Gastrointestinal Complications of Schistosomiasis

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Current Gastroenterology Reports 2001, **3**:293–303
Current Science Inc. ISSN 1522-8037

Schistosomiasis is an important disease in many parts of the world and has affected the course of human history many times over. The parasitic infection is acquired during contact with infected water. A chronic inflammatory response to schistosome eggs, mediated by both cellular and humoral mechanisms, is the root of the pathology seen in schistosomiasis. Hepatosplenic disease results in intrahepatic presinusoidal portal hypertension. The resultant esophageal and gastric varices are an important cause of morbidity and mortality. Standard treatment guidelines for managing varices can be applied to patients with schistosomiasis. Coinfection with viral hepatitis results in liver disease that progresses more rapidly and is more difficult to treat. Intestinal schistosomiasis may be confused with other disease states and can be an important cause of morbidity, especially in heavily infected patients. Diagnosis relies on demonstration of schistosome eggs in feces or tissue. Praziquantel is the treatment of choice. The development of a vaccine for schistosomiasis is an important goal in the attempt to control this disease.

Introduction

Schistosomiasis is a common disease of the tropical world, affecting an estimated 200 million or more individuals and causing an estimated 500,000 deaths every year. The disease has been described in humans for several millennia. Its current increased prevalence in many areas has numerous causes, including increased irrigation in areas with inadequate waste disposal and breakdown in public health infrastructure. The most common significant clinical effects of infection of two of the three important species infecting humans are intestinal and hepatic manifestations, which can result in serious illness or death.

History

Schistosome eggs have been identified in both Egyptian and Chinese mummies from antiquity [1]. The presence of hematuria, presumably as a result of *Schistosoma hematobium* infection, is noted repeatedly in Egyptian pharaonic writing [2], and schistosomiasis has been noted historically in other Middle Eastern cultures and in China. The disease affected many of Napoleon's troops during his campaign to conquer Egypt..

The causative organism was not identified until 1851 by Bilharz, who discovered the trematode during an autopsy at the Kasr-El-Ani Hospital in Cairo, Egypt. Although Manson speculated that the urinary and intestinal forms of schistosomiasis might be caused by two distinct species, it was not until 1907 that *S. mansoni* was identified as a separate species. In Japan, the illness of acute schistosomiasis, Katayama fever, was described in detail for the first time in 1847, and the causative pathogen, *S. japonicum*, was identified in 1904 by Katsurada.

The schistosome had a more recent impact on the history of Taiwan [3,4]. The People's Republic of China (PRC) had assembled an invasion force in 1950 to overcome the recently established nationalist Chinese in Taiwan. Because amphibious landing craft were not in adequate supply, most PRC soldiers needed to be able to swim during the anticipated invasion. Swimming instruction was given in canals in Chekiang and Fukien, areas endemic for *S. japonicum*. An estimated 30,000 to 50,000 cases of Katayama fever developed among the PRC forces, aborting the invasion plans. By the time the invasion force had regained collective strength, the Korean War and the presence of the US Seventh Fleet deterred further invasion plans. Because of these circumstances, the schistosome has been credited with "saving" Taiwan.

Epidemiology

Three main *Schistosoma* species cause disease in humans: *S. mansoni*, *S. haematobium*, and *S. japonicum* (Table 1). Additionally, a number of other species that are less widely distributed can infect humans. Schistosomiasis from all species is confined to tropical areas between the latitudes of 36° North and South. The distribution of the parasite is absolutely dependent on the distribution of the intermediate snail host, which lives in muddy banks of slow-moving fresh water sources. People may become infected when their skin is exposed to infested fresh water. However, the risk of infection may vary with the season, time of day, nature of exposure, and microclimate, as well as host factors. Therefore, the distribution of disease tends to be focal and irregular. Even

Table 1. Epidemiology of the main schistosome pathogens

	S. mansoni	*S. haematobium*	*S. japonicum*	*S. intercalatum*	*S. mekongi*
Distribution	Africa, Middle East, Caribbean, South America	Africa, Middle East, India	China, Philippines, Southeast Asia	Africa	Cambodia, Laos (Mekong River Basin)
Intermediate snail host	Biomphalaria	Bulinus	Oncomelania	Bulinus	Neotricula
Reservoir	Humans (main reservoir), rodents, baboons, insectivores	Humans	Humans, water buffalo, cattle, dogs, cats, pigs, and many others	Humans, rodents	Humans, dogs
Egg morphology	Oval egg with lateral spine	Oval egg with terminal spine	Round/oval egg with small lateral spine	Oval egg (Ziehl-Nielsen positive) with terminal spine	Round/oval smaller egg with small lateral spine
Disease predilection	Intestinal and liver	Urinary tract	Intestinal and liver	Intestinal	Intestinal and liver

From Bica *et al.* [24]; with permission.

within an endemic area, the burden of disease is not uniform. Children tend to be exposed more intensely to infection because of recreational water activities and are likely to expose a greater surface area to contaminated water. Peak intensity of infection is between the ages of 8 and 12 years in highly endemic areas and somewhat later in areas that are less endemic [5]. Adults tend to have lower prevalence and burden of disease. Epidemiologic studies, most notably chemotherapy/reacquisition studies, also point to an age-related acquired immunity to the parasite [6].

