122 Schistosomiasis

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Key features

- Schistosomiasis is caused by several species of blood flukes, with the three most important being *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum*
- Infection is focally widespread in most of Africa, Southeast Asia and large parts of South America. Two hundred million people are estimated to be infected; 85% of them live in sub-Saharan Africa. In countries where praziquantel therapy has been widely used, the burden of schistosomiasis is a fraction of what it was 30 years ago
- The lifecycle requires a snail intermediate host that is specific to each parasite species
- Schistosome ova that are deposited in surface water with stools or urine release primary larvae (miracidiae) that infect the snails and develop into free living secondary larvae (cercariae). Humans are infected when cercariae penetrate the skin during exposure to water
- In endemic areas, large proportions of the population can be infected, especially children. Many infections result only in vague, nonspecific or hidden morbidity
- The disease has both acute and chronic phases. Acute schistosomiasis (Katayama fever) occurs a few weeks after exposure and is caused by the body's reaction to developing larvae (schistosomula) migrating through the body. Chronic schistosomiasis occurs after years of infection and is primarily caused by cellular immunity and fibrosis as a reaction to ova retained in the tissues. Ectopic lesions may cause neurologic, pulmonary or genital schistosomiasis
- *Schistosoma mansoni* and *S. japonicum* primarily cause intestinal and hepatic pathology; *S. haematobium* primarily damages the urinary tract
- Diagnosis is based on microscopic detection of ova, serology or imaging
- Praziquantel provides safe, inexpensive and effective oral therapy. Extensive mass drug administration programs have, over the past 20 years, reduced morbidity and transmission in many countries

INTRODUCTION

Schistosomiasis is caused by trematodes (fluke worms) of the genus *Schistosoma* (Phylum Platyhelminthes, Class Trematoda) that live in blood vessels [1–3]. Humans become infected when infectious motile cercariae penetrate the skin during freshwater contact. Three main species infect humans. *Schistosoma mansoni* (Africa, Arabia and South America) and *S. japonicum* (China and the Philippines) causes intestinal and hepatosplenic schistosomiasis. *Schistosoma haematobium* causes urinary tract schistosomiasis in Africa and Arabia. *Schistosoma intercalatum* is only of local importance in some pockets in West and Central Africa, *Schistosoma mekongi* in the Mekong delta and *Schistosoma malayensis* in Malaysia [1–4]. Each schistosome species is transmitted by specific freshwater snails: *Biomphalaria* genus for *S. mansoni*, *Bulinus* for *S. haematobium* and *Oncomelania* (which are amphibious) for *S. japonicum* [5, 6].

The number of people with schistosomiasis is estimated by the World Health Organization (WHO) at more than 200 million in 74 countries, with over 700 million people at risk [7–9]. The actual figures may be lower, as the numbers of infections and people at risk are dwindling quickly in major historical foci, such as Egypt, Brazil and China [3]. Today, over 85% of cases occur in sub-Saharan Africa [8]. The WHO has classified schistosomiasis as one of the "Neglected Tropical Diseases" (NTD), a group of parasitic and infectious diseases that create considerable havoc among low-income and deprived populations in developing countries but that receive less attention than global threats such as HIV/AIDS, tuberculosis and malaria [9].

Transmission of schistosomes requires a tropical climate, the presence of suitable snail hosts, human settlement, contamination by excreta of the surface waters and human contact with these waters [1–3]. Notwithstanding these uniform conditions, the epidemiology of schistosomiasis varies greatly between continents, countries, regions and even neighboring villages. Snail populations, cercarial densities and human water contact show strong temporal and spatial variations, depending upon local ecology. The distribution of worms in local populations is often extensive, with prevalence commonly between 30% and 100%, but the severity of infection and disease can be very uneven. Typically, the highest prevalence and intensities of infection are found in children between the ages of 8 and 15 years, whereas adults usually have fewer exposures and develop acquired resistance to infection.

Severe disease is usually associated with heavy worm burdens, but may develop after only several years of silent, or mildly symptomatic, infection. Since the advent of safe schistosomicides, especially praziquantel, it has become possible to interrupt the insidious disease cycle, even in the face of continued transmission and re-infection [8, 10]. Therefore, modern control strategies focus primarily on the regular treatment of people at risk, especially school-aged children, or through mass drug administration (MDA) programs.

HISTORY

The evolutionary pathway of *S. japonicum* probably lies in the Yangtze River Valley, *S. mansoni* probably originated in the Nile River basin, and *S. haematobium* in the African Great Lake area [1–3, 11]. Calcified schistosome eggs and, more recently, specific antigens have been detected in Egyptian, Sudanese and Chinese mummies dating from several millennia BC. There are no comparable paleo-epidemiological traces in South America, where *S. mansoni* was imported with the slave trade in the 16th and 17th centuries.

In 1851, the young German pathologist Theodore Bilharz first identified *S. haematobium* as the etiologic agent of Egyptian endemic hematuria during an autopsy in Cairo. He also described the underlying pathology of the urinary system and bilharziasis, or bilharzia, is still used to denominate schistosomal disease. Association of chronic liver disease, characterized by hepatomegaly and splenomegaly, was not reported until Symmer described the typical "clay pipe stem fibrosis" in Egypt in 1904. The complete lifecycle of the parasite and the role of the snail intermediate host were described in 1913 by Miyairi and confirmed experimentally by Leiper in 1915. McDonough introduced the first effective chemotherapy using tartar emetic in 1918.

Schistosomiasis attracted little research attention in the USA until US troops became exposed to infection with *S. japonicum* on the island of Leyte, during the re-invasion of the Philippines in 1944. In the late 1950s, a mouse model of *S. mansoni* infection with hepatosplenomegaly, portal hypertension and esophageal varices was developed and the pathology was shown to be caused by schistosome ova trapped in the presinusoidal venules of the liver. In the 1960s, the immunologic complexities of the host's granulomatous response to the schistosome egg and the mechanisms of concomitant protective immunity began to be defined. It was determined in the 1970s that chronic disease often takes decades to develop and is associated with heavy worm burdens [12]. Until the 1980s, schistosomiasis could only be treated with toxic drugs, such as tartar emetic and, later, niridazole. The large-scale use of intravenous tartar emetic in Egypt between 1950 and 1980 is thought to have caused a massive iatrogenic spread of hepatitis C, considerably aggravating, and probably also obfuscating, schistosomal liver disease [13]. Most control programs in that period relied on the chemical destruction of the vector snails with copper sulphate or niclosamide (Bayluscid®), which was expensive, technically demanding and toxic to fish [1, 3].

In the 1970s, hycanthone, metrifonate and oxamniquine were developed, but these still had disadvantages, for example single-species activity, side effects or the need for repeated administration. The development of praziquantel in 1979, in a then unique public-private partnership between the WHO and the pharmaceutical industry, heralded a breakthrough for the treatment and control of schistosomiasis [1, 14]. It is highly effective and safe against all species in a single dose. More recently, less expensive generic brands, drug donations and renewed international support for neglected diseases control enabled the introduction of MDA, often combined with other anthelminthics, for the control of schistosomal morbidity. In 2001, the World Health Assembly officially recommended this strategy for all regions where schistosomiasis still constitutes a serious public health problem, along with integrated case management in primary healthcare, health education, safe water supply and improved sanitation [15].

BIOLOGY

SPECIES

The genus *Schistosoma* belongs to the class of Trematoda (flukes), phylum of Platyhelminthes (flatworms). They differ from other human flukes by: (i) having separate sexes; (ii) living in blood vessels; (iii) having non-operculated eggs; and (iv) lacking an encysted metacercarial stage. Humans are definitive hosts for *S. japonicum*, *S. mansoni*, *S. haematobium*, *S. mekongi*, *S. malayensis* and *S. intercalatum* [1].

Dozens of other schistosome species infect animals, some of which are occasionally found in humans, including *S. mattheei*, *S. bovis*, *S. curassoni*, *S. rodhaini*, *S. margrebowiei*, *S. spindale* and *S. incognitum*. Recent genetic studies confirmed that some of these species may form productive and pathogenic hybrids with human schistosomes [16]. The infective larvae or cercariae of other nonhuman schistosomes and related trematodes, mostly parasites of birds or small mammals, can attack or penetrate human skin causing dermatitis, but die without migration or maturation. These exposures also occur in temperate climates and cause "swimmers' itch" during summers in North America and Europe [17].

FIGURE 122.1 Morphology of adult male and female *Schistosoma mansoni*. *(Courtesy of the Armed Forces Institute of Pathology, Photograph Neg. No. 56-3334).*

MORPHOLOGY AND METABOLISM (Fig. 122.1)

Adult schistosomes are white-greyish worms with a cylindrical body, tend to be 10–20 mm long and 0.3–0.6 mm thick. The tegument of adult schistosomes consists of a double layer, of which the outer one is continuously shed and renewed. The male tegumental surface may be tuberculated or smooth, depending on the species; the surface of the female worm is smooth in all species. The adult male worm is shorter, thicker and flatter than the longer, slender female. With his flattened body, the male worm forms a groove or "gynecophoric channel", in which the female positions herself for most of her life. Copulation takes place permanently as the male and female genital orifices superpose in the gynecophoric channel.

Schistosomes feed on nutrients and cells in the blood, and metabolize globulins and hemoglobin through anaerobic glycolysis into pigment-like debris. As the gut terminates blindly, the debris is regurgitated into the host's bloodstream. The pigment may be deposited in the Kupffer cells and macrophages of the liver and other organs, showing as typical pigmentation in histologic stains.

REPRODUCTION AND TRANSMISSION

(Fig. 122.2)

Adult schistosome pairs live within the perivesical (*S. haematobium*) or mesenteric (other species) venous plexus. Studies in migrants show that live eggs, and thus adult worms, can still be found for more than 30 years after last exposure [18]. The average lifespan of adult schistosomes is estimated at 3–5 years, but may be shorter in areas with high levels of transmission and worm turn-over [19].

The favored location of the adult worms and, consequently, egg deposition and ensuing pathology, varies according to species. *Schistosoma haematobium* is concentrated near the bladder and around the ureters, *S. mansoni* in the inferior mesenteric vessels of the large intestine and *S. japonicum* in the superior mesenteric vessels of the large and small intestine.

The females produce large, oval or round ova of 100–170 μm in length with a typical terminal or lateral spine at a daily rate of hundreds (African species) to several thousands (Oriental species) with often clustered ova of 70–100 μm in length. The spines are formed during the release of the eggs from the ovipore and may serve as an anchor against the blood flow – helping eggs to start their journey through the vascular wall and into the tissues.

