80. Hirata T, Nakamura H, Kinjo N, et al. Increased detection rate of *Strongyloides stercoralis* by repeated stool examinations using the agar plate culture method. *Am J Trop Med Hyg*. 2007;77:683–684.
81. Buonfrate D, Sequi M, Mejia R, et al. Accuracy of five serologic tests for the follow up of *Strongyloides stercoralis* infection. *PLoS Negl Trop Dis*. 2015;9:e0003491.
82. Bisoffi Z, Buonfrate D, Sequi M, et al. Diagnostic accuracy of five serologic tests for *Strongyloides stercoralis* infection. *PLoS Negl Trop Dis*. 2014;8:e2640.
83. Ramanathan R, Burbelo PD, Groot S, et al. A luciferase immunoprecipitation systems assay enhances the sensitivity and specificity of diagnosis of *Strongyloides stercoralis* infection. *J Infect Dis*. 2008;198:444–451.
84. Rascoe LN, Price C, Shin SH, et al. Development of Ss-NIE-1 recombinant antigen based assays for immunodiagnosis of strongyloidiasis. *PLoS Negl Trop Dis*. 2015;9:e0003694.
85. Verweij JJ, Canales M, Polman K, et al. Molecular diagnosis of *Strongyloides stercoralis* in faecal samples using real-time PCR. *Trans R Soc Trop Med Hyg*. 2009;103:342–346.
86. Suputtamongkol Y, Premasathian N, Bhumimuang K, et al. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. *PLoS Negl Trop Dis*. 2011;5:e1044.
87. Marty FM, Lowry CM, Rodriguez M, et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. *Clin Infect Dis*. 2005;41:e5–e8.
88. Lichtenberger P, Rosa-Cunha I, Morris M, et al. Hyperinfection strongyloidiasis in a liver transplant recipient treated with parenteral ivermectin. *Transpl Infect Dis*. 2009;11:137–142.
89. Donadello K, Cristallini S, Taccone FS, et al. *Strongyloides* disseminated infection successfully treated with parenteral ivermectin: case report with drug concentration measurements and review of the literature. *Int J Antimicrob Agents*. 2013;42:580–583. Dec.
90. Zeitler K, Jariwala R, Restrepo-Jaramillo R, et al. Successful use of subcutaneous ivermectin for the treatment of *Strongyloides stercoralis* hyperinfection in the setting of small bowel obstruction and paralytic ileus in the immunocompromised population. *BMJ Case Rep*. 2018;2018:Jun 4.
91. Plieskatt J, Rezende W, Olsen C, et al. Advances in vaccines against neglected tropical diseases: enhancing physical stability of a recombinant hookworm vaccine through biophysical and formulation studies. *Hum Vaccin Immunother*. 2012;8.
92. Abraham D, Hess JA, Mejia R, et al. Immunization with the recombinant antigen Ss-IR induces protective immunity to infection with *Strongyloides stercoralis* in mice. *Vaccine*. 2011;29:8134–8140.
93. Forrester JE, Bailar JC 3rd, Esrey SA, et al. Randomised trial of albendazole and pyrantel in symptomless trichuriasis in children. *Lancet*. 1998;352:1103–1108.
94. Sandborn WJ, Elliott DE, Weinstock J, et al. Randomised clinical trial: the safety and tolerability of *Trichuris suis* ova in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2013;38:255–263.
95. Scholmerich J, Fellermann K, Seibold FW, et al. A Randomised, Double-blind, Placebo-controlled Trial of *Trichuris suis* ova in Active Crohn's Disease. *J Crohns Colitis*. 2017;11:390–399.
96. Bager P, Kapel C, Roepstorff A, et al. Symptoms after ingestion of pig whipworm *Trichuris suis* eggs in a randomized placebo-controlled double-blind clinical trial. *PLoS ONE*. 2011;6:e22346.
97. Kaisar MMM, Brienen EAT, Djuardi Y, et al. Improved diagnosis of *Trichuris trichiura* by using a bead-beating procedure on ethanol preserved stool samples prior to DNA isolation and the performance of multiplex real-time PCR for intestinal parasites. *Parasitology*. 2017;144:965–974.
98. Sirivichayakul C, Pojjaroen-Anant C, Wisetsing P, et al. The effectiveness of 3, 5 or 7 days of albendazole for the treatment of Trichuris trichiura infection. *Ann Trop Med Parasitol*. 2003;97:847.

287 Tissue Nematodes, Including Trichinellosis, Dracunculiasis, Filariasis, Loiasis, and Onchocerciasis

James W. Kazura

SHORT VIEW SUMMARY

Definition
- Tissue nematode infections cause a spectrum of disease manifestations ranging from asymptomatic cases to chronic pathologic processes and, occasionally, severe illness and death.

Epidemiology
- Infections with tissue nematodes occur throughout the world and have the highest prevalence in tropical regions where obligatory insect vectors are present.
- Trichinellosis
- Dracunculiasis
- Filariases

Microbiology
- The life cycles of these parasites are complex, with five distinct stages that involve their human host and, where applicable, insect vectors.
- Trichinellosis
- Dracunculiasis
- Filariases

Diagnosis
- Parasites are identified microscopically in body fluids, or diagnostic assays are used to detect parasite antigens.

Therapy
- Anthelmintic drugs are available for many infections.
- For trichinellosis, no drugs are available for treatment of newborn larvae or maturing first-stage larvae. Corticosteroids and mebendazole are sometimes utilized in severe disease. During the enteral stage of infection (1–2 weeks after eating contaminated meat), mebendazole or albendazole can be used to eliminate adult worms from the small intestine.
- For lymphatic filariasis, diethylcarbamazine is more active against *Wuchereria bancrofti* than *Brugia malayi*.
- Diethylcarbamazine is also used to treat tropical pulmonary eosinophilia and loiasis.
- Ivermectin is used to treat onchocerciasis.

Prevention
- Controlling insect vectors and mass administration of anthelmintic drugs to endemic populations reduces and may potentially eliminate transmission of medically significant tissue nematode infections.

Tissue-dwelling nematode (roundworm) infections are widely distributed throughout the world. The health and socioeconomic impacts of these infections are greatest in resource-poor settings in the tropics and subtropics, although populations in temperate and industrialized regions of the world continue to be at risk for infection and morbidity. Like all parasitic nematodes, the life cycle of these multicellular organisms includes five distinct stages: adult male or female worms and four larval stages distinguished from each other by a molting process that involves shedding of the parasite's surface cuticle and by organ system differentiation dictated by developmentally regulated changes in gene expression. With the exception of *Trichinella* spp., which are transmitted directly to humans by ingestion of contaminated meat, infection involves obligatory development in and subsequent transmission by blood-feeding invertebrate arthropods (the filariases) or swallowing of small freshwater crustaceans (copepods). Adult worms do not multiply in the human host and, therefore, the likelihood of developing a high enough worm burden to cause morbidity is directly related to the duration and intensity of exposure to vectors harboring infective larvae. Definitive diagnosis is made by microscopic visualization of parasites isolated from or present in host tissue, although this may be difficult or not indicated in all cases. Simple and inexpensive measures can be taken to avoid infection. Global efforts are underway to eliminate some tissue nematode infections as public health problems or even eradicate them by permanently stopping transmission. Effective and safe anthelmintic drugs are available for the majority of these infections.

Infections acquired by eating contaminated meat and swallowing copepods harboring infective larvae are considered first. Filarial infections transmitted by blood-feeding insects are described next.

TRICHINELLOSIS

Trichinellosis is acquired when undercooked meat of domestic pigs, horses, or game containing infective larvae of various *Trichinella* spp. is consumed. Symptomatic infections characterized by diarrhea, myositis, fever, and periorbital edema develop when large numbers of larvae are ingested.

Life Cycle of *Trichinella*

Members of the *Trichinella* genus are zoonotic nematodes that infect carnivorous and omnivorous mammals in various ecologic and climatic settings.[1] Recent genomic and phylogenetic analyses indicate that, of the 11 known species, there are two clades distinguished by the presence or absence of encapsulated third-stage larvae that have parasitized striated muscle cells (Table 287.1).[2,3] The two clades are estimated to have diverged from a common ancestor 15 to 20 million years ago. *Trichinella spiralis,* a species distributed throughout the world that infects pigs, rodents, and horses, has historically been the most common cause of human infection. *Trichinella* spp. of wild game are of increasing importance in areas where food safety measures and livestock practices have led to a reduction in *T. spiralis*.[4]

The parasite life cycle begins with the enteral phase when meat containing infective third-stage larvae is eaten. Larvae of approximately 1 mm in length are liberated after digestion of the encapsulated cyst wall in the acid-pepsin environment of the stomach. These larvae pass rapidly to the lumen of the small intestine, where they parasitize cells of the columnar epithelium. Four molts occur over 10 to 28 hours, culminating in the development of mature adult female and male worms in the epithelium of the small intestine. Fecund female worms produce and release first-stage (newborn) larvae that initiate the systemic phase of infection when they penetrate the gut wall and enter the lymphatics and eventually the blood circulation via the thoracic duct. Newborn larvae are dispersed in capillary beds throughout the body and ultimately parasitize striated muscle cells. After entering muscle, the larvae molt, encyst, and undergo development to become infective third-stage larvae within 15 days.[5] *T. spiralis* infective larvae encapsulated in collagenous cysts may remain viable for months to years. The cysts may calcify and be visible on radiographs.

Epidemiology

Trichinellosis historically has been associated with the consumption of undercooked pork products prepared from domestic swine. The epidemiologic significance of this source of infection has diminished over

TABLE 287.1 Hosts and Geographic Distribution of Species of the Genus *Trichinella*

SPECIES	CODE	COMMON HOSTS	GEOGRAPHIC DISTRIBUTION	ENCAPSULATED
Trichinella spiralis	T1	Pigs, rodents, horses, bears, foxes	Worldwide	Yes
Trichinella nativa	T2	Bears, foxes, dogs	Arctic, sub-Arctic	Yes
Trichinella britovi	T3	Dogs, cats, bears	Temperate areas, sub-Arctic	Yes
Trichinella pseudospiralis	T4	Birds, omnivorous mammals	Arctic, Tasmania	No
Trichinella murrelli	T5	Bears	North America	Yes
Not yet defined	T6	Bears	Sub-Arctic	Yes
Trichinella nelsoni	T7	Hyenas, cats	Tropical Africa	Yes
Not yet defined	T8	Lions, panthers	Southern Africa	Yes
Not yet defined	T9	Sylvatic carnivores	Japan	No

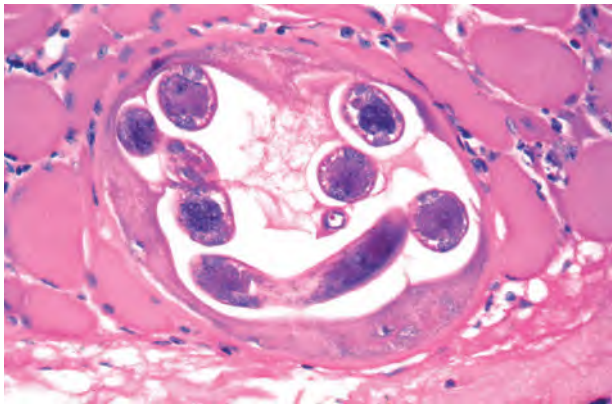

FIG. 287.1 Coiled *Trichinella spiralis* larvae within a skeletal muscle cell. *(From McAdam AJ, Sharpe AH. Infectious diseases. In: Kumar V, ed.* Robbins and Cotran Pathologic Basis of Disease. *8th ed. Philadelphia: Saunders; 2009.)*

the latter part of the 20th century as the practice to feed pigs garbage containing *Trichinella*-infested meat scraps or rodents has been eliminated. Notably, outbreaks of *T. spiralis* infection associated with the consumption of pork from domestic swine have recently been observed in several countries in eastern Europe and in western China.[6,7] Consumption of meat from horses and wild game (boar, deer, bear, cougar, and walrus in areas where sylvatic trichinellosis is endemic) may also be the source of human infection, and has been reported in the United States.[8–10] *T. spiralis* is the most common cause of human infection; *Trichinella britovi, Trichinella pseudospiralis,* and *Trichinella murrelli* often underlie cases associated with consumption of wild game.

Pathogenesis and Pathology

Pathologic manifestations of infection first appear in the gastrointestinal tract. Two to 3 weeks after ingestion of contaminated meat and establishment of adult worms in the upper small intestine, local villous atrophy and mucosal and submucosal infiltration with neutrophils, eosinophils, and macrophages develop. However, the most characteristic pathologic change induced by the parasite is evident in skeletal muscle fibers. Histologically, edema and basophilic degeneration are present. Coiled worms, cyst walls resulting from parasitization of muscle cells, and infiltrates consisting of eosinophils and lymphocytes may be observed (Fig. 287.1). Although nonstriated muscle and other host tissues do not support the complete development of *Trichinella* to infective third-stage larvae, newborn larvae that disseminate to the myocardium, lung, and central nervous system in heavily infected individuals may cause local inflammation and tissue damage that have serious pathologic consequences (e.g., myocarditis, encephalitis, meningitis).

Clinical Manifestations

Based on observations made under circumstances in which a common source of infested meat has been identified, the majority of infected people are asymptomatic. Morbidity is most likely to develop in individuals who have ingested the highest parasite inocula. Watery diarrhea is the most common manifestation during the enteral phase of infection. Vomiting, abdominal discomfort, and nausea may also be observed. Prolonged diarrhea, sometimes lasting for weeks, and other gastrointestinal symptoms in Native American adults who traditionally consume polar bear or walrus meat infested with *Trichinella nativa* have been suggested to reflect immunity acquired as a result of earlier infections. Facial and periorbital edema, fever, weakness, malaise, myalgia, urticarial rash, conjunctivitis, and conjunctival and subungual hemorrhages appear during the systemic phase when newborn larvae disseminate. These signs and symptoms are most severe and peak 2 to 4 weeks after ingestion of contaminated meat.[11–14] Weakness and myalgia appear first and are most severe in the extraocular, masseter, and neck muscles. Patients with high infection burdens may die of myocarditis, encephalitis, or pneumonia that becomes progressively severe after 4 to 8 weeks. It has been suggested that trichinellosis can lead to chronic muscle pain and weakness.

Diagnosis

Trichinellosis should be considered in the differential diagnosis of patients presenting with myositis, eosinophilia, fever, elevated creatine phosphokinase and lactate dehydrogenase levels, and signs consistent with systemic dissemination of newborn larvae as described previously. Questioning regarding a history of consumption of undercooked meat from wild or farmed game, such as bear and boar or pigs raised in noncommercial and unregulated farms, is informative. It is also helpful to determine whether a similar illness has developed in others who have consumed the same food. Antibodies to *Trichinella* spp. can be detected by a variety of techniques[15] (enzyme-linked immunosorbent assay is now used by the Centers for Disease Control and Prevention). Seroconversion usually occurs by approximately 3 weeks after ingestion of infective larvae. A biopsy specimen of painful muscle may reveal the presence of *Trichinella* spp., although this procedure is not recommended in most situations. It is useful to obtain a sample of the meat suspected to harbor the parasite because this can be used to confirm the origin of the infection. Various *Trichinella* spp. can be differentiated by DNA-based technologies such as polymerase chain reaction assay.[16]

The differential diagnosis of trichinellosis observed during the enteral phase of infection includes a wide variety of causes of gastroenteritis and diarrheal illnesses. During the systemic phase of infection, febrile illnesses including influenza and typhoid fever, connective tissue diseases such as dermatomyositis, and angioneurotic edema should be considered.

Therapy

Currently, no anthelmintic drug has proved effective against newborn larvae or maturing first-stage larvae that cause myositis and other signs

and symptoms that appear during the systemic phase of infection. Systemic corticosteroids in conjunction with mebendazole may be used in patients with severe illness, although proven benefit for this approach is lacking.

If the diagnosis is made during the enteral phase of infection (e.g., within 1–2 weeks of eating contaminated meat or when gastrointestinal signs and symptoms are present), mebendazole (200–400 mg orally three times daily for 3 days, then 400–500 mg orally three times daily for 10 days for all ages) may be used to eliminate adult worms from the small intestine.[17] Mebendazole is available in the United States only through compounding pharmacies. Albendazole (400 mg orally twice daily for 8–14 days) may also be used.

Prevention

Awareness of and compliance with safety regulations prohibiting the use of garbage as a source of food for domestic animals, control of rodents, segregation of livestock from wild animals, and proper preparation of meat from wild animals will reduce the risk for infection with *Trichinella* spp. Inspection of meat for *Trichinella* is ideally done by direct dissection and visualization of encysted larvae.

Cooking meat to a temperature of 55°C or higher (until pink fluid or flesh is not visible) kills *Trichinella* spp. Storage in a freezer (–15°C) for 3 or more weeks kills *T. spiralis* in pork, but this is not effective for *Trichinella* spp. larvae in horse and game meat. Drying, smoking as in the preparation of jerkies, and salting of meat should not be relied on to kill *Trichinella*.

HAYCOCKNEMA PERPLEXUM INFECTION

Haycocknema perplexum is a species of Muspiceoidia nematodes that has been observed in the tissues of Australian mammals and marsupials. Adult and larval stages of the nematode have been identified in muscle biopsy specimens of Australian patients from Tasmania and tropical northern Australia who present with chronic myositis, peripheral muscle weakness, and dysphagia accompanied by eosinophilia and elevated creatine kinase level.[18,19] Muscle weakness improved, and killing of parasites was observed, after administration of multiple doses of albendazole. Corticosteroids are not indicated because this class of drugs may exacerbate muscle weakness and lead to a reduction of eosinophilia that misleads the clinician to conclude that a beneficial effect on a connective tissue disease such as polymyositis has occurred.

DRACUNCULIASIS

Dracunculiasis, or guinea worm disease, is caused by the parasitic nematode *Dracunculus medinensis*. Once prevalent throughout southern Asia and parts of the Middle East, as of 2015–2016 indigenous infections were limited to Chad, Ethiopia, Mali, and South Sudan, with the majority in Chad.[20] Between 2016 and 2017, the number of reported cases worldwide fell from 10 to 8, a 20% decline in 1 year. The parasite causes debilitating skin lesions and secondary bacterial infections. Dracunculiasis has had great socioeconomic impact in affected rural communities.

Life Cycle of the Parasite

Humans are infected by swallowing fresh water from stagnant pools containing minute freshwater crustaceans (copepods) harboring infective larvae of *D. medinensis*. When the copepods are digested in the acid-pepsin environment of the stomach, larval forms are released from the body of the crustacean, after which they penetrate the wall of the small intestine and migrate through the thoracic musculature. Sexually mature male and female worms develop over 2 to 3 months. Gravid female worms mature over 10 to 14 months, migrate throughout the body, and ultimately reach the skin, particularly over the lower legs, ankles, and feet (Fig. 287.2). When skin comes into contact with water, the female worm (which may reach a length of 1 m) induces a local blister that eventually ruptures. Large numbers of larvae are released into the water when prolapsed loops of the uterine cavity contract. The motile free-swimming larvae infect copepods. *D. medinensis* larvae become infective for humans after further development in the intermediate copepod host over a 2-week period.

FIG. 287.2 ***Dracunculus medinensis*** **emerging from the skin over the foot.**

Epidemiology

Clinical manifestations of *D. medinensis* infection appear approximately 1 year after ingestion of contaminated water and are highly seasonal because they coincide with the appearance of stagnant pools of surface water that vary according to local climatic conditions. The prevalence of dracunculiasis is a strong indicator of socioeconomic development because communities are at highest risk where treatment of contaminated water, access to safe drinking water, and separation of bathing and drinking facilities are inadequate.