Disease within an infected area is related to the level of exposure, with more intense exposure related to greater prevalence of disease. Subtle signs of infection, such as anemia, fatigue, diarrhea, or hematuria, may be fairly common in a community, whereas severe illness may be present in as few as 10% of individuals in even the most heavily infected areas.

Humans are the only maintenance hosts for *S. haematobium*, and in most cases the important host for *S. mansoni*, although rodents and primates play a significant role in sustaining the life cycle in some areas. A number of mammals, including water buffalo, are natural reservoirs for *S. japonicum*.

Schistosomiasis is considered largely a disease of poor rural areas, and control efforts have not yet managed to show an impact in some of the most highly infected areas. The disease is spreading in some urban areas as well. Causes include irrigation efforts (which not only create new habitats for the snail intermediate host but also provide more water contact for residents), breakdown of public health infrastructure, and mass migration of infected populations to previously uninfected areas [7].

Natural History

The *Schistosoma* parasite requires both an intermediate host (snail) and a definitive host (human) (Fig. 1). When an egg passes into fresh water, a miracidium hatches. The miracidium is ciliated, and it searches for a suitable snail intermediate host. If the miracidium is successful in infecting a snail, the next stage of the organism develops (mother sporocyst). From germinal cells of this mother sporocyst grow daughter sporocysts, which in turn produce cercariae. The cercariae emerge directly from the snail into the water and swim about in hope of locating a suitable host. The cercariae cannot survive for more than 72 hours after emerging from the snail. If the cercaria locates a host, it attaches and penetrates the intact skin, shedding its tail in the process. The organism, now called a schistosomula, travels in the venous bloodstream to the lungs, where it squeezes through the pulmonary capillaries to enter the arterial bloodstream. After mating permanently, the worm pair eventually settles in its location of choice.

The preferred anatomic location varies by species and can change over the life of the worm: *S. mansoni* prefers the inferior mesenteric venules; *S. japonicum* the superior and inferior mesenteric venules; *S. mekongi* the superior mesenteric venules; and *S. hematobium* the plexi of the urinary bladder (Table 1). The eggs are deposited into the vascular lumen. Using irritative and digestive compounds, about half of the ova are able to penetrate through the wall of the blood vessel directly into the bowel or bladder. The rest of the eggs are carried to the liver (*S. mansoni* and *S. japonicum*) or the lungs (*S. haematobium* and others in advanced disease), where they are filtered from the circulation. The rates of egg deposition vary by species: *S. japonicum*, 500 to 3500/d; *S. mansoni*, 100 to 300/d; and *S. haematobium*, 20 to 200/d.

S. mekongi, *S. malayi*, *S. intercalatum*, and other species are also important pathogens, although they are limited in geographic distribution. The presentation of *S. malayi* and *S. mekongi*, which may cause severe disease, should be considered clinically analogous to that of *S. japonicum*