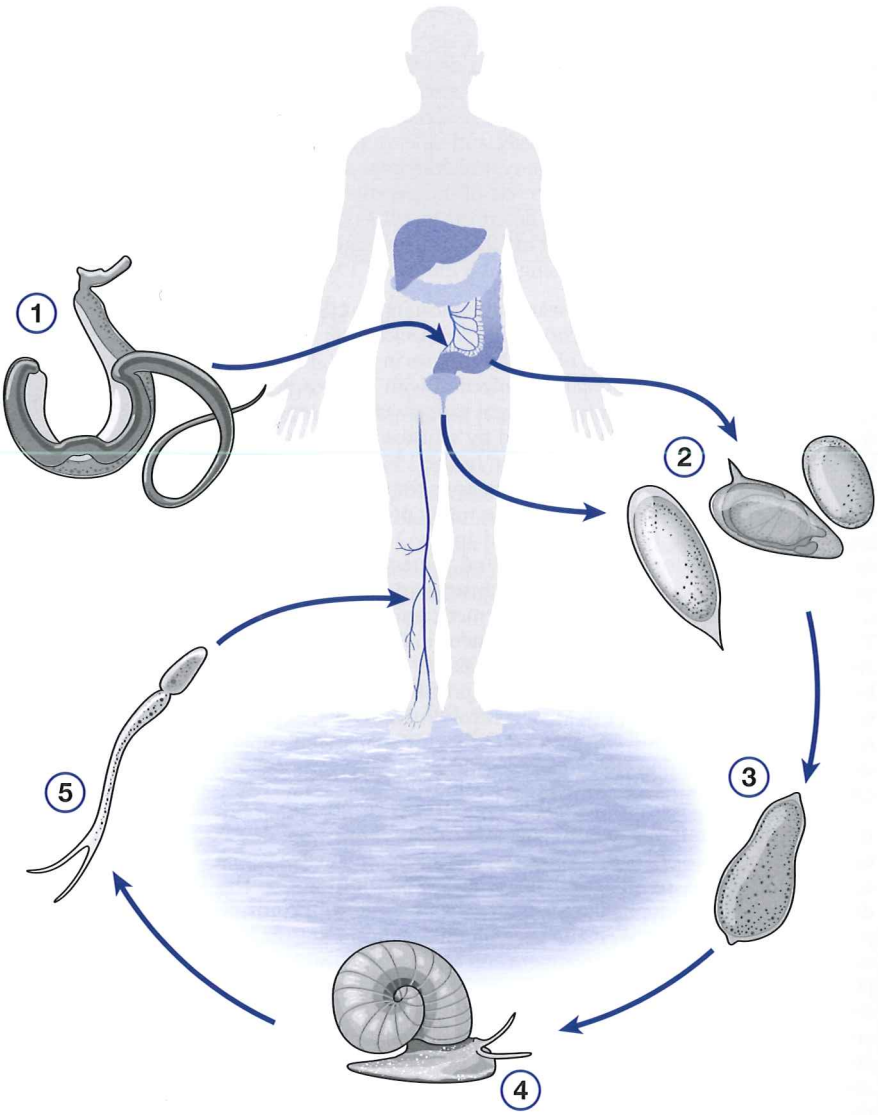


FIGURE 122.2 Transmission cycle of schistosomes. *(Reproduced with permission from Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006; 368:1106–18.)*

Each ovum contains one ciliated larva, called a miracidium, which matures over 6–10 days. The miracidium secretes proteolytic enzymes that help the eggs to penetrate through the vascular wall and into surrounding tissues into the lumen of the bladder (*S. haematobium*) or the intestine (other species). About 50% of the eggs are eventually excreted with the urine or the feces, where they may stay viable for seven days (African species) or up to several months (Oriental species), depending on the temperature and humidity in the environment. The other ova are dislodged and partly destroyed in the liver or spleen, but many remain stuck in the tissues of the bladder or ureters, the intestinal wall, or the liver or spleen (depending on species) where immune responses lead to most of the host's pathology.

The excreted ova release the miracidium upon contact with water of the right temperature (20–30°C), which then swims freely and swiftly around in search of its snail intermediate host. They are propelled by flagellating cilia and guided by positive phototaxis and chemotaxis (attracted by light and snail substances) and negative geotaxis (moving away from the bottom mud). In addition to this typical movement and cilia, the miricidia have pulsating flame and gland cells. They can remain infective for 6–12 hours and penetrate the snail intermediate host's soft parts by aid of lytic substances.

After snail penetration, the miracidium loses its cilia and transforms into a non-motile sac-like embryo: the mother sporocyst. Over the next 10–15 days, germinal cells in the mother sporocyst differentiate into motile daughter sporocysts. The daughter sporocysts migrate to, and grow in, the hepatic and gonadal tissue of the snail, where they metamorphose within 2–4 weeks into bifurcated, mobile larvae called cercariae. The entire non-sexual reproduction stage in the snail takes 4–6 weeks, but cercariae may be shed for up three months at a rate of dozens (*S. japonicum*) to thousands (*S. mansoni*, *S. haematobium*) per day. While snail life expectancy is reduced by schistosome infection because of damage to hepatic and gonadal tissue, one snail infected by one miracidium can shed thousands of cercariae every day for months and may produce up to 100,000 cercariae in its lifetime.

The cercariae are unisexual, highly mobile larvae measuring 400–600 µm in length. They feature a pear-shaped head with two embryonic suckers and a long slender tail ending in a typical short fork. Cercarial shedding is stimulated by direct sunlight and temperatures between 24–30°C, leading to peak transmission rates between 11.00 h and 15.00 h and, in subtropical regions, during summer months. *Schistosoma japonicum* cercariae may also be shed at night.

Cercariae may survive up to 48–72 hours, though infectivity starts to decrease after 12 hours. Activity in water varies with the species: *S. mansoni* and *S. haematobium* cercariae move vertically, alternating between active movements toward the surface and slow sinking; *S. japonicum* cercariae tend to remain at rest in the water surface film unless disturbed. When cercariae meet a suitable definitive host,

they attach themselves to its skin by their ventral or oral suckers, assisted by mucoid secretions. Vertical, vibratory movements and lytic secretions lead to penetration of the skin, usually complete within 3–5 minutes. Only some of the cercariae will develop further after penetration, depending on the physiologic and immunologic reactions of the host.

The cercariae lose their tail and undergo an intensive outer membrane modification to become schistosomula which are tolerant to a saline environment and, even more strikingly, to at least part of the hosts' immune responses. They remain in subcutaneous tissue for about 48 hours before beginning the 3–6 day migration through the bloodstream to the heart and then the lungs, where they are able to stretch the capillaries between the arterioles and venules. Within 5–10 days they reach the small vessels of the liver where they mature within another 3–4 weeks into adult male or female worms, mate and migrate against the blood flow to their perivesicular or mesenteric destination where the cycle starts all over again. Egg deposition and excretion thus starts 6–8 weeks after infection.

THE SNAIL INTERMEDIATE HOSTS AND OTHER RESERVOIR HOSTS

The snail intermediate hosts of *S. mansoni* and *S. haematobium* are red-brownish in color and are non-operculate, i.e. they have no cover or lid on the shells. The major intermediate hosts for *S. haematobium* and *S. intercalatum* are *Bulinidae*, with conic shells with a left-twisted spiral. The genus *Biomphalaria* serves as the intermediate host for *S. mansoni* and is characterized by its disk- or lens-shaped shells [1, 5, 6]. The snail intermediate hosts of *S. japonicum*, members of *Oncomelania hupensis* species, are operculate with conical or turriculate shells.

Other freshwater mollusks serve as intermediate hosts for incomplete avian schistosome infections (causing cercarial dermatitis) but may be difficult to distinguish from the intermediate hosts of human schistosomes, requiring the use of rigid determination keys or genetic analysis.

The aquatic snails important to the transmission of *S. mansoni* and *S. haematobium* live in lightly-shaded, slow-flowing shallow waters. *Biomphalaria*, and particularly *Bulinus*, can survive protracted droughts, hiding in moist mud until the next rains come and rivers swell again. The amphibious *Oncomelania* intermediate host of *S. japonicum* spends part of its time out of water, preferring moist soil in marshy habitats, at the edge of slow-flowing streams, or irrigation canals. It can survive dry periods, as well as long and cold winters. The population dynamics of the snails, and consequently the transmission dynamics of the parasite populations, may differ greatly from one area, one season or one year to another. The infective dynamics of the intermediate host are such that usually less than 0.5% is infected with schistosomes at any one time. As only a very small proportion of the total snail population can be sampled, it may be difficult to find any infected snails or cercariae even in highly endemic areas [20].

There is no identified functional reservoir host for *S. haematobium*. *Schistosoma mansoni* infects rodents and baboons living in some endemic areas and they can maintain the transmission cycle. However, humans are by far the main reservoir of infection. In contrast, *S. japonicum* is a zoonotic parasite that naturally infects dogs, cats, cattle, water buffaloes, pigs, horses, sheep, goats and rodents; some of these, i.e. cattle and water buffaloes, are as important for transmission as humans [6, 20].

IMMUNOLOGY

PROTECTIVE IMMUNITY

Epidemiologic and clinical observations show that people living in endemic areas develop acquired immunity, but only after several years of exposure [21]. Indeed, prevalence and intensities of infection decline after the age of 10–15 years. Cross-sectional data are, however, difficult to relate with exposure, as the worm burdens in adults were built up slowly over many years [21]. The availability of praziquantel has also allowed testing and confirming of this hypothesis by measuring re-infection rates after population-based treatment. After confirmed chemotherapeutic cure, egg counts usually rise much quicker to initial levels in children than in adults, with minimal correlation to exposures to contaminated water. This partial immunity is mediated by IgE against larval and adult worm antigens, which stimulate eosinophils to release cytotoxins targeting schistosomulae [22]. Efforts to develop a protective vaccine are ongoing but are unlikely to result in a commercially-available product in the near future [3, 22, 23].

MORBID IMMUNITY

The main pathology in schistosomiasis is actually caused by cellular immune responses against eggs retained in the tissues, rather than the adult worms [12, 24]. The enzymes and metabolites released by the ova that are trapped in the tissues provoke granulomatous reactions by eosinophils, monocytes and lymphocytes orchestrated by CD4+ T cells. In the early stages of infection, cytokine responses are predominantly of the TH1 type featuring interferon-γ. As egg production proceeds, they shift to a TH2 profile with high levels of IgE, interleukin (IL)-4 and eosinophilia. In long-standing chronic infection, this TH2 profile modulates to production of IL-10, IL-13 and IgG_4, which leads to the regression of the granulomas and their replacement by collagen. In most infected persons, however, anti-inflammatory IL-10, and possibly transforming growth factor (TGF)-β, induced by regulatory T cells, prevents excessive TH1 or TH2 polarization and, hence, severe disease manifestations in the late stages of the disease.

IMMUNE RESPONSES AND CO-INFECTIONS

Various bidirectional interactions between immune responses to schistosomiasis and HIV/AIDS have been described, but their clinical significance remains undetermined [3, 25]. Treatment of concomitant schistosomiasis appears to have little effect on HIV viral load or results, at most, in a lower HIV RNA increase in patients with a delayed intervention. Reduced CD4+ T cell counts may increase the susceptibility to schistosome infections and serodiagnostic reliabilities may be affected in concomitant infections.

There have been experimental animal and human studies reporting that chronic schistosomiasis, by downregulating the TH1 and upregulating the TH2 immune responses, could cause viral infections, notably hepatitis B and C, to become chronic and more severe [26]. The situation is complicated as parenteral treatment of schistosomiasis has caused the spread of some blood-borne viral infections [13], but the clinical importance of the immunosuppressive effects of schistosomiasis on hepatitis B and C is less than the pathophysiology caused by having multiple infections.

EPIDEMIOLOGY

GEOGRAPHIC DISTRIBUTION (Fig. 122.3)

The distribution of the different species depends primarily on the ecology of the snail hosts. The introduction and sustained transmission of *Schistosoma* infections requires suitable snail hosts, a tropical climate for at least 4–6 months a year, human settlement, fecal or urinary contamination of the surface waters harboring the snails and human contact with these waters. The geographic distribution of schistosomiasis is, thus, largely confined to an area between 36° north and 34° south latitude, where freshwater temperatures average 25–30°C and socioeconomic conditions impose regular contact with snail-infested water [1, 3, 4]. In addition, within populations and age groups, schistosomes are not evenly distributed – a small number of individuals carry most of the parasite burden [27].

