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parasites never develop fully. Pulmonary dirofilarial infection caused by the canine heartworm Dirofilaria immitis generally presents in humans as a solitary pulmonary nodule. Chest pain, hemoptysis, and cough are uncommon. Infections with Dirofilaria repens (from dogs) or Dirofilaria tenuis (from raccoons) can cause local subcutaneous nodules in humans. Zoonotic Brugia infection can produce isolated lymph node enlargement, whereas zoonotic Onchocerca species (par ticularly O. lupi) can cause subconjunctival masses. Eosinophilia levels and antifilarial antibody titers are not commonly elevated. Excisional biopsy is both diagnostic and curative. These infections usually do not respond to antifilarial chemotherapy. DRACUNCULIASIS (GUINEA WORM INFECTION) ■ ■ETIOLOGY AND EPIDEMIOLOGY The incidence of dracunculiasis, caused by Dracunculus medinensis, has declined dramatically because of global eradication efforts. How ever, between 2017 and 2020, there were increases in the number of human cases, followed by a decline in 2021 and 2022. At the end of 2022, there were a total of 13 human cases of Guinea worm disease across four African countries, with 6 cases in Chad, 5 cases in South Sudan, and 1 each in Ethiopia and Central African Republic. Low-level persistence of infection in animal reservoirs (dogs and cats) is a major challenge to ongoing eradication efforts. Humans acquire D. medinensis when they ingest water containing infective larvae derived from Cyclops, a crustacean that is the inter mediate host. Larvae penetrate the stomach or intestinal wall, mate, and mature. The adult male probably dies; the female worm develops over a year and migrates to subcutaneous tissues, usually in the lower extremity. As the thin female worm, ranging in length from 30 cm to 1 m, approaches the skin, a blister forms that, over days, breaks down and forms an ulcer. When the blister opens, large numbers of motile, rhabditiform larvae can be released into stagnant water; ingestion by Cyclops completes the life cycle. ■ ■CLINICAL FEATURES Few or no clinical manifestations of dracunculiasis are evident until just before the blister forms, when there is an onset of fever and gen eralized allergic symptoms, including periorbital edema, wheezing, and urticaria. The emergence of the worm is associated with local pain and swelling. When the blister ruptures (usually as a result of immer sion in water) and the adult worm releases larva-rich fluid, symptoms are relieved. The shallow ulcer surrounding the emerging adult worm heals over weeks to months.

Such ulcers, however, can become second arily infected, the result being cellulitis, local inflammation, abscess formation, or (uncommonly) tetanus. Occasionally, the adult worm does not emerge but becomes encapsulated and calcified. ■ ■DIAGNOSIS The diagnosis is based on the findings developing with the emergence of the adult worm, as described above. TREATMENT Dracunculiasis Gradual extraction of the worm by winding of a few centimeters on a stick each day remains the common and effective practice. Worms may be excised surgically. No drug is effective in treating dracunculiasis. ■ ■PREVENTION Prevention, which remains the only real control measure, depends on the provision of safe drinking water. Acknowledgment The authors wish to acknowledge and thank Peter F. Weller, MD, author of prior editions of this chapter.

■ ■FURTHER READING Hopkins DR et al: Progress toward global eradication of dracunculiasis—

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Schistosomiasis and

Other Trematode

Infections CHAPTER 241 Birgitte Jyding Vennervald,

Anna-Sofie Stensgaard Schistosomiasis and Other Trematode Infections
Trematodes, or flatworms, are a group of helminths that belong to the phylum Platyhelminthes. The adult flatworms share some common characteristics, such as macroscopic size (from one to several centi meters); dorsoventrally flattened, bilaterally symmetric bodies; and two suckers—oral and ventral. Except for schistosomes, which have separate sexes, all human parasitic trematodes are hermaphroditic. Their life cycles involve a mammalian/human definitive host, in which sexual reproduction by adult worms takes place, and an intermediate host (snails), in which asexual multiplication occurs. Some species of trematodes have more than one intermediate host. Humans are infected either by direct penetration of intact skin (schistosomiasis) or by ingestion of raw freshwater fish, crustaceans, or aquatic plants with metacercariae—the infective larval stage. Significant trematode infections of humans may be divided according to the location of the adult worms: blood, liver (biliary tree), intestines, or lungs (Table 241-1). Adult worms do not multiply within the mammalian host but can live for up to 30 years. Infections are often chronic. Although it is relatively rare to encounter patients with trematode infections in the United States, many millions of people are infected worldwide. Both schistosomiasis and food-borne trematode infections are poverty-related chronic diseases with high morbidity and a signifi cant public health impact. Various factors may increase the spread of the infections globally. Increasing temperatures may render new areas suitable for the intermediate host snails, and an increase in travel and

migration may increase the number of patients with trematode infections—for example, in the United States. APPROACH TO THE PATIENT Trematode Infection In the evaluation of a patient in whom trematode infection is sus pected, certain questions are highly relevant and can assist in estab lishing a diagnosis: Where have you been? If you have traveled, when