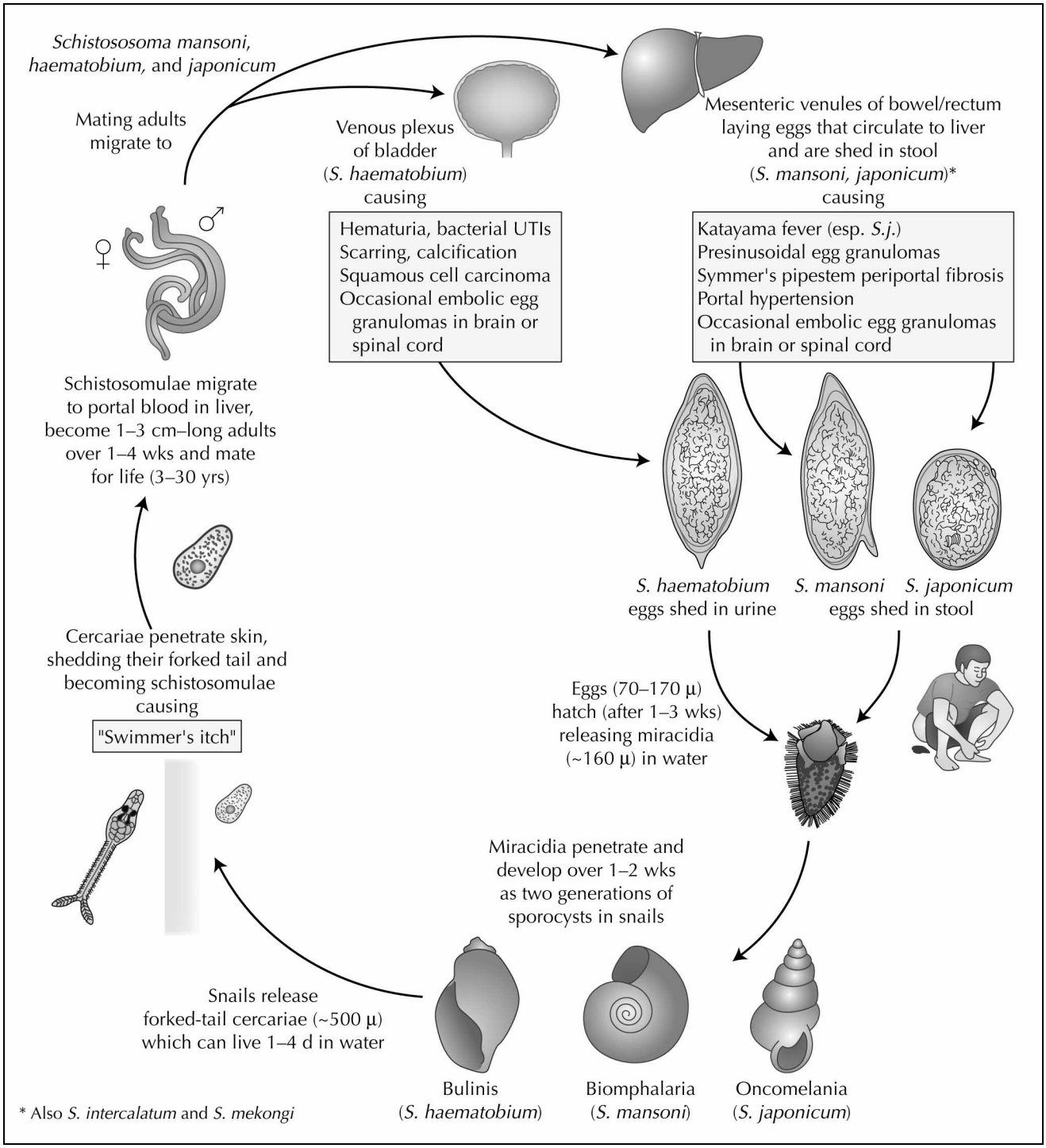

Figure 1. Life cycle of the important human *Schistosoma* species. *From* Melvin *et al*. [82].

infection. *S. intercalatum* infection causes mostly intestinal symptoms such as rectal bleeding and diarrhea.

Pathology/Pathogenesis

The disease in schistosomiasis is a result of host response to the worm at some point in its life cycle. The host may develop a response during the skin penetration phase, the pulmonary migration phase, the initial egg deposition, or the chronic egg deposition. The latter instance is responsible for virtually all the significant morbidity and mortality of schistosomiasis.

The exuberant inflammatory response to the schistosome eggs results in lesions composed of T cells and other inflammatory cells. These lesions progress to form granulomas made of T- and B-lymphocytes and large monocytes. Ultimately, non-caseating granulomas form [8,9].

The initial response by the host appears to require CD^{4+} cells; animals depleted of these cells are not able to form granulomas [10]. The CD4 response is initially a T-helper cell type 1 (Th1) response, with production of interleukin-12 (IL-12), interferon-gamma (IFN-γ), and IL-2 [11•]. The immune response may shift to a T-helper cell type 2 (Th2) response with production of transforming growth factor-beta (TGF-β) and IL-10, both of which appear to be beneficial in limiting disease. The Th2-type response has been noted in humans to be more closely associated with the "intestinal" form of *S. mansoni*, whereas the Th1-type response has been associated with the more debilitating "hepatosplenic" form of disease [11•]. Similarly, mice that are unable to mount a TGF-β response are noted to develop extensive hepatic fibrosis [12].

The phenomenon of immunomodulation, which manifests as a reduction in the size and change in composition of the granulomas coincident with gross changes such as reduction in portal vein inflammation and vascular obstruction, may be a result of the transition from a Th1 to a Th2 response [11•]. In addition, a segment of the human genome, 5q31-33, has been associated with resistance to infection with schistosomiasis [13••]. This chromosome segment seems to be associated with the Th2 immune response.

Humoral responses are also important in pathogenesis. Antibodies to soluble egg antigen (SEA) are vigorous in acute infection, whereas, in chronic infection, those with lower antibody responses to SEA have less pathology [14]. Elevated serum IgE levels also seem to protect against reinfection in endemic areas [15]. Furthermore, sera from chronically infected humans slows egg maturation and modulates granuloma development in mice [16]. TGF-β expression in mice is also associated with degree of fibrosis [17].

Clinical Syndromes

Schistosomiasis has many pulmonary, neurologic, renal, genital, and other manifestations that are beyond the scope of this review. One should note, however, that various *Salmonella* species and other enteric bacteria can cause a chronic bacteremia in individuals with schistosomiasis and result in an indolent presentation. A number of common clinical syndromes are described in the following sections.