The epidemiology of schistosomiasis is highly focal and can vary strongly from one area, village or hamlet to another [1, 3, 4]. While *S. haematobium* mostly occurs in warm plains, *S. mansoni* can be transmitted in a variety of ecotypes, from savannah to rain forest and highland areas of up to 2500 m. Transmission of both species takes place in the great lakes of Central and East Africa; in many other small

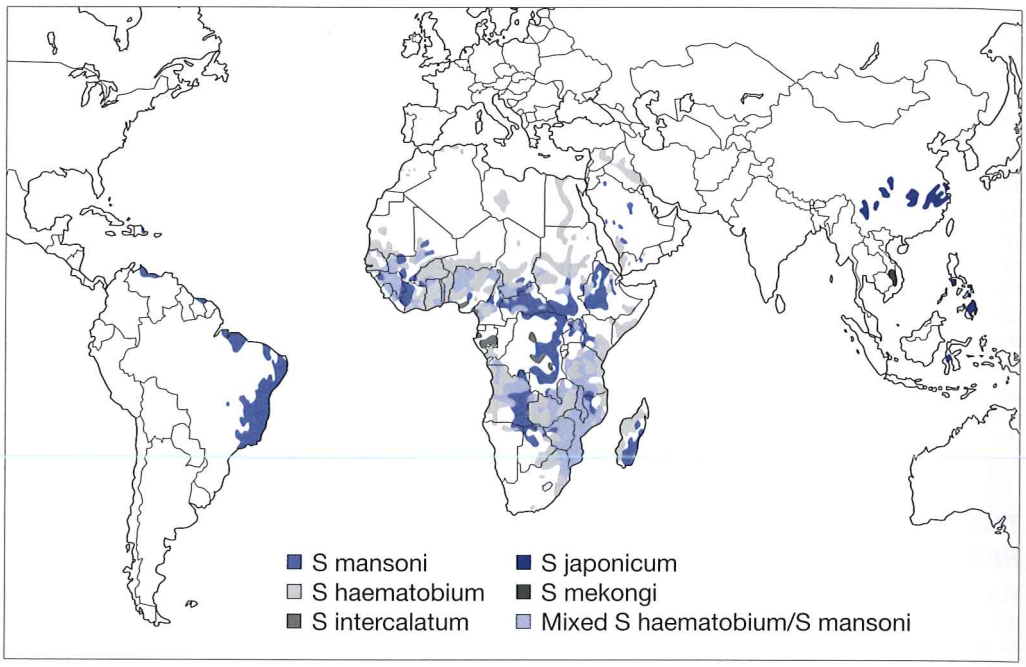


FIGURE 122.3 World distribution map of schistosomiasis *(Reproduced with permission from Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006;368: 1106–18.).*

and large, natural and artificial lakes throughout the continent; in surface irrigation and drainage systems; and in innumerable natural streams and ponds. Transmission of *S. japonicum* takes place in hot southern areas in China, as well as in the mountains of Sichuan and the central lakes, where winters are severe but summers are hot and long enough to allow intense seasonal transmission.

The main foci of *S. mansoni* are in sub-Saharan Africa, including Madagascar; Lower and Middle Egypt; the Arabian peninsula; northeast Brazil; Surinam; Venezuela; and parts of the Caribbean. *Schistosoma haematobium* occurs in large parts of sub-Saharan Africa, Madagascar, Middle and Upper Egypt, the Maghreb and the Arabian peninsula. *Schistosoma japonicum* is found along the central lakes and the Yangtze River in China, including the mountain areas of Sichuan and Yunnan; and Mindanao, Leyte and other small sites in the Philippines. It is not clear whether transmission still occurs in some small historical pockets in Indonesia. The distribution of *S. mekongi* is limited to the central Mekong basin in Laos and Cambodia, and of *S. intercalatum* to pockets in West and Central Africa.

Schistosomiasis is typically an infection of traditional rural areas, but it has also spread to many human settlements around artificial dams and irrigated lands [1–3, 28]. Examples are Lake Nasser and several newly reclaimed areas in Egypt; Lake Volta in West Africa; dams on the Senegal River in Mali, Mauritania and Senegal; hundreds of small village dams throughout Africa; the irrigated sugar estates in Brazil; canal systems in China, and, possibly in the future, the Three Gorges Dam area. Despite mandatory and elaborate risk assessments, food production and socioeconomic development take precedence over future health concerns. Urban schistosomiasis is becoming an increasing problem throughout Africa, South America and Asia. In many shantytowns, snail populations thrive in local canals, drains or small irrigated plots. As sanitation and water supply are often poor, migratory and other exchanges with rural endemic areas easily leads to the establishment of permanent transmission within city boundaries.

COMMUNITY EPIDEMIOLOGY

Our understanding of the epidemiology of schistosomiasis is based on indirect measures of worm burdens, i.e. the presence and number of eggs excreted by individuals in a known volume of excreta [1, 3, 27]. These are useful at the community and group level, but much less accurate in individuals owing to significant day-to-day and individual variations of egg excretion. Worm burdens have been directly counted in only a few autopsy studies, and further approximated in mathematical models or using circulating antigen levels. Other methodologic handicaps include difficulty measuring snail densities and infection rates, cercarial of miracidial densities, human water contact or acquired resistance [20].

The overall prevalence of infection in communities living under endemic conditions is usually between 30% and 100% [1]. However, particularly in areas with low intensities of transmission and infections, many light infections go undetected on routine screening, and the true prevalence may be 2–3 times higher than that observed [29]. In addition, many adults who are microscopically negative for ova have probably had earlier infections, as demonstrated by the persistence of specific antibodies.

Depending on the intensity of transmission and local habits, infections can be detected in toddlers from the age of 6 months onwards – sometimes even earlier [30]. In almost all foci, prevalence and intensities of infection, as measured by egg excretion, rise strongly from the age of 5–7 years to a peak in the age group between the age of 8 and15 years, and then decline substantially in adults [1, 3]. The peak age usually falls a few years earlier in heavily infected communities. Boys are usually more heavily infected than girls as they play more often and intensively in water. In adults, gender differences depend on occupational activities.

While these observations can be partly explained by water contact patterns, many epidemiologic, clinical and immunologic studies indicate that people living in endemic areas develop some form of acquired resistance after years of exposure [1, 22]. However, similar age-related infection rates are also observed in communities only recently exposed to transmission through migration or newly established transmission. As acquired immunity cannot be invoked in such cases, it might represent age-related innate resistance, possibly influenced by hormonal changes [21].

CLINICAL DISEASE AND PATHOLOGIC CORRELATES

The pathogenesis of schistosomiasis is largely based upon the host reaction against the different parasite stages, rather than their presence. The adult worms living in the bloodstream are seldom associated with clinical illness. They rarely cause vascular obstruction in ectopic areas, for example cerebral or spinal arteries. Early clinical manifestations associated with migratory schistosomulae include

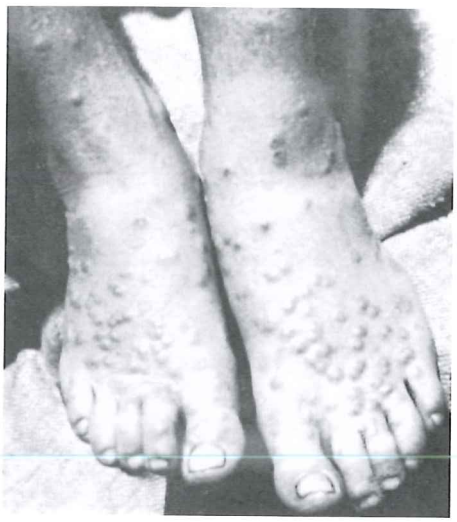


FIGURE 122.4 Swimmers' itch. *(Courtesy of Dr A J Bearup, School of Public Health and Tropical Medicine, University of Sydney, NSW, Australia).*

cercarial dermatitis and acute systemic schistosomiasis (Katayama fever). Chronic schistosomiasis is largely associated with the granulomatous and fibrotic responses to *Schistosoma* ova during mature, chronic infections [12]. Severity of clinical disease and susceptibility to praziquantel varies between geographic areas, suggesting *Schistosoma* subspecies, or strain differences, between and within countries and continents; apparently, immunogenetic traits among populations affect the epidemiology and pathophysiology of schistosomiasis as well [3].

CERCARIAL DERMATITIS (Fig. 122.4)

Non-sensitized and sensitized individuals respond with marked differences to the penetration of the skin by cercariae. Initial exposures produce only mild, transient reactions that can be unnoticed or cause only a mild prickling sensation as the water evaporates and the parasites penetrate the skin. Macules usually appear within 12 hours on the exposed skin in non-sensitized persons and rapidly disappear. However, in previously sensitized persons they are followed by pruritic papules, erythema and, in more severe cases, vesicles, edema and pruritus. Cercarial dermatitis most commonly occurs with *S. mansoni* and *S. haematobium* and is unusual with *S. japonicum*. A similar "swimmers' itch" is also frequently caused by cercariae of animal and bird trematodes in tropical areas or during summer in temperate climate zones, including Europe and North America [1, 17]. Pathologically, these focal lesions show edema and heavy dermal and epidermal eosinophil and mononuclear cell infiltrates resulting from subcutaneous cercarial death. Cercarial dermatitis resolves in 7–10 days without permanent tissue damage or scarring.

ACUTE SCHISTOSOMIASIS (KATAYAMA FEVER)

Acute schistosomiasis, or "Katayama fever" by its historical Japanese name, is a systemic hypersensitivity reaction against the migrating schistosomulae and/or the onset of egg production, occurring within a few weeks to months after a primary infection [31, 32]. It can be caused by all schistosome species. Usually, the onset is sudden with fever, fatigue, myalgia, malaise, nonproductive cough, marked peripheral eosinophilia, elevated IgE and patchy infiltrates on chest x-ray. Early symptoms are mostly caused by allergic reactions to the migratory schistosomulae as they congregate in the pulmonary microvasculature en route to the liver. A few weeks later, abdominal symptoms may develop because of the migration and positioning of the mature worms and the start of ovideposition in the tissues. Most patients recover spontaneously after 2–10 weeks, but some develop a persistent and serious illness with weight loss, dyspnea, diarrhea, diffuse abdominal pain, toxemia, hepatosplenomegaly and generalized rash. Intense infections occasionally are fatal.

Acute schistosomiasis caused by *S. mansoni* and *S. haematobium* is rarely reported within chronically exposed populations. It is not an infrequent diagnosis in tourists, travelers and others accidentally exposed to transmission. Most cases in Western travel clinics are imported from sub-Saharan Africa, often in family or group clusters [31, 33]. Exposures frequently occur in Lakes Malawi, Victoria and Volta, the Zambesi and Niger deltas, the Dogon country of Mali, and lake resorts in South Africa. The infective water contacts range from bathing and swimming to scuba diving, water skiing and rafting. Serious neurologic complications can occur as a result of ectopic worms or eggs in the spinal cord.