Clinical Manifestations

Signs and symptoms of dracunculiasis appear approximately 1 year after infection when fecund adult female worms appear near the surface of the skin. The initial presentation is a painful papule that enlarges over hours to days to form a blister that allows a portion of the worm to emerge from the skin. The blister may be accompanied by local erythema, urticaria, fever, nausea, and pruritus. The entire worm may emerge over a period of several weeks. Complications include secondary bacterial infections that may lead to sepsis, local abscesses, and pyogenic arthritis. Affected individuals are incapacitated for approximately 8 weeks. The vast majority of worms emerge from the lower leg, ankle, and foot, although aberrant sites of emergence have been reported (e.g., head, neck, genitalia).

Diagnosis and Therapy

Dracunculiasis is diagnosed by the appearance of the skin blister and adult worm (see Fig. 287.2). No anthelmintic drugs are known to be effective against *D. medinensis*. Application of wet compresses to the affected skin, administration of analgesics, and prevention of secondary bacterial infection by the use of topical antibiotics are recommended. Worms should be slowly and gently extracted over a period of several

TABLE 287.2 Filarial Diseases and Infections of Humans

DISEASE	GENUS AND SPECIES OF FILARIAL PATHOGEN	MAJOR CLINICOPATHOLOGIC MANIFESTATIONS	AREAS OF ENDEMICITY	INSECT VECTORS
Lymphatic filariasis	*Wuchereria bancrofti, Brugia malayi, Brugia timori*	Lymphedema of extremities and breasts, hydrocele, funiculitis, orchitis, tropical (pulmonary) eosinophilia	Sub-Saharan Africa, Southeast Asia, Oceania and western Pacific, Caribbean, limited areas of South America	*Anopheles, Culex, Aedes* spp. mosquitoes
Loiasis	*Loa loa*	Subcutaneous and conjunctival swelling	West and central Africa	*Chrysops* spp. tabanid flies
Onchocerciasis	*Onchocerca volvulus*	Dermatitis, keratitis, chorioretinitis	Sub-Saharan Africa, Arabian peninsula, parts of Central and South America	*Simulium* spp. black flies
Mansonellosis	*Mansonella ozzardi*	Rarely symptomatic	Caribbean, Central and South America	*Culicoides* spp. midges, *Simulium amazonicum* black flies
	Mansonella perstans	Rarely symptomatic	Sub-Saharan Africa, northern coast of South America, Tunisia, Algeria	*Culicoides* spp.
	Mansonella streptocerca	Dermatitis, inguinal lymphadenopathy	Central and West Africa	*Culicoides grahamii*

days using a small stick because breaking the worm can lead to allergic reactions and secondary bacterial infection.

Control and Eradication

The global effort to eradicate dracunculiasis began in 1986 when it was estimated that approximately 3.5 million cases occurred annually in 17 countries in Africa and in 3 countries in Asia. The program was closely linked with efforts to improve the safety of drinking water. Eradication is based on simple and cost-effective measures that include (1) filtration of drinking water through fine-meshed cloth to remove copepods, (2) killing copepods in sources of drinking water by application of temephos (Abate; BASF, Research Triangle Park, NC) larvicide, (3) provision of clean drinking water from boreholes or wells, and (4) educating residents of communities to avoid entering sources of drinking water if worms are emerging. The eradication effort has been largely successful, but a zoonotic reservoir in dogs and baboons along with civil unrest have been associated with incident cases. The total number of new cases in the world was estimated to be 25 in 2016.[20]

FILARIASES

Filarial parasites are threadlike nematodes transmitted to humans by obligatory blood-feeding insect vectors. The lymphatic system, skin, and eyes are the main areas of involvement (Table 287.2). Repeated and long-duration exposure to insect vectors harboring infective larvae is generally necessary for humans to acquire these infections, although travelers to endemic areas occasionally become infected.[21] All filariae of medical significance except for *Loa loa* harbor *Wolbachia* bacterial endosymbionts that are important in maintaining the reproductive capacity of adult female worms.

Lymphatic Filariasis

Wuchereria bancrofti, Brugia malayi, and *Brugia timori* are the causative agents of bancroftian and brugian (sometimes referred to as Malayan) filariasis. Approximately 1 billion persons worldwide are at risk; 120 million residents of developing countries were estimated to be infected before the initiation of a global elimination effort in the late 1990s.[22] In contrast to many other mosquito-borne infections of medical significance, lymphatic filariae are transmitted by not just one but several genera of mosquitoes. These include *Anopheles, Culex,* and *Aedes* spp., which differ greatly in their efficiency of transmission (*Anopheles* and *Culex* spp. being the least and most efficient, respectively).[23] The major pathologic manifestations are acute transient episodes of fever accompanied by painful inflammation of the lymphatics of the extremities and male genitalia and chronic lymphatic dysfunction that leads to gross disfigurement of the male genitalia and progressive lymphedema and swelling of the legs, arms, or breasts.

Life Cycle of the Parasite

Infection is initiated when female mosquitoes release infective third-stage larvae into the puncture site of the skin created during blood-feeding. These larvae pass rapidly through the dermis and enter local lymphatic vessels, where they molt to form fourth-stage larvae. Over 6 to 9 months, the parasites undergo another molt in afferent lymphatic vessels and eventually develop into sexually mature adult male and female worms. Adult worms largely reside in afferent lymphatic vessels of the upper and lower extremities and the lymphatics of the male genitalia, such as those draining the epididymis, testes, and spermatic cord. Other areas of the body, such as skin, may also harbor adult worms. Fecund female worms release as many as 10,000 first-stage larvae (commonly referred to as microfilariae) per day, which migrate from the lymphatics and enter the bloodstream. Microfilariae in peripheral blood are ingested by mosquitoes and undergo development to infective third-stage larvae after completing two molts in the mosquito over a period of 14 days. Adult worms are larger than microfilariae (100 × 0.25 mm vs. 150 × 7 μm, respectively; Fig. 287.3) and have a reproductive life span of 5 to 7 years. A characteristic feature of lymphatic filariasis in most endemic areas is the nocturnal periodicity of microfilaremia, whereby peak levels of parasites appear in peripheral blood at night when the mosquito vectors are seeking a blood meal. During the day, microfilariae are sequestered in deep vascular beds and may not be detectable in peripheral blood.

Epidemiology

Lymphatic filariasis is endemic in South Asia, sub-Saharan Africa, and Pacific regions. Countries with the highest prevalence include India, Indonesia, Papua New Guinea, Nigeria, Ghana, Kenya, and Tanzania. *W. bancrofti* is transmitted in nearly all endemic areas and constitutes 90% of cases worldwide. There is no animal reservoir for *W. bancrofti*. *B. malayi* is limited to southern and Southeast Asia and parts of the Pacific, and may infect cats and primates as well as humans. *B. timori* is found only in the islands of eastern Indonesia. The distribution of infection is heterogeneous within a given geographic region because the local spatial ecology is important in determining transmission and exposure to infective larvae (i.e., the proximity of mosquito breeding sites to human dwellings).[24] Because less than 1% of competent mosquito vectors contain infective larvae, intense exposure to mosquitoes is necessary to develop patent infection. Lymphatic filariasis has a profound detrimental effect on the economy and psychosexual health in societies where manual labor and subsistence agriculture are important in daily life.

Clinical Manifestations

The vast majority of individuals with patent infections documented by the presence of microfilaremia do not have clinically overt manifestations

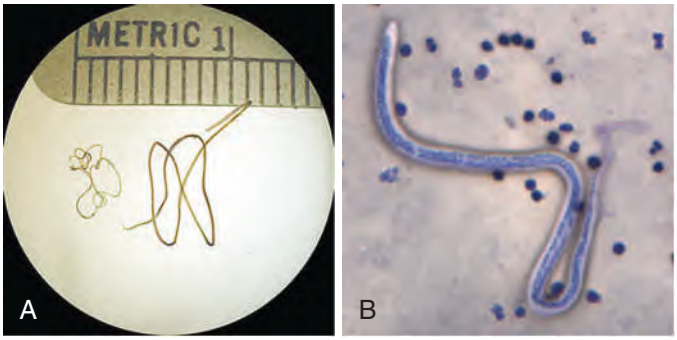

FIG. 287.3 Adult worms and microfilaria of *Wuchereria bancrofti.* (A) Male adult worm *(left)* and female adult worm *(right).* (B) Giemsa-stained microfilaria in a thick blood smear. *(From Lymphatic filariasis image gallery. In DPDx Laboratory Identification of Parasites of Public Health Concern.* https://www.cdc.gov/dpdx/lymphaticfilariasis/index.html.*)*

of a lymphatic pathologic process. Nevertheless, imaging studies indicate that asymptomatic infected adults and children may have compromised lymphatic function.[25,26] Overt pathologic sequelae first become apparent during adolescence and early adulthood, often as acute adenolymphangitis with fever and swelling of the leg, the arm, or the male genitalia. These episodes may last for 4 to 7 days in persons who have previously been asymptomatic or longer in persons who have experienced repeated attacks. The lymphatic inflammation typically progresses retrograde from axillary or inguinal lymph nodes, a feature that distinguishes acute adenolymphangitis from the more recently described entity of acute dermatolymphangioadenitis. The latter progresses toward the lymph node from a peripheral site and is believed to be due to secondary bacterial infection and not inflammation elicited by filarial worms.[27] A cut or entry wound of the skin may be observed in an interdigital area. So-called filarial fever in the absence of lymphatic inflammation may also be observed. In endemic populations, filarial fevers may be difficult to distinguish from other common causes of acute febrile illness.

Repeated episodes of acute filarial disease often precede the development of chronic lymphatic pathology that includes lymphedema of the legs, arms, and breasts and chronic disfigurement of the male genitalia (Fig. 287.4). Male genital involvement is very common in *W. bancrofti* infection and uncommon in *Brugia* spp. infection. Chronic swelling of the legs and compromised lymphatic drainage may result in secondary bacterial infections and sclerosis and verrucous changes of the overlying skin. The most severe cases are sometimes referred to as elephantiasis. Male genital involvement includes hydrocele, funiculitis, epididymitis, and orchitis. There is a poor understanding of the pathogenesis of the various genital manifestations of lymphatic filariasis.[28] Chyluria precipitated by the rupture of dilated lymphatic vessels into the genitourinary tract is an uncommon manifestation. Tropical pulmonary eosinophilia is described separately at the end of this section.

Pathogenesis and Pathology

Adult worms residing in afferent lymphatic vessels and lymph nodes draining the legs, arms, male genitalia, and occasionally other anatomic sites presumably initiate the disease process when poorly characterized parasite mediators produce local lymphatic dilation. Live motile worms exhibiting the "filaria dance" sign and nearby dilated lymphatic vessels can be detected by ultrasonography in the scrotum, inguinal lymph node, and breast[29,29a] (videos can be viewed at https://filariajournal.biomedcentral.com/articles/10.1186/1475-2883-2-3).

It is not clear why the majority of infected individuals remain asymptomatic, whereas others develop acute or chronic manifestations of lymphatic filariasis. With respect to acute filarial pathologic processes, the intensity of transmission and secondary bacterial infections may both be important in determining susceptibility.[30,31] The importance of worm burden as a determinant of a chronic lymphatic pathologic process is controversial. Many persons with chronic lymphedema of the extremities have no evidence of active infection (particularly in India), whereas

FIG. 287.4 Disfigurement of male genitalia with repeated episodes of acute filarial disease. Man with inguinal lymphadenopathy, large bilateral hydroceles, marked edema of the lower left limb (particularly the leg and foot), and early signs of elephantiasis in the foot.

this is not the case in other *W. bancrofti* endemic areas such as Papua New Guinea. Adaptive T-cell responses, genetic susceptibility, worm burden, and systemic inflammatory responses have been suggested to contribute to the complex clinical phenotypes of lymphedema and hydrocele, but a single unifying mechanism has not been defined.[32,33] An increased incidence of human immunodeficiency virus infection has been reported in individuals with lymphatic filariasis and may be due to the systemic immune activation induced by this disease.[34]

Diagnosis

Lymphatic filariasis is diagnosed by obtaining an appropriate history of exposure to mosquitoes in areas where the infection is endemic, observing pathologic signs, and performing a variety of laboratory tests. As described previously, a chronic lymphatic pathologic process such as lymphedema of an extremity or hydrocele primarily affects adults who are residents of endemic areas. A definitive diagnosis is made by microscopic detection of microfilariae in the blood or occasionally from other sites such as fluid aspirated from hydroceles. Blood to detect microfilaremia should generally be obtained at night when the peak density of parasitemia occurs. This is the case for most endemic areas except for *W. bancrofti* in some areas of Oceania. The sensitivity of detecting microfilaremia is enhanced by concentrating parasites by filtration of blood through polycarbonate (Nuclepore; Whatman/GE Healthcare Life Sciences, Pittsburgh, PA) filters that retain microfilariae. Enzyme-linked immunosorbent assay–format antigen capture assays that detect antigen secreted by *W. bancrofti* adult worms have been an important diagnostic advance because these tests allow point-of-care documentation of active infection in the absence of microfilaremia.[35,36] An analogous test for *Brugia* spp. is not yet available. Biopsy of lymphatic tissues to identify adult worms is not justified. As described earlier, adult worms can be imaged in vivo by the use of Doppler ultrasonography.

Therapy

Persons with asymptomatic parasitemia should be treated with diethylcarbamazine (6 mg/kg/day divided into two or three doses over 12 days to a total of 72 mg/kg). The drug is highly effective at eliminating microfilariae but has modest activity against adult worms. The filaricidal activity of diethylcarbamazine is greater against *W. bancrofti* than *B. malayi*. Side effects include fever and occasionally asthma-like symptoms in persons with high-level microfilaremia, and painful nodules may appear in the lymphatics, lymph nodes, skin, and male genitalia. The development of these nodules, usually less than 1 cm in diameter, is an inflammatory reaction to the death of adult worms or migrating larvae. They may appear days to weeks after taking antifilarial drugs, particularly diethylcarbamazine, because it has greater macrofilaricidal activity than albendazole or ivermectin. Systemic posttreatment reactions are likely related to innate immune reactions to *Wolbachia* endosymbionts released by dying microfilariae. The severity of acute side effects may be reduced by initiating treatment with a lower dose of diethylcarbamazine (50 mg on day 1, followed by 50 mg three times on day 2 and 100 mg three times on day 3). Hydroceles may be repaired surgically, but prevention of recurrence is contingent on drug treatment.

It is not known whether diethylcarbamazine or other antifilarial drugs such as ivermectin and albendazole ameliorate a preexisting lymphatic pathologic process because randomized clinical trials have not been performed. Some studies of mass drug treatment to control filariasis in endemic populations suggest that reducing transmission may decrease the incidence of chronic lymphatic pathologic processes.[37]

Prevention, Control, and Eradication

Lymphatic filariasis due to *W. bancrofti* has been targeted for elimination as a public health problem and for worldwide eradication by annual mass treatment with single-dose diethylcarbamazine combined with albendazole (in areas of the world where onchocerciasis and loiasis are not endemic) or ivermectin combined with albendazole (in areas where onchocerciasis and loiasis are endemic). By 2014, mass drug administration programs had been implemented in more than 60 countries, and it has been estimated that more than 5 billion doses of antifilarial medications have been administered.[38,39] *Brugia* spp. are less amenable to eradication because the parasite has an animal reservoir. It is currently believed that at least 5 years of annual mass treatment is necessary to stop transmission because this is the estimated reproductive life span of adult worms. Results of studies in Egypt indicate that this strategy will likely be successful in endemic areas where a good public health infrastructure exists.[40] It is not yet known whether similar success will be achieved in rural areas where population coverage with antifilarial drugs is suboptimal or vectors with greater transmission efficiency exist. The use of drugs that target the *Wolbachia* endosymbiont of filarial parasites (e.g., doxycycline) may provide added benefit because killing of these *Rickettsia*-like bacteria reduces the fecundity and shortens the reproductive life span of adult worms.[41] The use of insecticide-treated bed nets has been shown to significantly reduce the number of mosquitoes harboring infective larvae.[42]

Tropical Pulmonary Eosinophilia

This syndrome is associated with *W. bancrofti* and *B. malayi* infection. It is most commonly observed in South and Southeast Asia and endemic areas of Brazil and Guyana. Patients are typically middle-aged men (male-to-female ratio, 4 : 1) who present with nocturnal asthma, cough, fever, and weight loss. Microfilariae are not detectable in peripheral blood. High-level eosinophilia (>3000/μL blood) with elevated antifilarial antibodies and polyclonal immunoglobulin E are present. Chest radiographs typically show increased bronchovascular markings with a mottled appearance in the middle and lower lungs. Treatment with diethylcarbamazine leads to symptomatic improvement and reduces eosinophilia and immunoglobulin E levels. Re-treatment may be necessary in some cases. If the infection is not treated, progressive interstitial fibrosis and restrictive lung disease may develop.[43]

Loiasis

Adult worms of these nematodes migrate in subcutaneous tissue and occasionally the conjunctiva, where they elicit transient painful swelling. The infection is endemic in central and West Africa.

Life Cycle of the Parasite

Loa loa infective larvae are transmitted by female tabanid (red) flies (*Chrysops* spp.) that seek blood meals during the day. Adult worms measuring 30 to 70 × 0.3 mm develop over 6 to 12 months and migrate in subcutaneous tissues. Microfilariae released from fecund female worms migrate to the blood and have a diurnal periodicity. In contrast to other filarial pathogens of medical significance, *L. loa* do not harbor *Wolbachia* endosymbionts.

Epidemiology

Loiasis is endemic in coastal and rain forest regions of central and West Africa. The infection has been observed as far east as Uganda and Ethiopia. Infected individuals usually have a long history of residence in endemic areas with prolonged exposure to infected vectors; however, repeated short durations of intense exposure can also result in infection and morbidity, including in expatriate nonresidents who travel to endemic areas.[44]

Clinical Manifestations

Most infected individuals are asymptomatic. The main clinical presentation is a Calabar swelling, which represents an angioedematous response to adult worms migrating through subcutaneous tissue. The 10- to 20-cm swelling lesions most commonly appear on the face and extremities and are preceded by itching and pain. Calabar swellings are transient and persist from several days to weeks. Adult worms may also migrate to the conjunctiva and produce an "eye worm" (Fig. 287.5). Other manifestations include renal complications (hematuria and proteinuria) and encephalitis, which are usually precipitated by treatment with the antifilarial drug diethylcarbamazine. In the case of encephalitis, persons with high-level microfilaremia (>2500 microfilariae/mL) are at high risk.[45] Precautions for treating such individuals are described later under "Therapy."

Diagnosis

The diagnosis should be considered in persons who have resided in an endemic area and present with urticaria, an eye worm, or eosinophilia. Identification of microfilariae in the blood (which should be obtained during the day) or visualization of an adult worm in the conjunctiva confirms loiasis. Standardized and specific serologic tests for *L. loa* are not widely available outside the research laboratory setting. Molecular assays with high specificity and the ability to quantify *L. loa* microfilaremia are under development to address this gap.[46] The differential diagnosis includes other causes of angioedema such as C1 inhibitor deficiency, worm infections such as onchocerciasis and mansonellosis (both of which may overlap in endemicity with loiasis), and the various causes of high-level eosinophilia.