Cercarial dermatitis

Entry of cercariae into the skin can result in a typical eruption known as "swimmer's itch." This dermatitis can be caused by human or non-human cercariae and has little intrinsic clinical significance. However, the history of such a rash provides important information to clinicians attempting to make a diagnosis of schistosomiasis in a returning traveler. The dermatitis is self-limited and generally responds to topical steroids.

Katayama fever

The syndrome of acute schistosomiasis, known as Katayama fever, occurs in previously uninfected individuals. Katayama fever is named for a district in Japan, which harbored a high prevalence for *S. japonicum*. Visitors from other parts of Japan often became ill, sometimes severely. Katayama fever is now known to occur in *S. japonicum*, *S. mansoni*, and *S. haematobium* infections and occurs most commonly in those with heavy exposure, although it may occur in lightly infected people as well. Fever, headache, myalgias, diarrhea and loss of appetite characterize the illness. Marked eosinophilia is common. Katayama fever is usually self-limited, lasting 2 to 3 weeks. Rarely, the illness is life threatening.

Hepatosplenic schistosomiasis

Most of the chronic pathology from schistosomiasis results from fibrosis. The most important cause of chronic morbidity from schistosomiasis is portal hypertension, which occurs in 5% to 10% of patients [18]. Most fibrosis occurs around the intrahepatic portal veins and results from excess deposition of type I and type III collagen. The host immune response to the eggs, as described earlier, results in granulomatous fibrosis surrounding the intrahepatic portal vasculature. Eventually, the scarring causes fibrotic restriction of portal flow and intrahepatic presinusoidal portal hypertension. Fibrosis in early schistosomiasis is largely reversible, whereas that of chronic disease may be permanent. No significant impact on end-stage fibrosis is noted with eradication of the parasite.

Symmers [19] first described the gross appearance of schistosomal periportal fibrosis in 1904. He observed that "the cut surface of the liver looks as if a number of white clay-pipe stems had been thrust at various angles through the organ." This pattern of periportal fibrosis is now known as Symmers' pipestem fibrosis. Computed tomography (CT) may show the classic "turtle-back" pattern of scar distribution because of the resemblance to the scutes on the dorsal shell of turtles (Fig. 2).

Ultrasound has become important for staging and monitoring of liver disease in schistosomiasis. Numerous ultrasound staging systems have been developed to evaluate the extent and severity of periportal fibrosis. The Cairo classification is the most widely used [20]. Recent modifications to this scheme have been proposed to broaden applicability and improve reliability, especially in children, and to allow for differences in available ultrasound equipment [21•]. Correlation between ultrasound and histologic findings is satisfactory unless concomitant cirrhosis from other causes is present [22]. Recently, serum markers associated with fibrosis have been evaluated for noninvasive monitoring of liver fibrosis activity [23].

Schistosomal periportal hepatic fibrosis alone does not result in hepatocellular dysfunction. A compensatory increase in hepatic artery blood flow preserves oxygen delivery and thereby minimizes direct hepatocyte damage.

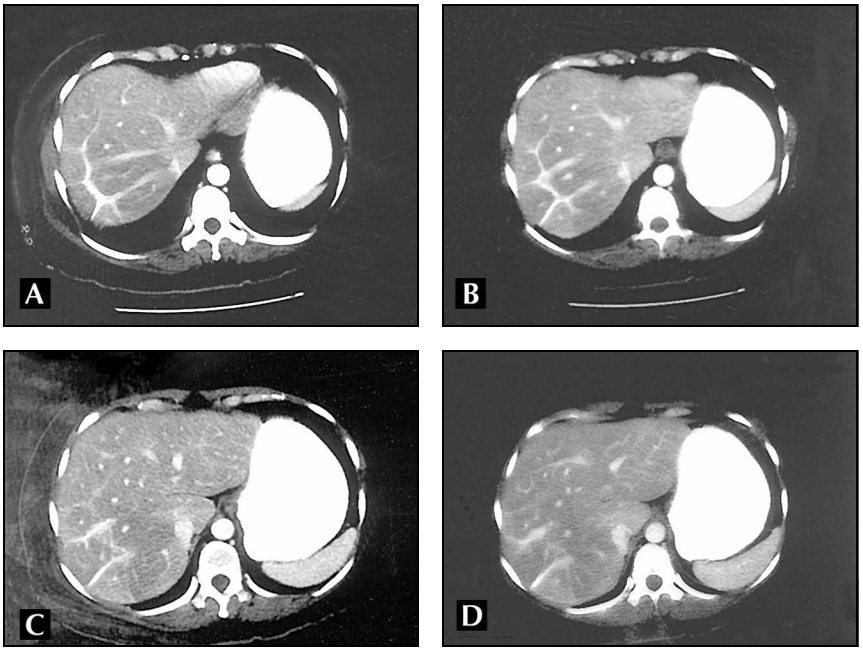

Figure 2. CT scan from a patient with hepatic schistosomiasis showing the "turtle-back" distribution of periportal fibrosis.

