8.11.1 Schistosomiasis 1540

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and Trevor N. Petney 8.11.3 Lung flukes (paragonimiasis) 1558 Udomsak Silachamroon and Sirivan Vanijanonta 8.11.4 Intestinal trematode infections 1562 Alastair McGregor 8.11.1 Schistosomiasis David Dunne and Birgitte Vennervald ESSENTIALS Schistosomiasis is caused by trematode worms Schistosoma spp., whose life cycle requires a definitive vertebrate host and an inter- mediate freshwater snail host. Transmission to humans occurs through exposure to fresh water containing infectious larvae, which can penetrate intact skin before developing into blood-dwelling adult worms. The disease is patchily distributed in parts of South America, Africa, the Middle East, China, and Southeast Asia, with about 200 million people infected and 20 million suffering severe consequences of infection. Clinical features Most infected people living in endemic areas have few (if any) overt symptoms, but clinical manifestations (when present) depend on the stage of infection. Larval invasion causes a transient immediate hypersensitivity reaction with intense itching (‘swimmer’s itch’) and rash (cercarial dermatitis). Early primary infection can cause a severe systemic reaction (acute schistosomiasis or Katayama fever) with fever, con- stitutional symptoms and (almost invariably) eosinophilia. Established infection can cause (1) Urinary schistosomiasis (Schistosoma haematobium)—active disease most commonly presents with painless, terminal haematuria; chronic disease is as- sociated with calcification, ulceration, and the development of papillomas in the bladder, and with ureteric fibrosis. (2) Intestinal schistosomiasis (S. mansoni and S. japonicum)—clinical features include diarrhoea, hepatomegaly, and splenomegaly. (3) Other manifestations—these include (a) nervous system—myelopathy and radiculopathy; (b) lungs—pulmonary hypertension and/or cor pulmonale;
(c) renal—glomerulonephritis. Diagnosis Should be suspected with a history of exposure to potentially con- taminated water. Definitive diagnosis depends on direct microscopic detection of eggs in urine or stool samples, or in tissue biopsies. Antigen detection and polymerase chain reaction-based tests can be useful in some circumstances. Treatment and prognosis Praziquantel is the drug of choice, with corticosteroids added in cases of Katayama fever. Acute schistosomiasis responds well, but chronic disease less so, but rapid re-exposure and reinfection are common (particularly in young children) unless control measures are implemented at the community level. Prevention In areas of high transmission, population-based chemotherapy or treatment of schoolchildren (who contribute most to ongoing trans- mission). Health education should be aimed at improving practices of water use and preventing indiscriminate urination and defecation. Introduction Schistosomiasis, also known as bilharzia, is caused by infection with parasitic

trematode worms (flukes) of the genus Schistosoma. Disease is usually associated with acute or chronic infections con- tracted by exposure to fresh water containing infective cercarial larvae that penetrate intact skin and develop into blood-dwelling worms. Most human infections are caused by one of three species, S. mansoni, S. haematobium, or S. japonicum. Two species, S. inter- calatum and S. mekongi, are less significant. Schistosomiasis is patchily distributed in parts of South America, Africa, the Middle East, China, and South-East Asia (Fig. 8.11.1.1). An estimated 800 million people are at risk of schistosomiasis worldwide, of whom at least 200 million are infected.

8.11.1 Schistosomiasis 1541 Diagnosis and treatment are often not available to exposed rural populations, and drug-based control programmes are ham- pered by the continued susceptibility to reinfection of those who have been treated, particularly children. Human schisto- somiasis is most often an insidious and chronic disease with a range of pathological manifestations involving the intestine and liver, or the urogenital tract. Mortality estimates are difficult, but 20 000–200 000 deaths might be directly associated with schisto- somiasis each year. Parasite life cycle The schistosome life cycle requires two host species: a definitive ver- tebrate host, in which adult male and female worms develop and sexual reproduction occurs, and an intermediate freshwater snail host, in which the parasite multiplies asexually. Transmission be- tween these hosts is achieved by two different free-swimming larval stages. For species that infect humans, miracidia hatch from eggs excreted in the faeces or urine, and then seek out and infect snails. Cercariae are released from the snail and are able actively to pene- trate intact human skin. Snails Different schistosome species have their own, often very restricted, range of snail hosts. Schistosomiasis is thus closely associated with particular freshwater habitats, and its geographical distribution is restricted by the availability of particular snail species. S. man- soni and S. haematobium are confined to aquatic snails (genera Biomphalaria and Bulinus, respectively) that inhabit ponds, lakes, irrigation canals, slow-flowing streams, and rivers. S. japonicum
is transmitted by amphibious snails of the genus Oncomelania that, in addition to a variety of freshwater habitats, are also present in damp soil and vegetation, such as paddy fields. Cercariae Once shed from freshwater snails, cercariae (Fig. 8.11.1.2) live for about 24 h, but their effective period of infectivity is probably shorter under field conditions. Cercarial behaviour and the timing of their release enhance their chance of contacting their vertebrate host of choice. Increasing temperature and light trigger the release of S. mansoni and S. haematobium cercariae during the day, and they use their tails actively to maintain their position near the water sur- face.
S. japonicum cercariae are shed late in the day and are closely associated with the meniscus, perhaps reflecting their wider host range, as species specific for rodents are shed at night. Skin penetration, transformation,
and migration Contact with skin triggers adherence mechanisms, and proteolytic enzymes and muscular movements allow penetration of the skin in minutes. Penetration initiates transformation into a schistosomular Fig. 8.11.1.1 Global distribution of the schistosomes that affect humans.
Fig. 8.11.1.2 The infective larva (cerceria) of Schistosoma mansoni, length approximately 200 µm. The head region has characteristic suckers; the muscular forked tail propels the free-swimming larva, but is discarded during skin penetration. This larva will develop into an adult worm in a human host.