Therapy

Diethylcarbamazine at a dose of 8 to 10 mg/kg/day for 21 days should be given to persons who do not have microfilaremia. Repeated

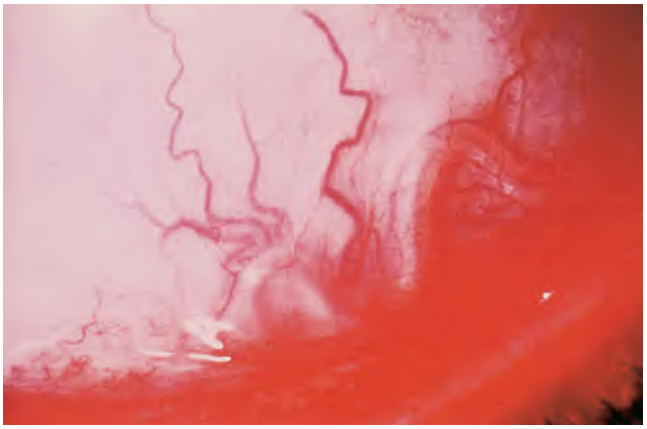

FIG. 287.5 **Serpentine adult *Loa loa* passing through the subconjunctiva.**

treatment courses with diethylcarbamazine may be necessary in 40% to 50% of patients. Calabar swelling, pruritus, and eye worms may be precipitated by treatment. Side effects can be minimized by concurrent administration of antihistamines or corticosteroids. In persons with high-level microfilaremia (>2500/mL), there is a significant risk for renal and central nervous system complications due to the rapid destruction of large numbers of microfilariae. Options include withholding anthelmintic drugs, cytapheresis to remove microfilariae before administration of diethylcarbamazine, and administration of a single dose of ivermectin. In the context of mass drug administration programs in West and central Africa aimed at elimination of onchocerciasis or lymphatic filariasis, it is important that prior screening for coendemic, high-level *L. loa* microfilaremia be performed to exclude treatment in order to avoid serious adverse events such as encephalitis.

Prevention and Control

Travelers who plan prolonged residence in endemic areas should take 300 mg diethylcarbamazine weekly as chemoprophylaxis.[47] There are currently no effective means to control the tabanid flies that transmit *L. loa.*

Onchocerciasis

Onchocerca volvulus is transmitted by blood-feeding *Simulium* spp. black flies. Infection can cause dermatitis, subcutaneous nodules, keratitis, and chorioretinitis. The disease has a great socioeconomic impact because it causes reduced vision ("river blindness") and chronic skin disease in adults.

Life Cycle of the Parasite

Infection is acquired when female *Simulium damnosum* sibling species (in Africa) and several other *Simulium* spp. (in the Americas and Arabian peninsula) take blood meals. Infective third-stage larvae migrate to subcutaneous tissue, undergo two molts, and eventually over 6 to 12 months develop into threadlike sexually mature adult male (300 × 0.3 mm) or female (400 × 0.3 mm) worms. Adult worms aggregate in nodules in subcutaneous tissue and muscle. Fecund female worms release unsheathed microfilariae (200 × 8 µm) that migrate to the dermis and eye.

Epidemiology

Onchocerciasis is endemic in West Africa, limited areas of East Africa, and the Arabian peninsula. Mass administration of ivermectin in six endemic countries in the Americas has resulted in interruption of transmission in all geographic regions with the exception of remote border areas of southern Venezuela and northern Brazil.[48] The greatest number of infected individuals live in West Africa, particularly Nigeria and the Democratic Republic of the Congo.[49,50] Although there is great variability in the frequency of disease manifestations in various endemic areas, the majority of infected individuals are asymptomatic. Onchocerciasis in savanna regions of West Africa is characterized by a greater likelihood of reduced vision and blindness compared with rain forest regions. Dermatologic manifestations of infection are common in areas of Africa outside either the rain forest or savanna.

Pathology and Clinical Manifestations

Adult worms of both sexes reside in nonpainful vascularized fibrous nodules (0.5 × 3.0 cm) in a subcutaneous or intramuscular site. The lesions may be palpable. The major pathologic sequelae of clinical significance are due to inflammatory responses to microfilariae. In the skin, these include acute and chronic papular dermatitis, lichenified dermatitis, atrophy, and depigmentation.[51] Pruritus is usually the presenting symptom. In the eye, microfilariae that have migrated to the cornea initially elicit punctate keratitis. This can progress to a sclerosing keratitis that causes blindness. As described previously, this outcome is most common in savanna forms of onchocerciasis in West Africa. Iridocyclitis and chorioretinitis are less common. *Onchocerca volvulus* infection may also cause inguinal lymph node fibrosis and atrophy of the overlying skin that leads to the appearance of hanging groin.

Diagnosis

The diagnosis should be considered when the previously described signs are present in an individual who has resided in an endemic area. Because transmission is inefficient, residence of months to years is usually (but not always) required to acquire *O. volvulus* infection. Identification of microfilariae in the skin or eye or adult worms in nodules is required for definitive diagnosis. Microfilariae in the skin are accessed by using a corneoscleral instrument to obtain a 1- to 2-mg biopsy specimen of the dermis overlying both scapulae, iliac crests, and calves. The skin snips are placed in microtiter plates containing saline held at 37°C for 60 minutes to 24 hours (depending on the microfilarial burden) to allow the parasites to emerge. The parasites are identified under low-power microscopy. Microfilariae in the eye can be identified by slit-lamp examination. In the research setting, polymerase chain reaction assay can be used to identify persons with light infections that are not detectable by microscopy.[52] The differential diagnosis of onchocercal dermatitis includes scabies and the many other infectious and noninfectious causes of dermatitis. Eye disease may be mimicked by other infectious and noninfectious causes of chorioretinitis. Eye worms similar to those observed for loiasis do not occur because adult *O. volvulus* parasites do not migrate to the conjunctiva.

Therapy

Ivermectin, which is effective in killing microfilariae but not adult *O. volvulus* worms, is the drug of choice. The dose is 150 to 200 µg/kg given as a single dose. A reduction in skin microfilariae is detectable within 2 weeks but may be incomplete. For expatriates who are more prone than lifelong residents of endemic areas to develop severe pruritus, more frequent treatment with ivermectin (e.g., every 3 months) may be necessary to control symptoms. Doxycycline, which kills the obligatory *Wolbachia* endosymbiont of *O. volvulus,* is highly effective in reducing microfilarial production by adult worms and may represent a novel strategy for reducing transmission and disease pathogenesis.[53,54] However, there is no indication that this approach offers benefit for the treatment of the individual patient. In cases in which loiasis coexists with onchocerciasis (both infections are endemic in some areas of West Africa), the use of ivermectin carries a risk for precipitating encephalopathy in persons with high levels of *L. loa* microfilaremia. Cytapheresis may be used to reduce the level of *L. loa* microfilariae before treatment, but this is usually not an option in resource-poor settings.

Prevention and Control

Control of the *Simulium* vector by aerial dispersion of larvicides from 1974 to 2002 was highly successful in reducing blindness in 11 countries in West Africa where the savanna form of onchocerciasis was common. The African Program for Onchocerciasis Control is based on mass distribution of ivermectin to reduce morbidity and possibly stop transmission. The latter goal has recently been emphasized as feasible with programmatic changes that include improved mapping of endemic foci, better monitoring tools, and use of drug combinations that kill adult worms.[55]

Mansonellosis

Mansonellosis is a poorly understood infection of humans that is asymptomatic in most individuals. Transmission is by blood-feeding midges (*Culicoides* spp. for *Mansonella ozzardi, Mansonella perstans,* and *Mansonella streptocerca*) or the black fly (*Simulium amazonicum* for *M. ozzardi*).

M. ozzardi infection is endemic in northern South America, Central America, and some Caribbean islands. Unsheathed microfilariae circulate in the blood. Most infections are asymptomatic. Lymphadenopathy, urticaria, pruritus, pulmonary symptoms, and keratitis have been described. Ivermectin reduces microfilariae, but optimal treatment has not been defined.[56]

M. perstans infection is endemic in parts of central and northern Africa, South America, and the Caribbean. Adult worms reside in serous cavities of the body and sheathed microfilariae circulate in the blood. Angioedema, urticaria, and pruritus have been attributed to the infection. Diethylcarbamazine lowers the level of microfilaremia. Doxycycline has been shown to be effective in reducing microfilaremia, likely through its ability to eliminate adult worms by killing *Wolbachia* bacterial endosymbionts.[57]

M. streptocerca is endemic in rain forest regions of central Africa and parts of Uganda.[58,59] Many infected individuals are asymptomatic,

although some people develop inguinal lymphadenopathy and a chronic dermatitis with pruritus. The latter may be similar to that seen in persons with onchocerciasis. Microfilariae reside in the dermis and can be identified by obtaining a skin snip and identifying the parasite microscopically as described for onchocerciasis. *M. streptocerca* microfilariae are distinguished from those of *O. volvulus* by the hook-shaped tail of the former.[60] Treatment is with diethylcarbamazine at a dose similar to that described for lymphatic filariasis.

Zoonotic Filariae Reported to Cause Human Disease

Dirofilaria repens is a parasite of felids and canids transmitted by mosquitoes. Humans are nonpermissive hosts, but the parasite may undergo incomplete development in the eye. Subconjunctival, intraocular, and orbital lesions have been described. Treatment is by excision.[61] Subconjunctival infections with the canine parasite *Onchocerca lupi* and with *Setaria labiatopapillosa* have been reported.

References

1. Pozio E. World distribution of *Trichinella* spp. infections in animals and humans. *Vet Parasitol*. 2007;149:3–21.
2. Mitreva M, Jasmer DJ. Biology and genome of Trichinella spiralis. In: C. elegans Research Community. Wormbook. http://www.wormbook.org. Accessed November 23, 2006.
3. Zarlenga DS, Rosenthal BM, La Rosa G, et al. Post-Miocene expansion, colonization, and host switching drove speciation among extant nematodes of the archaic genus *Trichinella*. *Proc Natl Acad Sci U S A*. 2006;103:7345–7359.
4. McIntyre L, Pollock SL, Fyfe M, et al. Trichinellosis from consumption of wild game meat. *CMAJ*. 2007;176:449–451.
5. Gottstein B, Pozio E, Nöckler T. Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev*. 2009;127–145.
6. Pozio E. New patterns of *Trichinella* infection. *Vet Parasitol*. 2001;98:133–148.
7. Cui J, Wang ZQ, Zu BL. The epidemiology of trichinellosis in China during 2004-2009. *Acta Trop*. 2011;118:1–5.
8. Springer YP, Casillas S, Helfrich K, et al. Two outbreaks of trichinellosis linked to consumption of walrus meat - Alaska, 2016-2017. *MMWR Morb Mortal Wkly Rep*. 2017;66:692–696.
9. Holzbauer SM, Agger WA, Hall RL, et al. Outbreak of *Trichinella spiralis* infections associated with a wild boar hunted at a game farm in Iowa. *Clin Infect Dis*. 2014;59:1750–1756.
10. Heaton D, Huang S, Shiau R, et al. Trichinellosis outbreak linked to consumption of privately raised raw boar meat - California, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67:247–249.
11. Kociecka W. Trichinellosis: human disease, diagnosis and treatment. *Vet Parasitol*. 2000;93:365–383.
12. Ancelle T, Dupouy-Camet J, Desenclos JC, et al. A multifocal outbreak of trichinellosis linked to horse meat imported from North America to France in 1993. *Am J Trop Med Hyg*. 1998;59:615–619.
13. Barennes H, Sayasone S, Odermatt P, et al. A major trichinellosis outbreak suggesting a high endemicity of *Trichinella* infection in northern Laos. *Am J Trop Med Hyg*. 2008;78:40–44.
14. Schellenberg RS, Tan BJ, Irvine DJ, et al. An outbreak of trichinellosis in French hunters due to consumption of bear meat infected with *Trichinella nativa* in two northern Saskatchewan communities. *J Infect Dis*. 2003;188:835–843.
15. Dupouy-Camet J, Kociecka W, Bruschi F, et al. Opinion on the diagnosis and treatment of human trichinellosis. *Expert Opin Pharmacother*. 2002;3:1117–1130.
16. Zarlenga DS, Chute MB, Martin A, et al. A multiplex PCR for unequivocal differentiation of all encapsulated and non-encapsulated *Trichinella*. *Int J Parasitol*. 1999;29:1859–1867.
17. Watt G, Saison D, Sacchi L, et al. Blinded, placebo-controlled trial of antiparasitic drugs for trichinosis myositis. *J Infect Dis*. 2000;182:371–374.
18. Dennet X, Siejka SJ, Andrews JR, et al. Polymyositis caused by a new genus of nematode. *Med J Aust*. 1998;168:226–227.
19. Vos LJ, Robertson T, Binotto E. *Haycocknema perplexum*: an emerging cause of parasitic myositis in Australia. *Commun Dis Intell Q Rep*. 2016;40:E496–E499.
20. Hopkins DR, Ruiz-Tiben E, Eberhard ML, et al. Progress toward global eradication of drucunculiaisis, January 2016-June 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66:1327–1331.
21. Klion AD. Filarial infections in travelers and immigrants. *Curr Infect Dis Rep*. 2008;10:50–57.
22. Michael E, Bundy DA, Grenfell BT. Re-assessing the global prevalence and distribution of lymphatic filariasis. *Parasitology*. 1996;112:409–428.
23. Gambhir M, Michael E. Complex ecological dynamics and eradicability of the vector borne macroparasitic disease, lymphatic filariasis. *PLoS ONE*. 2008;3:e2874.
24. Rwegoshora RT, Simonsen PE, Meyrowitsch DW, et al. Bancroftian filariasis: house-to-house variation in the vectors and transmission—and the relationship to human infection—in an endemic community of coastal Tanzania. *Ann Trop Med Parasitol*. 2007;101:51–60.
25. Figueredo-Silva J, Dreyer G. Bancroftian filariasis in children and adolescents: clinical-pathological observations in 22 cases from an endemic area. *Ann Trop Med Parasitol*. 2005;99:759–769.
26. Fox LM, Furness BW, Haser JK, et al. Ultrasonographic examination of Haitian children with lymphatic filariasis: a longitudinal assessment in the context of antifilarial drug treatment. *Am J Trop Med Hyg*. 2005;72:642–648.
27. Dreyer G, Medeiros Z, Netto MJ, et al. Acute attacks in the extremities of persons living in an area endemic for bancroftian filariasis: differentiation of two syndromes. *Trans R Soc Trop Med Hyg*. 1999;93:413–417.
28. Noroes J, Addiss D, Cedenho A, et al. Pathogenesis of filarial hydrocele: risk associated with intrascrotal nodules caused by death of adult *Wuchereria bancrofti*. *Trans R Soc Trop Med Hyg*. 2003;97:561–566.
29. Mand S, Debrah A, Batsa L, et al. Reliable and frequent detection of adult *Wuchereria bancrofti* in Ghanaian women by ultrasonography. *Trop Med Int Health*. 2004;9:1111–1114.

29a. Mand S, Marfo-Debrekyei Y, Dittrich M, et al. Animated documentation of the filaria dance sign (FDS) in bancroftian filariasis. *Filaria J*. 2003;2:3.

30. Tisch DJ, Alexander ND, Kiniboro B, et al. Reduction in acute filariasis morbidity during a mass drug administration trial to eliminate lymphatic filariasis in Papua New Guinea. *PLoS Negl Trop Dis*. 2011;5:e1241.
31. Esterre P, Plichart C, Huin-Blondey MO, et al. Role of streptococcal infection in the acute pathology of lymphatic filariasis. *Parasite*. 2000;7:91–94.
32. Ottesen EA. Lymphatic filariasis: treatment, control and elimination. *Adv Parasitol*. 2006;61:395–441.
33. Anurada R, George PJ, Pavan Kumar N, et al. Circulating microbial products and acute phase proteins in lymphatic filarial disease. *PLoS Pathog*. 2012;8:e1002749.
34. Kroidl I, Saathoff E, Maganga L, et al. Effect of *Wuchereria bancrofti* infection on HIV incidence in southwest Tanzania: a prospective cohort study. *Lancet*. 2016;388:1912–1920.
35. Tisch DJ, Hazlett FE, Kastens W, et al. Ecologic and biologic determinants of filarial antigenemia in bancroftian filariasis in Papua New Guinea. *J Infect Dis*. 2001;184:898–904.
36. Weil GJ, Curtis KC, Fakoli L, et al. Laboratory and field evaluation of a new rapid test for detecting *Wuchereria bancrofti* antigen in human blood. *Am J Trop Med Hyg*. 2013;89:11–15.
37. Bockarie MJ, Tisch DJ, Kastens W, et al. Mass treatment to eliminate filariasis in Papua New Guinea. *N Engl J Med*. 2002;347:1841–1848.
38. Hopkins DR. Disease eradication. *N Engl J Med*. 2013;368:54–63.
39. Global programme to eliminate lymphatic filariasis: progress report, 2014. *Wkly Epidemiol Rec*. 2015;90:489–504.
40. Ramzy RM, El Setouhy M, Helmy H, et al. Effect of yearly mass drug administration with diethylcarbamazine and albendazole on bancroftian filariasis in Egypt: a comprehensive assessment. *Lancet*. 2006;367:992–999.
41. Hoerauf A. Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis. *Curr Opin Infect Dis*. 2008;21:673–681.
42. Reimer LJ, Thomsen EK, Tisch DJ, et al. Insecticidal bed nets and filariasis transmission in Papua New Guinea. *N Engl J Med*. 2013;369:745–753.
43. Babu S, Nutman TB. Immunopathogenesis of lymphatic filarial disease. *Semin Immunopathol*. 2012;34:847–861.
44. Klion AD, Massougbodji A, Sadeler BC, et al. Loiasis in endemic and nonendemic populations: immunologically mediated differences in clinical presentation. *J Infect Dis*. 1991;163:1318–1325.
45. Carme B, Boulesteix J, Boutes H, et al. Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. *Am J Trop Med Hyg*. 1991;44:684–690.
46. Fink DL, Kamgno J, Nutman TB. Rapid molecular assays for specific detection and quantitation of *Loa loa* microfilaremia. *PLoS Negl Trop Dis*. 2011;5:e1299.
47. Nutman TB, Miller KD, Mulligan M, et al. Diethylcarbamazine prophylaxis for human loiasis: results of a double-blind study. *N Engl J Med*. 1988;319:752–756.
48. Centers for Disease Control and Prevention. Progress toward elimination of onchocerciasis in the Americas—1993-2012. *MMWR Morb Mortal Wkly Rep*. 2013;62:405–408.
49. Mathers CD, Ezzati M, Lopez AD. Measuring the burden of neglected tropical diseases: the global burden of disease framework. *PLoS Negl Trop Dis*. 2007;1:e114.
50. Hopkins DR, Richards FO Jr, Ruiz-Tiben E, et al. Dracunculiasis, onchocerciasis, schistosomiasis, and trachoma. *Ann N Y Acad Sci*. 2008;1136:45–52.
51. Timmann C, Abraha RS, Hamelmann C, et al. Cutaneous pathology in onchocerciasis associated with pronounced systemic T-helper 2-type responses to *Onchocerca volvulus*. *Br J Dermatol*. 2003;149:782–787.
52. Zimmerman PA, Guderian RH, Aruajo E, et al. Polymerase chain reaction–based diagnosis of *Onchocerca volvulus* infection: improved detection of patients with onchocerciasis. *J Infect Dis*. 1994;169:686–689.
53. Tamarozzi F, Halliday A, Gentil K, et al. Onchocerciasis: the role of *Wolbachia* bacterial endosymbionts in parasite biology, disease pathogenesis, and treatment. *Clin Microbial Rev*. 2011;24:459–468.
54. Debrah AY, Specht S, Klarmann-Schulz U, et al. Doxycycline leads to sterility and enhanced killing of female *Onchocerca volvulus* worms in an area with persistent microfilaridermia after repeated ivermectin treatment: a randomized, placebo-controlled, double-blind trial. *Clin Infect Dis*. 2015;61:517–526.
55. Mackenzie CD, Homeida MM, Hopkins AD, et al. Elimination of onchocerciasis from Africa: possible? *Trends Parasitol*. 2012;28:16–22.
56. Medeiros JF, Py-Daniel V, Barbosa UC, et al. Current profile of *Mansonella ozzardi* (Nematoda: Onchocercidae) in communities along the Ituxi river, Labrea municipality, Amazonas, Brazil. *Mem Inst Oswaldo Cruz*. 2008;103:409–411.
57. Coulibaly YI, Dembele B, Diallo AA, et al. A randomized trial of doxycycline for *Mansonella perstans* infection. *N Engl J Med*. 2009;361:1448–1458.
58. Fischer P. Tukesiga E, Büttner DW. Long-term suppression of *Mansonella streptocerca* microfilariae after treatment with ivermectin. *J Infect Dis*. 1999;180:1403–1405.
59. Bamuhiiga JT. *Mansonella streptocerca*: another filarial worm in the skin in Western Uganda. *Community Eye Health*. 1998;11:28.
60. Orihel TC. The tail of the *Mansonella streptocerca* microfilaria. *Am J Trop Med Hyg*. 1984;33:1278.
61. Gautam V, Rustagi IM, Singh S, et al. Subconjunctival infection with *Dirofilaria repens*. *Jpn J Infect Dis*. 2002;55:47–48.