Thus, in the absence of other disease states leading to cirrhosis there are no peripheral stigmata of chronic liver disease. Palmar erythema, gynecomastia, testicular atrophy, spider angioma, and jaundice do not develop.

Patients suffering from hepatosplenic schistosomiasis typically have normal serum aminotransferase levels with mild increases in alkaline phosphatase and serum IgG [24]. Evidence of hypersplenism, especially in the form of thrombocytopenia, is common [18].

Physical examination classically reveals left-lobe hepatomegaly and moderate splenomegaly. The right hepatic lobe is often atrophic. Late disease is manifested as hepatic atrophy and marked splenomegaly with substantial ascites and peripheral muscle wasting.

Varices

Hemodynamic studies of schistosomiasis patients demonstrate hyperdynamic systemic and splanchnic blood flow [25]. Furthermore, patients who develop portal hypertension frequently develop impressive portosystemic collateral blood flow, most often in the form of esophageal and/or gastric varices.

Esophageal varices and subsequent hemorrhage are the most common serious complications of schistosome-induced portal hypertension [26]. Although these patients tend to fare better than cirrhotic patients with variceal bleeding, mortality is still high.

Bleeding prophylaxis with nonspecific beta blockers has been studied in schistosomiasis patients with varices. Based on a classic study and other investigations of non-schistosomiasis patients, these drugs are recommended for prevention of first variceal bleed [27,28]. Furthermore, when possible, these agents should be used as adjunctive treatment for patients who have already had an index bleed.

Band ligation is widely recognized as the treatment of choice and standard of care for elective treatment of bleeding esophageal varices. The applicability of this standard to the discrete subset of patients with schistosomal portal hypertension can be questioned because most studies of variceal bleeding are done in regions where schistosomiasis is not an important cause of esophageal varices. However, based on small studies of patients with either "pure" schistosomal intrahepatic presinusoidal portal hypertension or those with mixed schistosomiasis and cirrhosis (mostly viral), treatment for variceal bleeding seems to be applicable to patients with schistosomiasis. Specifically, endoscopic band ligation [29] and endoscopic sclerotherapy [30] achieve good rates of hemostasis with lower complication rates than in patients with other causes of portal hypertension. Relative efficacy is consistent with larger studies in other groups.

A subset of patients with esophageal varices develops gastric fundal varices. Band ligation and injection sclerotherapy are less effective for bleeding from gastric varices caused by cirrhosis. However, results from one small study (n=20) of injection sclerotherapy suggest that this modality is an effective bridge to surgery for bleeding gastric varices in patients with schistosomiasis [31].

A study of cyanoacrylate injection in 80 schistosomiasis patients with bleeding esophageal and gastric varices produced a short-term hemostasis rate of 95%, with one treatment-related death. Overall mortality was 7.5% [32•]. This method uses *N*-butyl-cyanoacrylate mixed with iodized oil. The mixture is injected directly into the lumen of the varix, where it polymerizes and hardens almost instantly, thus occluding and sclerosing the vessel. Cyanoacrylate injection for hemostasis in variceal bleeding is not approved for use in the United States.

Surgical treatment for control of variceal bleeding includes various methods of portosystemic shunting such as the distal splenorenal shunt. Devascularization procedures are another surgical option. The more common of these—the gastroesophageal decongestion and splenectomy (GEDS)—is a manual ligation of collateral flow with splenectomy [33]. Generally, surgical methods have the advantage of long-term reduction in recurrent bleeding with minimal long-term morbidity [34,35].

The transjugular intrahepatic portosystemic shunt (TIPS) is one method that appears to be less effective in patients with schistosomiasis than in other patients with portal hypertension [36]. Extrapolating from studies of non-schistosomiasis patients, stent patency diminishes over time [37]. Higher rates of stent occlusion in schistosomiasis patients can be expected because the underlying hepatic parenchyma is normal. These patients therefore have greater longevity along with normal foreign body and healing responses.

Aside from TIPS, studies of treatments for non-schistosomal variceal hemorrhage can be extrapolated to patients with schistosomiasis. From a therapeutic point of view, it seems clear that the cause of the variceal bleeding, whether from schistosomal portal hypertension or another etiology, is not important. Practitioners can be reassured that interventions to treat variceal bleeding in the setting of schistosomiasis are likely to be at least as successful (if not more so) as they would be in patients with other causes of portal hypertension. These results are not unexpected, given the normal hepatic function in schistosomiasis. Therefore, current guidelines for managing the serious complication of portal hypertensive bleeding are appropriate in the setting of schistosomiasis [38••]. Of course, eradication of the parasite is also crucial.

Comorbid liver disease and schistosomiasis

Hepatitis C virus (HCV) infection is hyperendemic in Egypt, where schistosomiasis is also very common. HCV prevalence is reported at 10% to 20% in Egyptian volunteer blood donors [39]. The rate of HCV seroprevalence exceeds 50% in the subgroup of patients aged 40 to 67 years. These authors also found a rate of antischistosomal antibodies of 89% in the same age group [40]. Hepatitis B virus (HBV) infection is also very common in Egypt, approaching a prevalence of 60% in some age groups [40,41]. Overall seroprevalence of HBV in Egypt of about 40% is reported, demonstrating the importance of this infection [42].