section 8 Infectious diseases 1542 larva, with loss of the tail and of the protective outer glycocalyx layer, and the addition of an extra lipid bilayer to the surface membrane of the parasite’s syncytial outer tegument. This tegument now forms the main parasite–host interface and so has

physiological and im- munological functions vital to long-term survival in the mamma- lian bloodstream. These include uptake of nutrients, response to injury, and surface adsorption of host antigens to provide an im- munological disguise. Newly transformed schistosomula remain in the epidermis for several days before migrating, via the blood- stream, lungs, and systemic circulation, to the hepatic portal system. Here the schistosomula mature and differentiate into adult worms, pair, and migrate against the portal blood flow to the small venules draining the genitourinary tract (S. haematobium) or the large and, to a lesser extent, small intestine (S. mansoni, S. japonicum, S. inter- calatum, S. mekongi). Adult schistosomes Male and female worms are 1 to 2 cm long and morphologically dis- tinct. Paired worms remain permanently coupled, with the shorter, flatter, more muscular male gripping the female in its gynaecophoric canal (Fig. 8.11.1.3). Worms ingest blood cells into their blind- ending bifurcated gut, producing a haematin-like pigment that is regurgitated into the blood. Adult worms have average lifespans in humans of 3 years (S. haematobium) to 7 years (S. mansoni), al- though active infections are reported in individuals who have left endemic areas more than 20 years previously. Schistosme eggs and miracidiae Female worms start to produce eggs between 5 and 12 weeks after infection, at rates of 300 (S. mansoni) to 3000 (S. japonicum) per day. A few days after an egg is laid, a single miracidium develops within the rigid eggshell, the shape and size of which is character- istic for each species. S. mansoni (Fig. 8.11.1.4) and S. haemato- bium eggs are ellipsoid, 65 × 150 µm, the former having a lateral spine and the latter a terminal spine. S. japonicum eggs are more spherical, 70 × 90 µm, with a small lateral knob that is not always apparent microscopically. Embryonated eggs pass from the venules into the gut or bladder lumen. This is facilitated by host immune responses to secreted egg antigens, as egg excretion is inhibited in immunosuppressed experimental hosts and HIV infected in- dividuals. The passage of the eggs causes tissue damage, as does the granulomatous reactions to eggs that fail to escape from the bloodstream and get swept into the liver by the portal blood flow. Eggs deposited in fresh water rapidly hatch in response to osmotic changes, releasing the miracidium. This ciliated and actively swim- ming larva lives for about 6 h, and can chemically detect the prox- imity of snails, modifying its swimming behaviour as it approaches a potential host. The parasite actively penetrates the snail’s tissues and transforms into a primary sporocyst. Asexual replication gives rise to daughter sporocysts that migrate to the snail’s hepatopan- creas where cercariae are asexually generated within each sporo- cyst. Thus, snails infected with a single miracidium release cercariae that are all of the same sex. Cercariae are first released from snails 3–6 weeks after infection, depending on parasite species and am- bient temperature. Infected snails can shed hundreds of cercariae daily over several months. Epidemiology Distribution Schistosomiasis is associated with poor living conditions and inad- equate sanitation and water supply. Its distribution has changed over the last 50 years. In some areas sustained control strategies have been successful. However, environmental and climatic changes, develop- ment of water resources, population increases, and migration, have led to its spread into previously nonendemic areas or areas with a low rate of infection. S. japonicum and S. haematobium have decreased, whereas S. mansoni has increased to become the most prevalent and widespread species. S. japonicum has been controlled effectively in many areas and is now endemic only in China, where it is much re- duced, Indonesia, the Philippines, and Thailand. S. mekongi is found in Cambodia and Laos, and S. intercalatum is found in 10 countries within the rainforest belt of central Africa. S. mansoni is present in most countries of sub-Saharan Africa, and in Madagascar, the Nile Delta and valley, as well as Saudi Arabia, Yemen, Oman, Libya, nor- thern and eastern Brazil, Suriname, Venezuela, and some Caribbean islands. S. haematobium is widespread in sub-Saharan Africa and Fig. 8.11.1.3 Adult worms of S. mansoni. The shorter male

encloses the female in its gynaecophoric canal, the characteristic haematin-like pigment can be seen in the female worm's gut. Fig. 8.11.1.4 Egg of S. mansoni containing a fully developed miracidium and showing the characteristic lateral spine of this species.