Katayama fever caused by *S. japonicum* infections can present as serious, sometimes fatal, serum sickness-like disease which possibly results from the early release of large quantities of egg antigens that cross-react with antibodies to schistosomula, resulting in immune complexes that cause hypertrophy of lymphoreticular tissue [1–3, 32. This prototypic Katayama syndrome is characterized by fever, hepatosplenomegaly and cachexia which may evolve directly to severe hepatosplenic fibrosis and portal hypertension. Unlike African schistosomiasis, it is not restricted to primary infection, but also occurs in people living in endemic areas and in those with a history of previous infections. In China, true "rebound epidemics" have been reported in endemic communities exposed to floods.

CHRONIC PATHOLOGY AND ILLNESS

In chronically established infections most pathology is caused by cellular and fibrotic immune reactions against eggs that are trapped in the tissues during their perivesical or peri-intestinal migration, or after embolization to the liver, spleen, lungs or cerebrospinal system [12, 34, 35]. The ova secrete proteolytic enzymes that sensitize local lymphocytes which in turn mobilize macrophages, lymphocytes, eosinophils and fibroblasts that encapsulate the egg with a typical granuloma. Early, acute granulomas are usually composed of eosinophils and neutrophils, as well as mononuclear cells. Macrophages, lymphocytes, fibroblasts and multinucleated giant cells dominate the chronic granuloma. The acute granuloma is large and diffuse, whereas the more chronic granuloma is smaller and better circumscribed (Fig. 122.5).

The egg granuloma is thought to be protective, as well as pathogenic. In healthy hosts it reduces, or confines, tissue necrosis. Granuloma formation is largely a product of TH2 cytokines. As cell-mediated immunity reactions are downregulated over time, the granulomas are reduced in size and gradually replaced by collagen depositions. In some, but not all patients, this balance is disturbed and the collagen deposition leads to fibrosis. Depending on the tissue egg load, a great number of microlesions may merge into the typical fibrotic streaks that cause most of the irreversible pathology in all forms of schistosomiasis. The severity of chronic diseases is thus related to the intensity of infection on one hand, and individual immune responses on the other. Severe forms are mostly seen in individuals with previously high parasite loads, and probably some form of immunogenetic predisposition [3, 24].

While in such cases schistosomiasis is a serious and sometimes life-threatening disease, many infections remain asymptomatic or cause only mild, vague or intermittent symptoms of malaise, drowsiness, abdominal discomfort and mucus or blood-specked diarrhea [1–3]. In endemic areas, it is common to detect many infected persons without, at first sight, noticeable consequences. Often, however, treatment is followed by spontaneous, widespread reports of improved wellbeing, fitness and appetite. Also in tourists or migrants, infection is regularly a chance finding, sometimes decades after exposure.

URINARY SCHISTOSOMIASIS

The eggs of *S. haematobium* provoke granulomatous inflammation, ulceration and pseudopolyposis of the mucosa and submucosa of the bladder and the ureters [3, 36]. Obstructive uropathy occurs when such lesions are located in the ureter or in the bladder near the ureteral inlet. Bladder and ureteral obstruction may result in urine stasis,

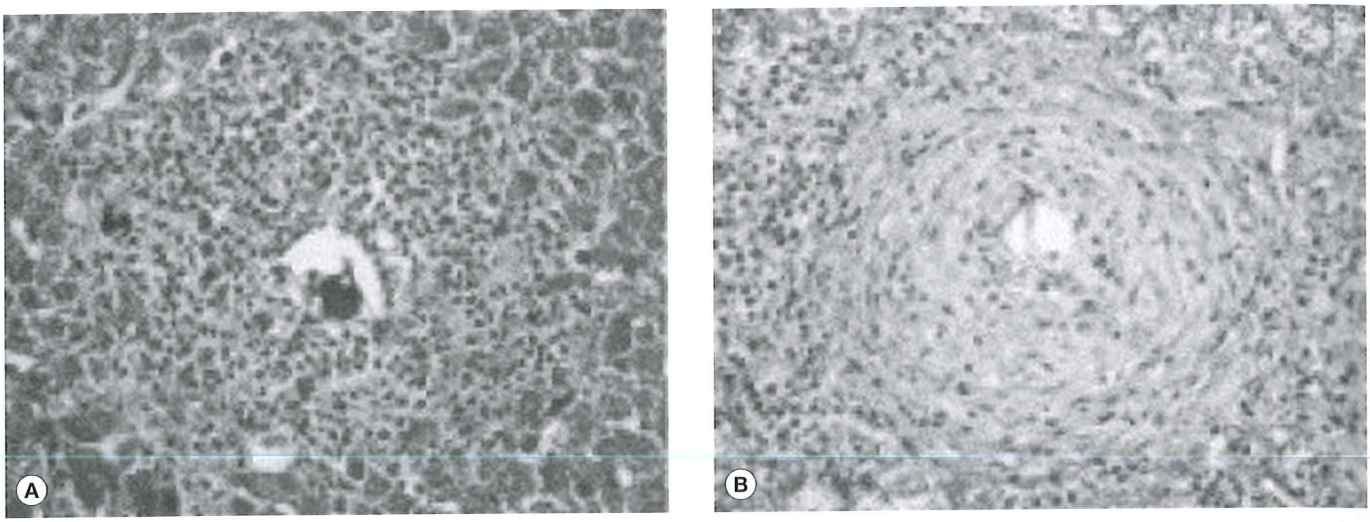


FIGURE 122.5 Histopathology in schistosomiasis: early **(A)** and late **(B)** egg granulomas in the liver. *(Reproduced with permission from Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006;368:1106–18.)*

FIGURE 122.6 Urinary schistosomiasis: macroscopic hematuria, the "red flag" of urinary schistosomiasis in children. *(Reproduced with permission from Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006;368: 1106–18.)*

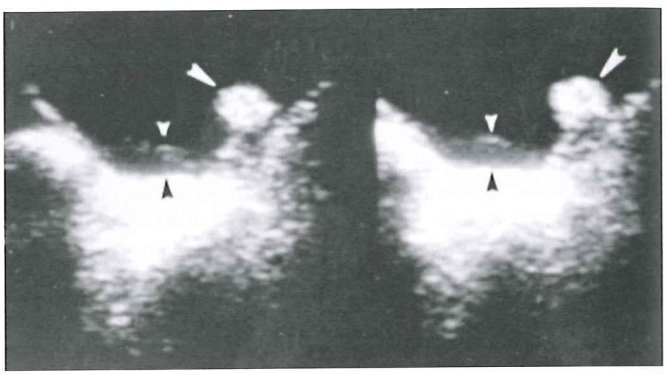


FIGURE 122.7 Urinary schistosomiasis. Ultrasonographic view of bladder. Thickening and irregularity of the bladder wall (small arrows) and a large polyp (large arrows) are present.

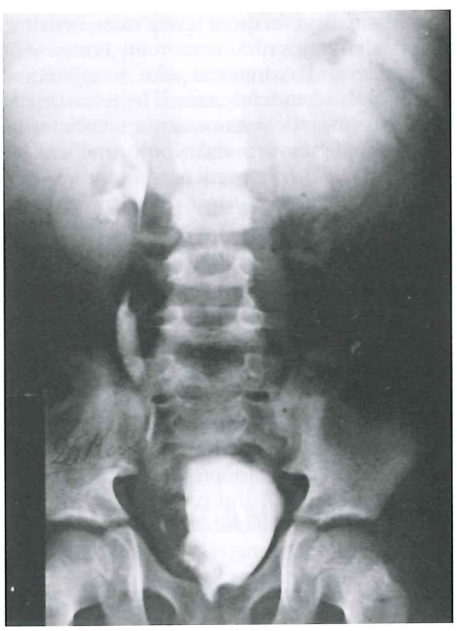


FIGURE 122.8 Urinary schistosomiasis. Intravenous pyelogram showing a large bladder filling defect caused by granulomatous polyp formation. Early right hydronephrosis and hydroureter are also present. *(Courtesy of U.S. Naval Medical Research Unit No.3, Cairo, Egypt).*

disruption of the normal bacteriostatic mechanisms of the bladder mucosa and urinary tract infection. Although rarer following the widespread use of antischistosomal chemotherapy, abdominal radiographs may show calcium deposits around extensive deposits of calcified *Schistosoma* eggs in the bladder wall.

Common early symptoms of urinary schistosomiasis include dysuria, urinary frequency and urgency, proteinuria and, particularly, hematuria. In endemic areas, the latter is the "red flag of schistosomiasis" in children between the age of 5 and 10 years old, sometimes mistakenly considered as the onset of menstruation in girls, or even as a similar coming of age in boys (Fig. 122.6). Typically, blood is first seen in the terminal urine; in more severe cases, the urine can be dark-colored and bacterial super-infection is a common complication. These symptoms mostly wane as the child becomes older. In non-treated populations exposed to *S. haematobium*, microhematuria can be present in 40–100% of infected children [39]. Bladder pathology and upper urinary tract lesions can be detected by ultrasound or radiology in many infected people (Figs 122.7 and 122.8). Many cases with serious morphologic lesions show a surprisingly preserved renal function.

Lesions can reverse spontaneously with age and usually heal well after antischistosomal therapy. Chronic infection may lead to obstructive uropathy, renal failure and bladder cancer.

Obstructive Uropathy (Figs 122.7 and 122.8)

Fibrosis of the bladder and lower ureters with hydroureter and hydronephrosis occurs in the lower third of the ureter or in the bladder. It may remain clinically silent for years, while being easily visualized in pyelograms or ultrasound, and is usually reversible with chemotherapy. Hydronephrosis is initially caused by compression; the parenchyma can eventually be destroyed leading to renal failure. Secondary chronic bacteriuria and pyelonephritis, sometimes complicated by septicemia, may be the presenting manifestation and can be fatal.

Bladder Cancer

Chronic urinary schistosomiasis is epidemiologically associated with high incidences of squamous cell bladder carcinoma in Egypt and, less clearly, in some other African foci [3, 37]. In Egypt, the incidence of bladder cancer has decreased over the past 2–3 decades along with the prevalence of urinary schistosomiasis following praziquantel MDA. In addition to causing chronic inflammation of the bladder wall, the schistosomal lesions may enhance the exposure of the bladder epithelium to carcinogenic substrates. Apart from gross hematuria, bladder cancer often presents with frequency, urgency, dysuria, weight loss and metastasis to the inguinal, femoral and retroperitoneal lymph nodes.

INTESTINAL SCHISTOSOMIASIS

The eggs of *S. mansoni*, *S. japonicum* and other species migrate through the intestinal wall where they provoke mucosal granulomatous inflammation, pseudopolyposis, micro-ulcerations and superficial bleeding. Most lesions are situated in the large bowel and the rectum; small bowel pathology is rare [38].

Most common symptoms attributed to intestinal schistosomiasis are chronic or intermittent abdominal pain and discomfort, loss of appetite and mucous diarrhea with or without blood, although occult blood in the stool is very common [1–3, 39]. Physical examination may be normal or show moderate abdominal distention, diffuse mild abdominal tenderness and hyperactive bowel sounds.

Intestinal polyposis, ulcers, fistula and strictures have been attributed to *S. mansoni*. In such cases, diffuse, protein-losing enteropathy may occur, with chronic mucohemorrhagic diarrhea, weight loss and anemia. Physical examination reveals a distended abdomen with diffuse tenderness or localized tenderness over the transverse and descending colon. Severe, long-standing granulomatous or polypous lesions may result in partial or complete bowel obstruction and, in rare cases, appendicitis or perforation. Intense dysenteric syndromes are exceptional, but in some cases fatal. *Schistosoma japonicum* and *S. mansoni* have both been associated with colon cancer, but the evidence for causation is weak.

