercalatum*, and *S. mekongi, and, occasionally, S. haematobium*.
- Among children and adolescents, the predominant pathological process consists of nonfibrotic granulomatous inflammation around trapped eggs in the presinusoidal periportal spaces of the liver. There are generally no apparent signs of liver dysfunction. At this stage, the changes are largely reversible with treatment.
- Among adults with chronic infection, the predominant pathologic process consists of collagen deposition in the periportal spaces by activated hepatic stellate cells, which causes periportal fibrosis (Symmers' pipestem fibrosis). This leads to occlusion of the portal veins, portal hypertension with splenomegaly, portocaval shunting, and gastrointestinal varices. Again, the liver function is not impaired.
- Pulmonary complications: Pulmonary manifestations of schistosomiasis occur most commonly among patients with hepatosplenic disease due to chronic infection with S. mansoni, S. japonicum, or S. haematobium. Presinusoidal portal hypertension leads to formation of portosystemic collateral vessels, through which the schistosome eggs may embolize into the pulmonary circulation, producing a granulomatous pulmonary endarteritis, with subsequent development of pulmonary hypertension and cor pulmonale. Progression of disease may be associated with cardiac enlargement and pulmonary artery dilatation. Chest radiography demonstrates fine miliary nodules, which may be confused with tuberculosis in India/endemic regions.
- Genitourinary schistosomiasis: Genitourinary schistosomiasis is caused by infection due to *S. haematobium*. It can result in infertility and increased risk for HIV transmission. Patients present with microscopic or macroscopic hematuria and/or pyuria. The schistosoma eggs provoke granulomatous inflammation, ulcerations, and development of pseudopolyps in the vesical and ureteral walls. Urinary tract lesions are largely reversible with treatment prior to the onset of fibrosis and calcification. Hydronephrosis, bladder polyps, and tumors can also form in long-standing infections. Female genital manifestations may include hypertrophic and ulcerative lesions of the vulva, vagina, and cervix and involvement of the ovaries/fallopian tubes, leading to infertility. Involvement of the epididymis, spermatic cord, and prostate occurs in males. Genital lesions in both males and females are partially reversible with treatment. Genital schistosomiasis may be an independent risk factor for an HIV infection.
- Glomerular disease: Infection due to any schistosomal species may cause glomerulopathy, leading to proteinuria and nephrotic syndrome.
- Neuroschistosomiasis: Schistosomiasis-N can involve the spinal cord (acute myelopathy) and/or the brain.

Diagnosis

Eosinophilia is observed in 30–60% of patients with acute schistosomiasis. Other hematological abnormalities seen are anemia (chronic blood loss) and thrombocytopenia (splenic sequestration in an enlarged spleen). Liver enzymes are rarely elevated, even in established hepatic fibrosis due to schistosomiasis. Hematuria and/or leukocyturia are common with S. haematobium infection.

The diagnosis of schistosomiasis requires detection of infection either by direct assays (demonstration of eggs in the stool or urine via microscopy or demonstration of schistosome antigen or DNA in the blood, urine, and/or stool) and indirect assays (demonstration of antibody in blood via serology).[11,13]

- Microscopy: Identification of schistosome eggs in a stool or urine sample via microscopy is the gold standard for the diagnosis of active schistosomiasis. Eggs of S. mansoni, S. japonicum, S. haematobium, S. mekongi, and S. intercalatum are found in stool and those of S. haematobium are mainly found in urine. The sensitivity of stool microscopy is enhanced by concentration techniques that can detect even up to 10 eggs/gm of stool. The sensitivity of urine microscopy is the highest for examination of samples collected between 10:00 am and 2:00 pm, and it can be much improved by examining the precipitate after centrifugation or filtration of urine (minimum volume 10 mL).
- Serology: Serologic tests serve as an important diagnostic tool in the absence of egg detection via microscopy, particularly for travelers, who generally have a low parasite burden. These assays become positive only after 6–12 weeks of acute infection. Available include ELISA, radioimmunoassay, indirect hemagglutination, immunofluorescent antibody test, Western blot, and complement fixation. The adult worm antigen immunofluorescent immunoglobulin (Ig)M antibody assay (AWA-IFA) is the most sensitive test used in exposed travelers but its commercial availability is limited. Most commercially produced antibody test assays are not species-specific; therefore, these assays are generally used as screening tests for schistosomal infections. In addition, antibody titers do not correlate with parasite burden. None of the tests can distinguish between active disease and previous infection. Antibodies usually persist for many months to years even after successful treatment, therefore not reliable for posttreatment follow-up.
- Antigen detection: Point-of-care antigen detection kits are commercially available and have a role useful for schistosomal eradication programs in low-endemic settings and in travelers with low parasite burden. Soluble schistosome antigen titers correlate well with infection intensity and with the clinical severity of disease. In addition, they can also be used to assess treatment efficacy as antigen assays become negative soon after successful therapy. Two gut-associated genus-specific schistosome glycoproteins, circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) [more sensitive in *S. mansoni* infections], are present in blood and excreted in urine during active infection, and detection of these water-soluble antigens indicates active infection. CAA is detectable the earliest after exposure. The detection threshold is 30 pg CAA/mL serum, which is equivalent to about 10 worm pairs. The schistosome-circulating antigen test using an up-converting phosphor reporter lateral flow chromatography is even more sensitive in urine and in serum.
- Molecular tests: PCR assays for stool, urine, and serum have been developed for the diagnosis of schistosomiasis. Its role is still limited to research.