8.11.1 Schistosomiasis 1543 Madagascar, and is more prevalent than S. mansoni in North Africa and the Middle East. Transmission and epidemiology Each successful cercarial penetration of human skin has the po- tential to give rise to a single male or female adult worm, but it is probable that many cercariae die naturally in the epidermis. People tend to accumulate worms with continued exposure to infection. However, human populations in endemic areas do not just continue to accumulate worms with age. Intensities of infec- tion increase in children during their younger years (as estimated by numbers of excreted eggs), peaking around the age of 12 years, before falling to lower levels in adulthood (Fig. 8.11.1.5a). This is probably due to the death of older worms, which are not re- placed at a similar rate in older people. This age–infection in- tensity profile is more pronounced if study populations are given chemotherapy to remove existing infections and then monitored for levels of reinfection over several subsequent years. In these circumstances, it is clear that young children are much more susceptible to reinfection than older children or adults, and that a striking change in susceptibility to reinfection occurs after 12 years of age. Age-dependent resistance to infection The slower acquisition of worms in adulthood could be due to re- duced exposure to infection or to age-dependent changes in innate resistance or acquired immunity. In many endemic areas children have more contact with water than adults, but careful observation of water-associated behaviour has shown that age profiles of water contact are variable between communities, whereas profiles of re- infection intensities are remarkably consistent (Fig. 8.11.1.5b). This suggests that host-related factors other than exposure influ- ence susceptibility to reinfection. This has been most convincingly shown in fishing communities in areas with high S. mansoni trans- mission on Lake Albert, Uganda. Here occupational water contact results in adults having greater exposure to infection than their children, yet, within 12 months of treatment, it is the children under 12 years of age that suffer much higher reinfection inten- sities. Current research is focused on assessing the relative roles of innate and acquired immunity in this age-dependent resistance and whether the onset of puberty or the length of time spent living in endemic areas might be important. For example, it is not known if this age-dependent resistance to infection holds true for travel- lers exposed to infection for the first time. Immune responses to schistosomes also differ between children and adults. Specific IgE and other characteristically Th2-type responses against the para- site are associated with resistance to reinfection. Whatever mech- anisms underlie the contrasting susceptibilities of children and adults, continued exposure can be expected to result in reinfection, especially among younger children. Pathogenesis Schistosome eggs can be trapped in the tissues, often the walls of the intestines or, depending on species, the urinary bladder, ureters, and genital organs where they may be seen in cone biop- sies of the uterine cervix. The eggs of S. mansoni and S. japonicum are swept into the liver via the portal system, where they embolize into the portal radicles and give rise to vascular and granuloma- tous changes (Fig. 8.11.1.6). Granulomatous pyelophlebitis and peripyelophlebitis is responsible for development of portal hyper- tension, while granulomata with subsequent fibrosis may be re- sponsible for the periportal fibrosis. The characteristic lesion in the liver is a presinusoidal periportal fibrosis (Symmers' fibrosis, Fig. 8.11.1.7). There is typically no bridging between the fibrous tracts, no nodule formation, and no hepatic cell damage. Increased portal pressure can result in the development of portosystemic 350 (a) 300 250 200 150 100 50 0 Geometric mean eggs per gram faeces (b) 12 10 6 4 2 Scaled geometric mean eggs per gram faeces 8 0 0 10 20 30

40 50 60 Mean age (years) 0 10 20 30 40 50 60 Mean age (years) Fig. 8.11.1.5 (a) Age–intensity profiles of S. mansoni infection
from six communities in Kenya. (b) Age–reinfection intensity
profiles of S. mansoni after chemotherapy in the same six communities in Kenya, assessed between 12 and 36 months after treatment. (a) From Fulford, AJ, et al. (1992). On the use of age-intensity data to detect immunity to parasitic infections, with special reference to Schistosoma mansoni
in Kenya. Parasitology 105: 219–227, reproduced with permission.