The reported frequency of intestinal disease in people living in endemic areas infected with *S. mansoni* or *S. japonicum* is usually 10–50% [39]. In general, intestinal morbidity is strongly correlated with intensities of infection, both at the population and at the individual level.

HEPATOSPLENIC SCHISTOSOMIASIS

(Figs 122.9 and 122.10)

Hepatic schistosomiasis can be caused by *S. mansoni*, *S. japonicum* and *S. mekongi*. The pathologic impact of *S. intercalatum* is restricted to mild intestinal disease. Hepatic and hepatosplenic schistosomiasis can be caused by either early inflammatory or late fibrotic hepatic disease, with quite different underlying pathology and prognoses [1–3].

Inflammatory Hepatic Schistosomiasis

This is an early reaction to ova trapped in the hepatic presinusoidal periportal spaces where many granulomas are produced (Fig. 122.5A).

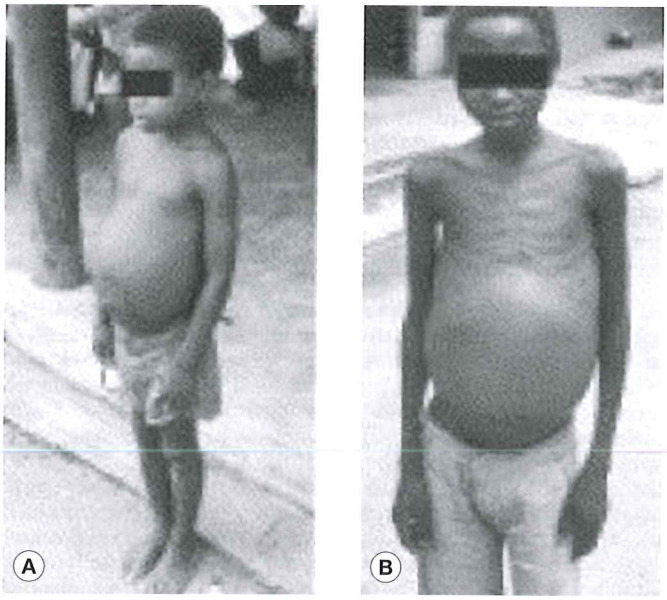


FIGURE 122.9 Early **(A)** and late **(B)** hepatosplenic schistosomiasis mansoni. *(Reproduced with permission from Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006;368:1106–18.)*

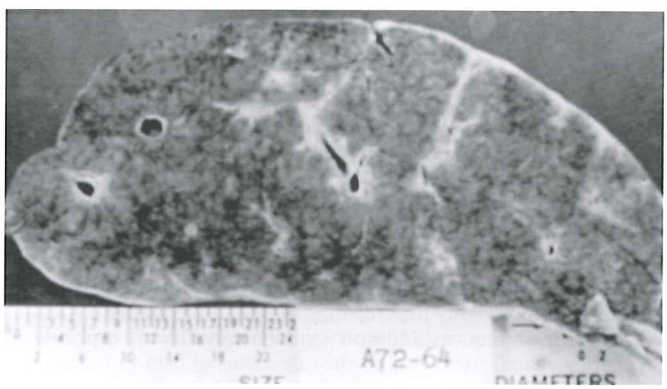


FIGURE 122.10 Cut surface of the liver showing Symmer's clay pipe stem fibrosis in a patient infected with *Schistosoma mansoni*. *(Courtesy of U. S. Naval Medical Research Unit No. 3, Cairo, Egypt).*

It is the main cause of schistosomal hepatomegaly in children and adolescents, often associated with hyperplastic splenomegaly and strongly correlated with the intensity of infection. Typical features include sharp-edged enlargement of the left lobe of the liver and nodular splenomegaly. In most cases, the organomegaly is mild but sometimes the liver and spleen may extend below the umbilicus and into the pelvis (Fig. 122.9A). Usually, liver cell function is normal and jaundice is absent. In young children, clinical differentiation from malaria may be difficult. In heavily endemic areas, this type of hepatomegaly, with or without splenomegaly, is present in 30% or more of infected children and adolescents, but much less in adults. The frequency and severity correlate with intensities of infection, but are also subject to methodologic variations, immunogenetic predisposition and other confounding factors [39].

Fibrotic or Chronic Hepatic Schistosomiasis

This complication develops years later in the course of infection and in a minority of those infected. It is believed to be a consequence of long-standing intense infection, as well as dysfunctional or overpolarized immune responses which fail to downregulate granulomatous and fibrotic reactions [24]. Diffuse collagen deposits in the periportal spaces occur (Fig. 122.5B) and confluence of the resulting fibrotic streaks leads to the pathognomic "Symmer's pipe stem

fibrosis", in which the elongated periportal fibrotic lesions resemble clay pipe stems (Fig. 122.10). Physical occlusion of the portal veins leads to portal hypertension, increased splenic vein pressure and tortuosity and splenomegaly. Portal hypertension results in collateralization of the abdominal venous circulation, which may show externally as a "caput medusa", and leads internally to portocaval shunting and gastrointestinal varices. This condition also facilitates the distribution of *Schistosoma* eggs into the general circulation and the occurrence of ectopic lesions in the lungs, spinal cord (Fig. 122.11) or the brain. End-stage hepatosplenic schistosomiasis can be marked by ascites (Fig. 122.9B).

The extent of exposure, immunogenetic predisposition, concomitant infections and nutritional deficiencies all contribute to the severity of the disease. The liver is not necessarily enlarged, but is usually hard and nodular on palpation. In contrast to cirrhosis, the parenchyma, hepatocellular functions and its biologic parameters remain largely unaffected. Fibrotic hepatic schistosomiasis is mainly seen in young and middle-aged adults, although it can occur in heavily infected adolescents. In *S. mansoni* infections, this takes at least 5–15 years to develop, by which time ova may not be present or detectable. In *S. japonicum*, the progression may be more rapid, in some cases with little, or no, interval between acute and chronic disease.

Bleeding from gastro-esophageal varices is the most serious, and often fatal, complication of fibrotic hepatic schistosomiasis. In *S. mansoni* infections, it tends to recur and become more severe over time; in *S. japonicum*, bleeding is often sudden and massive. Repeated or occult bleeding may lead to anemia, hypoalbuminemia, cachexia and growth retardation. Ascites can be caused by a combination of hypoalbuminemia and portal hypertension, or concomitant infection with hepatitis B or C.

Advanced liver fibrosis caused by schistosomiasis used to be a frequent and severe health problem in large parts of Egypt, Brazil, China, the Philippines and other countries. Over the past few decades, chemotherapy and general socioeconomic development have led to a dramatic reduction of such morbidity worldwide. Symptomatic liver fibrosis has always been less frequent in sub-Saharan Africa, except for some East-African foci, for example West Nile in Uganda, Machakos in Kenya and Gezirah in Sudan [39]. These varying continental and regional morbidity patterns may be partially explained by ethnic and genetic factors, in addition to the intensities of exposure to infection.

OTHER COMPLICATIONS AND ECTOPIC SCHISTOSOMIASIS

Pulmonary Schistosomiasis

This syndrome is a complication of portocaval shunting caused by portal hypertension in chronic *S. mansoni* infection which allows ova to pass into the peri-alveolar capillary beds [1, 3, 40]. The ensuing granulomas cause obliterative arteritis which leads to fibrosis resulting in pulmonary hypertension, increased right heart pressure, pulmonary artery and right atrial dilatation, and right ventricular hypertrophy. Schistosomal cor pulmonale has been mostly described in Brazil and Egypt, but appears to have become much less frequent over the last decades.

Schistosomal Glomerulonephritis

Immune complexes can be deposited in the renal glomeruli during *S. mansoni* infections [41]. Schistosomal glomerulonephritis used to be found quite commonly in renal biopsies from patients with *S. mansoni* infection in Brazil, but this finding was usually asymptomatic or clinically insignificant. Nephrotic syndrome is seen occasionally in patients with *S. mansoni* or *S. haematobium* infections, sometimes associated with chronic *Salmonella* bacteremia or bacteriuria.

Genital Schistosomiasis

Schistosoma haematobium and *S. mansoni* ova that are trapped in the reproductive organs remain mostly occult in endemic areas, but are a regular finding in travelers. Hypertrophic and ulcerative lesions of the vulva, vagina and cervix may facilitate the transmission of sexually transmitted infections, including HIV. Lesions of the ovaries and the fallopian tubes can lead to infertility. In males, the epididymis, testicles, spermatic cord and prostate may be affected; hemospermia is a common symptom [42].

Neuroschistosomiasis

This severe complication is caused by inflammation around ectopic worms or eggs in the cerebral or spinal venous plexus, which can evolve to irreversible fibrotic scars if left untreated [1–3, 43]. Ectopic *S. mansoni* and *S. haematobium* infections mainly cause spinal cord pathology with transverse myelitis, which is also a potential complication of acute schistosomiasis in travelers [31, 33]. Symptoms vary with the location and the degree of the myelitis, and may include paraplegia and loss of bladder and/or anal sphincter control. Sometimes, the patient may have pain or loss of sensation; rarely there will be a rash around the body affecting the dermatome at the level of the spinal cord lesion.

Schistosoma japonicum, possibly because of the larger number and smaller size, or the clustering of the eggs, is associated with cerebral granulomatous lesions that can be either diffuse or focal, possibly depending on whether eggs have been randomly embolized from a distance or locally-released by ectopic worm pairs. Depending on type and location, the resulting syndrome may have an epileptic, paralytic or meningo-encephalitic character. The acute phase, which occurs months after exposure, may be accompanied by fever, urticaria, eosinophilia and angioneurotic edema suggesting an allergic encephalopathy. There may be delirium, confusion, personality changes, incontinence, coma, nuchal rigidity, pyramidal track signs and cerebellar symptoms. The acute phase may merge into a chronic phase, which could be asymptomatic or mimic intracranial neoplasm. Epileptic syndromes often include Jacksonian or grand mal seizures, stemming from lesions in the parietal lobe. Other neurologic signs and symptoms are headaches, speech difficulties, visual disturbances, papilledema and cerebellar symptoms [43].

Other Sites

Ectopic schistosomal lesions in the skin can present as maculopapules or wart-like protuberances, the latter particularly in the genital area [2]. Schistosomal granulomas in the peritoneum may be mistaken for endometriosis, miliary tuberculosis or cancer metastasis. Granulomas around stray eggs have also been documented in the pancreas, gallbladder, stomach, heart, kidney and adrenal glands, with or without recognized clinical manifestations.

ASSOCIATION OF SCHISTOSOMIASIS AND OTHER INFECTIONS

Chronic *Salmonella* Co-Infections

Schistosomiasis has been associated with the presence of several co-infections, especially chronic persistent *Salmonella* bacteremia [1]. Possible explanations include immunologic tolerance caused by schistosomiasis and the physical attachment and proliferation of *Salmonella* bacteria on, or in, adult worms. The syndrome was seen mainly in males between the age of 15–30 years, but has become rare. It is characterized by a long history of indolent febrile disease, bacteremia with one or more *Salmonella* species and chronic active schistosomiasis. It differs from enteric fever caused by *S. typhi* by negative stool cultures, a petechial rash on the lower extremities rather than on the abdomen, and the absence of systemic complications, for example prostration, delirium or localized infections.