288 Trematodes (Schistosomes and Liver, Intestinal, and Lung Flukes)

James H. Maguire[a]

SHORT VIEW SUMMARY

Definition
- Trematodes or flukes are flatworms that live in blood vessels, biliary tract, intestines, and lungs of humans and lower animals.
- Included are the schistosomes and the foodborne trematodes: liver flukes *(Fasciola, Clonorchis, Opisthorchis),* intestinal flukes (various species), and lung fluke *(Paragonimus).*

Epidemiology
- Schistosomes are prevalent in tropical and subtropical Africa, the Middle East, Southeast Asia, East Asia, the Philippines, and limited areas in the Caribbean and South America in areas with inadequate sanitation or access to clean water.
- Foodborne trematodes are most prevalent in Southeast and East Asia but also in other parts of the world where persons ingest raw or undercooked fish, crayfish, or plants produced in fresh water contaminated with human or animal feces or, for *Paragonimus*, sputum.

Microbiology
- Persons become infected with schistosomes when the larval parasites (cercariae) shed by freshwater snails (intermediate hosts) penetrate bare skin.
- Persons become infected with foodborne trematodes by ingesting the larval parasites (metacercariae) encysted in fish, aquatic vegetation, or crustaceans (second intermediate host) that were infected with cercariae shed from snails (first intermediate host).

Diagnosis
- Trematode infections are frequently light and may cause few or no symptoms but often elicit peripheral blood eosinophilia.
- Suggestive clinical syndromes during the first weeks after initial infection include acute illness with fever, urticaria, eosinophilia, and other symptoms when larval flukes are migrating through the body and maturing; ectopic migration can lead to disease of the central nervous system, the skin, and other parts of the body.
- Suggestive clinical syndromes during chronic infections include: intestinal schistosomes (diarrhea, intestinal polyps, portal hypertension), urinary schistosomes (hematuria, bladder cancer), liver flukes (biliary obstruction), intestinal flukes (diarrhea, abdominal discomfort), and lung flukes (cough, hemoptysis, cavitary lung lesions).
- Diagnosis is made by microscopic identification of characteristic eggs in stool, urine, or sputum or by identification of larval or adult worms in tissue.
- Serology, available for some trematode infections, may be more sensitive than microscopic examination, especially during acute infections.

Therapy
- Praziquantel is the drug of choice for all trematode infections except fascioliasis, for which triclabendazole is preferred (see Table 288.1).

Prevention
- For schistosomiasis, preventive methods include sanitation, provision of clean water, snail control, and avoidance of contact with contaminated fresh water.
- For foodborne trematodes, prevention of infection includes maintaining freshwater bodies free of contamination by humans and lower animals, snail control, and proper cooking of aquatic fish, plants, and crustaceans.
- Periodic screening and treatment or mass drug administration for populations at risk for infection are essential.

The trematode flatworms that infect humans include the schistosomes, which live in venules of the gastrointestinal (GI) or genitourinary tract, and other flukes, which inhabit the bile ducts, intestines, or lungs.[1] The geographic distribution of each species of trematode parallels the distribution of the specific freshwater snail that serves as its intermediate host (Table 288.1).[1a] Six species of schistosomes infect more than 230 million persons, and more than 100 species of other trematodes infect at least 65 million persons.[2–6]

Trematodes vary in length from 1 mm to more than 10 cm, are flattened dorsoventrally, and have an anterior and ventral sucker and a blind bifurcate intestinal tract. Schistosomes differ from other trematodes in several ways: The sexes of adult worms are separate, transmission is through penetration of skin by larvae, and there is only a single intermediate host, whereas other trematodes are hermaphroditic and are transmitted through ingestion of infected fish, crustaceans, or aquatic plants that serve as second intermediate hosts. Unusually, free-swimming larvae of nonschistosomal trematodes directly invade the human conjunctiva or anterior chamber and cause ocular granulomata, as in the case of *Procerovum varium*, a parasite of fish-eating birds in Asia and the western Pacific.[6a] Only a small proportion of persons with trematode infections harbor large numbers of worms and are at risk for severe disease; most are asymptomatic or experience subtle morbidity, such as fatigue and cognitive or physical impairment.[3,4,7–10]

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

SCHISTOSOMES

Of more than 230 million persons infected with schistosomes in 78 countries and territories, about 120 million have symptoms, 20 million have severe disease, and as many as 200,000 or more die each year.[1,1a,2,4,6–8] Although control programs and socioeconomic development have eliminated or nearly eliminated transmission of schistosomiasis in more than a dozen countries, progress has been slow elsewhere, especially in sub-Saharan Africa, where greater than 90% of cases occur.[2,4,8] Moreover, water resource development projects and population movements continue to spread the disease into regions where it was not previously endemic.[5a] Three main species, namely, *Schistosoma mansoni, Schistosoma japonicum,* and *Schistosoma haematobium,* and three species with narrow geographic distribution, namely, *Schistosoma mekongi, Schistosoma intercalatum,* and *Schistosoma guineensis,* cause human schistosomiasis or bilharziasis, named after Theodor Bilharz who first identified the parasite in 1852.[8] A dozen or more other species of animal schistosomes can cause human infection, including schistosomes of birds and small mammals that cannot mature in the human host but die

TABLE 288.1 Features of Schistosomes and Other Important Trematodes

PARASITE	SNAIL INTERMEDIATE HOST (GENUS)	SECOND INTERMEDIATE HOST	GEOGRAPHIC DISTRIBUTION	LOCATION OF ADULT WORMS	TREATMENT
Schistosomes[a]					
Schistosoma mansoni	*Biomphalaria*	None	Brazil, Venezuela, Suriname, Sub-Saharan Africa, Caribbean, Middle East	Mesenteric venules	Praziquantel, 40 mg/kg/day in 1 or 2 doses × 1 day Oxamniquine[b]
Schistosoma japonicum	*Onchomelania*	None	China, Philippines, Indonesia	Mesenteric venules	Praziquantel, 60 mg/kg/day in 3 doses × 1 day
Schistosoma mekongi	*Neotricula*	None	Cambodia, Laos	Mesenteric venules	Praziquantel, 60 mg/kg/day in 3 doses × 1 day
Schistosoma intercalatum, Schistosoma guineensis	*Bulinus*	None	Central and West Africa	Mesenteric venules	Praziquantel, 40 mg/kg/day in 1 or 2 doses × 1 day
Schistosoma haematobium	*Bulinus*	None	Africa, Middle East, Corsica (France)	Venules of lower urinary tract	Praziquantel, 40 mg/kg/day in 1 or 2 doses × 1 day Metriphonate[b]
Liver Flukes					
Clonorchis sinensis	*Bithynia, Parafossarulus*	Freshwater fish	China, Taiwan, Korea, Japan, Vietnam	Bile, pancreatic ducts	Praziquantel, 75 mg/kg/day in 3 doses × 1–2 days Albendazole,[c] 10 mg/kg/day × 10 days
Opisthorchis viverrini	*Bithynia*	Freshwater fish	Thailand, Laos, Cambodia	Bile, pancreatic ducts	Praziquantel, 75 mg/kg/day in 3 doses × 1–2 days Albendazole,[c] 10 mg/kg/day × 10 days
Opisthorchis felineus	*Bithynia*	Freshwater fish	Eastern Europe, former Soviet Union	Bile, pancreatic ducts	Praziquantel, 75 mg/kg/day in 3 doses × 1–2 days Albendazole,[c] 10 mg/kg/day × 10 days
Fasciola hepatica	*Lymnaea*	Watercress, other aquatic plants	Americas, Europe, Asia, western Pacific, North Africa	Bile ducts	Triclabendazole,[d] × 10 mg/kg × 1 day Nitazoxanide[e]
Intestinal Flukes					
Fasciolopsis buski	*Segmentina*	Aquatic plants	Far East, India	Small intestine	Praziquantel, 25 mg/kg/day × 1 day Niclosamide,[c] 1 g × 1 day Triclabendazole[e]
Heterophyes heterophyes	*Pirenella, Cerithidea*	Freshwater fish	Far East, Egypt, Middle East, southern Europe	Small intestine	Praziquantel, 25 mg/kg/day × 1 day Triclabendazole[e]
Metagonimus yokogawai	*Semisulcospira*	Freshwater fish	Far East, Russia, southern Europe	Small intestine	Praziquantel, 25 mg/kg/day × 1 day Triclabendazole[e]
Lung Flukes					
Paragonimus westermani; other species	*Semisulcospira, Onchomelania, Thiara*	Freshwater crabs, crayfish	Far East, South Asia, Philippines, West Africa, South and Central America, USA	Lungs	Praziquantel, 75 mg/kg/day in 3 doses × 2 days Triclabendazole,[c] 10 mg/kg day × 3 days

[a]Some experts recommend higher doses (e.g., praziquantel 60 mg/kg/day in divided doses for all species), multiple doses (e.g., for 2 or 3 days), or a repeated dose at 4 to 6 weeks to achieve higher rates of cure in persons not exposed to reinfection.[9]
[b]Not available or limited availability.
[c]Alternative drug.
[d]In the United States it is available from the Centers for Disease Control and Prevention Drug Service after approval by the US Food and Drug Administration.
[e]Limited data.

in the skin, where they cause a dermatitis.[7,9,11,11a,12] Hybrid schistosomes infective for human beings result from crossbreeding of different species of human schistosomes or human and zoonotic schistosomes.[5a]

Life Cycle

Adult worms, measuring 1 to 2 cm in length and 0.3 to 0.6 mm in width live, mate, and feed on blood in the portal and mesenteric vessels (*S. japonicum, S. mekongi, S. mansoni, S. intercalatum,* and *S. guineensis*) or vesical plexus *(S. haematobium).*[8,11] The male worm folds around and encloses the female in its gynecophoral canal. Egg production varies from about 300 eggs per day for female *S. mansoni* and *S. haematobium* and 3000 eggs daily for *S. japonicum* (Fig. 288.1). Eggs, measuring 145 × 55 µm for *S. mansoni* and *S. haematobium* and 85 × 60 µm for *S. japonicum* (Fig. 288.2), are deposited in the venules and make their way into the urine or feces and hatch in fresh water, where the miracidium, a 0.1-mm ciliated larva, emerges. The miracidium penetrates the body of the appropriate snail intermediate host and multiplies asexually. Within 4 to 6 weeks, thousands of motile, forked-tail cercariae, 0.1 to 0.2 mm long, emerge. On encountering human skin, the cercariae penetrate with the help of their glandular secretions, and within minutes they lose their tails and change into schistosomula. This transformation from a freshwater environment to parasitic existence in the human host

is associated with the unique formation of a heptalaminate membrane and other dramatic changes in morphology, metabolism, and physiology.[13] The schistosomula migrate to the lungs and liver and, in about 6 weeks, they mature to adult worms and descend through the venous system to their final habitat. Eggs appear in the feces or urine 4 to 6 weeks after cercariae penetrate the skin. Adult schistosomes live an average of 3 to 5 years but can survive for 30 years or more.[7,8,11]

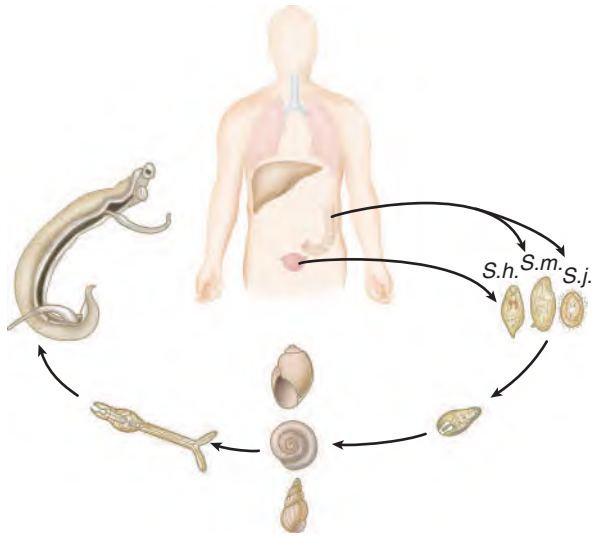

FIG. 288.1 Life cycle of schistosomes. Eggs are passed in stools for *Schistosoma mansoni (S.m.)* and *Schistosoma japonicum (S.j.)* and in urine for *Schistosoma haematobium (S.h.).* The eggs hatch in fresh water, miracidia invade specific snail intermediate hosts, and, in a few weeks, forked-tail cercariae are liberated. These infective forms penetrate human skin, pass through a migratory phase in the lung and the liver, and then pass to their final habitat in the portal venous system (*S.m.* and *S.j.*) or the urinary bladder venous plexus *(S.h.).* Three other species infect humans, although less frequently. *Schistosoma intercalatum* and *Schistosoma guineensis* produce terminal spined eggs that may be found in feces, whereas *Schistosoma mekongi* produces eggs similar to, but smaller than, those of *S. japonicum,* which may also be found in stools. These two species of schistosomes have characteristic snail intermediate hosts.

Epidemiology

Transmission of schistosomiasis requires an appropriate snail intermediate host; fecal or urinary contamination of warm, slowly moving fresh water; and human entry into the snail-infested water. The snail host is specific for each species and strain of schistosome, which have a specific geographic distribution (Table 288.1).[1a,11] *S. mansoni* occurs in three South American countries, several Caribbean islands, and, along with *S. haematobium,* in Africa and the Middle East, often in areas where the two species overlap.[8] *S. intercalatum* and *S. guineensis* also can overlap with *S. haematobium* in parts of West and Central Africa but are less common. *S. japonicum* is found in China, the Philippines, and Indonesia; and *S. mekongi* is found in Cambodia and Laos.[8] Cattle, water buffaloes, pigs, dogs, and other mammals are naturally infected with *S. japonicum* and *S. mekongi* and act as reservoir hosts, with a major role in transmission. Infections of rodents, sheep, primates, and other animals occur with *S. mansoni* and, rarely, *S. haematobium;* although they seem to contribute little to maintenance of the life cycle, they may jeopardize public health efforts to eliminate transmission and lead to the emergence of zoonotic parasitic hybrids infective to humans.[7,8,11,13a]

Transmission is focal in endemic countries and most intense in poor rural areas with inadequate sanitation and water supplies. The distribution of schistosomiasis is changing in many areas. The risk for infection is now nonexistent or negligible in previously highly endemic countries, including Japan, Morocco, Tunisia, Algeria, Oman, Jordan, Turkey, Iran, Mauritius, and the Caribbean countries.[2,13b,13c] Control programs have significantly reduced the incidence of infection and morbidity in Brazil, Venezuela, China, Saudi Arabia, Egypt, Cambodia, and the Philippines. Since 2000 strategies to reduce morbidity from schistosomiasis have been successfully implemented in several African countries, but in most of sub-Saharan Africa, high levels of endemicity persist, including in areas where dams and irrigation projects have led to major increases in the prevalence and extension of transmission to new areas.[4,7,8] An outbreak of urogenital schistosomiasis, likely related to arrival of infected individuals from endemic regions of Africa, was detected in Corsica, France, which marked the first instance of European transmission since the 1960s.[5a] New foci of schistosomiasis have been

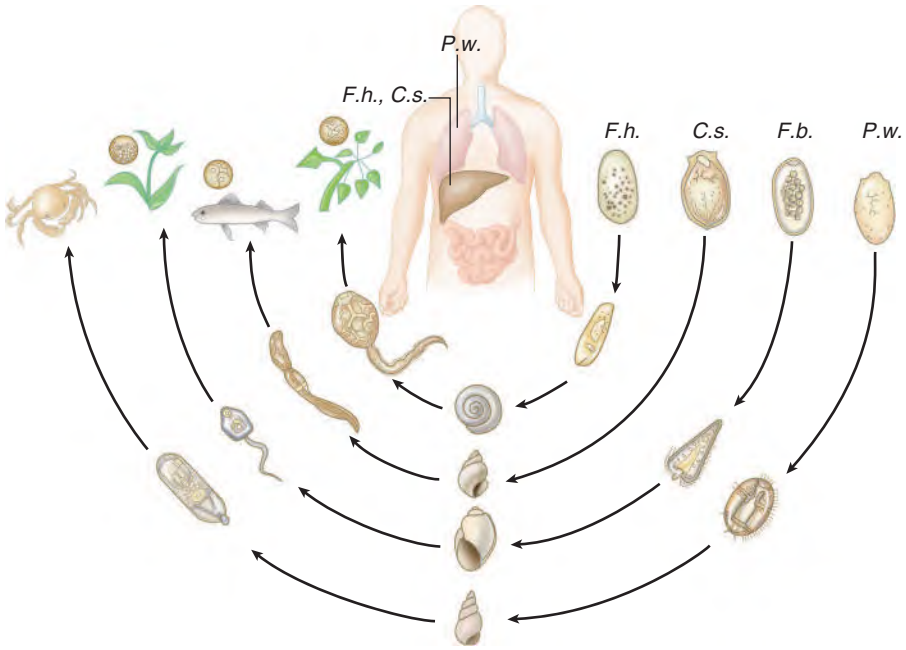

FIG. 288.2 Life cycle of important parasitic flukes. Eggs are passed in stools for *Fasciola hepatica (F.h.), Clonorchis sinensis (C.s.),* and *Fasciolopsis buski (F.b.)* or in sputum for *Paragonimus westermani (P.w.)* infections. The next stage of multiplication occurs in specific snail intermediate hosts, followed by liberation of cercariae, which encyst on the second intermediate hosts (aquatic plants, fish, or crabs). These metacercariae represent the infective stage, and humans develop the infection after consumption of the second intermediate hosts. The final habitats of these flukes are the liver (*F.h.* and *C.s.*), intestines *(F.b.),* or lungs *(P.w.).*

identified in Myanmar.[13d] Urban transmission occurs in some large cities of Brazil and Africa, and global climate change is predicted to increase transmission in many areas.[13e]

In endemic communities the distribution of the infection fits a negative binomial curve, with most infected persons harboring low worm burdens and only a small proportion, usually children ages 8 to 12 years, having heavy infections.[4,7,8] Aggregation of the worm burden in a small proportion of infected individuals probably reflects a combination of factors, including the amount of water exposure, partial acquired immunity, age, and genetic susceptibility.[4,7,8,14,15] Typically, the intensity of infection declines after the early teenage years as partial immunity to new infections builds up, older worms die, and contact with fresh water decreases. Because worms do not multiply in the host, the intensity of the infection depends on the number of cercariae encountered. Persons with heavy infections are at most risk for developing severe disease.