TABLE 241-1 Major Human Trematode Infections GEOGRAPHIC DISTRIBUTION TREMATODE TRANSMISSION ROUTE Blood Flukes Intestinal schistosomiasis Schistosoma mansoni Skin penetration by cercariae released from snails (Biomphalaria spp.) Africa, Brazil, Venezuela, Surinam, the Caribbean

(low risk) Shistosoma japonicum Skin penetration by cercariae released from snails (Oncomelania spp.) China, Indonesia, Philippines Schistosoma guineensis and Schistosoma intercalatum Skin penetration by cercariae released from snails (Bulinus spp.) Rainforest areas of Central Africa Schistosoma mekongi Skin penetration by cercariae released from snails (Neotricula aperta) Several districts of Cambodia and Lao People's Democratic Republic (PDR) Urogenital schistosomiasis Schistosoma haematobium Skin penetration by cercariae released from snails (Bulinus spp.) Africa, Middle East, Corsica (France) Liver Flukes Clonorchis sinensis Ingestion of metacercariae in freshwater fish Asia, including Republic of Korea, China, Taiwan, Vietnam Opisthorchis viverrini Ingestion of metacercariae in freshwater fish Northeast Thailand, Lao PDR, Cambodia, Vietnam Opisthorchis felineus Ingestion of metacercariae in freshwater fish Former Soviet Union, Kazakhstan, Ukraine,

Turkey PART 5 Infectious Diseases Fasciola hepatica Ingestion of metacercariae on aquatic plants or in

water Worldwide Fasciola gigantica Ingestion of metacercariae on aquatic plants or in

water Africa, Asia Intestinal Flukes Fasciolopsis buski Ingestion of metacercariae on aquatic plants Bangladesh, China, India, Indonesia, Lao PDR, Malaysia, Taiwan, Thailand, Vietnam Echinostoma spp. Ingestion of freshwater fish, frogs, mussels, snails China, India, Indonesia, Japan, Malaysia, Russia, Republic of Korea, Philippines, Thailand Heterophyes heterophyes, several other species Ingestion of metacercariae in freshwater or brackishwater fish Egypt, Greece, Islamic Republic of Iran, Italy, Japan, Republic of Korea, Sudan, Tunisia, Turkey Lung Flukes Paragonimus westermani Ingestion of metacercariae in crayfish or crabs Tropical and subtropical areas of eastern and southern Asia and

sub-Saharan Africa Paragonimus kellicotti Ingestion of metacercariae in crayfish or crabs North America did you return? What activities have you been involved in (trekking, swimming, whitewater rafting)? What have you been eating (local dishes while traveling; raw, poorly cooked, or pickled freshwater fish or crustaceans)? Definitive diagnosis is based on detection of parasite eggs in stool, urine, sputum, and sometimes tissue samples or on serologic tests. The presence of eosinophilia and a history of travel to endemic areas should raise suspicion of trematode infection. The U.S. Centers for Disease Control and Prevention (CDC) can provide guidance with respect to diagnosis and treatment.

SCHISTOSOMIASIS Human schistosomiasis is caused by six species of the parasitic genus Schistosoma: S. mansoni, S. japonicum, S. mekongi, S. intercalatum, and the recently described S. guineensis cause intestinal disease, and S. haematobium causes urogenital disease (Table 241-1). The infection may cause considerable intestinal, hepatic, and genitourinary morbid ity. Avian schistosomes may penetrate human skin but die in subcuta neous tissue, producing only cutaneous manifestations. ■ ■ETIOLOGY Schistosoma infection is contracted through contact with freshwater bodies harboring infected intermediate-host snails (Fig. 241-1). Cer cariae, the infective larval stage released from the snail, penetrate intact human skin within a few minutes after attaching to the skin. After pen etration, the cercariae transform to schistosomula, which then enter a small vein or lymphatic vessel, circulate in the bloodstream through the lung capillaries, and are pumped via the heart to all parts of the body to reach the portal vein. There, the worms mature into adult males or females, pair, and migrate to their final location in the mesenteric or pelvic venous plexus. The interval from cercarial penetration to sexual maturation and egg production, termed the prepatent period, lasts 5–7 weeks (up to 12 weeks for S. haematobium). The female worm then begins to produce eggs, which are excreted via feces or, for S. haematobium, urine. Approxi mately 50% of eggs are retained in tissue, where they are responsible for organ-specific morbidity (see “Pathogenesis,” below). When excreted eggs reach water, they hatch and release a free-swimming larval stage (miracidium), which, after penetrating a host snail, undergoes sev eral rounds of asexual multiplication. After ~4–6 weeks, infective cercariae are shed from the infected snails into the water. One snail, infected by one miracidium, can shed thousands of cercariae per day for several months; thus, the transmission potential of schistosomes is enormous. Environmental temperature is an important determinant of the development rate and the number of cercariae produced and released by the snails. The schistosome egg (Fig. 241-2) is the only stage of the parasites’ life cycle that can be detected in humans, either in excreta or in tissue biopsies. The eggs are large and can easily be distinguished morpho logically from other helminth eggs. S. haematobium eggs are ~140 μm long, with a terminal spine; S. mansoni eggs are ~150 μm long, with a lateral spine; and S. japonicum eggs are smaller, rounder, and ~90 mm long, with a small lateral spine or knob. Adult schistosomes are ~1–2 cm long. The male worm is flat, and the body forms a groove or gynecophoric canal in which the mature adult female is held like a sausage in a hotdog roll. Females are longer, thinner, and rounded. The females produce hundreds (African species) to thousands (Asian species) of eggs per day. Each ovum contains a ciliated miracidium larva, which secretes proteolytic enzymes that help the eggs to migrate into the lumen of the bladder (S. haematobium) or the intestine (other species). The lifespan of an adult schistosome aver ages 3–5 years but can be as long as 30 years. Schistosome worms feed on red blood cells; the debris is regurgitated in the host’s blood, where it can be detected as circulating antigens (see “Diagnosis,” below). Adult schistosomes persist in the bloodstream for years and have evolved strategies of evading attack using immune effector mecha nisms. This immune evasion is a result of several processes, such as binding of host proteins to the schistosome surface, which renders the parasite invisible to the host immune system. The genome of schistosomes is relatively large (~300 Mb). Wholegenome sequences are available for S. mansoni, S. japonicum,