Co-Infections with Hepatitis B and C

Chronic *S. mansoni* infected patients co-infected with hepatitis B or C are prone to have clinically more severe infections. Prior parenteral treatment for schistosomiasis may also have substantially increased the risk for hepatitis infections in some areas, especially Egypt [13,

26]. Patients with co-infections more often develop jaundice, intractable ascites and hepatic failure. In fact, patients with chronic schistosomiasis who have elevations in serum alanine transaminase (ALT) or aspartate transaminase (AST) have a high probability of having concomitant hepatitis B and/or C infections. Proper precautions should be taken in the management of the patient and the handling of blood samples.

INDIRECT PATHOLOGY AND MORBIDITY

Before the advent of modern treatment and control, *S. japonicum* infection was believed to be related to reduced stature, weight, weight-for-height, skin-fold thickness, muscle mass and other anthropometric measures, especially during childhood and adolescence. These clinical and epidemiologic observations, although historical and not always rigorously documented, indicate an independent effect of the infection on nutrition, growth and development. This impact on physical development was widespread and is thought to have substantially reduced economic productivity in China at one time, when schistosomiasis was considered "the plague of gods" and its control received high political priority [2].

However, early studies to establish an association between general wellbeing, anthropometric indices, nutritional status and physical or cognitive performance, and the presence or intensity of *S. mansoni* or *S. haematobium* infection were largely inconclusive or contradictory [39]. Possibly, they were obscured by the frequent comorbidities from malarial, intestinal helminths, protozoa, bacterial and viral infections. As severe disease from *Schistosoma* infections has waned in many areas, subtle or "indirect" morbidity has become the target of more focused research efforts and is providing a rationale for sustained control strategies. Significant associations have now been demonstrated for anemia, nutritional status, cognitive and physiologic capacities [44].

GLOBAL BURDEN OF DISEASE (GBD)

Schistosomiasis is highly prevalent but the associated morbidity is low and variable. The GBD of schistosomiasis, as expressed in Disability-Adjusted Life Years (DALY), depends on the number of people infected on one hand, and the mortality and disability attributed to it on the other [45]. The total number of cases in the world is estimated by the WHO at 200 million, a figure that is consistently quoted in the literature but may need to be revised downward in view of recent trends [2, 7–9]. The GBD estimates report up to 15,000 lives lost to schistosomiasis annually, and applies a "disability weight" of 0.06. The total number of DALYs lost to schistosomiasis is estimated at 1.75–2.0 million, of which 85% are in sub-Saharan Africa. This is a fraction of the GBD of AIDS, malaria or tuberculosis, and puts it in the same league as lymphatic filariasis, leishmaniasis and trypanosomiasis. Schistosomiasis would account for 0.1% of the GBD in the world and 0.4% of the GBD in sub-Saharan Africa.

These figures have been contested by many schistosomiasis experts when advocating for global control efforts [8, 44, 46, 47]. Upgrades of as much as a 40-fold increase of schistosomiasis mortality in sub-Saharan Africa, and a 4–30-fold upgrade of the disability weight have been proposed. These revised data have not been empirically validated, however, and remain inconsistent with total mortality and GBD data. This does not reduce the need, however, to bring treatment and control to affected populations.

DIAGNOSIS

MEDICAL HISTORY AND EXAMINATION

Within endemic areas, schistosomiasis must be suspected in all patients presenting any symptom, however vague, that can be related to the infection. In travelers and migrants, a careful residence or travel history can help establish the diagnosis of schistosomiasis [31, 33]. In several sub-Saharan areas, both *S. mansoni* and *S. haematobium*, and even *S. intercalatum*, can be contracted. The patient who has lived in, or visited, endemic areas must be asked about skin contact with freshwater of any kind, even if considered locally as safe or snail-free. Contacts of any type or duration can lead to infection. The patient may, or may not, report itching or rash shortly after the water contact. Visual inspection may help diagnose "swimmers' itch" after recent exposure.

A medical history may reveal intermittent symptoms since the potential exposure, including flu-like syndromes in the weeks or months thereafter. Malaise, fatigue, muscle pains, appetite loss, intermittent diarrhea, vague abdominal pain and red or dark urine are potential warning signs – partly depending on the suspected species. A neurologic history and examination is performed to exclude early cerebrospinal involvement. Abdominal palpation may reveal hepatomegaly or splenomegaly of varying degrees and abdominal tenderness or distention, but also may be entirely negative.

LABORATORY FINDINGS

Rapid tests can include a visual inspection or a hematuria dip-stick test of the urine for *S. haematobium*, or occult blood in the stools for *S. mansoni* and *S. japonicum*; these are very useful tools for rapid diagnosis and community screening in the endemic areas [1–3, 39]. In tourists and migrants, the most important hematologic indicator is eosinophilia, which is usually elevated in acute schistosomiasis but may be negative in chronic cases. Other hematologic or biochemical parameters, including liver function tests, are often within normal limits but abnormal values can indicate chronic complications, for example anemia or renal failure, or comorbidities, such as hepatitis. Mild anemia is not unusual in infected persons living in endemic areas and the serum alkaline phosphatase level may be elevated. If the ALT or AST levels are elevated, a concomitant hepatitis B and/or C infection should be suspected. Recently, DNA detection in serum was shown to be very sensitive and specific for the early diagnosis of schistosomiasis [48].

SCHISTOSOMA *OVA* IDENTIFICATION BY MICROSCOPY (Fig. 122.11)

The microscopic demonstration and identification of eggs in excreta remains the gold standard for the diagnosis of active schistosomiasis, but has low sensitivity in light infections [29]. In rare cases, incidental exposure may lead to infection with only male or female worms, in which case there is no ova production. If eggs are found, their size and shape allows easy detection and identification under low magnification. Direct microscopic examinations of wet-mounted slides are not reliable, as they contain only a few milligrams of feces or milliliters of urine. Concentration methods and repeated examinations in different urine or stool specimens on different days may be required to confirm the presence of active infections. Stools may be concentrated with general techniques, for example Ritchie's formol-ether method, or more specific ones, such as conical flask sedimentation in glycerine water, sieving or miracidial hatching. Urine may be centrifuged, sedimented or passed through paper or nylon filters with a variety of devices [1, 49, 50]. Sensitivity increases considerably with the weight or volume of the sample examined. The excretion of *S. haematobium* eggs in the urine is not uniform over a day, and samples collected between 10.00 h and 14.00 h are more likely to be positive. Also, physical exercise before sampling increases the chance of finding eggs in the urine. The microscopic examination of crushed rectal snips, obtained during proctoscopy or sigmoidoscopy, is remarkably sensitive for *S. mansoni* and *S. japonicum*, as well as *S. haematobium* infection. Rectal biopsies can be performed during proctoscopy or sigmoidoscopy by taking 1–3 small mucosal samples from inflamed or granulomatous lesions, or from random areas of normal-appearing mucosa. The mucosal sample is pressed between a cover slip and a glass slide until it becomes transparent. If ova are present, they can be seen under low power microscopy. Also, bladder biopsies obtained during cystoscopy can be directly examined for eggs. The biopsies can be partly fixed in formalin for histologic staining and examination, which may reveal eggs, as well as inflammation and typical granulomas.

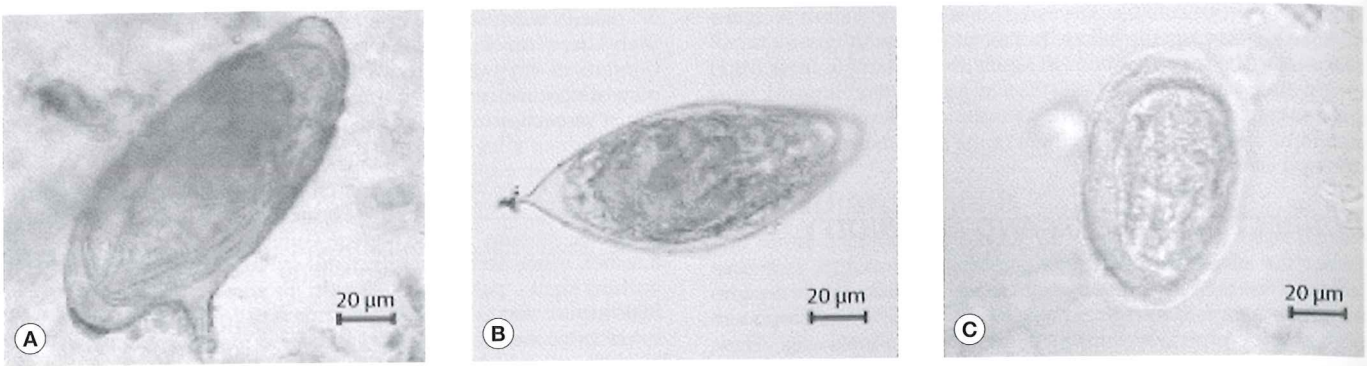


FIGURE 122.11 Schistosome eggs under the microscope. **(A)** *S. mansoni* (from lateral spine); **(B)** *S. haematobium* (from terminal spine); **(C)** *S. japonicum* (from small lateral spine). *(Reproduced with permission from Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet 2006;368:1106–18.)*

Egg counts in calibrated samples provide a quantitative assessment of the infection. Quantitative egg counts after standardized urine filtration or in calibrated fecal thick smears (Kato-Katz method) are especially useful for epidemiologic surveys and control, as they correlate reasonably well with worm burdens and morbidity. For the Kato-Katz method, a 50 mg sample of feces is pressed through a 105-mesh steel sieve and fitted in the hole of a punched template, which rests on a glass microscope slide. This calibrated sample of filtered feces is then covered with a cellophane cover-slip impregnated with glycerin, inverted and pressed onto a bed of filter paper. The slide is left for 24–48 hours while the fecal matter clears. Then, all eggs on the slide are counted under a microscope. Multiplying by 20 gives the number of eggs per gram of feces (EPG). Limitations of the test are that formed stools are desirable, light infections tend to be missed when examining small amounts of feces, and the microscopist must be reliable. The most common quantitative technique for urine is filtrating 10 ml with a syringe through a paper, nucleopore or nytrel filter, which is then examined under a microscope and the number of eggs counted. This method provides a measure of eggs per 10 ml of urine [49, 50].

In clinical settings and in field surveys requiring accuracy, 3–5 repeated examinations with Kato-Katz or 10 ml urine filtration may be needed. It may be important to verify the ova's viability, particularly to determine whether drug treatment has been successful. Dead *Schistosoma* ova in the tissues can be excreted in the urine and stool for months after adult worms are dead. Eggs passed more than one week after treatment are usually not viable. Microscopic examination of viable eggs will reveal clear, transparent structures with moving organelles (flame cells) of the miracidium. Dead eggs are often deformed, dark or half-empty, and show no internal movement. Alternatively, ova may be hatched to demonstrate their viability by diluting a small amount of urine or stool sediment in distilled water at room temperature and exposing it to light for 15–20 minutes. Ideally, it is put in a covered, darkened flask with a narrow top, which is left exposed to the light. Examination with a hand-held lens will reveal swimming miracidia.