In the United States and other temperate areas, infection cannot be transmitted because of the absence of the appropriate snail intermediate host. Schistosomiasis is seen among immigrants from endemic areas and returning travelers, and sometimes it appears in small epidemics among travelers engaging in adventure and nature tourism.[16–19]

Pathogenesis

The disease associated with schistosomiasis is largely due to the host's immune response to the larvae and eggs.[14,20,21] Mature adult worms evade the host's immune defenses by binding host antigens to their tegument and regenerating their tegument, along with other mechanisms, thus contributing little to the immunopathology of the disease.[22] Different mechanisms are responsible for tissue injury during the stage of larval penetration, the acute stage, and the chronic infection.

In previously exposed persons a protective response consisting primarily of specific immunoglobulin E (IgE) antibodies, eosinophils, and macrophages is directed against the schistosomula after cercarial penetration of the skin.[14,21] As a result, some organisms die in the skin and are surrounded by edema and cellular infiltrates in the dermis and epidermis that can give rise to a papular dermatitis.

The syndrome of acute schistosomiasis occurs 2 to 12 weeks after a heavy first exposure to larvae during worm maturation and the initiation of egg deposition.[12,19,23,24] A febrile illness with features of serum sickness results from formation of circulating immune complexes in response to larval and egg antigens and production of high levels of proinflammatory cytokines. Acute disease develops primarily in previously unexposed persons and less commonly in heavy reinfections, usually due to *S. japonicum*. Symptomatic acute infections are rarely reported among persons who grow up in an endemic area, perhaps because of sensitization in utero as a result of maternal infection.[12]

Disease during the chronic stage of infection is due to the presence of eggs in host tissues and the immune response directed against the egg antigens.[14,20,21] Miracidia in the eggs secrete antigenic glycoproteins through pores in the eggshell that induce an inflammatory response that facilitates passage of the eggs through blood vessel walls and tissues en route to the lumen of the intestinal or urinary tract. One-third to one-half of eggs reach the environment, with the remainder trapped in tissues or embolized to a distant site. The host response to toxic egg antigens and eggs retained in the tissues includes acute eosinophilic inflammation, followed by granuloma formation, initially consisting of neutrophils, eosinophils, and mononuclear cells and, later, mostly lymphocytes, macrophages, multinucleated giant cells, and fibroblasts.[14,25,26] In *S. mansoni* and *S. haematobium* infections the granulomatous response has been shown to be orchestrated by $CD4^+$ T lymphocytes and is tightly regulated by various immunologic mechanisms.[21,23,27,28] They involve balanced helper T cell type 1 and 2 responses and the production of cytokines locally in the granulomas and systemically; these responses in turn are regulated by numerous other mediators and mechanisms.[14,27–29] In addition to destroying eggs, granulomas may mediate their passage into the lumen of the bowel or urinary tract. This hypothesis is supported by the finding of reduced egg output in persons with advanced human immunodeficiency virus (HIV) disease.[30]

Granulomas initiate tissue injury first through the inflammatory infiltrate and replacement of normal tissue and later through extensive collagen deposition and scarring.[14,21,31,31a] Large granulomas and fibrosis cause the major pathologic lesions in chronic schistosomiasis. In the case of schistosomes that inhabit the mesenteric vessels, the pathologic process is greatest in the intestines and the liver, the major site of egg embolism. With *S. haematobium* infection, the main system involved is the urinary tract. The result is inflammatory lesions and ulcerations of the mucosa; fibrotic scarring of the bowel, bladder, and lower ureteral walls; and obstruction of portal blood flow in the liver and urine flow through the ureters and bladder. During the early stages of schistosome infection, the granulomatous response is exuberant. Later, modulation of granulomatous hypersensitivity results in smaller granulomas and less fibrosis, which in turn probably play a significant role in limiting progression of the disease.[21,27] Treatment of children during the early stage can completely resolve the granulomatous inflammation.[8] A subset of untreated persons immunoregulate their response to egg antigens poorly and develop extensive fibrosis and severe disease.[4,14]

The severity of disease in schistosomiasis is determined in part by the duration and intensity of the infection.[32–34] This relationship is not exact, however, and other variables, such as genetic susceptibility to disease, parasite strain, and coinfections with malaria, hepatitis viruses, HIV, and other infectious agents, may be important.[4,30,35–37] Chronic schistosomiasis appears to be associated with a partial degree of resistance to reinfection directed against invading immature worms and mediated by IgE antibodies, eosinophils, and cytokines, such as interleukin-4 (IL-4) and IL-5.[14,21,38]

Clinical Syndromes

Infections with human schistosomes are frequently asymptomatic. Illness, when present, is strongly influenced by location in endemic versus nonendemic sites and related to factors such as prevalence of immunity and intensity of infection.[16,39–40] Acute symptomatology is more frequent in previously uninfected individuals, and chronic illness, which is associated with a higher burden of infection, occurs most often in endemic areas.

Schistosome Dermatitis ("Swimmer's Itch")

During penetration of cercariae, some previously exposed and unexposed persons experience a prickling sensation and may note urticaria, followed by a macular rash several hours later.[8,11a,12,19,41] In persons exposed for the first time, this rash disappears quickly, but in previously sensitized persons, it may persist and progress to a pruritic maculopapular rash that lasts for days. The rash is most severe in persons infected with schistosomes of birds or aquatic mammals, which die in the skin. This "swimmer's itch" is common in the Great Lakes region, New England, and other parts of the United States, Canada, Europe, and elsewhere in the world (see Chapter 290).

Acute Schistosomiasis (Katayama Fever)

Previously uninfected persons from nonendemic areas may have no symptoms after first exposure or may develop symptoms of acute schistosomiasis (Katayama syndrome) 2 to 12 weeks after exposure, particularly to *S. japonicum* or *S. mansoni*.[8,12,16,19,23,24] The Katayama fever syndrome is unusual with *S. haematobium* and most severe with heavy infections, especially with *S. japonicum*. It may occur in persons previously infected with *S. japonicum*. Onset of fever is often acute and accompanied by chills, fatigue, headache, myalgia, abdominal pain, diarrhea, and occasionally bloody stools. As many as 70% of patients develop nonproductive cough, dyspnea, chest pain, and diffuse and nodular infiltrates seen on chest radiography.[42] In a few cases in which lung nodules were biopsied, granulomas around eggs were seen.[43] The liver, spleen, and lymph nodes are often enlarged. Urticaria is common, and eosinophilia occurs in nearly all cases, but eggs may not be seen in the stools until late in the illness. Symptoms and signs usually disappear after 2 to 10 weeks, but persistent and more serious disease and even death may occur with heavy infections. Lesions of the central nervous system (CNS), genital tract, and skin are due to aberrant migration of adult worms and ectopic deposition of eggs, which occurs in a small number of cases of acute infection, including in persons without systemic manifestations.[12] In some cases eosinophil-mediated toxicity leading to vasculitis and small vessel thrombosis may be responsible for neurologic disease during acute infection.[44] Patients with acute schistosomal

encephalopathy present with headache, altered mental status, and often seizures and focal deficits. Computed tomography (CT) and magnetic resonance imaging (MRI) show edema and multifocal enhancing lesions and occasionally border zone infarctions.[45]

Chronic Schistosomiasis

Symptoms may be absent or mild in many patients who have light or moderate worm burdens. However, careful analysis of clinical and epidemiologic data has demonstrated subtle but important morbidity in persons with even light infections.[46] Chronic granulomatous inflammation and elevated levels of proinflammatory cytokines are believed to contribute to poor caloric intake, undernutrition, anemia of chronic inflammation, stunting, and impairment of work capacity and cognitive development in persons with chronic schistosomiasis.[46,46a] Similar mechanisms, along with placental infection and inflammation, may be responsible for decreased birth weight and poor birth outcomes in infants born to mothers with chronic schistosomiasis.[47] When these previously underappreciated sequelae of infection have been taken into account, estimates of the disability associated with schistosomiasis suggest a burden of disease as much as 50 times greater than previously reported.[48] Regardless of symptoms, eosinophilia is often present in persons with chronic schistosomiasis.

Intestinal and Hepatosplenic Schistosomiasis

Patients with light infections caused by the intestinal schistosomes *S. mansoni, S. japonicum,* and *S. mekongi* may complain of fatigue, intermittent abdominal pain, and diarrhea.[8,49,50] In heavy infections blood loss from ulcerations or dysentery may lead to a moderate degree of anemia. Intestinal polyps have been observed, most commonly in Egypt, and strictures or large inflammatory masses may cause obstruction or mimic carcinoma.[51] An association between intestinal schistosomiasis and cancer of the bowel has been suggested but not yet confirmed.[52,52a]

An early sign of chronic schistosomiasis caused by *S. mansoni, S. japonica,* or *S. mekongi* is hepatomegaly from granulomas around embolized eggs that become trapped in small portal venules. Such inflammatory hepatomegaly is common during childhood and diminishes or resolves with time; it should be distinguished from hepatomegaly due to periportal, or Symmers "pipestem," fibrosis that is seen after years of infection in up to 5% to 10% of infected young and middle-aged adults.[8,31] Granulomas and fibrosis cause a presinusoidal block to portal blood flow and eventually portal hypertension, splenomegaly, hypersplenism, and development of portosystemic collateral blood vessels. In most cases of hepatosplenic schistosomiasis, liver cell perfusion is not reduced, hepatic function is preserved, and levels of hepatic aminotransferases remain normal.[53] Persons with coexisting alcoholic cirrhosis, chronic hepatitis B, or hepatitis C may develop jaundice and ascites.[54] Natural progression of schistosomal disease occurs more rapidly in persons with schistosomiasis from *S. japonicum* than from *S. mansoni* and occasionally leads to decompensated liver disease as well. Repeated episodes of hematemesis from bleeding esophageal varices occur, which usually are associated with low mortality in persons with compensated disease but may lead to hepatic failure and death in persons with decompensated disease. Persons with both schistosomiasis mansoni and chronic hepatitis B or C are at higher risk for cirrhosis and perhaps hepatocellular carcinoma than persons infected with hepatitis viruses alone.[54]

Infections with *S. intercalatum* and *S. guineensis* tend to be lighter and produce less pathology than infections due to *S. mansoni* or *S. japonicum*.[55] Egg deposition occurs primarily in the colon, and patients may present with blood and mucus in the stool; in these cases endoscopy shows polyps and inflamed rectal mucosa. More severe disease can be seen in persons with *S. mekongi* infections, with advanced hepatosplenic disease similar to that seen in *S. mansoni* and *S. japonicum* infections.[56]

Genitourinary Schistosomiasis

In infection with *S. haematobium,* hematuria and dysuria from inflammation and small ulcerations in the bladder mucosa may appear within 3 to 4 months of infection.[57,58] In endemic areas most children have microhematuria by age 10 years, and gross hematuria is common as well. Later, polyps, hypertrophic nodules, and "sandy patches" around egg deposits may be visible on cystoscopy. Granulomas, fibrosis, and, ultimately, calcification of the bladder wall cause reflux and obstruction of urine flow, with hydroureter, hydronephrosis, chronic bacteriuria, bladder cancer, and, in a small percentage of cases, renal failure. Deposition of *S. haematobium* eggs in the genital tract occurs in up to 75% of women and causes sandy patches with mucosal bleeding, abnormal blood vessels, and occasionally ulcerative, nodular, or papillomatous lesions of the vulva, perineum, and cervix.[59–61] These lesions, which are illustrated in WHO's pocket atlas for health care professionals (available at https://www.who.int/schistosomiasis/genital_schistosomiasis), increase the patient's susceptibility to HIV infection and other sexually transmitted diseases, and lesions of internal pelvic organs may cause bleeding and infertility. Antischistosomal treatment of infected girls can cause regression of lesions before they become irreversible. Hematospermia results from involvement of the prostate and seminal vesicles with schistosomiasis haematobia, which has been implicated in male infertility as well.[62,63] Associations have been demonstrated between *S. haematobium* infection and squamous cell carcinoma of the bladder; the latter has especially affected young and middle-aged men in Egypt.[57,63–66]

Pulmonary Hypertension and Glomerulopathy

With infection with *S. mansoni* and *S. japonica,* eggs may bypass the liver through portosystemic collateral vessels and cause pulmonary disease; in infection with *S. haematobium,* eggs escape the vesical plexus and reach the lungs directly.[65,66] Pulmonary hypertension develops in 10% to 20% of persons with hepatosplenic schistosomiasis, but only in the most severe cases does obstruction to pulmonary blood flow due to granulomatous inflammation and arteritis of small pulmonary arteries lead to cor pulmonale. Subclinical glomerulonephritis is not uncommon in persons with chronic schistosomiasis; kidney biopsy has shown deposits of immune complexes containing schistosomal antigens in the glomerular basement membrane.[58,67] Clinically important glomerulopathy occurs most commonly in persons with hepatosplenic disease; its prevalence has decreased in areas where cases of severe schistosomiasis have become uncommon.[68]

Ectopic Egg Deposition and Central Nervous System Schistosomiasis

Ectopic egg deposition from aberrant migration of adult worms and embolization of eggs from distant sites are common with all species of schistosomes and can involve almost any organ. In most cases the resulting lesions do not produce symptoms, but involvement of the CNS can cause serious cerebral and spinal cord disease.[45,69] CNS schistosomiasis is most common with *S. japonicum* infection, occurring in as many as 2% to 5% of infections and accounting for high rates of epilepsy in endemic areas. The brain is the usual site of CNS disease with *S. japonicum* infection, only occasionally with *S. mansoni* infection, and virtually never with *S. haematobium* infection. Patients present with focal or generalized seizures, focal neurologic deficits, signs of increased intracranial pressure due to the mass effect, and diffuse encephalitis. CT and MRI of the head show nodular and ring-enhancing lesions with surrounding edema. With *S. haematobium* and *S. mansoni* infections, eggs reach the lower spinal cord through the Batson plexus and produce either transverse myelitis with back pain and paraplegia or myeloradiculopathy from granulomatous lesions of the conus medullaris and cauda equina.[69]

Coinfections

Concurrent infection with other organisms may affect the clinical course of schistosomiasis. Prolonged bacteremia with *Salmonella typhi* and other *Salmonella* species has been reported in persons chronically infected with *S. mansoni, S. japonicum, S. intercalatum,* and *S. haematobium*.[70,71] Unlike typhoid fever, the illness is indolent, with persistent fever, weight loss, and continuous bacteremia, and it can last months. Treatment of the bacterial infection without treating the schistosomiasis may result in relapse of bacteremia and symptoms. *Salmonella* can attach to the tegument and gut of schistosomes, and there is evidence that schistosomes and *Salmonella* share antigens that elicit immunologic tolerance to the bacterial infection.[70,71] Chronic *Salmonella* bacteriuria can complicate infection with *S. haematobium. Salmonella* bacteremia and bacteriuria have been associated with glomerulonephritis and nephrotic syndrome in persons infected with either *S. haematobium* or *S. mansoni*.[58,68]

Chronic coinfection with hepatitis B or C worsens the prognosis of persons with hepatosplenic schistosomiasis, as already described.[54,72] The high rate of hepatitis C coinfection noted in Egypt probably reflects widespread transmission associated with parenteral antischistosomal treatment that was practiced until the 1980s.[72] HIV coinfection has been associated with decreased egg excretion in persons with *S. mansoni* and *S. haematobium* infections and decreased hematuria with *S. haematobium* infections because of impaired granuloma formation and increased trapping of eggs in tissue.[30] Schistosomiasis appears to increase susceptibility to HIV infection by as much as threefold to fourfold in women with genital lesions.[61,73] Infection with schistosomes may increase HIV viral load, accelerate progression of HIV disease, and increase HIV transmission by the vertical and horizontal routes.[73] Treatment of schistosomiasis in persons with HIV coinfection has led to a decrease in HIV viral load, an increase in $CD4^+$ T-cell counts, and a decrease in schistosomal fecundity and egg excretion but poor killing of adult worms.[73–75] An immune reconstitution syndrome after initiation of antiretroviral therapy among persons previously treated for schistosomiasis may present with worsening manifestations of schistosomiasis, such as new or increasing bloody diarrhea or hematuria, increasing hepatomegaly or splenomegaly, rash, or constitutional symptoms.[76]

Diagnosis

Schistosomiasis should be suspected in persons who have a history of freshwater exposure in endemic areas even in the absence of suggestive clinical findings or eosinophilia.[9,12,77] Hematuria is common with *S. haematobium* infections, and screening children for blood in their urine by using dipsticks has provided reliable estimates of the prevalence of infection in areas of high endemicity.[57] Commonly used diagnostic tests for schistosomiasis include serologic tests and microscopic examination of stool, urine, or tissue for eggs.[77]

Parasitologic Tests

Microscopy on a simple smear of feces or a drop of urine can detect heavy infections, but because eggs may be passed intermittently or in small numbers, concentration procedures and repeated examinations are needed to detect lighter infections. Several concentration procedures also allow quantification of egg output, such as the Kato-Katz technique, which uses 20 to 50 mg of fecal material, or filtration of a standard volume of urine through a Nuclepore membrane.[77] Counts higher than 400 eggs per gram of feces or 10 mL of urine are considered heavy and are associated with an increased risk for complications. Even repeated concentration procedures may miss low-intensity infections, which are common in low-prevalence areas or in travelers or expatriates with chronic infections. Microscopic examination of snips of rectal or bladder mucosa obtained at proctoscopy or cystoscopy may reveal eggs when the stool or urine examination is negative. Because persons with inactive infections may continue to shed dead eggs into stool or urine for months, tests for egg viability, such as egg hatching or microscopic examination of eggs for movement of flame cells, should be performed

Antigens shed by adult worms into the blood can be detected by enzyme-linked immunosorbent assay (ELISA) or monoclonal lateral flow assays in serum and urine.[8,77] A point-of-care lateral flow assay that detects *S. mansoni* antigens in urine is available commercially in some countries outside of the United States; its sensitivity is equal or superior to that of duplicate Kato-Katz smears for light infections, and it can detect acute infections several weeks before eggs are shed in the stool.[77–79] Polymerase chain reaction (PCR)-based assays that detect schistosome DNA in stool, urine, serum, or plasma have sensitivities greater than that of microscopy of duplicate samples in chronic infections and microscopy or serology in acute infections.[80,81]

Serologic Tests

Serologic tests for antibodies to schistosomes are available at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and some commercial laboratories.[82] The CDC uses a combination of tests with purified adult worm antigens. Its Falcon assay screening test–ELISA (FAST-ELISA) is 99% specific for all species and has a sensitivity of 99% for *S. mansoni* infection, 95% for *S. haematobium,* but less than 50% for *S. japonicum.* Because the FAST-ELISA may miss some *S. haematobium* and *S. japonicum* infections, immunoblots using species-specific antigens are performed in cases of potential exposure to these parasites. Serologic tests cannot distinguish active from past infections but are useful for screening previously unexposed travelers and expatriates.[19] In such persons a positive serologic test is presumptive evidence of infection even if microscopic examination of stool or urine fails to reveal schistosome eggs. In acute schistosomiasis eggs do not appear in the feces or stool for 30 to 50 days (or longer after treatment).[19] Serologic tests and PCR-based assays typically turn positive sooner than microscopic studies but may not be readily available, and seroconversion may not occur for 2 months or longer after exposure.[82a] In such cases the diagnosis rests on the epidemiologic history and clinical picture.[19,82a]