section 8 Infectious diseases 1544 collaterals and eggs can then pass directly from the portal vein to the pulmonary circulation (Fig. 8.11.1.8). Here the combin- ation of vascular and granulomatous changes is responsible for pulmonary hypertension. Clinical features Stage of invasion: Cercarial dermatitis
or ‘swimmer’s itch’ When cercariae penetrate the skin, they can cause a skin reaction, called cercarial dermatitis or ‘swimmer’s itch’. This is frequently seen after exposure to avian schistosomes, and is associated with the death of cercariae in the skin. It is seen both in areas endemic for human schistosomiasis and in nonendemic areas. In people exposed for the first time, the invasion causes a transient immediate hyper- sensitivity reaction with intense itching. Within 12 to 24 h, it is fol- lowed by a delayed reaction characterized by a small, red, pruritic, macular rash progressing to papules after 24 h. The rash can per- sist for up to 15 days and residual pigmentation might persist for months. Following repeated exposure, the signs and symptoms in-crease dramatically and start earlier. A similar reaction can be seen after re-exposure to human cercariae, predominantly S. mansoni and S. japonicum. Treatment, if needed, is symptomatic. Stage of maturation: Acute schistosomiasis
or Katayama fever The early stages of a primary infection can be associated with a severe systemic reaction that resembles serum sickness. This acute illness, called acute toxaemic schistosomiasis or Katayama fever, can occur following initial infection with any schistosome infecting humans, although it is more common in S. japonicum and S. mansoni infections. Acute schistosomiasis is most marked in primary infections in nonimmune adults, but acute S. japoni- cum infection can occur in re-exposed individuals. Symptoms appear 2 to 6 weeks after exposure. The clinical picture resembles an acute pyrexial illness with fever as a prime characteristic. The patient feels ill, and may have rigors, sweating, headache, mal- aise, muscular aches, profound weakness, weight loss, and a non productive irritating cough. Anorexia, nausea, abdominal pain, and diarrhoea can occur. Physical examination may reveal a generalized lymphadenopathy, an enlarged tender liver, and, sometimes, a slightly enlarged spleen Fig. 8.11.1.6 Schistosomal granuloma in the appendix. (a) (b) Fig. 8.11.1.7 The liver in S. mansoni infection in South Africa. Symmers’ clay pipe stem fibrosis: (a) macroscopic views; (b) microscopic view. Copyright Gareth Turner. Fig. 8.11.1.8 Schistosomal granuloma in the lung. Copyright Gareth Turner.

8.11.1 Schistosomiasis 1545 and an urticarial rash (Fig. 8.11.1.9). Eosinophilia is almost always present. Patients might become confused or stuporose or present with visual impairment or papilloedema. Severe cerebral or spinal cord manifestations may occur, and this is an indication for urgent investigative measures. Even light infections may cause severe illness and the syndrome can, in rare cases, be fatal. Differential diagnoses include infections such as typhoid (leuco- penia, no eosinophilia), brucellosis, malaria, infectious mononucle- osis, miliary tuberculosis, leptospirosis, and other conditions with fever of unknown origin. Fever and eosinophilia occur in trichin- osis,

tropical eosinophilia, invasive ankylostomiasis, strongyloid- iasis, visceral larva migrans, and infections with Opisthorchis and Clonorchis species. Established infections Urogenital schistosomiasis (Schistosoma haematobium) The signs and symptoms of S. haematobium infection relate to the worms' predilection for the veins of the urogenital tract, and result from deposition of eggs in the bladder, ureters, and to some extent the genital organs. In the phase of established infection two stages can be recognized: • an active stage mainly in children, adolescents, and younger adults with egg deposition in the urinary tract, egg excretion in the urine with proteinuria and macroscopic or microscopic haematuria • a chronic stage in older individuals with sparse or absent urinary egg excretion but the presence of urogenital tract pathology In the active stage many patients will have minimal symptoms. The most frequently encountered complaint is a painless, characteristic- ally terminal, haematuria, the prevalence and severity of which is related to the intensity of infection. In communities where S. hae- matobium is highly endemic, macroscopic haematuria among boys may be considered a natural sign of puberty. Dysuria, frequency, and suprapubic discomfort or pain is associated with schistosomal cystitis and may continue throughout the course of active infection. Initially the eggs may give rise to an intense inflammatory response in the mucosa. This may cause ureteric obstruction leading to hydroureter and hydronephrosis. Cytoscopy reveals friable masses or polyps ex- tending into the bladder, petechiae, and granulomas. These early in- flammatory lesions, including the obstructive uropathy, are usually reversible after treatment with antischistosomal drugs. The bladder lesions and obstructive uropathy can be visualized by ultrasonog- raphy (Fig. 8.11.1.10). As the infection progresses, the inflammatory component de- creases, possibly due to modulation by the host immune response, and fibrosis increases. Various changes occur in the bladder, including calcification, ulceration, and the development of papil- lomas. Cytoscopy reveals 'sandy patches' composed of large numbers of calcified eggs surrounded by fibrous tissue and an atrophic mu- cosal surface. The bladder lesions may lead to nocturia, precipitancy, retention of urine, dribbling, and incontinence. The ureters are less commonly involved, but ureteric fibrosis can cause irreversible ob- structive uropathy which can progress to uraemia. Bilateral ureteric involvement can occur. Despite damage to the ureters, symptoms are often absent or minimal. (a) (b)
Fig. 8.11.1.9 Katayama fever (S. mansoni infection): (a) giant urticarial rash; (b) rash in a traveller. Courtesy of Dr Tom Doherty, London Hospital for Tropical Diseases. Fig. 8.11.1.10 Bladder pseudopolyps as seen by ultrasound in S. haematobium infection. Courtesy of Ms Hilda Kadzo, Kenyatta National Hospital, Nairobi, Kenya.