and S. haematobium. ■ ■EPIDEMIOLOGY Because of the complex life cycle of schistosomes, with snails as an intermediate host and humans as the final host, transmission is depen dent on freshwater habitats that are suitable for the snails, are areas of human activity, and have climatic conditions favoring the survival of the snails and the development of the parasites inside the snail host. These requirements are reflected in the global distribution of

Infected definitive host Definitive host Cercaria Snail (intermediate host) FIGURE 241-1 Life cycle of schistosomiasis. schistosomiasis as well as in its microgeographic distribution within an endemic area. For S. mansoni, S. haematobium, S. intercalatum, and S. guineensis, humans are the most important definitive host.

S. japonicum and S. mekongi are zoonotic parasites, with a wide range of definitive hosts such as pigs, water buffaloes, and various rodents. It is estimated that at least 251.4 million people required preven tive treatment in 2021, of whom more than 75.3 million people were reported to have been treated. Schistosomiasis transmission has been reported from 78 countries, of which 51 endemic countries have mod erate to high transmission (Fig. 241-3). More than 70% of infected people live in sub-Saharan Africa. Schistosomiasis is the most impor tant of the neglected tropical diseases and is second only to malaria in public health impact. It is a poverty-related disease, and infection is prevalent in areas where adequate water supplies and sanitary facilities are lacking. In these areas, people come into contact with infested water through a variety of activities, including bathing, washing clothes, and collecting water for drinking or cooking. In some areas, adults have a high occupational risk of exposure; fishermen, canal cleaners, and workers in rice fields fall into this category. Among children, playing in FIGURE 241-2 Schistosoma haematobium eggs.

water and swimming pose a risk. Large-scale irri gation and hydroelectric power operations can create suitable habitats for host snails and thus increase the risk of schistosomiasis transmission.

In general, children living in endemic areas initially acquire infection at ~3–4 years of age— i.e., when they are old enough to walk and come into contact with infested water. However, infection does occur in much younger chil dren. As children grow older, the prevalence and intensity of infection increase, peaking around puberty. A characteristic feature of schistosomia sis infection in human populations is a convex age–prevalence curve, with low prevalence in very young children, higher prevalence in older children with a peak at 10–15 years of age, and declining prevalence in adults. The same pat tern is observed between age and intensity of infection and is attributable to various factors. Generally, children have more frequent, pro longed, and extensive water contact than adults through activities like playing and swimming. Furthermore, several studies have indicated that acquired immunity to schistosomiasis develops slowly over several years, so that adults are reinfected to a much lesser extent than children. These factors, combined with progressive spon taneous death of adult worms from infections acquired during childhood, lead to lower levels of infection in the adult population. Eggs shed in urine and stool Eggs CHAPTER 241 It is important to note that ongoing climate change, resulting in ris ing water temperatures and altered precipitation patterns, affects the distribution, reproduction, survival, and dispersal of the intermediate host snails, as well as the rate of parasite development within the snail. Therefore, climate change could considerably alter the distribution and abundance of the intermediate host snail and its schistosome parasites, resulting in notable shifts in the global distribution, disease dynamics, and transmission of schistosomiasis in the future. Schistosomiasis and Other Trematode Infections

■ ■PATHOGENESIS Cercarial invasion may be associated with dermatitis arising from dermal and subdermal inflammatory reactions in response to dying cercariae that trigger innate immune responses. However, most mani festations of schistosomiasis—in the acute, established, and chronic phases of infection—are due to immunologic reactions to eggs retained in host tissues. Around the time when oviposition commences, acute schistoso miasis (Katayama fever) may occur