Evaluation of Persons With Confirmed Schistosomiasis

Persons with confirmed schistosomiasis should be evaluated for evidence of disease. Urinalysis, urine culture, and serum creatinine determination are indicated for persons with *S. haematobium* infection. Any abnormality should prompt an ultrasound or CT scan to detect complications, such as thickening or calcification of the bladder wall, hydroureter, hydronephrosis, polyps, stones, or carcinoma of the bladder.[57,83] Evaluation of infections due to the intestinal schistosomes includes liver function tests, tests for chronic hepatitis B and C, and imaging to document periportal fibrosis and signs of portal hypertension.[49,50,84] Contrast studies, CT, MRI, and ultrasonography are sensitive means of detecting and evaluating urinary tract and hepatic pathologic processes, although ultrasonography has become the preferred modality in endemic countries after standardized protocols developed by World Health Organization (WHO) for use in hospitals and the field.[83,84] Biologic markers, such as hyaluronic acid, procollagen peptides, and others, can identify persons with hepatic fibrosis but do not replace ultrasonography for assessing portal hypertension.[85] Liver biopsy may be necessary to identify any pathologic process in addition to schistosomiasis in persons with decompensated hepatosplenic disease. Esophageal varices are visualized by barium swallow or endoscopy.[8]

Therapy

Treatment is indicated for all persons with schistosomiasis. Cure of infection is desirable because even a single pair of worms may be responsible for a catastrophic neurologic complication, such as transverse myelitis. Successful deployment of antischistosomal medication at the individual level not only prevents the development of complications, but, if given early and reinfection is avoided, it also can cause partial or complete regression of intestinal lesions, urinary bladder wall thickening, bladder polyps, urinary obstruction, genital sandy patches, and periportal fibrosis.[86–88] For control of schistosomiasis at the population level in endemic areas where reinfection is inevitable, the goal is to reduce worm burdens to levels that are unlikely to produce disease, decrease prevalence of infection, and, if feasible, eliminate transmission.[5,8,89,89a]

Praziquantel for Treatment of Schistosomiasis

The drug of choice for treating all species of schistosomes is praziquantel (see Table 288.1), which affects membrane permeability to calcium ions in the parasite.[90] Paralysis and vacuolation of the tegument immobilize the worm and expose it to attack by the host immune system. After a single treatment, cure rates of chronic infections range from 65% to 95%, and in persons not cured, egg excretion is reduced by greater than 90%.[8,91] A second dose several weeks later may increase the rate of cure in persons not exposed to reinfection.[12] Praziquantel does not affect developing schistosomula or eggs and may not abort an early infection.[90,92] Treatment with praziquantel has beneficial effects on host immunity: Damage to the tegument exposes parasite antigens to the immune system and thus accelerates the development of protective acquired immunity that otherwise would take years to acquire naturally.[92a] Resistance to praziquantel has been documented in the laboratory, and there have been reports of decreased responsiveness in the field and anecdotal reports of returned travelers who required multiple courses of praziquantel to clear their infections.[91,93–95]

Adverse effects, which are usually mild and last less than 24 hours, are largely due to reactions to dying worms rather than drug toxicity.

Patients may report headache, dizziness, or abdominal discomfort and, less commonly, nausea, vomiting, diarrhea, bloody stools, fever, and urticaria. Pediatric formulations of praziquantel in a smaller, orally dispersible tablet that masks the drug's bitter taste appear promising in clinical trials.[96]

Pregnant women were formerly restricted from receiving praziquantel, but WHO now recommends that praziquantel be given to pregnant and lactating women with schistosomiasis during mass treatment campaigns.[97] Two randomized controlled trials of pregnant women who received praziquantel after 12 weeks of gestation did not detect an increased risk of adverse maternal or neonatal outcomes.[98,99] The safety of praziquantel during the first trimester has not been well assessed, but animal data, observations on treatments inadvertently given during the first trimester, and decades of postmarket surveillance suggest that it is safe.[97] Praziquantel is excreted in breast milk in minute amounts. Suspending breast feeding for 3 days after praziquantel therapy and avoiding praziquantel during the first trimester seems advisable for individual patients.

Persons with known or suspected cysticercosis should remain under observation during praziquantel therapy because of the risk for seizures or other neurologic consequences of dying cysticerci; treatment should be withheld in persons with intraocular cysticerci. Persons with schistosomal disease of the CNS should also receive corticosteroids to reduce the inflammation and edema around eggs because miracidia in eggs in tissues remain viable and secrete antigenic proteins for several weeks.[44,45]

Other Antischistosomal Drugs: Oxamniquine and Artemisinin Derivatives

Oxamniquine, an alternative for treatment of *S. mansoni* infections but with limited availability, is as effective as praziquantel for infections acquired in the Western Hemisphere.[4,100] Higher doses are needed for strains of the parasite from Africa, and drug resistance has been documented. Metrifonate is effective only against urinary schistosomes; it requires three doses 2 weeks apart and is currently not available.[57]

The antimalarial drugs artemether and artesunate are active against all species of schistosomes, can kill schistosomula during the first 3 weeks of infection, and are synergistic with praziquantel in killing adult worms.[101,102] They are effective as prophylactic agents against *S. japonicum* when given every 2 weeks and have been used for chemoprophylaxis in China.[101–103] Artesunate combined with pyrimethamine-sulfadoxine or mefloquine can cure chronic *S. haematobium* or *S. mansoni* infections but is less effective than praziquantel alone.[102,104] Most trials of artesunate in combination with praziquantel have shown superiority of the combination over praziquantel alone for treatment of chronic infections.[102,103] Widespread use of artemisinin derivatives for treatment or prophylaxis in malaria-endemic areas should be avoided because of the risk for promoting artemisinin-resistant plasmodia, but the deployment of praziquantel with an artemisinin derivative might hasten elimination of transmission of schistosomiasis in nonmalarious areas.[102–105]

Management of Acute Schistosomiasis

The symptoms of Katayama syndrome often require administration of corticosteroids to suppress the inflammatory process (e.g., prednisone 40 mg/day orally for 5 days), but there is no consensus about proper anthelmintic treatment.[8,12,19,23,24] Most authorities administer praziquantel shortly after administration of corticosteroids and treat *S. mansoni* and *S. haematobium* infections for up to 3 days and *S. japonicum* infections for up to 6 days in the doses listed in Table 288.1.[8,12] Other authors believe that praziquantel should not be used during the acute phase because of its limited effectiveness against schistosomula, the lowering of serum levels by concomitant corticosteroid therapy, and the risk for reactions that develop in response to killing of parasities.[93,16,106] Data on effectiveness of artemisinin compounds alone or with praziquantel for treatment of acute schistosomiasis are limited, and in one study the efficacy of the combination of artemether and praziquantel was not superior to that of praziquantel alone.[16,19,105] In all cases of acute schistosomiasis a second course of therapy is recommended 4 to 6 weeks after the onset of symptoms. Treatment of asymptomatic persons with praziquantel 28 to 40 days after exposure seems to prevent acute illness but not chronic infection, whereas treatment of persons within 10 to 15 days of exposure has precipitated an acute illness, including severe complications, such as bronchospasm and cerebral microinfarcts.[44,93,106]

Evaluation of Therapy

Because antischistosomal drugs may temporarily inhibit egg laying by adult worms, stool and urine should be examined 6 to 8 weeks after completion of therapy and again 3 to 6 months later for both acute and chronic infections; persons who remain infected should receive a single dose of praziquantel, 40 to 60 mg/kg.[8,12,44] Eosinophilia, hematuria, or persistence of symptoms should prompt repeat parasitologic studies. Serologic tests may remain positive for several years after successful treatment.

New Medications for Schistosomiasis

Development of new chemotherapeutic agents for treatment of schistosomiasis is essential because of the incomplete efficacy of praziquantel and the threat of emerging resistance.[8,107] Current efforts include investigating existing drugs (such as antimalarials, anthelmintics, and anticancer drugs), combinations of existing drugs, and natural products, as well as exploring differences between host and parasitic metabolic pathways and analyzing genomes and transcriptomes to identify new drug targets.[107] The publication of genomic sequences of the three major human schistosome species is stimulating the search for new drug targets.[8] Unfortunately, at this time no new antischistosomal candidate is undergoing human trials, and it is unlikely that an alternative to praziquantel will be available in the next decade.[8,107]

Prevention and Control of Schistosomiasis

Travelers to areas where schistosomiasis is endemic should avoid contact with fresh water that may be infested with cercariae.[18] If contact is unavoidable, vigorous toweling of the skin may limit cercarial penetration after leaving the water, and medical follow-up should be sought after return from travel. With the possible exception of 50% DEET (*N,N*-diethyl-*m*-toluamide), topical lotions and soaps do not reliably prevent infection after contact with cercariae.[19] Further data are needed before recommending artemether for prophylaxis, which at any rate should not be used in malarious areas.

In theory transmission of schistosomiasis in endemic communities can be interrupted by provision of sanitation and safe water supplies and elimination of snail intermediate hosts or their habitats, and indeed persons with safe water and adequate sanitation are at lower risk of infection.[108,109] However, the scale and cost of these interventions are beyond the reach of many countries, and the cornerstone of schistosomiasis control programs has been the WHO-recommended strategy of regular administration of antischistosomal drugs (along with drugs for soil-transmitted helminthiases, onchocerciasis, and lymphatic filariasis in areas where these infections are endemic) to populations at risk, primarily to maintain individual worm burdens at levels below those that cause morbidity and mortality and secondarily to decrease transmission and prevalence of infection.[2,5,92a] More than 180 million tablets of praziquantel were donated in 2016, and almost 90 million persons received treatment, representing approximately 36% of the persons thought to be in need of treatment.[5] Although mass drug administration has achieved reduction in intensity of infection and infection-related morbidities, it is not sufficient to interrupt transmission in most endemic areas.[89a,110] Moreover, difficulties in sustaining large-scale drug administration programs and the potential emergence of praziquantel resistance may make this strategy merely a temporary solution.

Interruption of transmission in many regions will require integrated and intensive strategies, as demonstrated by a highly successful community-based trial in China that used regular chemotherapy, removing cattle from snail-infested grasslands, providing farmers with mechanized farm equipment, supplying tap water, building lavatories and latrines, providing boats with fecal-matter containers, and implementing an intensive health-education program.[111] These strategies have markedly reduced transmission in China, but factors such as population movements, flooding, and socioeconomic changes pose difficult challenges that require intensified efforts and new tools.[13c,112] Snail control

can increase the impact of mass drug administration, for instance, in the Senegal River Basin, where the reintroduction of the river prawn, a natural predator of the intermediate snail host, significantly decreased schistosomiasis prevalence and egg burden.[112a,112b] Development of a vaccine to prevent heavy infections seems possible based on experimental studies in animals and evidence of acquired immunity in human populations.[113,114] Numerous vaccine candidates have been identified, and several antigens have entered clinical trials.[113,114] Vaccines and other new tools and scaled-up efforts will be necessary to achieve WHO's goals of eliminating schistosomiasis as a public health problem by 2025 and interrupting transmission in all endemic countries (except for a number of countries in the African region, where a marked reduction in prevalence is the goal).[2]

LIVER FLUKES

The major liver flukes of humans are *Clonorchis sinensis* and several species of *Opisthorchis* (largely found in the Far East, Southeast Asia, and Russia) and *Fasciola hepatica,* which is widely distributed throughout the world (see Table 288.1).[1a,3,115,116,116a] Less common liver flukes include *Fasciola gigantica* in South America, Africa, and Southeast Asia; *Metorchis conjunctus* in North America and *Metorchis bilis* in Russia; and *Opisthorchis guayaquilensis* in the Americas.[116,117] All are infections of various lower animals, particularly cats and dogs, and are transmitted through food. The lancet fluke, *Dicrocoelium dendriticum,* which inhabits the biliary tree of ruminants and humans, is the exception: It is transmitted by accidental ingestion of infected ants, the second intermediate host.[118,119] Most commonly found in sheep-raising countries of the Mediterranean, it produces mild right upper quadrant pain and loose stools. Ingestion of raw or undercooked liver of an infected animal can lead to an allergic pharyngitis (halzoun), with adult worms present in expectorated secretions, or, more commonly, to false or spurious infection from swallowed eggs found in the stool.[120]

Clonorchiasis and Opisthorchiasis

Clonorchis sinensis, Opisthorchis viverrini, and *Opisthorchis felineus* have similar life cycles, eggs, and capacity to produce disease; they differ primarily in their geographic distribution, the morphology of the adult worms, and the frequency with which the clinical syndromes occur.[3,10,121–123] *C. sinensis* is found primarily in East and Southeast Asia, with *O. viverrini* in Southeast Asia and *O. felineus* in the regions of the former Soviet Union and western Europe.[1a,122–124] Millions of persons are infected, and in some endemic areas it is not uncommon to find prevalence rates of 20% to 80%.

The hermaphroditic adult flukes are flat, elongated worms measuring 5 to 25 mm × 2 to 5 mm that inhabit the intrahepatic bile ducts (see Fig. 288.2). Their yellow-brown operculated eggs (30 × 12 µm) are fully embryonated when they pass out of the body in feces into fresh water (Fig. 288.3). The eggs are ingested by specific snails, inside of which they hatch into miracidia that develop and replicate to produce large numbers of cercariae. Cercariae are released into the water and penetrate susceptible freshwater fish, primarily carp, and then encyst as metacercariae. Several species of freshwater shrimp can also serve as the second intermediate host of *C. sinensis.*[122,123,125] Humans, cats, dogs, and other fish-eating mammals become infected by ingesting the metacercariae in raw or inadequately cooked fish; through the action of trypsin and cysteine proteases the metacercariae excyst in the duodenum and pass through the ampulla of Vater to the bile ducts, where adult worms mature and begin egg laying in about 3 to 4 weeks and live as long as 30 years, feeding on lipids in the bile. An adult worm can produce 4000 eggs or more per day.

Clinical Manifestations

Most patients are asymptomatic but may have eosinophilia; symptoms are related to worm burden. An acute illness resembling acute schistosomiasis with fever, abdominal pain, hepatomegaly, urticaria, and

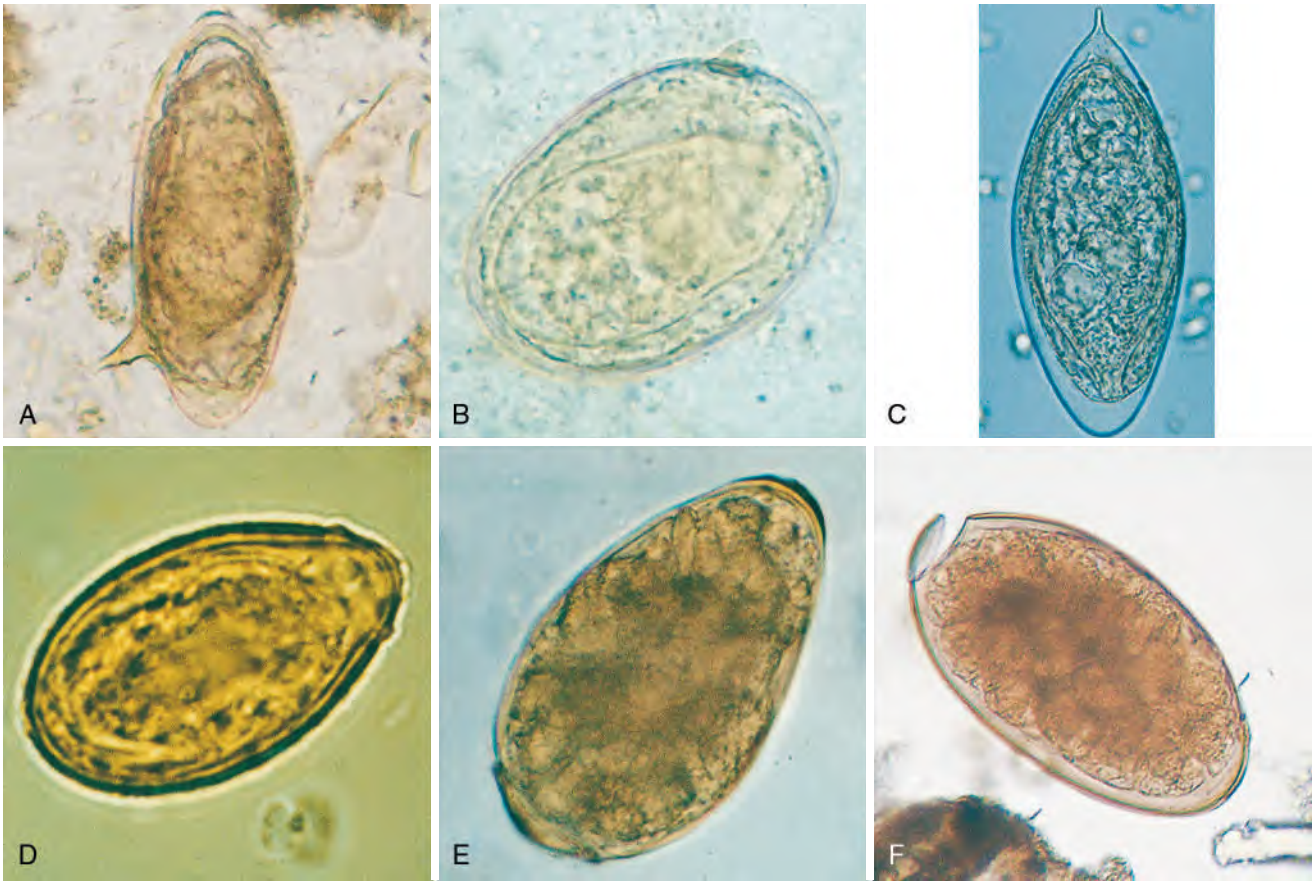

FIG. 288.3 Eggs of common human trematodes. (A) *Schistosoma mansoni.* (B) *Schistosoma japonicum.* (C) *Schistosoma haematobium.* (D) *Clonorchis sinensis.* (E) *Paragonimus westermani.* (F) *Fasciola hepatica* (note the partially open operculum). *(From Centers for Disease Control and Prevention. DPDx—Laboratory Identification of Parasitic Diseases of Public Health Concern.* http://www.dpd.cdc.gov/DPDx/*.)*

eosinophilia occasionally develops 2 to 4 weeks after the initial exposure.[126] In acute *O. felineus* infection, increased liver enzymes and enhancing hypodense nodules on CT have been reported.[124] Irritation of bile duct walls by the suckers of the flukes and secreted metabolic products leads to inflammation and thickening of bile duct walls and localized obstruction in about 10% of persons with heavy chronic infections (1000–25,000 or more eggs per gram of stool). Patients complain of right upper quadrant discomfort, anorexia, and weight loss. On physical examination the liver is palpable and firm. Periductal fibrosis, pigment stones, recurring episodes of cholangitis with bacterial sepsis, cholecystitis, liver abscess, and occasionally pancreatitis occur in the most heavily infected persons.[122,127,128] Developmental retardation has been reported in children with heavy infections.[122] Immune-complex glomerulonephritis may account for the frequent finding of high levels of IgG antibodies to *O. viverrini* in the urine of infected persons in Thailand.[128] An increased incidence of cholangiocarcinoma, an adenocarcinoma originating from hyperplastic biliary epithelium, has been associated strongly with *O. viverrini* infection in Thailand and also with *C. sinensis* infections in China and elsewhere.[116,122,129,130] The pathogenesis is thought to be related to injury and inflammation from feeding activities of worms, obstruction of bile ducts, bacterial infection, and toxicity of worms' excreted products.[122]

Diagnosis and Therapy

Liver fluke infection is diagnosed by finding eggs in the stool or by identifying adult worms during surgery or endoscopic retrograde cholangiopancreatography.[115,126,131] Eggs may not be found in the stool in the presence of biliary obstruction or in infections with fewer than 20 adult flukes; multiple examinations of concentrated specimens may be necessary unless the highly sensitive multivalent flotation method (FLOTAC) is used.[115,131] Serologic tests, antigen detection tests, and PCR-based assays are not widely available outside endemic areas or research laboratories.[131a,131b,132] Molecular techniques can discriminate species of *Clonorchis, Opisthorchis*, and several intestinal flukes that produce small morphologically similar eggs that are difficult to distinguish microscopically.[133] Ultrasonography, CT, or MRI can demonstrate dilation and stricture of bile ducts, thickening of the gallbladder wall, stones, and cholangiocarcinoma.[131] Flukes within bile ducts are difficult to visualize and require high-resolution equipment, but flukes in the gallbladder are more readily seen.[131] M-mode ultrasonography may demonstrate moving worms, which appear as thin linear echoes in ducts or can be seen floating in the gallbladder.