Treatment[11-13]

It has been shown that prompt treatment of schistosomiasis reverses the acute or early chronic diseases and prevents/reverses complications associated with chronic infections (neuroschistosomiasis, hydronephrosis, and periportal fibrosis/portal hypertension). Treatment is not beneficial for reversing late-stage fibrosis of the hepatic or urinary tract or reversing secondary complications, such as esophageal varices or cor pulmonale. The primary aim of treatment is to decrease schistosoma egg production.

- Acute infection
- Swimmer's itch: The rash usually is self-limiting and clears within a few days. Treatment consists of symptomatic management for pruritus.
- Acute schistosomiasis syndrome (Katayama fever)[12]: It is a systemic hypersensitivity reaction to schistosome antigens and circulating immune complexes that occurs 3 to 8 weeks after infection. Prednisolone 20 to 40 mg daily for 5 days reduces the acute inflammation rapidly. Praziquantel is not effective against the larval stages of schistosomes and is effective only when the worms have fully matured that usually occurs 4 to 6 weeks after an acute infection.
- Chronic infection: Administration of praziquantel to patients with recent infection may induce symptoms of acute schistosomiasis within a few days of therapy. However, prolonged delay prior to administration of praziquantel (up to 12 weeks after infection) may increase the risk of the development of neuroschistosomiasis. In endemic areas, a single dose of praziquantel is curative in more than 85% of cases; retreatment of patients with residual infection further increases cure rates. Among travelers with a low parasite burden, a single dose of praziquantel is generally sufficient for reducing the worm burden.

Alternative drugs: Oxamniquine is an artemisinin derivative and has been recommended to be used for the treatment of refractory diseases. It acts on the glucose metabolism of immature schistosomes and has shown some potential if used very early into an infection. Mefloquine is another alternative drug but has limited action on mature worms.

Follow-up

This includes monitoring of clinical manifestations, eosinophil count (in patients with initial eosinophilia), and microscopic evaluation for eggs in stool or urine (after 6 weeks–6 months of treatment). Serology is not a useful monitoring tool as it remains positive for prolonged periods following treatment.

Special Situations

- Reinfection/persistent infection: It is defined as the presence of viable eggs 6–12 weeks after initial therapy. This warrants repeat treatment with praziquantel. The same dose of praziquantel may be used for reinfection. Genitourinary schistosomiasis: Early treatment with praziquantel substantially reduces HIV incidence and female infertility.

Table 5: Treatment[9]

Gambiense HAT			
Patients <6 years or <20 kg	CSF ≤ 5 cells/μL no trypanosomes	Pentamidine 4 mg/kg/day	IM or IV for 7 days
	CSF >5 cells/μL and/or trypanosomes ++ or lumbar puncture CI	NE combination therapy—nifurtimox 15 mg/kg +	Orally in three doses for 10 days
		eflornithine 400 mg/kg/day	IV over 2 hours for 7 days
Patients ≥6 years and ≥20 kg	CSF <100 cells/μL	Fexinidazole	For 10 days
	CSF ≥100 cells/μL, or if lumbar puncture CI	NE combination therapy	
Rhodesiense HAT			
	Empirical	Suramin 4–5 mg/kg	IV day 1
	First-stage disease	Suramin 4–5 mg/kg, alternately pentamidine/melarsoprol	IV day 1 followed by 20 mg/kg (max 1 gm) IV weekly five inj.
	Second-stage disease	Melarsoprol 2.2 mg/kg/day (max 180 mg/day)	IV for 10 days
		plus prednisolone 1 mg/kg/day (max 50 mg)	po for 10 days, taper every 3 days 25%

Table 6: Dosage

Praziquantel		
	S. haematobium, S. mansoni, or S. intercalatum	40 mg/kg, two divided doses
	S. japonicum or S. mekongi	60 mg/kg, two divided doses

- Hepatosplenic schistosomiasis: Treatment options include surgical portosystemic shunt or esophagogastric devascularization with splenectomy.
- Neuroschistosomiasis: Praziquantel with corticosteroids (prednisone 1–2 mg/kg) is essential to prevent the intense inflammatory response to treatment. The steroids prevent tissue damage that may occur as a result of inflammation. Steroids should be continued for 2 weeks to 6 months and should always be tailored to individual circumstances. Initiation of treatment with praziquantel can cause paradoxical worsening of neurologic symptoms and should always be administered a few days/a week after initiation of corticosteroid treatment.

Prevention

Schistosomiasis control strategies for endemic areas include water sanitation programs, mass treatment, and vaccine development. Minimizing contact with freshwater containing infectious cercarial larvae is an important control measure. Direct contact with freshwater can be reduced by the provision of safe water supplies with proper sewage control as well as community education regarding wearing protective clothing and footwear in the setting of freshwater contact. Other measures may include vigorous toweling of exposed skin and/or applying insect repellent DEET (N,N-diethyl-m-toluamide) after exposure to freshwater. Annual mass treatment with praziquantel in endemic regions has shown some potential.[14] Praziquantel is administered as 40 mg/kg orally once in adults and children ≥4 years. There is no effective vaccine against schistosomiasis.

Take-home Message

A variety of infections may be possible in a returning traveler, and the etiology would vary depending on the geographic area traveled to. A variety of host factors and environmental conditions along with "host-vector-parasite" interaction would decide the clinical presentation. Since some acute or chronic clinical manifestations would overlap with the commonly occurring diseases in the "host" country, these should always be kept in mind while evaluating a returning traveler for exotic illnesses. One should never forget the dictum, "Uncommon clinical manifestations of common diseases are far more common than the common manifestations of uncommon diseases. Routine investigations do provide some clues but specific tests/investigations may be needed to evaluate illnesses in returning traveller."

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