 Egg deposition can also cause granulomas and lesions to de- velop in the genital organs, most commonly in the cervix and vagina in women and the seminal vessels in men leading to syn- dromes termed female and male genital schistomasis, respectively. This may result in dyspareunia, abnormal vaginal discharge, con- tact bleeding, and lower back pain in women, and perineal pain, painful ejaculation, and haematospermia in men. Genital symp- toms like bloody discharge and genital itch are associated with S. haematobium infection in school- age girls. Symptoms such as haematospermia and perineal discomfort have been described in travellers returning from Malawi. In some of these patients, eggs have been demonstrated in seminal fluid but not in urine. An asso- ciation between female genital schistosomiasis and HIV infection has been demonstrated but the impact of genital lesions caused by S. haematobium infection on the spread of HIV needs to be eluci- dated. Although small numbers of S. haematobium eggs are fre- quently detected in faeces and rectal biopsies, intestinal symptoms are uncommon. S. haematobium infection is associated with squamous cell car- cinoma of the urinary bladder and

significant positive associations between the occurrence of urinary bladder cancer and infection with S. haematobium has been reported in several case studies. S. haematobium has been classified as definitely carcinogenic to humans (group 1 carcinogens). The aetiological significance of the parasite in the causation of this cancer is also supported by the finding that the prevalence of squamous cell carcinoma of the bladder is correlated with intensity of S. haematobium infection. Chronic inflammation occurring with continuous infection and reinfection plays a central role in the initiation of S. haematobium related bladder cancer. In the established stage, S. haematobium should be distin- guished from renal tuberculosis with haematuria, haemoglobin- uria, and cancer of the urogenital tract. Differential diagnosis for genital schistosomiasis includes sexually transmitted infections and sexual abuse. Intestinal schistosomiasis In most early S. mansoni and S. japonicum infections, symptoms are mild or absent. Clinical features are generally encountered in those with high-intensity infections. They include diarrhoea, sometimes with blood or mucus in the surface of the stool, abdominal discom- fort, and hypogastric pain or colicky cramps. Severe dysentery is rare, but can occur. The liver, especially the left lobe, may be en- larged; the spleen may also be enlarged, but is usually soft. At this stage, the condition is entirely reversible by antischistosomal treat- ment, but the relative lack of symptoms may cause it to pass un- noticed until irreversible complications set in. Later stages present as intestinal or hepatosplenic disease. Intestinal schistosomiasis is associated with granuloma formation (Fig. 8.11.1.6), inflammation, and fibrosis, primarily in the large intestine. Focal dense deposits of S. mansoni or S. japonicum eggs as well as eggs migrating through the intestinal wall provoke mucosal granulomatous inflamma- tion, pseudopolyposis, microulcerations, and superficial bleeding. The major clinical manifestation is intermittent diarrhoea with or without passage of blood or mucus, occasionally associated with protein-losing enteropathy and anaemia. Intestinal schistosomiasis in S. japonicum infection can also involve the stomach, with gastric bleeding and pyloric obstruction. Differential diagnosis includes irritable bowel syndrome, amoeb- iasis, giardiasis, intestinal helminth infection, ulcerative colitis, Crohn’s disease, and tuberculosis. Hepatosplenic schistosomiasis is a manifestation of S. mansoni and S. japonicum infection caused by schistosome eggs trapped in liver tissue. The term covers two distinct clinical entities: early in- flammatory and late hepatosplenic disease with periportal fibrosis. Early inflammatory hepatosplenic schistosomiasis is the main cause of hepatosplenic schistosomiasis in children and adolescents. The liver is enlarged, especially the left lobe, and is smooth and firm. The spleen is enlarged, often extending below the umbilicus and firm or hard. Generally, no hepatic fibrosis can be demonstrated by ultrasonography. Early inflammatory hepatosplenic schistosom- iasis may be found in up to 80% of infected children and the se- verity is related to intensity of infection (Fig. 8.11.1.11). This type of hepatosplenomegaly may also be associated with concomitant chronic exposure to malaria. Presinusoidal periportal fibrosis (clay pipe stem or Symmers’ fi- brosis) (Figs. 8.11.1.12 and 8.11.1.7) develops later in life, gener- ally in young and middle-aged adults with long-standing intense exposure to infection. Patients with periportal fibrosis may excrete very few or no eggs in faeces. During the early stages the liver is enlarged, especially the left lobe; it is smooth, firm, and sometimes tender. Later, in many cases, it becomes small firm and nodular. The spleen is enlarged, often massively, due to passive congestion and reticuloendothelial hyperplasia (Fig. 8.11.1.12). The patient can be asymptomatic or might complain of a left hypochondrial mass with discomfort and anorexia. Anaemia might be present. There may be reduced growth, infantilism, and amenorrhoea, especially in S. japonicum infection. Severe hepatosplenic schistosomiasis can lead to portal hypertension, but hepatic function usually remains normal. Ascites, attributable both to the portal hypertension and to Fig. 8.11.1.11 Kenyan child with severe hepatosplenic schistosomiasis

mansoni.