A single course of praziquantel (75 mg/kg in three doses for 1–2 days) eradicates the infection in more than 85% of cases.[132] A single dose regimen of 30 to 40 mg/kg was as effective for treatment of light and moderate infections with *O. viverinni* in Thailand.[134] Tribendimidine (available in China, 400 mg/day orally for 1 to 3 days) results in cure rates of 58% for *C. sinensis*.[135] Albendazole in a dose of 10 mg/kg for 7 days may also be used.[132] Rarely, surgery is needed to relieve biliary tract obstruction. Prevention of infection can be achieved by freezing fish or cooking fish adequately. In areas where opisthorchiasis is endemic, mass treatment with praziquantel has been effective.[136,137]

Fascioliasis

Infection with the sheep liver fluke *Fasciola hepatica* results from ingesting uncooked watercress or other fresh aquatic vegetation in 61 countries worldwide, especially in sheep- and cattle-raising areas.[3,138–140] Estimates of the global prevalence of human infection range from 2.4 to 17 million.[6,10] Infections have been reported from all continents except Antarctica, with the highest rates of infection in Bolivia, Peru, Egypt, Iran, Portugal, and France. The ability of *F. hepatica* to adapt to new definitive hosts and new environments, such as the Bolivian Altiplano at 3800 to 4100 meters, accounts for its continued spread from its Near Eastern and European origins.[115,138,139] A small number of cases have been reported in the United States; most have been imported, but fascioliasis occurs in domesticated herbivores in the United States, and several cases of domestically acquired infection have been reported.[141–143] The closely related but larger *F. gigantica* has a more limited distribution, and its distribution often overlaps that of *F. hepatica* in parts of Africa and Asia.[144]

The hermaphroditic adult fluke is flat, brown, and leaf shaped, and it measures about 3 × 1.5 cm. Mature worms in their natural hosts (mainly sheep and cattle) live in the common and hepatic bile ducts, where they deposit their eggs (see Fig. 288.2). The large oval, yellowish brown, operculate ova measuring 140 × 75 µm (see Fig. 288.3) pass to the intestines, are evacuated in the feces, and complete their development in fresh water. Within a few days miracidia hatch and invade their specific snail intermediate host, within which they undergo asexual replication, resulting in the release of cercariae that encyst as metacercariae on aquatic plants, including watercress, water caltrops, water lettuce, mint, and parsley. Whether embedded in plants or free floating in contaminated water or juice made from plants, the infective metacercariae excyst after being swallowed, and the larvae penetrate the intestinal wall into the peritoneum, from whence they migrate through the liver capsule and feed on liver parenchyma before entering the biliary tract.[3,115,116,144a] Three to 4 months are needed from infection to oviposition in humans. Adult flukes can live as long as 10 years.

Clinical Manifestations

Infection with *F. hepatica* has two distinct clinical phases corresponding to (1) the hepatic migratory phase of its life cycle and (2) the presence of the worms in their final habitat in the bile ducts.[10,115] Symptoms corresponding to the initial acute migration of the larval fluke appear within 6 to 12 weeks of ingestion of metacercariae and can last 4 months or longer. Marked eosinophilia is seen in most infected persons, and abdominal pain, intermittent high fever, weight loss, and urticaria are common.[145] There may be tender hepatomegaly, jaundice, anemia, and elevated results of liver function tests. Cough and chest pain occur in 10% to 15% of infected persons, sometimes accompanied by an eosinophilic pleural effusion. Aberrant migration may produce migratory nodules in the skin, painful inflammation of the intestinal wall, and lesions in the lung, brain, genitourinary tract, or elsewhere. CT or MRI shows hypodense lesions, measuring 1 cm or more in diameter, that move to various parts of the liver over the course of several weeks.[131,146,147] Hypodense tortuous and branching linear tracks under the capsule correspond to necrosis, and eosinophilic inflammatory infiltrates are seen along the path of larval migration.[148,149]

Within several weeks to months the symptoms and signs of the acute phase subside as the worms enter the bile ducts. The chronic phase of fascioliasis is usually subclinical, although eosinophilia is common, and anemia may develop in children.[150] Some persons have symptoms of biliary colic and cholecystitis due to inflammation and intermittent obstruction of bile ducts; on occasion, there is ascending cholangitis.[151] Ultrasonography or cholangiography may show masses in the common bile duct corresponding to adult worms, and worms have been visualized directly by cholangioscopy and removed after sphincterotomy for identification.[152] Pancreatitis may also occur and has been reported in up to 30% of cases.[153]

Ectopic fascioliasis may also occur, either bloodborne or from migration through soft tissues. It consists of tender, erythematous nodules or occasionally localized abscesses. Most commonly, they involve the subcutaneous tissue of the abdominal wall, but they have also been reported to be in muscle, heart, lung, GI tract, eye, and brain.[154,155]

Diagnosis

The diagnosis during the acute stage is based on epidemiology, the clinical picture, and, often, characteristic lesions seen on CT or MRI. Biopsy of nodules on the surface of the liver, in the skin, or elsewhere may show inflammatory tracts or immature worms. Serologic tests are useful during acute infection because symptoms develop 1 to 2 months before eggs are detectable in the stool. Whole-worm antigens, coproantigens, and excretory-secretory proteins have been used in enzyme immunoassays and immunoblots; sensitivities of greater than 90% are reported, but the specificity may be less, owing to cross-reactivity with other helminths.[156] CDC offers an enzyme immunoassay combined with a confirmatory immunoblot based on a recombinant *F. hepatica* antigen (FhSAP2) that has a specificity of greater than 98% for chronic fascioliasis.[157] The definitive diagnosis is made by demonstrating eggs in samples of stool, bile, or duodenal aspirates or by recovering worms at surgery. Repeat examinations and concentration procedures may be

necessary to detect eggs in the stool. A duplex PCR-based method can identify and discriminate *F. hepatica* and *F. gigantica* in stool, and a recombinase polymerase amplification method has potential for deployment in resource-limited settings.[158]

Therapy

Unlike infections with other flukes, fascioliasis responds poorly to praziquantel. First-line treatment is with a single oral dose of triclabendazole, a well-tolerated benzimidazole used in veterinary practice that is highly effective against mature and immature flukes.[115,159,160] Rates of cure of 78% to 99% have been reported, and persons not cured with a single dose usually respond to a second dose. Treatment should be repeated if radiographic findings or eosinophilia fail to resolve or the titers of serologic tests do not decrease.[161] Resistance of *F. hepatica* to triclabendazole is widespread in cattle and has been observed in human fascioliasis.[161a,161b] Triclabendazole is not available commercially in the United States but can be obtained through the CDC Drug Service under a special protocol requiring CDC and FDA approval.

Rates of cure with an alternative regimen, nitazoxanide, 500 mg twice daily for 6 to 7 days, have been as high as 95% in several small trials but lower in others.[162,163] Another alternative, bithionol, requires 10 to 15 doses, causes frequent side effects, and is no longer available from the CDC Drug Service. Artesunate has activity against *F. hepatica,* but cure rates are less than those with triclabendazole, and artemether had little effect in a trial in Egypt.[164,165]

INTESTINAL FLUKES

More than 70 flukes are known to infect the human GI tract.[3,6,116,166,167] Most are found in parts of Asia where the appropriate intermediate hosts and animal reservoirs are found.[1a] Cases in the United States occur primarily in immigrants from endemic areas, and less commonly among persons who ingested imported food, such as sushi made from infected fish.[141] Consumption of raw or undercooked local freshwater fish has led to *Heterophyes* infection in Hawaii.[141] *Nanophyetus salmincola,* which is transmitted in the Pacific Northwest of the United States, is discussed in Chapter 290. The best-known intestinal flukes include *Fasciolopsis buski;* the heterophytid flukes *Heterophyes, Metagonimus,* and *Haplorchis;* and *Echinostoma* spp.

Fasciolopsiasis

Human infection with the large intestinal fluke *Fasciolopsis buski* occurs in the Far East, Southeast Asia, and southern Asia, where pigs are the major reservoir of infection.[139,167,168] The thick, fleshy adult worms range in length from 2 to 7.5 cm and in breadth from 0.8 to 2 cm, making them the largest intestinal flukes that parasitize humans. They inhabit the duodenum and jejunum, where they produce large operculated eggs (135 × 80 µm) (see Fig. 288.2). On reaching fresh water the eggs hatch, releasing miracidia that penetrate a specific snail intermediate host in which they multiply and develop into free-living cercariae. The cercariae encyst into metacercariae on almost any aquatic plant. The metacercariae survive in most environments for up to 1 year. When raw or poorly cooked infected plants, frequently water chestnut, bamboo, caltrop, and hyacinth and roots of the lotus, are ingested by humans, the metacercariae excyst in the intestines, and, within 3 months, the parasites develop into mature worms that survive 6 months or more in the human host.

Adult flukes live in the upper portion of the small intestine, where they attach to the mucosa and produce local inflammation, ulceration, and abscesses. Fasciolopsiasis is usually asymptomatic, but anemia and eosinophilia are common.[10,18,116,168a] In some cases epigastric pain and diarrhea develop 1 or 2 months after exposure; rare cases of upper GI bleeding and appendicitis have been reported.[168b,168c] With heavy infections, flukes may cause transient obstruction and ileus. Edema of the face and extremities may result from hypersensitivity to worm metabolites or from hypoalbuminemia due to malabsorption or protein-losing enteropathy.

Heterophyiasis, Metagonimiasis, and Haplorchiasis

There are at least 22 species of flukes in the family Heterophyidae, of which *Heterophyes heterophyes* and *Metagonimus yokogawai* are the most common. *H. heterophyes* is found primarily in the Nile delta region, Tunisia, Turkey, and Iran, whereas *M. yokogawai* is most prevalent in the Far East.[4,138,169] *Haplorchis taichui* infection is common in parts of Southeast Asia, where its eggs are often confused with those of *O. viverrini.*[170,171] The adult flukes of all species measure less than 2 mm in length and inhabit the small intestine of human, animal, or avian hosts, where they produce small operculate eggs (30 × 15 µm). The life cycle is similar to that of other trematodes and involves snails and fish living in fresh or brackish water. The metacercariae encyst under the scales of the fish. Infection is acquired by consumption of undercooked or salted fish. Adults begin producing eggs in about 9 days and live only a few months to less than 1 year.

Flukes attach to the small intestine wall, where they produce focal inflammation and ulcerations. Asymptomatic eosinophilia occurs with light infections, whereas moderate infections have been associated with irritable bowel syndrome–like symptoms, and heavy infections may lead to colicky abdominal pain, dyspepsia, and diarrhea.[10,166,172] Flukes may penetrate the mucosa and deposit eggs that pass through lymphatics into the bloodstream. Eggs may embolize to the heart or CNS, where they can cause myocarditis or focal lesions of the brain or spinal cord and occasionally death.

Echinostomiasis

At least 20 species of *Echinostoma* infect humans, primarily in Southeast and East Asia, where infection is acquired by ingestion of raw or undercooked clams, frogs, snakes, snails, and fish, which can serve as the second intermediate host.[116,167,173,173a] Rare cases have been reported in India and Nepal, and a group of six travelers became infected after eating raw fish caught in Lake Tanganyika in Tanzania.[173b,173c] Illness in heavy infections tends to be more severe than that observed in other intestinal trematode infections and includes abdominal pain, diarrhea, malnutrition, anemia, intestinal ulceration, and perforation.

Diagnosis and Therapy

A definitive diagnosis of intestinal trematode infection depends on demonstration of eggs or adult worms in stools. Proper identification of the species by examining eggs is difficult because the morphology and size of eggs of different species are similar.[115] Eggs of *F. buski* can be confused with those of *F. hepatica,* and eggs of *Heterophyes, Metagonimus,* and *Haplorchis* can be confused with each other and with the eggs of *C. sinensis* and *Opisthorchis.* Species identification is best made by examining adult worms expelled after treatment or by PCR-based methods applied to stool specimens.[132,170,174]

The treatment of choice of all intestinal trematodes infections is praziquantel. Niclosamide has been used to treat *Fasciolopsis* and *Heterophyes* infections, and triclabendazole may be effective, but experience using this drug is limited.[115,132]

LUNG FLUKES

Paragonimiasis

More than 40 species of *Paragonimus* are recognized as parasites of mammals, and of these about 15 cause significant infections in humans.[10,116,175–177] *Paragonimus westermani,* the most important species infecting humans, is found in the Far East, principally in Korea, Japan, Taiwan, China, and the Philippines. Other important species are *Paragonimus miyazaki* (Japan), *Paragonimus skrjabini* and *Paragonimus hueitungensis* (China), *Paragonimus heterotrema* (China, Southeast Asia), *Paragonimus uterobilateralis* and *Paragonimus africanus* (Central and West Africa), *Paragonimus mexicanus* (Central and South America), and *Paragonimus kellicotti* (North America).[176–178] More than a dozen cases of locally acquired paragonimiasis have been reported in the United States among persons who ate raw or undercooked crayfish, most often while canoeing or camping in the Mississippi River drainage basin.[141,176–178]

Reddish brown adult worms measuring 7 to 16 mm × 4 to 7 mm live in encapsulated cystic cavities in the parenchyma of the lung, usually close to the bronchioles. Worms produce golden-brown operculate eggs (80–120 µm × 50–65 µm) that pass into the bronchioles and are coughed up; they are then either passed in sputum or swallowed and passed in feces (see Figs. 288.2 and 288.3). On reaching fresh water they require 2 to 3 weeks to develop before miracidia hatch at 29°to 32°C. After 3

to 5 months of development and reproduction in the snail, stumpy-tailed cercariae emerge. They encyst in the muscles and viscera of crayfish and freshwater crabs. Human infection is initiated by consumption of these freshwater crustaceans if they are uncooked, partially cooked, salted, or pickled. Cases in Japan have been reported from consumption of wild boar and deer, which can serve as paratenic hosts.[178a] Metacercariae excyst in the duodenum, penetrate the intestinal wall, and enter the peritoneal cavity. After several days they migrate through the diaphragm to the pleural cavities and then into the lungs. A fibrous cyst wall develops around them, and egg deposition starts 5 to 6 weeks after infection. Worms may develop also in extrapulmonary sites, including the liver, lymph nodes, skin, spinal cord, and brain. Adults may live as long as 20 to 25 years but generally have much shorter lives.

Clinical Manifestations

At 2 to 15 days after ingestion of metacercariae, some persons develop abdominal pain and diarrhea, followed by fever, chest pain, cough, urticaria, and eosinophilia. However, these initial symptoms are often absent, and light or moderate infections may remain undetected until first seen on a radiograph obtained for other reasons. In cases of North American paragonimiasis diagnosed in Missouri, cough, fever, eosinophilia, and pleural effusions developed within 2 to 12 weeks of ingesting raw crayfish.[178]

The inflammatory reaction to adults encapsulated in the lungs and the shedding of eggs into the bronchial tree are responsible for chronic symptoms. Cough productive of brownish sputum with intermittent hemoptysis are the initial manifestations of chronic infection.[179] Later the clinical picture resembles chronic bronchitis or bronchiectasis with profuse expectoration and pleuritic chest pain, dyspnea, chronic cough, chest pains, and occasional hemoptysis.[176] Radiographs may be negative or show diffuse infiltration, cysts measuring about 4 cm in diameter, nodules, calcifications, pleural effusion, and pneumothorax.[180] In North American cases, CT has shown nodules, internal mammary and cardiophrenic lymphadenopathy, pericardial thickening or effusion, linear tracks between nodules and pleura, and inflammation of the omentum, corresponding to the worm's migratory path.[181] Pleural and pericardial fluid is exudative and may contain large numbers of eosinophils. The illness is often confused with pulmonary tuberculosis, but eosinophilia and the lack of fever suggest the true diagnosis.[176] Lung cancer may be suspected in patients with nodular or mass lesions, especially in the absence of other symptoms.[182]

The most commonly recognized form of extrapulmonary disease is involvement of the CNS, which is seen in as many as 25% of hospitalized cases.[175,176,183] Parasite-induced meningitis may be the first manifestation, usually occurring within a year of pulmonary infection; eosinophilic meningitis has been seen in US cases of *P. kellicotti* infection with migration of parasites in the brain.[183a] Cerebral infections present as space-occupying tumors, with seizures, headaches, visual disturbances, and motor or sensory deficits. Radiographs of the skull may show clusters of calcified cysts that resemble soap bubbles, and MRI and CT show aggregates of ring-enhancing lesions with surrounding edema.[180,183b]

Other extrapulmonary infections result in migratory allergic skin lesions similar to those seen with cutaneous larva migrans; these lesions are most common during infections with *P. skrjabini* but also occur with infections with *P. westermani* and other species. Flukes can migrate through the liver and enter the biliary tree and have been found in the liver, spleen, peritoneum, intestinal wall, intraabdominal lymph nodes, and elsewhere.[176,183,184,184a]

Diagnosis and Therapy

The diagnosis of paragonimiasis is established by identifying expectorated eggs in the sputum, swallowed eggs in the feces, or worms and eggs in biopsy specimens. Multiple examinations of stool and sputum may be necessary. Serologic tests are useful for diagnosing early, light, or extrapulmonary infections.[185] Enzyme immunoassay tests are available, and an immunoblot assay performed at the CDC that uses a crude antigen extract of *P. westermani* has a sensitivity of 96% and a specificity of almost 100%.[186,187] A Western blot that uses *P. kellicotti* antigens recognized all 11 cases of North American paragonimiasis examined, including 2 cases negative by *P. westermani* immunoblot.[188]

The treatment of choice for paragonimiasis is praziquantel. The alternative, triclabendazole, also has a high rate of cure.[132,176] A patient with *P. westermani* infection and a severe allergy to praziquantel failed to respond to several courses of triclabendazole but was successfully treated after desensitization to praziquantel.[189] Bithionol is no longer used because of more frequent side effects. Because an inflammatory reaction to dying worms may precipitate seizures or other neurologic complications, corticosteroids should be used simultaneously with praziquantel for cerebral paragonimiasis.