SEROLOGY

Antibody-Based Serum Assays

Many serologic methods have been developed for the indirect diagnosis of schistosomiasis [49–52]. These are quite sensitive but can not distinguish a past infection from a present active one. Some tests also may cross-react with other helminths and they are not easily applicable in the field. Serologic assays are important, however, for diagnosis in travelers, migrants and other occasionally-exposed people. They can also provide important circumstantial evidence when complications of schistosomiasis are suspected, especially neuroschistosomiasis, even when urine and stools are microscopically negative. Most routine techniques detect IgG, IgM or IgE against soluble worm antigen (SWA) or crude egg antigen (CEA) by enzyme immune assays (EIA). Seroconversion takes place usually within 4–8 weeks after infection, but, rarely, antibodies might not be detected for 4–5 months after infection. Most assays remain positive for at least two years after cure, and often much longer.

Circulating Schistosome Antigens

Circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) can be detected and quantified in serum or urine with labeled monoclonal antibodies in different formats, including reagent strips [50, 52, 53]. These are *Schistosoma* gut glycoproteins regurgitated with the metabolized blood particles into the circulation of the human host. Antigen detection in serum is not sensitive in light infections, however, and therefore not very useful for clinical applications. These assays are primarily used in epidemiologic and therapeutic studies. Urine-based assays are more sensitive, but less specific.

CHEMICAL TESTING

Using reagent strips to test for blood in urine and simple questionnaires for visible hematuria are inexpensive, easy and effective tools for the screening and rapid assessment of urinary schistosomiasis [1–3, 29, 49, 50]. Indirect diagnostic methods for intestinal or hepatic schistosomiasis, for example examining the stool for mucus and blood, are reasonably sensitive, but less specific.

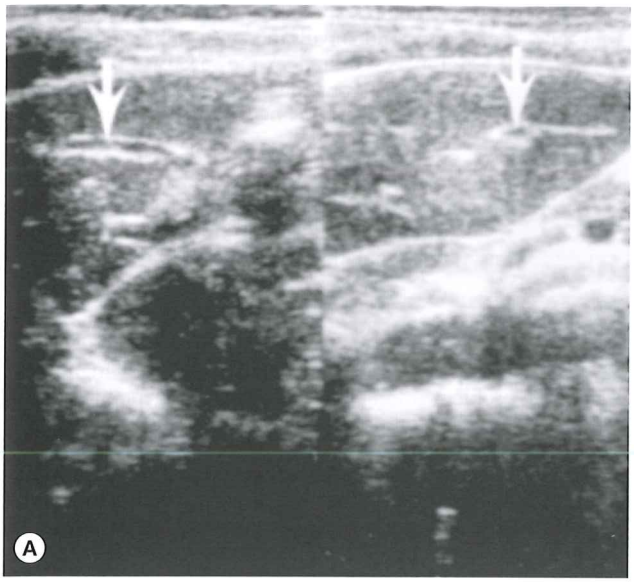
ENDOSCOPY AND CYSTOSCOPY

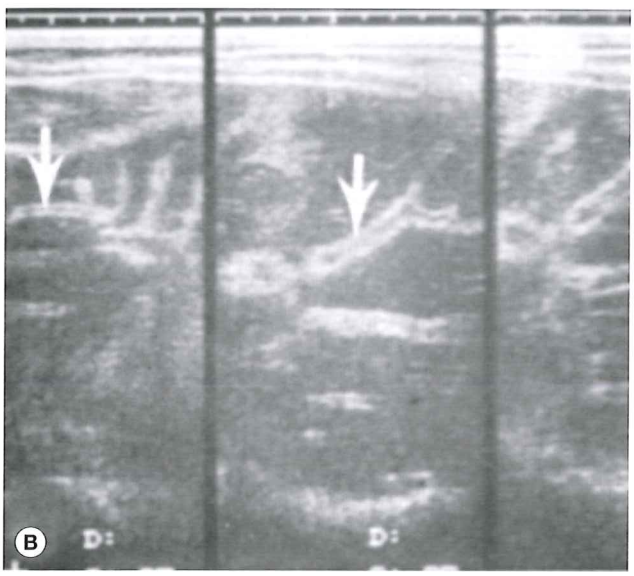
Endoscopy can visualize esophageal varices; sigmoidoscopy and colonoscopy allow visualizing of typical schistosomiasis lesions and provide access to biopsy specimens for tissue egg identification [1, 54]. The endoscopist can visualize small petechiae in otherwise normal rectal mucosa, dull patches with a sandpaper-like appearance, superficial erosions, stellate superficial ulcerations, hyperemic, easy bleeding areas, and granulomatous or polyp disease; the latter can be removed during the procedure. Laparoscopy can reveal granulomatous inflammation or periportal fibrosis. Needle biopsies of the liver may not sample the hard fibrotic lesions; wedge biopsies may be needed, for instance, to differentiate periportal fibrosis from post-infectious or alcoholic cirrhosis. Cystoscopy may reveal hemorrhagic inflammation, granulomatosis, polyposis, fibrosis or calcification of the bladder, and allow biopsy sampling.

IMAGING (Figs 122.7, 122.8, 122.12)

X-Rays and Scans

Intravenous pyelography and ultrasonography allow visualization of renal, ureteral and bladder pathology quite easily and plain x-rays may show calcified tissues and lesions, including renal or bladder stones (Figs 122.7 and 122.8) [55]. In hepatic schistosomiasis, contrast radiology can demonstrate portal vein distension or





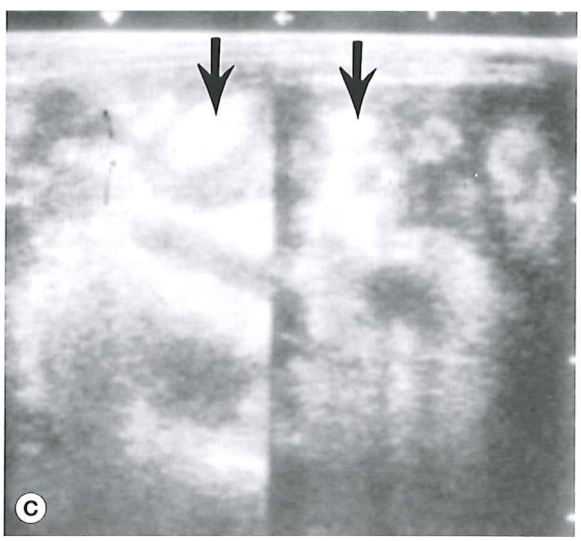


FIGURE 122.12 Minimal **(A)**, moderate **(B)** and extensive **(C)** periportal fibrosis of the liver demonstrated by ultrasonography. The arrows point to typical lesions.

gastro-esophageal varices. Computerized tomography, myelography and magnetic resonance can be useful for detailed imaging, especially for neuroschistosomiasis.

Ultrasound

Over the past three decades, ultrasonography has provided marked improvement in the diagnosis and study of schistosomiasis pathology [56, 57]. Sonography is an excellent noninvasive technique to demonstrate the pathognomonic periportal fibrosis and can estimate the degree of portal hypertension by measuring the distension of the portal vein (Fig. 122.12). Standardized protocols have been developed in order to classify hepatic fibrosis and urinary tract lesions. These protocols require specific expertise and experience, and results may be subject to considerable inter- and intra-observer variation.

TREATMENT

Once active infection is confirmed by detection of ova, or a clinical diagnosis of schistosomiasis is made, specific chemotherapy is indicated.

CHEMOTHERAPEUTIC AGENTS

Praziquantel, the drug of choice, is effective against all schistosome species, as well as other flukes (e.g. *Clonorchis sinensis* and *Paragonimus westermani*) and cestodes (e.g. *Taenia saginata, Taenia solium, Diphyllobothrium latum* and *Hymenolepis nana*) [2, 3, 54, 58]. Praziquantel is mostly marketed as scored 600-mg tablets. The drug acts within an hour after ingestion by provoking tetanic contraction of the adult worms and damaging their tegument, but the precise molecular mechanisms remain unknown. The antigens revealed induce humoral and cellular immune responses, enhancing the direct drug action. Side effects are mild and include nausea, vomiting, malaise and abdominal pain. In heavy infections, acute colic with bloody diarrhea may occur, probably provoked by massive worm shifts and antigen releases induced by praziquantel.

The original brand of praziquantel, Biltricide® (Bayer), has lost most market share to about 30 generic brands. Consequently, the price falling from $2.00–4.00 to less than $0.20 per treatment has made the drug widely available for control purposes [58]. On the downside of this development, large pharmaceutical companies have given up investments to find new schistosomicides [14].

The quality of generic praziquantel may vary and counterfeit praziquantel has been reported in Sudan [59]. The toxicity, mutagenicity and embryotoxicity of praziquantel are very low in animal models and, after 30 years of widespread application, no significant safety problems have been documented in humans. It is therefore no longer recommended to withhold treatment from young children and pregnant women [60].

The standard single dose of 40 mg/kg of body weight for treating *S. mansoni, S. haematobium* or *S. intercalatum* may be subcurative [1–3, 54]. Higher regimens are not always well-tolerated, however, and should be given in split doses, several hours apart. For population-based treatment, in which the reduction of egg loads and morbidity is the main objective, 40 mg/kg remains recommended [10]. People with high egg counts may be given two doses of 30 mg/kg, 3–6 hours apart. This higher split-dose is also routinely recommended for treatment of *S. japonicum, S. mekongi* and *S. malayensis* infections.

Praziquantel does not act on ova or on immature worms. Viable, tissue-dwelling eggs may be excreted for several weeks after successful treatment and schistosomulae or young adult worms may survive treatment and become viable adult worms. The optimal course, therefore, if cure is the goal, is to repeat the microscopic examination of the stool and/or urine for ova 4–6 weeks after treatment. After a single dose of 40 mg/kg, intensities of infection, as measured by egg counts or antigen levels, are almost invariably reduced by 90–95%. Parasitologic cure is usually achieved in 70–95% of treated

patients, but these percentages may be considerably lower in populations with high initial egg counts and exposed to intense transmission and re-infection [61]. For individual case-management, or when there is no risk of re-infection, 60–120 mg/kg in split doses may be given. Repeat treatment 6–12 weeks later can be used to cure prepatent infections, particularly if eosinophilia, high antibody titers or symptoms persist. Definitive parasitologic cure in people leaving endemic areas is proven by the disappearance of viable eggs from the excreta for at least six months after treatment. In some cases, egg release is interrupted but starts again a few weeks later. Adult worms may be incapacitated temporarily by chemotherapy and resume mating and activity later. A few remaining schistosomes may cause little or no harm, but if complete eradication of all worms is envisaged, a conclusive laboratory evaluation may have to consist of thorough examination of excreta on three consecutive days, serologic reconversion, clearing of eosinophilia and, possibly, examination of a rectal or vesical biopsy. For population-based treatment in endemic areas, aiming more at morbidity rather than infection control, pursuing complete cure in all those treated is impractical and not pertinent.

The cure rate (percentage of infected people converting to negative stools or urine) can vary according to the sensitivity of method used, the timing of the follow-up, and the intensity of transmission. The optimal time of follow-up is 4–6 weeks after treatment. However, in areas and periods of intense transmission, residual surviving of worms in those with high worm burdens, maturation of prepatent infections and rapid re-infection may result in seemingly low cure rates [61]. A better measure of success is the reduction of mean egg counts as an indicator of the risk for severe morbidity, and the impact on the long-term resolution of pathology as measured by ultrasound, hematuria reagent strips testing for blood, or clinical evaluation [62, 63].