The situation in Egypt is unique, with an extremely high rate of HCV infection directly related to well-intentioned schistosome control efforts. Beginning in the 1920s and continuing until the mid-1980s, massive efforts were made to control schistosomiasis using parenteral drugs such as potassium antimony tartrate. The re-use of injection equipment during the antischistosome campaigns directly spread HCV and possibly HBV [43••]. In other countries where schistosomiasis is common, such as Brazil, the rates of HCV are substantially lower: between 1.2% and 4.6% [44]. Thus, the Egyptian population provides an unfortunate opportunity to evaluate the impact of combined infection with schistosomiasis and chronic viral hepatitis.

The implications of coinfection with schistosomiasis and chronic viral hepatitis are important. Patients with schistosomiasis have a relative risk of 5.22 (95% CI 2.93 to 9.31) for developing hepatocellular carcinoma (HCC) [45•]. HCV and HBV are also substantial risk factors for the subsequent development of HCC. Thus, the combined effects of schistosomiasis and chronic viral hepatitis, with significant overlap in worldwide distribution, are relevant both to individual patients and to public health.

In a small study, Kamal *et al.* [46•] found that patients coinfected with schistosomiasis had higher HCV viral titers, higher histologic activity index scores, and less likelihood of achieving sustained response to anti-HCV therapy when compared with patients who had HCV alone. They propose that the mechanism is the known effect of schistosomiasis in downregulating the Th1 response [47] and conclude that coinfection with schistosomiasis results in HCV that progresses faster and is more resistant to treatment than in HCV alone. Whether combination therapy with IFN-α2b and ribavirin will be successful in this group of patients remains to be seen.

No recommendations about treatment in coinfected individuals have appeared in published reports. However, given that schistosomiasis results in poorer response to antiviral therapy, it seems reasonable to treat schistosomiasis first in coinfected patients before embarking on antiviral therapy. The importance of preventing reinfection with schistosomiasis, especially during treatment for viral hepatitis, should be obvious. Furthermore, vaccination against HBV in nonimmune individuals is vital in controlling this risk factor.

Intestinal schistosomiasis

The preferred home of *S. mansoni*, *S. japonicum*, and the less commonly encountered *S. intercalatum* and *S. mekongi*, is the venous splanchnic vasculature. As noted earlier, the flukes will selectively inhabit certain vessels and their branches (Table 1). As the adult worms move through the vessels, the female lays numerous eggs, again the root of pathology in this disease. The eggs produce a local inflammatory response, which can be massive. To complete the life cycle, some of the eggs eventually penetrate into the lumen of the bowel, where they are shed in the feces. Some of the eggs, however, remain trapped within intestinal tissue and cause intestinal pathology (Fig. 3).

As expected, there is a wide spectrum of presentation in intestinal schistosomiasis relative to location of egg deposition, intensity of infection, and host factors in response to infection. Acute symptoms are often nonspecific and can include bloody mucoid diarrhea, tenesmus, abdominal pain, bowel obstruction, fever, and weight loss [48]. The differential diagnosis is broad (Table 2).

Chronic infection leads to granulomatous polyp formation, which can be extensive [49]. Large, mass-like