(see “Clinical Features,” below). Antigen excess from eggs results in the formation of soluble immune complexes, which may be deposited in several tissues and initiate a serum sickness–like illness. All evidence suggests that schistosome eggs, and not adult worms, induce the organ-specific morbidity caused by schistosome infections. Approximately half of the eggs are not excreted via feces or urine but are trapped in intestinal or hepatic tissue (S. mansoni, S. japonicum, and S. mekongi) or in the bladder and urogenital system (S. haematobium). The eggs induce a granulo matous host immune response composed primarily of lymphocytes, eosinophils, and alternatively activated macrophages. The lymphocytes produce various TH2 cytokines such as interleukins 4, 5, and 13. Later, in the chronic phase of infection, regulatory cytokines are respon sible for immunomodulation or downregulation of host responses to schistosome eggs and play an important role in reducing the size of granulomas. When S. mansoni or S. japonicum eggs are swept into the small portal branches of the liver via the portal vein, they lodge in the pre sinusoidal periportal tissues. The formation of granulomas around the eggs can cause significant enlargement of the spleen and liver. High-intensity infections in children are often accompanied by hepa tosplenomegaly that generally decreases over time, partly because the

B A FIGURE 241-3 Global distribution of human schistosomiasis. A. Schistosoma mansoni infection (dark blue) is endemic in Africa, the Middle East, South America, and a few Caribbean countries. S. intercalatum infection (green) is endemic in sporadic foci in West and Central Africa. B. Schistosoma haematobium infection (purple) is endemic in Africa and the Middle East. The major endemic countries for S. japonicum infection (green) are China, the Philippines, and Indonesia. Schistosoma mekongi infection (red) is endemic in sporadic foci in Southeast Asia. (Reprinted from CH King, AAF Mahmoud: Schistosomiasis and other trematode infections, in DL Kasper et al [eds], Harrison’s Principles of Internal Medicine, 19th ed. New York, McGraw-Hill Education, 2015, pp 1423–1429.) PART 5 Infectious Diseases number of eggs being deposited in the tissue gradually declines after the early teenage years as partial immunity to new infections develops and partly because of immunologic downregulation of the granulo matous response. However, in some infected individuals, egg-induced granulomatous responses lead to severe periportal fibrosis (Symmers clay pipestem fibrosis), with deposition of collagen around the portal vein, occlusion of the smaller portal branches, and severe, often irre versible, pathology. Occlusion of the portal branches may result in marked portal hypertension (Fig. 241-4). The signs and symptoms of S. haematobium infection relate to the worms’ predilection for the veins of the urogenital plexus and result from deposition of eggs in the bladder, ureters, and genital organs. During established active infection, clusters of living eggs in the urogenital tissues can be found surrounded by intense inflammatory reactions and intense tissue eosinophilia. Movement of egg clusters into the lumen of the bladder is often followed by sloughing off of the FIGURE 241-4 Portal hypertension with ascites. (Photo courtesy of Birgitte J. Vennervald.)

epithelial surface, ulceration, and bleeding. Intense egg-induced tissue inflammation can result in bladder wall thickening and development of masses and pseudopolyps. Inflammation and granuloma formation around the ureteral ostia can lead to hydronephrosis. Generally, late chronic-stage infections are characterized by accu mulation of dead calcified eggs in tissue. Characteristic cervical lesions are found in S. haematobium infections, including active-stage lesions with intense tissue inflammation around live eggs and chronic-stage sandy patches with clusters of calcified eggs. ■ ■CLINICAL FEATURES In general, disease manifestations of schistosomiasis occur in three stages—acute, active, and chronic—according to the duration and intensity of infection. Cercarial

Dermatitis (“Swimmer’s Itch”) Cercarial penetra tion of the skin may result in a maculopapular rash called cercarial dermatitis or “swimmer’s itch.” Cercarial dermatitis can develop in people who have not previously been exposed to schistosomiasis (e.g., travelers), whereas it is rare among people living in endemic areas. A particularly severe form of cercarial dermatitis is commonly seen after exposure to cercariae from avian schistosomes. These cercariae cannot complete their development in humans and die in the skin, causing an inflammatory allergic reaction. This form of cercarial dermatitis can occur in people who have been in contact with water from lakes (e.g., in Europe or the United States) where various species of water birds, such as ducks, geese, and swans, are found. The rash may last for 1–2 weeks. This condition normally requires no treatment, but sys temic antihistamines, topical antihistamines, or glucocorticoids can be used to reduce symptoms. Acute Schistosomiasis (Katayama Fever) Symptomatic acute schistosomiasis, also known as Katayama fever or Katayama syndrome, is usually seen in travelers who have contracted the infection for the first time. The onset occurs between 2 weeks and 3 months after expo sure to the parasite. The symptoms may appear suddenly and include fever, myalgia, general malaise and fatigue, headache, nonproductive cough, and intestinal symptoms such as abdominal tenderness or pain. Various combinations of these symptoms are often accompanied by eosinophilia and transient pulmonary infiltrates. Many patients