8.11.1 Schistosomiasis 1547 hypoalbuminaemia, may be seen, especially in S. japonicum infec- tion. Patients with severe hepatosplenic disease and portal hyper- tension can develop oesophageal varices detectable by endoscopy or ultrasound (Fig. 8.11.1.13). These patients might experience re- peated bouts of haematemesis, melaena, or both. This is the most severe, potentially fatal, complication of hepatosplenic schistosom- iasis, and death may result from massive loss of blood. Differential diagnoses of hepatosplenic schistosomiasis include kala-azar (visceral leishmaniasis), tropical splenomegaly syndrome associated with malaria, leukaemia, lymphoma, alcoholic, or viral cirrhosis, and some of the haemoglobinopathies. Some regression of periportal fibrosis may occur after specific antischistosomal therapy, as judged by ultrasonography examination of the liver, but in most individuals with periportal fibrosis and clinical manifestations of se- vere hepatosplenic disease, regression does not occur. In comparison with S. japonicum and S. mansoni infections, clin- ical symptoms of disease in S. intercalatum infection are commonly mild or absent, and it is not regarded as a serious public health problem. Active infection is seen in children and adolescents and pathology is detected only in those with egg excretion exceeding 400 eggs/g faeces. The usual clinical presentation is one of diarrhoea, often with blood in the stool and lower abdominal pain or discom- fort. S. mekongi infections are usually asymptomatic but may pro- duce a clinical picture similar to that of S. japonicum, although the infections are usually milder. Hepatosplenomegaly can occur. Other manifestations Nervous system manifestations Nervous system involvement in S. mansoni and S. haematobium infections most frequently affect the spinal cord following acute infection. This manifestation is not related to the intensity of infec- tion. Myelopathy and radiculopathy result from the inflammatory reaction, caused by the deposition of eggs around the spinal cord, and presents as an ascending flaccid paralysis with sensory level and sphincter involvement. The lesion is usually in the region of the cauda equina. Although paraparesis is seen most commonly during acute schistosomiasis, it might also be a late-stage complication of S. mansoni infection in endemic areas with high rates of transmis- sion. Myelography, CT, and magnetic resonance imaging (MRI) are of diagnostic value. In acute cases lesions are seen on MRI scans as a diffuse swelling of the lumbar cord with central softening or cyst formation. The brain is the major site of central nervous system involvement in S. japonicum infections. About 2% of acutely infected patients experi- ence symptoms that mimic acute encephalitis or a focal neurological process. CT shows multiple enhancing lesions. In chronic infections, patients may present with focal brain lesions that can resemble tu- mours and present as focal epilepsy. These lesions contain masses of eggs and granulomas. Antischistosomal drugs, corticosteroids, and surgery are the types of treatment available for neuroschistosomiasis, and uncontrolled studies suggest that treatment with a combination of praziquantel and corticosteroids is effective. However, a con- sensus regarding the best treatment of the different presentations of neuroschistosomiasis has not been reached. Pulmonary manifestations Eggs may be deposited in the lungs. Granulomatous reactions and fibrosis develop in the pulmonary vasculature leading to pulmonary hypertension and/or cor pulmonale (Fig. 8.11.1.8). This is normally seen secondary to hepatosplenic schistosomiasis in patients with portal fibrosis and portal hypertension, but pulmonary hyperten- sion can also result from accumulation of S. haematobium eggs in the lungs. A syndrome of cough with multiple small radiographic lesions and eosinophilia has been described. Symptoms include fa- tigue, palpitations, dyspnoea, cough, and sometimes haemoptysis. Patients may progress to decompensation with congestive cardiac failure. In endemic areas schistosomiasis must always be considered as a possible cause of pulmonary hypertension and cor pulmonale.

Renal manifestations Glomerulonephritis can be associated with chronic S. mansoni infection, especially hepatosplenic disease. Immunoglobulins, Fig. 8.11.1.12 Hepatic periportal fibrosis as seen by ultrasound in S. mansoni infection. Fig. 8.11.1.13 Oesophageal varices as seen by ultrasound in S. mansoni infection.