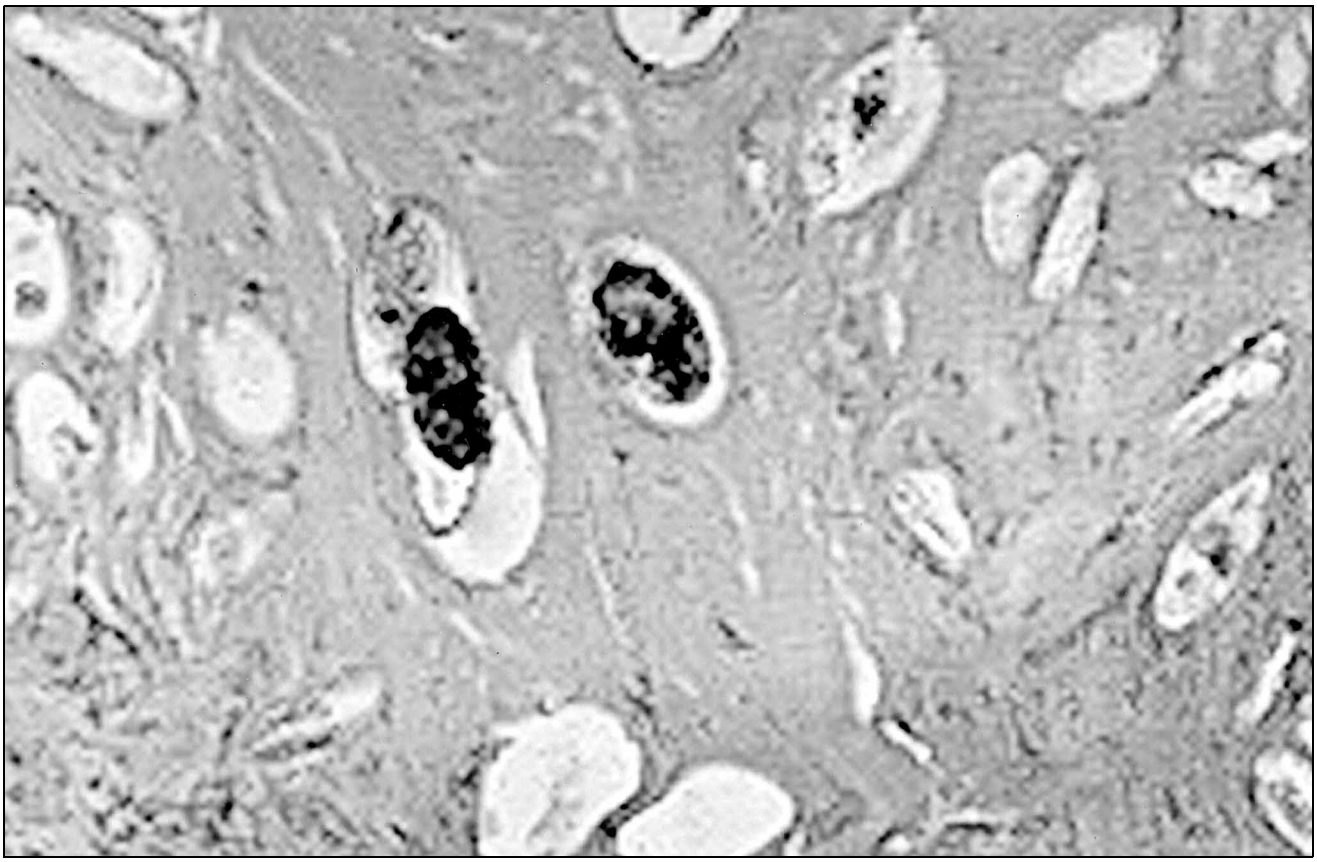

Figure 3. Endoscopic biopsy specimen of a polyp discovered in a patient on routine colonoscopy. Note the *Schistosoma japonicum* eggs surrounded by fibrous tissue.

lesions called bilharziomas can cause intestinal obstruction [50] or be confused with malignancy [51,52]. Histopathologic examination reveals the characteristic schistosome eggs within the inflammatory mass.

A more common finding in intestinal disease is diffuse polyposis, present in up to 20% of cases [53]. The polyps are inflammatory in nature (not adenomatous) and can lead to chronic gastrointestinal blood and protein loss. The resultant anemia and hypoalbuminemia are often clinically significant. Treatment with antischistosomal medications can reduce the density and number of polyps [54,55]. Endoscopic polypectomy can be pursued in cases of residual polyps. Elimination of polyps has been shown to dramatically improve anemia and hypoalbuminemia [56].

Fibrotic strictures [57], fistulas [58,59], bowel perforation [60–62], and other consequences of chronic bowel inflammation in schistosomiasis have been reported [63,64] but are less common than polyposis. These disease manifestations usually require surgical treatment, obviously in concert with antischistosomal chemotherapy.

Diagnosis

For physicians practicing in areas where schistosomiasis is rarely encountered, the key diagnostic hurdle is suspicion of the disease. Schistosomiasis should be considered in the differential diagnosis for patients presenting with any of the aforementioned clinical entities when potential exposure has occurred. A history of contact with fresh water in endemic areas is required, and a recollection of swimmer's itch may provide an important clue to the diagnosis of schistosomiasis.

The traditional diagnosis of schistosomiasis depends on the identification of ova in the stool or urine. The Kato–Katz method of preparation is the most widely accepted, using a 25-mg or 50-mg stool sample [65]. Because of the inconstant nature of egg shedding, the sensitivity of a single test is poor. With tests repeated daily for 3 days, sensitivity improves to 90% [66]. The Kato–Katz method also allows quantification of the egg count per volume of feces, which in turn correlates to worm burden and severity of infection. However, the technique appears to be less sensitive in *S. japonicum* infection [67]. Also, particularly in lighter infections, it is possible to have multiple negative stool studies in the setting of schistosomiasis. Another means of obtaining eggs is through endoscopic colon or rectal biopsy, which has superior sensitivity compared with stool studies if multiple biopsies are obtained [68].

Serologic study has become useful for diagnosis of schistosomiasis, and both circulating antigen and antibody tests are available. Antibody testing is only marginally useful for residents of schistosomiasis-endemic areas,

Table 2. Diseases presenting similarly to intestinal schistosomiasis

Tuberculosis
Infectious dysentery
Shigellosis
Salmonellosis
Entamoeba histolytica infection
EHEC
EIEC
Campylobacteriosis
Clostridium difficile infection
Trichuris trichuria infection
Hookworm
Malaria
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Gastrointestinal lymphoma
Colorectal adenocarcinoma

EHEC—enterohemorrhagic *E. coli*; EIEC—enteroinvasive *E. coli*.

because the antibody persists for years after infection and cannot distinguish between light and heavy infection. However, antibody testing may be used in travelers returning to areas where schistosomiasis is not present, or for hosts that would be expected to have no antibody to *Schistosoma* antigens.