recover spontaneously from acute schistosomiasis after 2–10 weeks, but the illness follows a more severe clinical course in some individuals, with weight loss, dyspnea, diarrhea, and hepatomegaly. Severe cerebral or spinal cord manifestations may occur, and even light infections may cause severe illness. The syndrome can, in rare cases, be fatal. Differential diagnosis includes many other febrile infectious dis eases with acute onset, including malaria, salmonellosis, and acute hep atitis. Fever and eosinophilia occur in trichinosis, tropical eosinophilia, invasive ankylostomiasis, strongyloidiasis, visceral larva migrans, and infections with Opisthorchis and Clonorchis species. Katayama fever is rare in people chronically exposed to infection in areas endemic for S. mansoni or S. haematobium. Intestinal Schistosomiasis (S. mansoni, S. japonicum) In intes tinal schistosomiasis, adult worms are located in the mesenteric veins, and disease manifestations are associated with parasite eggs passing through or becoming trapped in intestinal tissue. This event induces mucosal granulomatous inflammation with microulcerations, super ficial bleeding, and sometimes pseudopolyposis. The symptoms tend to be more pronounced with a high intensity of infection and include intermittent abdominal pain, loss of appetite, and sometimes bloody diarrhea. The clinical manifestations of S. intercalatum, S. guineensis, and S. mekongi infection are generally milder. Hepatosplenic Schistosomiasis Hepatosplenic schistosomiasis is caused by schistosome eggs trapped in liver tissue and occurs in S. mansoni and S. japonicum infections. There are two distinct clinical entities: early inflammatory hepatosplenomegaly and late hepatosplenic disease with periportal fibrosis. Early inflammatory hepatosplenic schistosomiasis is the main entity seen 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 is firm or hard. Generally, ultraso nography shows no hepatic fibrosis. This form of hepatosplenic schis tosomiasis may be found in up to 80% of infected children. Its severity is closely associated with the intensity of infection and may also be associated with concomitant chronic exposure to malaria. Late hepatosplenic schistosomiasis with periportal or Symmers fibrosis may develop in young and middle-aged adults with long-standing, high-level exposure to infection. Patients with periportal fibrosis may excrete very few or no eggs in feces. During the early stage, the liver is enlarged, especially the left lobe; it is smooth and firm or hard. The spleen is enlarged, often massively, and is firm or hard. The patient

may report a left hypochondrial mass with discomfort and anorexia. Ultrasonography reveals typical periportal fibrosis and dilation of the portal vein. Other complications include delayed growth and puberty, especially in S. japonicum infections, and severe anemia. Severe hepa tosplenic schistosomiasis may lead to portal hypertension, but hepatic function usually remains normal, even in cases with marked periportal fibrosis and portal hypertension. Ascites, attributable both to portal hypertension and to hypoalbu minemia, may be seen, especially in S. japonicum infection. Patients with severe hepatosplenic disease and portal hypertension may develop esophageal varices detectable by endoscopy or ultrasound. These patients may experience repeated bouts of hematemesis, melena, or both. Hematemesis is the most severe complication of hepatosplenic schistosomiasis, and death may result from massive loss of blood. Urogenital Schistosomiasis (S. haematobium) The signs and symptoms of S. haematobium infection relate to the worms' predilec tion for the veins of the urogenital tract. Two stages of infection are recognized. An active stage occurring mainly in children, adolescents, and younger adults is characterized by egg excretion in the urine, with proteinuria and macroscopic or microscopic hematuria and deposi tion of eggs in the urinary tract. A chronic stage in older individuals is characterized by sparse or no urinary egg excretion despite urogenital tract pathology. A characteristic sign in the active stage is painless, terminal hema turia. Dysuria and suprapubic discomfort or pain are associated with active urogenital schistosomiasis and may persist throughout the

course of active infection. Eggs deposited in the bladder mucosa may give rise to an intense inflammatory response of the bladder wall, which may cause ureteric obstruction and lead to hydroureter and hydronephrosis. These early inflammatory lesions, including obstruc tive uropathy, can be visualized by ultrasonography.

As the infection progresses, the inflammatory component decreases and fibrosis becomes more prominent. The symptoms at this stage are nocturia, urine retention, dribbling, and incontinence. Cystoscopy reveals "sandy patches" composed of large numbers of calcified eggs surrounded by fibrous tissue and an atrophic mucosal surface. The ureters are less commonly involved, but ureteral fibrosis can cause irreversible obstructive uropathy that can progress to uremia. Egg deposition may cause granulomas and lesions in the genital organs, most commonly in the cervix and vagina in women and the seminal vessels in men. The results may include dyspareunia, abnormal vaginal discharge, contact bleeding, and lower back pain in women and perineal pain, painful ejaculation, and hematospermia in men. Genital symptoms like bloody discharge and genital itch are associated with S. haematobium infection in school-aged girls living in schistosomiasis-endemic areas. Symptoms such as hematospermia and perineal discomfort have been described in travelers, and eggs have been demonstrated in seminal fluid. An association between female genital schistosomiasis and HIV infection has been demonstrated, but the impact of genital schistosomiasis on HIV transmission needs further elucidation. S. haematobium has been classified by the International Agency for Research on Cancer (IARC) as definitely carcinogenic to humans (i.e., a group 1 carcinogen). Chronic S. haematobium infection is associated with squamous cell carcinoma of the urinary bladder. CHAPTER 241 Other Manifestations Worms and eggs can sometimes be located in ectopic sites, causing site-specific manifestations and symptoms. Neuroschistosomiasis is one of the most severe clinical forms of schis tosomiasis and is caused by the inflammatory response around eggs in the cerebral or spinal venous plexus. S. mansoni and S. haematobium worms can end up in the spinal venous plexus, where they may