section 8 Infectious diseases 1548 complement components, and schistosome antigens are depos- ited in the mesangial area. The condition is manifested clinic- ally as proteinuria and/or nephrotic syndrome, sometimes with hypertension. Miscellaneous manifestations Patients infected with any of the three major schistosome species and subsequently infected with salmonella may develop a prolonged intermittent febrile illness. Prolonged excretion of salmonella in the urine and intermittent bacteraemia has been demonstrated in S. hae- matobium infection. Treatment for the salmonella infection alone is often not effective without treatment of the underlying schistosome infection. Ectopic schistosomiasis lesions can sometimes be found in the skin, the peritoneum, or other organs. Diagnosis and clinical investigations Information about geographical area and history of exposure by wading, bathing, washing, or showering in potentially contamin- ated fresh water is important for diagnosis of schistosomiasis, espe- cially in travellers and immigrants. This can indicate the likelihood of infection and point to the schistosome species involved. A de- finitive diagnosis is made by the direct demonstration of schisto- some eggs by microscopy of urine or stool samples, biopsies or, on rare occasions, secretions such as seminal fluid. In epidemiological studies it is usually important to obtain quantitative estimates of egg output to provide information about intensity of infection within a population. Direct parasitological methods In S. haematobium infection, eggs can be detected in urine after fil- tration, sedimentation, or centrifugation followed by microscopy. Ideally, urine should be passed around midday and the terminal part of the stream examined. The most commonly used method in epidemiological studies in endemic areas is filtration of 10 to 20 ml of urine using a syringe and a polycarbonate (e.g. Nucleopore), poly- amide (e.g. Nytrel), or paper filter. Infection intensity is expressed as eggs/10 ml of urine. This may not be sufficiently sensitive for detec- tion of low-intensity infections in travellers. In such cases, diagnosis is often based on filtration of 24-h urine samples. For S. mansoni, S. japonicum, S. mekongi, and S. intercalatum eggs in the faeces, sedimentation of the eggs followed by micros copy is a useful and simple technique. However, the Kato thick smear technique is the most widely used method in epidemio- logical studies. This is based on microscopic examination of a smear of a small but fixed amount of faecal sample (usually 20–50 mg). Coarse particles and fibrous material are first removed from the sample by passing it through a sieve. A fixed sample volume is obtained by the use of a template. This is placed on a microscope slide and squashed with either a piece of cellophane soaked in glycerol or a glass coverslip. After leaving the slide for 6 to 24 h to allow the preparation to clear, the eggs are counted and the level of infection expressed as eggs/g faeces. Unfortunately, watery or diarrhoeal stools cannot be processed this way, and low- intensity infections may not be detected, since only small faecal samples are examined and eggs may be clumped unevenly in the stool. Increased sensitivity is obtained by increasing the number of samples examined. For diagnosis of light infections in previ- ously unexposed travellers, microscopic examination of a rectal tissue snip crushed between glass slides is often the most sensitive direct parasitological method. This method can also be used for biopsies. The crushed tissue sample is far better than a sectioned biopsy for the detection and identification of eggs. Other direct methods Detection of circulating schistosome antigens Sensitive enzyme immune assays (ELISA) have been developed to detect circulating schistosome antigens in serum or urine. These antigens, circulating anodic antigen (CAA) and circulating cathodic antigen (CCA), are

derived from the gut of the adult schistosomes. The assays have almost 100% specificity and high sensitivity, and are excellent epidemiological tools as they provide a direct estimate of worm burden and can be used to monitor the efficacy of chemo- therapy since presence of CAA or CCA is an indication of an active infection. They are less well suited for diagnosis of light infections in travellers. A rapid point-of-care assay (Rapid Medical Diagnostics, Pretoria, South Africa) for CCA in urine is now commercially avail- able. It has been evaluated in several endemic locations and seems to be more sensitive than the Kato thick smear method in mapping S. mansoni endemic areas and is now widely used for screening of infected communities in relation to mass drug administration programmes. Polymerase chain reaction-based methods Polymerase chain reaction-based detection of parasite DNA in stool or urine is more sensitive than parasitological methods and is now increasingly being employed for diagnosis and as a useful tool in epi- demiological studies. Multiplex polymerase chain reaction analysis which includes detection of several intestinal parasites in a single stool sample can be an advantage when diagnosing infections in travellers. Schistosome DNA can also be detected in vaginal lavage and cerebrospinal fluid samples for diagnosis of genital schistosom- iasis or neuroschistosomiasis. Indirect diagnostic techniques In S. haematobium infections, chemical reagent strips for detection of microhaematuria are widely used in endemic areas as a diag- nostic measure. The method can be used in areas of both high and low transmission and there is a consistent significant correlation between microhaematuria and intensity of infection. In intestinal schistosomiasis, blood may be found in the stools, but it is not as useful an indicator of infection. In urinary schistosomiasis, eosinophiluria, with high numbers of eosinophil granulocytes in the urine, is a characteristic finding. Detection of the eosinophil granule protein ECP (eosinophil cat- ionic protein) in urine has been used for the qualitative assessment of eosinophil infiltration of the bladder mucosa, and hence local in- flammation and can be used to follow post-treatment resolution of urinary tract morbidity in endemic areas. Eosinophilia, sometimes exceeding 50%, is often found in acutely infected travellers. In cases where eggs are difficult to find, eosino- philia plus a history of exposure might suggest the need for further examination for schistosomiasis including serodiagnosis.