The antibody tests have shown variable rates of sensitivity and specificity, according to the antigens used, but the commonly used immunofluorescent antibody test (IFAT) has good sensitivity for acute infection in travelers. Currently, the US Centers for Disease Control (CDC) performs a Falcon assay screening test enzyme-linked immunoassay (FAST-ELISA) using adult worm antigens, also with excellent sensitivity and specificity in acute infection [69].

Antigen testing, developed over the past several decades, is gaining acceptance as a reliable diagnostic technique for both chronic and acute infections. The most accepted antigen tests are the circulating anodic antigen (CAA) and the circulating cathodic antigen (CCA). These antigens are detectable by ELISA, very stable, genus specific, and correlated to worm burden [70••]. The sensitivity of these tests in combination is between 65% and 100%, depending on the burden of infection and thoroughness of the parasitologic evaluation. The test becomes rapidly negative after treatment. The SEA is another useful worm antigen test because egg antigen may persist in the serum for a longer period of time following therapy [71].

Treatment of Infection

Three drugs are available for treatment of schistosomiasis: praziquantel, oxamniquine, and metrifonate, although metrifonate is no longer manufactured and is difficult to acquire. Praziquantel is the drug of choice for all *Schistosoma* species infections, with once-daily dosing. Metrifonate can only be used for *S. haematobium* infections because the response to the other pathogens is not predictable [72].

Praziquantel has rapid activity against adult worms with changes in the tegument and muscular activity, possibly resulting from calcium ion flux within the worm [73]. The drug may cause paralysis of the worm with dislodgment. Also important may be exposure of previously "hidden" worm antigens to which the host might respond. In animal models, hosts depleted of CD4 cells were unable to clear infection when praziquantel was administered, implying that the host response is important to the drug activity [74]. However, the true mechanism of action remains unknown.

The dose of praziquantel for *S. haematobium* and *S. mansoni* infections is generally 40 mg/kg once daily, and for *S. japonicum* it is 60 mg/kg/d usually divided into two doses. The medication is generally well tolerated, with neurologic side effects most common, including dizziness, headache, and malaise occurring in up to 90% of patients. Gastrointestinal side effects are also very common and include nausea, vomiting, and abdominal discomfort [75].

Oxamniquine is useful for *S. mansoni* infections, although its mode of action is not well understood. There is some evidence that oxamniquine may cause genome damage to the worm, but there is no evidence of mutagenicity to humans [72]. The drug is more effective in South America, the Caribbean, and West Africa than in other areas, such as North Africa, where a much higher dosage may be required. A single dose of 15 mg/kg/d is generally used in sensitive strains, with typical neurologic side effects of drowsiness, headache, and dizziness occurring in about 30% to 50% of patients [73]. Nausea, orange discoloration of the urine, and occasional fever (possibly caused by host response to release of worm antigen) are also reported [76]. Community treatment with this compound has been well tolerated and effective.

The success of therapy for schistosomiasis seems to be related to the burden of disease, and it is clear that some strains are resistant to chemotherapeutic agents. However, resistance to praziquantel does not seem to confer resistance to oxamniquine, and vice versa. Also, a recent study suggests that resistance to praziquantel does not appear to be rapidly increasing despite widespread control efforts using this drug [77].

Future Research

Although mass chemotherapy with praziquantel has demonstrated value in control efforts, concern remains that rapid reinfection in areas of high prevalence will require more sustained and durable effects. A vaccine against schistosomiasis has been a focus of research for several decades.

A number of promising vaccine modalities have been explored, including native and recombinant peptide vaccines, DNA vaccines, cytokine-modulating vaccines and irradiated products [78–81]. Six candidate vaccines

have shown some promise in animal models: Sm28GST (glutathione-*S*-transferase), Sm97 (paramyosin), IrV-5 (irradiation-associated vaccine antigen), TPI (triose-phosphate isomerase), Sm23, and Sm14 (fatty acid binding protein). Any schistosome vaccine faces substantial barriers prior to implementation in humans.

Conclusions

Schistosomiasis remains an important disease in many parts of the world. With international travel increasing, physicians from all corners of the globe need to keep a high index of suspicion for this parasitic infection. Recognizing and treating the consequences of chronic infection, especially hepatosplenic disease, is crucial.

Developments in immunology and advances in our understanding of the complex inflammatory response to *Schistosoma* infection demonstrate how much work remains toward development of a vaccine. Parallel work in public health and sanitation, ecology, and pharmacology are needed if there is to be any hope of controlling or eliminating schistosomiasis.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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