cause transverse myelitis—an acute complication sometimes seen in travelers returning home with schistosomiasis. S. japonicum is mainly associated with granulomatous lesions in the brain, causing epileptic seizures, encephalopathy with headache, visual impairment, motor deficit, and ataxia. Pulmonary schistosomiasis is caused by portacaval shunting of eggs into the lung capillaries, where they induce granulomas in the perialveolar area. The consequences may be fibrosis, pulmonary hyper tension, and cor pulmonale. Schistosomiasis and Other Trematode Infections ■ ■DIAGNOSIS Anamnestic information on recent travels to endemic areas and expo sure to freshwater bodies through recreational or other activities is important in the diagnosis of schistosomiasis in travelers. Information about exact geographic locations can facilitate identification of the relevant species of Schistosoma. Eosinophilia is a common finding and is often associated with helminthic infections such as schistosomiasis. Detection of schistosome eggs in stool or urine is indicative of active infection and is the standard diagnostic method. The diagnosis is often based on the detection of eggs in a fixed small amount of excreta—e.g., 50 mg of stool or filtration of 10 mL of urine. This method is widely used among populations in endemic areas and allows quantitation of the level of infection (eggs per gram of feces or per 10 mL of urine). However, levels of egg excretion in people from nonendemic areas may be very low, in which case a larger sample and concentration methods (e.g., formol-ether concentration) may be needed. Eggs can also be detected in rectal biopsies (both S. mansoni and S. haematobium) and occasionally in Pap smears and semen samples (S. haematobium). Polymerase chain reaction (PCR)–based detection of parasite DNA in stool or urine is more sensitive than parasitologic methods and is increasingly used. Schistosoma DNA can be detected in cerebrospinal fluid samples for diagnosis of neuroschistosomiasis. Serology, with detection of specific antibodies to schistosomes, is useful in travelers but less so in people from endemic areas where

transmission is ongoing. The serologic assays employed at the CDC are a Falcon assay screening test/enzyme-linked immunosorbent assay (FAST-ELISA) using S. mansoni adult microsomal antigen and a con firmatory species-specific immunoblot assay performed in light of the patient’s travel history.

Schistosome proteoglycans—circulating anodic and cathodic anti gens (CAAs and CCAs)—regurgitated into the bloodstream by the feeding worms can be detected in serum and urine by ELISA or monoclonal antibody–based lateral flow assays. The presence of CAA or CCA is an indication of active infection, and levels of these antigens correlate well with the intensity of infection. However, detection of CAAs and CCAs is not currently suitable for diagnosis in travelers, who are likely to have low levels of infection and very few worms, but promising results have been obtained using an ultrasensitive lateral flow assay. A commercially available point-of-care assay (Rapid Medical Diagnostics, Pretoria, South Africa) that detects CCA in urine is now widely used for screening of infected communities in relation to mass drug administration programs. TREATMENT Schistosomiasis The drug of choice for treatment of schistosomiasis is praziquantel. It is administered orally, is available as 600-mg tablets, and is effec tive against all schistosome species infecting humans. The drug is safe and well tolerated. Standard regimens are shown in Table 241-2. In patients who are not cured by initial treatment, the same dose can be repeated at weekly intervals for 2 weeks. Since praziquantel does not affect the young migrating stages of the schistosomes, it may be necessary to repeat the dose 6–12 weeks later, especially if eosinophilia or symptoms persist despite treatment. PART 5 Infectious Diseases As a general principle, all patients with acute schistosomiasis should be treated with praziquantel. Glucocorticoids can be added in

Katayama fever to suppress the hypersensitivity reaction. How ever, treatment for acute schistosomiasis or Katayama fever must be adjusted appropriately for each case, and in the most severe cases, management in an acute-care setting is necessary. Praziquantel is effective in cerebral S. japonicum infections, resulting in rapid dissipation of cerebral edema and resolution of TABLE 241-2 Treatment of Schistosomiasis and Food-Borne Trematode Infections INFECTION DRUG OF CHOICE ADULT DOSEa Schistosoma mansoni,

S. haematobium,

S. intercalatum, S. guineensis Praziquantelb 40 mg/kg PO in 2 divided doses for 1 day S. japonicum, S. mekongi Praziquantel 60 mg/kg PO in 3 divided doses for 1 day Clonorchis sinensis, Opisthorchis viverrini, Opisthorchis felineus Praziquantel 25 mg/kg PO tid for

2 consecutive days Fasciola hepatica, Fasciola gigantica Triclabendazolec 2 doses of 10 mg/kg PO given 12 h apart Fasciolopsis buski Praziquantel 75 mg/kg PO in 3 divided doses for 1 day Echinostoma spp., Heterophyes heterophyes, several other species Praziquantel 25 mg/kg PO tid Paragonimus westermani, Paragonimus kellicotti Praziquantel Triclabendazolec 25 mg/kg PO tid for

2 consecutive days 10 mg/kg PO once (or twice, 12–24 h apart) aThe pediatric dose is the same as the adult dose in all instances. bThe safety of praziquantel in children <4 years old has not been established, although many children in this age group have been treated with praziquantel during mass drugadministration programs. cIn February 2019, the U.S. Food and Drug Administration (FDA) approved triclabendazole for treatment of fascioliasis in patients at least