Most schistosome-induced pathology resolves after praziquantel treatment. Clinical, radiologic and sonographic studies have demonstrated regression over weeks-to-months of intestinal and vesical lesions, reactive hepatomegaly, and even severe upper urinary tract lesions and liver fibrosis. Thus, the prognosis is usually good, except in advanced cases with parenchymal hydronephrosis or renal failure in urinary schistosomiasis, or severe liver fibrosis with established portal hypertension with recurrent bleeding from esophageal varices and ascites in hepatosplenic schistosomiasis.

Resistance against praziquantel was feared in some high transmission foci, but the low local cure rates were shown to be caused by intense continuing transmission [61]. Tolerant *S. mansoni* strains were reported in Egypt, but have not been independently confirmed. If existent, they have not spread further in spite of intense drug pressure. To date, true drug resistance to praziquantel in human populations has not been convincingly documented.

Recently, derivatives of artemisinin, a drug for the treatment of malaria, were shown to be effective against the immature stages of *S. japonicum*, *S. mansoni* and, possibly, *S. haematobium* [64]. They could, in principle, be used to treat acute schistosomiasis or as a prophylactic agent. In a clinical trial in China, repeated administration throughout the transmission season greatly reduced parasite burden of *S. japonicum* and prevented early manifestations of infection. Trials in Africa, as a stand-alone drug or in combination with praziquantel, showed prophylactic but no curative potential. However, their preventive application is not recommended, as artemisinin should be preserved for treatment of drug-resistant malaria.

TREATMENT OF ACUTE SCHISTOSOMIASIS AND COMPLICATIONS

Topical steroid creams and oral antihistamines can provide symptomatic relief for cercarial dermatitis. Katayama fever is primarily treated with corticosteroids, for example prednisone 40 mg daily for 5–14 days, to suppress the hypersensitivity reaction. This treatment should be followed by praziquantel to eliminate the adult worms [31, 32, 54].

Neuroschistosomiasis requires specialized care, again with corticosteroids and, if necessary, anticonvulsants prior to praziquantel treatment [43, 54]. Caution is required in the rare case of concurrent neurocysticercosis, on which praziquantel is also active but may provoke epileptic seizures owing to the destruction of the cerebral cysts.

Bleeding from esophageal varices may be treated symptomatically with β-blockers, endoscopic sclerotherapy, splenectomy, or splenorenal or portocaval shunts. In advanced urinary schistosomiasis, destructed and non-functional kidneys may have to be removed [54].

CONTROL AND PREVENTION

Until late in the 20th century, schistosomiasis was a high-priority public health problem among the populations in Egypt, the Maghreb, Brazil, China and the Philippines [1–3, 11, 26]. Large-scale national control programs, based on the chemical or physical destruction of the snail intermediate hosts, case-finding and general improvement in hygiene, involved large teams of malacologists, epidemiologists, clinicians and laboratory technicians in specialized programs. Apart from a few research or pilot projects, most of the lower-income endemic countries, especially in sub-Saharan Africa, remained devoid of such efforts and often lacked the means to diagnose and treat clinical cases.

SNAIL CONTROL

Attempts to exterminate the snail populations with chemicals (molluscicides) are expensive, logistically demanding and often inconclusive. An efficient application requires considerable human and material resources, as well as detailed epidemiologic and malacologic surveillance. Snail populations can be reduced but rarely exterminated, requiring molluscicide treatment to be repeated regularly and for a long period. The toxicity of molluscicides to fish and other aquatic organisms causes ecologic concerns. Focal application in specific "hot spots" where schistososome-infected snails reside and human infections are occurring may be useful in preventing local infections. In general, however, chemical snail control has been all but abandoned as a standard control strategy. Snail control can also be pursued in some cases by thorough and regular weeding, hydraulic engineering and alternative irrigation practices, but such measures are tedious and expensive. The introduction of competitor snails, natural predators such as ducks or fish, or plant molluscicides, is not effective in practice.

MASS DRUG ADMINISTRATION (MDA) PROGRAMS

The introduction of praziquantel heralded a shift in control strategies to interventions aimed at the definitive human host, rather than at the intermediate snail host. This strategy of "morbidity control" has a more immediate impact on infection and disease and requires much less expertise. It was officially adopted by the WHO in 2002 and has become the standard approach in most endemic countries [1–3, 6, 8, 10, 58]. Its main objective is to reduce community-wide infection rates and intensities of infection in order to prevent schistosomal morbidity (by reducing ova retained in the host's body) and, over time, transmission of infection (by reducing ova passed from the host into the environment). Various chemotherapy strategies can be applied, including indiscriminate mass treatment, treatment of particular risk groups, especially school-aged children, and active case-finding followed by treatment (Fig. 122.13). Thirty years of experience have shown that population-based treatment is feasible and safe, and effectively reduces prevalence and intensity of infection, as well as morbidity. Its impact on transmission is more difficult to measure, and a limited number of residual eggs passing into the environment can maintain considerable transmission potential. However, in most areas where MDA has been applied over a number of years, transmission appears to have waned. Still, regular surveillance and/or regular re-treatment must be envisaged.

FIGURE 122.13 Schistosomiasis control in the field **(A)** Mass treatment with praziquantel in the community. **(B)** Safe water suppy, **(C)** Snail control with molluscicides. *(Reproduced with permission from Bruno Gryseels; Infectious Disease Clinics of North America; vol 26; Issue 2; 383-397; Elsevier Inc ©2012).*

INTEGRATED CONTROL METHODS

Schistosomiasis can be eliminated by behavioral changes, safe water supply and sanitary engineering. This happened in Japan in the 1950s, far before modern drugs were developed [65]. In low-income countries, the prevention of schistosomiasis necessitates more than providing safe drinking water. Sites free of exposure to infective cercariae for washing, bathing, laundering, swimming and crop irrigation are also required. Moreover, these must be adapted to local attitudes and circumstances, and long-term maintenance is a frequently problematic necessity. Specific educational programs can enhance the knowledge and perception of schistosomiasis, but is often insufficient in reducing exposure in the absence of adequate alternatives for water contact.

In several countries with sufficient resources and the political will to implement and sustain population-based therapy, the public health impact of schistosomiasis has decreased dramatically over the past decades. These middle-income nations are usually characterized by general socioeconomic progress and substantial improvements in water supply, sanitation and healthcare. While residual transmission pockets may remain difficult to extinguish, general prevalence and intensities of infection are kept low by regular MDA. It is estimated that the number of remaining infections in Brazil and China, and possibly even Egypt, has been reduced to less than one million. Even more strikingly, severe morbidity in these countries has all but disappeared; cases of advanced hepatosplenic disease with hematemesis, advanced hydronephrosis or schistosomiasis-associated bladder cancer, once common, have become anecdotal. In Morocco, Tunisia, Iraq and Puerto Rico the infection has been eliminated.

CONTROL IN SUB-SAHARAN AFRICA

Early pilot projects with population-based chemotherapy in sub-Saharan Africa showed promising results in the short-term, but the re-treatment schedules and vertical structures employed were not sustainable once foreign assistance was withdrawn [2, 8, 20]. Quick wins were as quickly lost to rapid re-infection, while regular health services were left deprived and demotivated for further action. National resources and capacities are limited, while decision makers are faced with many priorities. Some programs that were built up more gradually, by improving passive or active case finding through regular healthcare structures, have had less impressive short-term results but appeared to be more sustainable. However, as the disease continues to spread to new development areas and city slums, efforts to control schistosomiasis remain a public health priority in large parts of the continent.

GLOBAL TARGET TO CONTROL SCHISTOSOMIASIS

Renewed efforts have been launched to control schistosomiasis in resource-poor countries following a call by the WHO to international agencies, charities and pharmaceutical companies to provide praziquantel and other anthelminthic drugs at low, or no, cost [9, 10, 15]. The joint "Global Target" is to annually treat at least 75% of all school-aged children at risk of infection using a standardized strategy based on local epidemiologic characteristics of schistosomal infections. Active MDA programs are being launched in an increasing number of sub-Saharan African countries [47]. An important new asset is the integration of schistosomiasis control with MDA for

TABLE 122-1 Other Schistosome Species Causing Human Intestinal Disease

	Schistosoma intercalatum	*Schistosoma mekongi*	*Schistosoma mattheei*
Distribution	African disease only. Endemic in parts of Cameroon, Gabon, Democratic Republic of Congo and other areas of Central and West Africa; although occasionally co-existent with *S. mansoni* and *S. haematobium*, usually found as the sole species in known transmission foci	Lower Mekong River basin in Laos and Cambodia	South Africa. Natural infection of sheep, cattle, horses and antelope that occasionally infects humans. Always found in association with *S. mansoni* or *S. haematobium*
Clinical manifestations	Anorexia, nausea, abdominal pain, diarrhea with blood and mucus; rectal and genital lesions; hepatomegaly and rectal bleeding pain in left iliac fossa with tenesmus	Similar to *S. japonicum*; acute schistosomiasis in non-immune travelers; generalized weakness, diarrhea and abdominal distress; hepatomegaly and splenomegaly. CNS and cardiopulmonary complications not described	Relatively mild intestinal disease, mucoid diarrhea; diffuse intermittent abdominal pain and cramping, malaise, hepatomegaly
Diagnosis	Eggs are similar to *S. haematobium* in shape and in possessing a terminal spine but are usually longer (140–240 μm), often have a central bulge and are shed in stool, not urine; terminal spine is characteristically bent; eggs are Ziehl-Neelsen (acid-fast) positive	Eggs in stool and rectal biopsy. The eggs are similar to *S. japonicum* but are generally smaller (50–80 μm by 40–65 μm); they also contain a small, inconspicuous spine. Elevated alkaline phosphatase	Eggs resemble *S. intercalatum* and measure 120–180 μm in length and have a terminal spine; eggs present in stool or occasionally urine
Treatment	Praziquantel at 40 mg/kg body weight in single dose	Praziquantel at 60 mg/kg single dose or 2 × 30 mg/kg in divided doses	Praziquantel at 40 mg/kg single dose

CNS, central nervous system.

other neglected parasitic diseases, for example lymphatic filariasis, onchocerciasis and intestinal helminths, as well as provision of vitamins and nutritional supplements [66]. To increase sustainability, these campaigns are carried out wherever possible through community health workers or regular health services rather than vertical mobile teams. However, many health systems may still be too weak and overburdened to sustain these programs, or to execute them with the necessary epidemiologic vigor [67]. The over-reliance on drugs may also reduce efforts for the implementation of the other, more structural, elements of the WHO resolution, for example accessible care for clinical cases, safe water supply, improved sanitation and behavioral changes [68]. The massive, and sometimes uncontrolled, use of praziquantel brings along a risk for the development of drug resistance, while there are no alternative antischistosomal drugs in the pipeline [69]. Thus, while further progress towards the elimination of schistosomiasis as a public health problem can be expected, the global efforts need to be accompanied with national and local expertise and vigilance.

Although a vaccine to prevent schistosomiasis is unlikely to be available during the next decades, one that would reduce infection rates may improve a multifaceted approach to control schistosomal morbidity and transmission. A combination of chemotherapy, reduction of water contact and contamination, and possibly snail control and vaccination, could lead to the elimination of schistosomiasis in much of the world. However, the ultimate challenge in the eradication of schistosomiasis is to improve living standards and alleviate poverty, which is the underlying cause of this and many other health problems in the tropics.

OTHER HUMAN SCHISTOSOME INFECTIONS

Characteristics of three other *Schistosoma* species causing human disease are outlined in Table 122-1.

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