8.11.1 Schistosomiasis 1549 Immunodiagnosis In cases of suspected schistosomiasis in which eggs have not been detected, serology can be used to demonstrate specific antibodies. An indirect immunofluorescence test using sections of adult worms for detection of specific immunoglobulins (IgM and IgG) is widely used. For travellers, a positive antibody result combined with a history of exposure should lead to treatment. Serodiagnosis is not useful in endemic areas because of the high levels of specific anti- bodies found in naturally exposed populations. Ultrasonography Ultrasonography is noninvasive, portable, has no biological hazards for the patient, and can be used to either complement or replace many invasive diagnostic techniques. It is the technique of choice for grading schistosomal periportal fibrosis, portal hypertension, hydronephrosis, and urinary bladder lesions. A protocol for stand- ardized investigations and methods of reporting has been produced by the World Health Organization (WHO) (http://www.who.int/schistosomiasis/resources/tdr_str_sch_00.1/en/). Ultrasonography is especially useful for monitoring decreases in morbidity after chemotherapy programmes. Lesions in the female genital tract, especially cervical lesions, can be visualized directly by colposcopy and a pocket atlas with pictures showing the lesions has been developed for use in health facilities in endemic areas (http://www.who.int/schistosomiasis/resources/ 9789241509299/en/). Endoscopy and cystoscopy can be used in demonstrating oe- sophageal varices in hepatosplenic schistosomiasis and urinary bladder lesions, respectively. CT and especially MRI are methods of choice when diagnosing neuroschistosomiasis Treatment The drug of choice is praziquantel, available as 600 mg tablets. It

is administered orally and is effective against all schistosome spe- cies infecting humans. It is also effective for most other trematode infections and against adult cestodes. The drug is safe and well tolerated. The standard effective clinical regimen for praziquantel has been shown, in randomized control trials, to be 40 mg/kg in divided oral doses over one day (2 × 20 mg/kg does 4-hourly) for S haematobium, S intercalatum and S mansoni, and 60 mg/kg in divided oral doses over one day (2 × 30 mg/kg either 4- or 6-hourly or 3 × 20 mg/kg doses 4-hourly) for S mekongi and S japonicum. In patients who are not cured by the initial treatment, the same dose can be repeated at weekly intervals for 2 weeks. A repeat dose 6–12 weeks later can be administered to cure prepatent infections, especially if eosinophilia or symptoms persist despite treatment. In schistosomiasis control programmes based on mass drug administration, a single dose of praziquantel (40 mg/kg) is re- commended by WHO. Praziquantel has not been shown to be teratogenic in animals and based on extensive experience with the drug and review of the veterinary and human evidence WHO now recommends that pregnant and lactating women are treated during control campaigns. Similarly, WHO reports that there is growing evidence that infected children as young as 1 year old can be effectively treated with praziquantel without serious side effects; however, currently there is no paediatric formulation of praziquantel available. Any side effects are generally mild, resolving spontaneously over a few hours and rarely requiring medication. Gastrointestinal side effects include abdominal pain or discomfort and sometimes vomiting. They occur more frequently in individuals with high in- fection intensities. Urticarial skin reactions and periorbital oedema may occur in about 2% of treated individuals. General side effects including headache, dizziness, fever, and fatigue can also occur, but less frequently. As a general principle, all patients with acute schistosomiasis should be treated with praziquantel. Corticosteroids can be added in case of Katayama fever to suppress the hypersensitivity reac- tion. Since immature schistosomes are not susceptible to prazi- quantel, treatment should be repeated 4–6 weeks later. Use of praziquantel for cerebral S. japonicum infections is effective, re- sulting in rapid dissipation of cerebral oedema and resolution of cerebral masses. However, corticosteroids and anticonvul- sants are sometimes needed in addition to praziquantel in cases with neuroschistosomiasis. Praziquantel should be administered with great caution in the case of concurrent neurocysticercosis. Chemotherapy is only part of the management of schistosomiasis- associated portal hypertension, since the main complications are due to obstructive pathology. Management of portal hypertension and prevention of bleeding from oesophageal varices is beyond the scope of this chapter. Praziquantel has largely replaced other drugs for treatment of schistosomiasis. Artemisinin derivatives are effective against immature stages (schistosomulae) of S. japonicum, S. mansoni, and S. haematobium and clinical trials in China has shown that repeated oral doses of artesunate or artemether prevented patent S. japonicum infections. In order to reduce the risk of inducing drug-resistant malaria para- sites, artemisinin-based combination therapies are used in treat- ment of malaria. So far two large-scale trials have examined the effect of these therapies on S. haematobium in Mali and S. mansoni in Kenya, respectively. Taken together, the evidence suggests that the efficacy of artemisinin-based combination therapies against the two major schistosome species is only moderate and inferior to a single dose of praziquantel, so these treatments should be reserved for the management of malaria. Prognosis Most infected people have few, if any, overt symptoms. Acute schis- tosomiasis can be fatal or can lead to severe residual damage to the nervous system if not treated, but responds well to antischistosomal therapy if started early. Early infections respond extremely well to treatment and the pathological lesions regress leaving little residual damage. However, in endemic areas individuals, particularly young children, are rapidly re-exposed and reinfected, unless control meas- ures are taken at the community level. Chronic infections with se- vere periportal fibrosis respond less well to specific

antischistosomal treatment, although some regression of hepatosplenic disease with periportal fibrosis has been seen after treatment. The lifetime prog- nosis is worst in patients with severe hepatosplenic schistosomiasis

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