6 years of age.

cerebral masses. However, glucocorticoids and anticonvulsants are sometimes needed in neuroschistosomiasis. The effect of antischistosomal treatment on disease manifesta tions depends on the stage and severity of the lesions. Early hepa tosplenomegaly, mild or moderate fibrosis, and urinary bladder lesions seen during active infection resolve after chemotherapy. However, for late-stage manifestations (e.g., severe fibrosis with portal hypertension), praziquantel treatment is only one com ponent of management, since the main complications are due to obstructive pathology. Management of portal hypertension and prevention of bleeding from esophageal varices should follow clini cal guidelines for treatment of these conditions. ■ ■PREVENTION AND CONTROL Schistosomiasis is contracted through direct contact with infested freshwater. Travelers should be made aware of the risk of infection if they come into contact with freshwater sources in schistosomiasisendemic areas. For people living in rural areas where schistosomiasis is endemic, it may be very difficult, if not impossible, to avoid water contact—for example, during occupational activities such as fishing and working in rice fields. Schistosomiasis is a poverty-related disease, and access to safe water and good sanitary facilities may rarely be avail able. Because S. japonicum is a zoonotic parasite, preventive measures should target not only the human population but also animals such as water buffalo, which act as reservoirs for infection. Praziquantel treatment of infected people, often during mass drugadministration programs, is a cornerstone of the management and control of schistosomiasis. Regular treatment will reduce the level of schistosomiasis morbidity in affected populations. However, treatment should be combined with other relevant strategies, such as control of the intermediate host snails, improved water-

quality and sanitation facilities, and health education. Schistosomiasis control measures should be integrated into local health programs. There have been intensive efforts to develop vaccines, but none is yet available. Three vaccine candidates have been tested in clinical phase 1 or 2 trials. Only one candidate, S. haematobium 28GST, has been tested in a clinical phase 3 trial in populations living in an endemic area. The vaccine candidate was immunogenic and well tolerated by infected children, but a sufficient efficacy was not reached. FOOD-BORNE TREMATODE INFECTIONS Food-borne trematode infections are a group of zoonotic diseases caused by hepatic, intestinal, and pulmonary parasitic flukes. These infections are contracted by ingestion of infective parasites in under cooked aquatic food or water plants. Infections can cause severe liver and lung disease, and together, this may result in 2 million life-years lost to disability and death worldwide every year. ■ ■LIVER FLUKES The most important liver flukes causing human infections are the related species Opisthorchis viverrini and Opisthorchis felineus, which cause opisthorchiasis; Clonorchis sinensis, which causes clonorchiasis; and Fasciola hepatica and Fasciola gigantica, which cause fascioliasis (Table 241-1). Opisthorchiasis and Clonorchiasis O. viverrini is found mainly in northeastern Thailand, Laos, and Cambodia; O. felineus mainly in Europe and Asia, including the former Soviet Union; and C. sinensis in Asia, including Korea, China, Taiwan, Vietnam, Japan, and Asian regions of Russia. Parasite eggs excreted from infected humans or animals are ingested by a host snail (the first intermediate host), where they undergo several developmental stages. Cercariae are then released from the snail and penetrate freshwater fish (the second intermediate host), encysting as metacercariae in the muscles or under the scales. Humans become infected by eating raw or undercooked fish from endemic countries. After ingestion, the metacercariae excyst in gastric juices and migrate via the duodenum, the ampulla of Vater, and the extrahepatic biliary system to the intrahepatic bile ducts.

TABLE 241-3 Clinical Features of Food-Borne Trematode Infections SYMPTOMS OR SIGNS INFECTION COMPLICATIONS EARLY OR ACUTE STAGE ESTABLISHED OR CHRONIC STAGE Liver Flukes Clonorchis sinensis, Opisthorchis viverrini, Opisthorchis felineus Often asymptomatic; sometimes hepatitis-like symptoms and high fever (especially with O. felineus) Fasciola hepatica, Fasciola gigantica Acute onset (1–4 weeks after infection) with high fever, weight loss, sometimes urticaria and liver tenderness Intestinal Flukes Fasciolopsis buski, Echinostoma spp., Heterophyes heterophyes, several other species Often asymptomatic; sometimes nonspecific gastrointestinal symptoms Lung Flukes Paragonimus westermani, Paragonimus kellicotti Often asymptomatic; sometimes insidious onset with anorexia and weight loss aCarcinogenesis has not yet been established for O. felineus. The clinical manifestations of infection with Opisthorchis species and C. sinensis are similar. Pathologic changes are typically seen in the bile ducts, liver, and gallbladder (Table 241-3). Tissue damage and intense inflammation are caused by mechanical and chemical irrita tion and immune responses to worms or worm products, and chronic inflammation may result in the development of cholangiocarcinoma. Both O. viverrini and C. sinensis are classified by the IARC as definitely carcinogenic (class 1). Acute and light infections are mostly asymptom atic, but hepatitis-like signs and symptoms, with high fever and chills, have been reported, especially in O. felineus infections. In general, only heavily infected people have symptoms and severe complications (Table 241-3). The diagnosis of these infections is based on microscopic identifica tion of parasite eggs in stool specimens. The eggs of Opisthorchis are indistinguishable from those of Clonorchis. Fascioliasis Fascioliasis occurs in many areas of the world and usu ally is caused by Fasciola hepatica, a common liver fluke of sheep and cattle. F. hepatica is found in more than 50 countries on all continents except Antarctica; F. gigantica is less widespread. The areas with the

highest known rates of human Fasciola infection are in the Andean highlands of Bolivia and Peru. In other areas where fascioliasis is found, human cases are sporadic. Unlike the other liver flukes, Fasciola species have no second intermediate host, as their infectious metacercariae adhere directly to aquatic plants. Humans usually acquire infection by ingesting aquatic plants, such as watercress, that contain viable metacercariae or by drinking water with free metacercariae. After metacercariae have excysted in the duodenum, Fasciola spe cies migrate through the intestinal wall into the body cavity, penetrate the liver capsule, and move through the liver into the bile ducts. This migration route is different from that of other liver flukes and gives rise to symptoms during the acute migratory phase; the parasites may cause tissue destruction, focal bleeding, and inflammation. Some migrating flukes may deviate from their usual route to cause ectopic infections. In the established latent stage of infection, the parasites may cause bile duct inflammation, resulting in thickening and expansion of the ducts, fibrosis, and ultimately biliary obstruction (Table 241-3). Although some infected people are asymptomatic in the latent phase, others may experience repeated relapses of acute manifestations. The most widely used diagnostic approach is direct detection of Fasciola eggs by microscopic examination of stool or of duodenal or

Biliary colic, cholestatic jaundice, recurrent cholangitis and cholelithiasis; hepatomegaly, gallbladder enlargement, periductal fibrosis. Light infections are often asymptomatic and remain so for years. Pancreatitis, cholangiocarcinomaa Biliary colic, cholestatic jaundice, recurrent cholangitis and cholelithiasis; thickening, enlargement, and fibrosis of biliary ducts; sometimes repeated relapses of acute symptoms Pancreatitis. In rare cases: ectopic infections in the central nervous system, orbital area, gastrointestinal tract, lungs, and other organs. Rarely, fascioliasis can be fatal. Heavy infection may lead to ulceration of intestinal mucosa and malabsorption. Mild infections are often asymptomatic. Malnutrition, anemia; rarely, ectopic infection in the central nervous system Bronchitis-, asthma-, and tuberculosis-like symptoms and signs such as chronic cough, dyspnea, bloody (“rusty”) sputum Pulmonary cyst formation; ectopic infection in the central nervous system, eyes, skin, heart, abdominal and reproductive organs biliary aspirates. Eggs generally cannot be detected until 3–4 months after exposure, whereas antibodies to the parasite may become detect able 2–4 weeks after exposure. More than one stool specimen may be needed for diagnosis, especially in light infections. CHAPTER 241 ■ ■INTESTINAL FLUKES More than 70 species of intestinal flukes can cause human infection. These parasites are found in different geographic areas, with a relatively high prevalence in Southeast Asia. Humans are infected by ingestion of infective metacercariae attached to aquatic plants (Fasciolopsis buski) or encysted in freshwater fish. Flukes mature in the human intestines, and eggs are passed with feces. Mechanical irritation of the intestinal wall and inflammation may lead to nonspecific gastrointestinal symptoms such as diarrhea, constipation, and abdominal pain. Most individuals infected with intestinal flukes are asymptomatic, but heavy infections can be severe, with intestinal mucosal ulcerations and malabsorption (Table 241-3). The diagnosis is established by detection of eggs in stool samples. However, eggs from various intestinal trematodes are often morphologically similar, and it is very difficult to distinguish among species. A cautionary note: Fasciola eggs can be difficult to distinguish on the basis of morphologic criteria from the eggs of the intestinal fluke F. buski. The distinction has implications for therapy: infection with F. buski is treated with praziquantel, which is not effective against fascioliasis (Table 241-2). Schistosomiasis and Other Trematode Infections ■ ■LUNG FLUKES Paragonimiasis is a parasitic lung infection caused by lung flukes of the genus Paragonimus. It is a food-borne parasitic zoonosis, with most cases reported from Asia and attributable to consumption of raw or undercooked freshwater crustaceans. Paragonimus westermani and related species (e.g., Paragonimus africanus) are endemic in West Africa, Central

and South America, and Asia. The United States has one indigenous species of lung fluke, Paragonimus kellicotti. Paragonimus species require two intermediate hosts: first, a freshwa ter snail; and second, a freshwater crustacean, such as a freshwater crab. Humans are infected by consuming raw or undercooked infected crus taceans containing Paragonimus metacercariae. Paragonimus infects other carnivores such as cats, dogs, foxes, rodents, and pigs in addi tion to humans. After ingestion, metacercariae quickly penetrate the duodenum and traverse the peritoneal cavity, diaphragm, and parietal pleura to mature into hermaphroditic worm pairs in the pleural spaces or lungs within 6–10 weeks. Adults cross-fertilize in cystic cavities

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