PREVENTION OF FOODBORNE FLUKE INFECTIONS

As aquaculture for production of freshwater fish, crustaceans, and aquatic vegetables continues to expand and provide a rapidly growing percentage of the supply for local and international markets, efforts to prevent and control nonschistosomal trematode infections are critical at all stages of the food chain. The focus is on food production and preparation, because elimination of snail and animal hosts is neither desirable nor feasible. Educational interventions focus on preventing contamination of water sources with human and animal feces, especially ponds used for the cultivation of fish and aquatic plants. Effective education about proper preservation, cooking, or other preparation of food takes cultural practices and beliefs into account. WHO's current strategy to control foodborne trematodiases also includes control of morbidity and mortality by widespread screening of populations and anthelmintic treatment of confirmed cases or, in areas of high prevalence, mass treatment of persons at risk for infection. National programs in Southeast Asia have delivered hundreds of thousands of doses of praziquantel for control of clonorchiasis and opisthorchiasis, and in Egypt, Bolivia, and Peru, triclabendazole has been administered to populations with high rates of fascioliasis.[2,190]

Key References

The complete reference list is available online at Expert Consult.

1a. Lu XT, Gu QY, Limpanont Y, et al. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. *Infect Dis Poverty*. 2018;7:28.

4. Colley DG, Bustinduy AL, Secor WE, et al. Human schistosomiasis. *Lancet*. 2014;383:2253–2264.

5. World Health Organization (WHO). Schistosomiasis and soil-transmitted helminthiases: number of people treated in 2016. *Wkly Epidemiol Rec*. 2017;92:749–760.

5a. Boissier J, Grech-Angelini S, Webster BL, et al. Outbreak of urogenital schistosomiasis in Corsica (France): an epidemiological case study. *Lancet Infect Dis*. 2016;16:971–979.

5b. Mutapi F, Maizels R, Fenwick A, et al. Human schistosomiasis in the post mass drug administration era. *Lancet Infect Dis*. 2017;17:e42–e48.

6a. Arya LK, Rathinam SR, Lalitha P, et al. Trematode fluke *Procerovum varium* as cause of ocular inflammation in children, South India. *Emerg Infect Dis*. 2016;22:192–200.

11a. Horák P, Mikeš L, Lichtenbergová L, et al. Avian schistosomes and outbreaks of cercarial dermatitis. *Clin Microbiol Rev*. 2015;28:165–190.

13a. Catalano S, Sène M, Diouf ND, et al. Rodents as natural hosts of zoonotic *Schistosoma* species and hybrids: an epidemiological and evolutionary perspective from West Africa. *J Infect Dis*. 2018;218:429–433.

13b. Zoni AC, Catalá L, Ault SK. Schistosomiasis prevalence and intensity of infection in Latin America and the Caribbean countries, 1942–2014: a systematic review in the context of a regional elimination goal. *PLoS Negl Trop Dis*. 2016;10:e0004493.

13c. Bergquist R, Zhou XN, Rollinson D, et al. Elimination of schistosomiasis: the tools required. *Infect Dis Poverty*. 2017;6:158.

13d. Soe HZ, Oo CC, Myat TO, et al. Detection of *Schistosoma* antibodies and exploration of associated factors among local residents around Inlay Lake, Southern Shan State, Myanmar. *Infect Dis Poverty*. 2017;6:3.

13e. Yang GJ, Bergquist R. Potential impact of climate change on schistosomiasis: a global assessment attempt. *Trop Med Infect Dis*. 2018;3:E117.

14. Colley DG, Secor WE. Immunology of human schistosomiasis. *Parasite Immunol*. 2014;36:347–357.

16. Lingscheid T, Kurth F, Clerinx J, et al. Schistosomiasis in European travelers and migrants: analysis of 14 years TropNet Surveillance data. *Am J Trop Med Hyg*. 2017;97:567–574.

31a. Carson JP, Ramm GA, Robinson MW, et al. Schistosome-induced fibrotic disease: the role of hepatic stellate cells. *Trends Parasitol*. 2018;34:524–540.

41. Gordy MA, Cobb TP, Hanington PC. Swimmer's itch in Canada: a look at the past and a survey of the present to plan for the future. *Environ Health*. 2018;17:73.

43. Coron N, Le Govic Y, Kettani S, et al. Early detection of *Schistosoma* egg-induced pulmonary granulomas in a returning traveler. *Am J Trop Med Hyg*. 2016;94:611–614.

46a. Ezeamama AE, Bustinduy AL, Nkwata AK, et al. Cognitive deficits and educational loss in children with schistosome infection—a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2018;12:e0005524.

52a. Hamid HKS. *Schistosoma japonicum*-associated colorectal cancer: a review. *Am J Trop Med Hyg*. 2019;100:501–505.

54. Abruzzi A, Fried B, Alikhan SB. Coinfection of *Schistosoma* species with hepatitis B or hepatitis C viruses. *Adv Parasitol*. 2016;91:111–231.
59. Christinet V, Lazdins-Helds JK, Stothard JR, et al. Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease. *Int J Parasitol*. 2016;46:395–404.
60. Miller-Fellows SC, Howard L, Kramer R, et al. Cross-sectional interview study of fertility, pregnancy, and urogenital schistosomiasis in coastal Kenya: documented treatment in childhood is associated with reduced odds of subfertility among adult women. *PLoS Negl Trop Dis*. 2017;11:e0006101.
61. Kjetland EF, Hegertun IE, Baay MF, et al. Genital schistosomiasis and its unacknowledged role on HIV transmission in the STD intervention studies. *Int J STD AIDS*. 2014;25:705–715.
63. Abdel-Naser MB, Altenburg A, Zouboulis CC, et al. Schistosomiasis (bilharziasis) and male infertility. *Andrologia*. 2019;51:e13165.
64. Ishida K, Hsieh MH. Understanding urogenital schistosomiasis-related bladder cancer: an update. *Front Med (Lausanne)*. 2018;5:223.
65. Gavilanes F, Fernandes CJ, Souza R. Pulmonary arterial hypertension in schistosomiasis. *Curr Opin Pulm Med*. 2016;22:408–414.
71. Hsiao A, Toy T, Seo HJ, et al. Interaction between *Salmonella* and schistosomiasis: a review. *PLoS Pathog*. 2016;12:e1005928.
73a. Wall KM, Kilembe W, Vwalika B, et al. Schistosomiasis is associated with incident HIV transmission and death in Zambia. *PLoS Negl Trop Dis*. 2018;12:e0006902.
76. Goovaerts O, Mwinzi PNM, Muok EMO, et al. Aberrant plasma MMP and TIMP dynamics in *Schistosoma*-immune reconstitution inflammatory syndrome (IRIS). *PLoS Negl Trop Dis*. 2018;12:e0006710.
77. Weerakoon KGAD, Gobert GN, Cai P, et al. Advances in the diagnosis of human schistosomiasis. *Clin Microbiol Rev*. 2015;28:939–967.
79. He P, Gordon CA, Williams GM, et al. Real-time PCR diagnosis of *Schistosoma japonicum* in low transmission areas of China. *Infect Dis Poverty*. 2018;7:8.
80. Al-Shehri H, Koukounari A, Stanton MC, et al. Surveillance of intestinal schistosomiasis during control: a comparison of four diagnostic tests across five Ugandan primary schools in the Lake Albert region. *Parasitology*. 2018;145:1715–1722.
82a. Röser D, Bjerrum S, Helleberg M, et al. Adventure tourism and schistosomiasis: serology and clinical findings in a group of Danish students after white-water rafting in Uganda. *JMM Case Rep*. 2018;5:e005141.
84. Richter J, Botelho MC, Holtfreter MC, et al. Ultrasound assessment of schistosomiasis. *Z Gastroenterol*. 2016;54:653–660.
85. Olveda DU, Inobaya M, Olveda RM, et al. Diagnosing schistosomiasis-induced liver morbidity: implications for global control. *Int J Infect Dis*. 2017;54:138–144.
89a. Secor WE, Colley DG. When should the emphasis on schistosomiasis control move to elimination? *Trop Med Infect Dis*. 2018;3:85.
90. Vale N, Gouveia MJ, Rinaldi G, et al. Praziquantel for schistosomiasis: single-drug metabolism revisited, mode of action, and resistance. *Antimicrob Agents Chemother*. 2017;61:e02582-16.
91. Zwang J, Olliaro P. Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: a meta-analysis. *Parasit Vectors*. 2017;10:47.
92a. Mutapi F, Maizels R, Fenwick A, et al. Human schistosomiasis in the post mass drug administration era. *Lancet Infect Dis*. 2017;17:e42–e48.
96. Osakunor DNM, Woolhouse MEJ, Mutapi F. Paediatric schistosomiasis: what we know and what we need to know. *PLoS Negl Trop Dis*. 2018;12:e00061444.
97. Friedman JF, Olveda RM, Mirochnick MH, et al. Praziquantel for the treatment of schistosomiasis during human pregnancy. *Bull World Health Organ*. 2018;96:59–65.
99. Olveda RM, Acosta LP, Tallo V, et al. Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2016;16:199–208.
103. Bergquist R, Elmorshedy H. Artemether and praziquantel: origin, mode of action, impact, and suggested application for effective control of human schistosomiasis. *Trop Med Infect Dis*. 2018;3:125.
107. Bergquist R, Utzinger J, Keiser J. Controlling schistosomiasis with praziquantel: how much longer without a viable alternative? *Infect Dis Poverty*. 2017;6:74.
108. Grimes JET, Croll D, Harrison WE, et al. The roles of water, sanitation and hygiene in reducing schistosomiasis: a review. *Parasit Vectors*. 2015;8:156.
109. Campbell SJ, Biritwum NK, Woods G, et al. Tailoring water, sanitation, and hygiene (WASH) targets for soil-transmitted helminthiasis and schistosomiasis control. *Trends Parasitol*. 2018;34:53–63.
110. Andrade G, Bertsch DJ, Andrea Gazzinelli A, et al. Decline in infection-related morbidities following drug-mediated reductions in the intensity of *Schistosoma* infection: a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2017;11:e0005372.
112. Sun LP, Wang W, Hong QB, et al. Approaches being used in the national schistosomiasis elimination programme in China: a review. *Infect Dis Poverty*. 2017;6:55.
112b. Lo NC, Gurarie D, Yoon N, et al. Impact and cost-effectiveness of snail control to achieve disease control targets for schistosomiasis. *Proc Natl Acad Sci U S A*. 2018;115:e584–e591.
113. Tebeje BM, Harvie M, You H, et al. Schistosomiasis vaccines: where do we stand? *Parasit Vectors*. 2016;9:528.
114. Siddiqui AA, Siddiqui SZ. Sm-p80-Based schistosomiasis vaccine: preparation for human clinical trials. *Trends Parasitol*. 2017;33:194–201.
116a. Harrington D, Lamberton PHL, McGregor A. Human liver flukes. *Lancet Gastroenterol Hepatol*. 2017;2:680–689.
118. Azmoudeh-Ardalan F, Soleimani V, Jahanbin B. *Dicrocoelium dentriticum* in explanted liver: report of an unusual finding. *Exp Clin Transplant*. 2017;15(suppl 1):178–181.
120. Moure Z, Zarzuela F, Espasa M, et al. *Dicrocoelium dendriticum*: an unusual parasitological diagnosis in a reference international health unit. *Am J Trop Med Hyg*. 2017;96:355–357.
121. Sripa B, Tesana S, Yurlova N, et al. A historical review of small liver fluke infections in humans. *Parasitol Int*. 2017;66:337–340.
122. Qian MB, Utzinger J, Keiser J, et al. Clonorchiasis. *Lancet*. 2016;387:800–810.
124. Pakharukovaa MY, Mordvinov VA. The liver fluke *Opisthorchis felineus*: biology, epidemiology and carcinogenic potential. *Trans R Soc Trop Med Hyg*. 2016;110:28–36.
125. Tang ZL, Huang Y, Yu XB. Current status and perspectives of *Clonorchis sinensis* and clonorchiasis: epidemiology, pathogenesis, omics, prevention and control. *Infect Dis Poverty*. 2016;5:71.
127. Xia J, Jiang SC, Peng HJ. Association between liver fluke infection and hepatobiliary pathological changes: a systematic review and meta-analysis. *PLoS ONE*. 2015;10:e0132673.
129. Zheng S, Zhu Y, Zhao Z, et al. Liver fluke infection and cholangiocarcinoma: a review. *Parasitol Res*. 2017;116:11–19.
131a. Worasith C, Kamamia C, Yakovleva A, et al. Advances in the diagnosis of human opisthorchiasis: development of *Opisthorchis viverrini* antigen detection in urine. *PLoS Negl Trop Dis*. 2015;9:e0004157.
131b. Li HM, Qian MB, Yang YC, et al. Performance evaluation of existing immunoassays for *Clonorchis sinensis* infection in China. *Parasit Vectors*. 2018;11:35.
133. Buathong S, Leelayoova S, Mungthin M, et al. Molecular discrimination of *Opisthorchis*-like eggs from residents in a rural community of central Thailand. *PLoS Negl Trop Dis*. 2017;11:e0006030.
134. Sayasone S, Meister I, Andrews JR, et al. Efficacy and safety of praziquantel against light infections of *Opisthorchis viverrini*: a randomized parallel single-blind dose-ranging trial. *Clin Infect Dis*. 2017;64:451–458.
138. Cwiklinski K, O'Neill SM, Donnelly S, et al. A prospective view of animal and human fasciolosis. *Parasite Immunol*. 2016;38:558–568.
142. Ashrafi K, Bargues MD, O'Neill S, et al. Fascioliasis: a worldwide parasitic disease of importance in travel medicine. *Travel Med Infect Dis*. 2014;12:636–649.
144a. Cabada MM, Goodrich MR, Graham B, et al. Fascioliasis and eosinophilia in the highlands of Cuzco, Peru and their association with water and socioeconomic factors. *Am J Trop Med Hyg*. 2014;91:989–993.
146. Patel NU, Bang TJ, Dodd GD III. CT findings of human *Fasciola hepatica* infection: case reports and review of the literature. *Clin Imaging*. 2016;40:251–255.
151. Ishikawa T, Stephenson VM, Heitman SJ. Biliary obstruction caused by the liver fluke, *Fasciola hepatica*. *CMAJ*. 2016;188:524–526.
152. Dolay K, Hasbahçeci M, Hatipoğlu E, et al. Endoscopic diagnosis and treatment of biliary obstruction due to acute cholangitis and acute pancreatitis secondary to *Fasciola hepatica* infection. *Ulus Travma Acil Cerrahi Derg*. 2018;24:71–73.
157. Shin SH, Hsu A, Chastain HM. Development of two FhSAP2 recombinant–based assays for immunodiagnosis of human chronic fascioliasis. *Am J Trop Med Hyg*. 2016;95:852–855.
159. Cabada MM, Malaga JL, Castellanos-Gonzalez A, et al. Recombinase polymerase amplification compared to real-time polymerase chain reaction test for the detection of *Fasciola hepatica* in human stool. *Am J Trop Med Hyg*. 2017;96:341–346.
161a. Kelley JM, Elliott TP, Beddoe T, et al. Current threat of triclabendazole resistance in *Fasciola hepatica*. *Trends Parasitol*. 2016;32:458–469.
161b. Cabada MM, Lopez M, Cruz M, et al. Treatment failure after multiple courses of triclabendazole among patients with fascioliasis in Cusco, Peru: a case series. *PLoS Negl Trop Dis*. 2016;10:e0004361.
164. Lama NS, Longa X, Sub XZ, et al. Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis. *Pharmacol Res*. 2018;133:77–100.
168a. Saurabh K, Ranjan S. Fasciolopsiasis in children: clinical, sociodemographic profile and outcome. *Indian J Med Microbiol*. 2017;35:551–554.
168b. Cao YH, Ma YM, Qiu F, et al. Rare cause of appendicitis: mechanical obstruction due to *Fasciolopsis buski* infestation. *World J Gastroenterol*. 2015;21:3146–3149.
168c. Sarma MS, Yachha SK, Srivastava A, et al. Endoscopic extraction of *Fasciolopsis buski* presenting as acute upper GI bleeding in a child. *Gastrointest Endosc*. 2015;82:743.
171. Lamaningao P, Kanda S, Laimanivong S, et al. Development of a PCR assay for diagnosing trematode (*Opisthorchis* and *Haplorchis*) infections in human stools. *Am J Trop Med Hyg*. 2017;96:221–228.
173a. Toledo R, Esteban JG. An update on human echinostomiasis. *Trans R Soc Trop Med Hyg*. 2016;110:37–45.
173b. Sah R, Khadka S, Hamal R, et al. Human echinostomiasis: a case report. *BMC Res Notes*. 2018;11:17.
173c. Chunge RN, Chunge CN. Infection with *Echinostoma* sp. in a group of travellers to Lake Tanganyika, Tanzania, in January 2017. *J Travel Med*. 2017;24:1–3.
177. Diaz JH. Paragonimiasis acquired in the United States: native and nonnative species. *Clin Microbiol Rev*. 2013;26:493–504.
178a. Yoshida A, Matsuo K, Moribe J, et al. Venison, another source of *Paragonimus westermani* infection. *Parasitol Int*. 2016;65:607–612.
179. Kagawa FT. Pulmonary paragonimiasis. *Semin Respir Infect*. 1997;12:149–158.
183a. Bahr NC, Trotman RL, Samman H, et al. Eosinophilic meningitis due to infection with *Paragonimus kellicotti*. *Clin Infect Dis*. 2017;64:1271–1274.
183b. Xia Y, Chen J, Ju Y, et al. Characteristic CT and MR imaging findings of cerebral paragonimiasis. *J Neuroradiol*. 2016;43:200–206.
184a. Liang T, Liang G, Du Y, et al. Scrotal paragonimiasis in adults: two case reports and review of literature. *Medicine (Baltimore)*. 2018;97:1–4.

References

1. Muller R. The nematodes. In: Muller R, ed. *Worms and Human Disease*. 2nd ed. Wallingford: CABI Publishing; 2002:109–235.

1a. Lu XT, Gu QY, Limpanont Y, et al. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. *Infect Dis Poverty*. 2018;7:28.

2. World Health Organization (WHO). *Integrating Neglected Tropical Diseases Into Global Health and Development. Neglected Tropical Diseases: Fourth WHO Report on Neglected Diseases*. Geneva: WHO; 2017.

3. Crompton DWT, Savioli L. *Handbook of Helminthiases for Public Health*. Boca Raton, FL: CRC Press-Taylor and Francis Group; 2007:91–125.

4. Colley DG, Bustinduy AL, Secor WE, et al. Human schistosomiasis. *Lancet*. 2014;383:2253–2264.

5. World Health Organization (WHO). Schistosomiasis and soil-transmitted helminthiases: number of people treated in 2016. *Wkly Epidemiol Rec*. 2017;92:749–760.

5a. Boissier J, Grech-Angelini S, Webster BL, et al. Outbreak of urogenital schistosomiasis in Corsica (France): an epidemiological case study. *Lancet Infect Dis*. 2016;16:971–979.

5b. Mutapi F, Maizels R, Fenwick A, et al. Human schistosomiasis in the post mass drug administration era. *Lancet Infect Dis*. 2017;17:e42–e48.

6. Fürst T, Keiser J, Utzinger J. Global burden of human food-borne trematodiasis: a systemic review and meta-analysis. *Lancet Infect Dis*. 2012;12:210–221.

6a. Arya LK, Rathinam SR, Lalitha P, et al. Trematode fluke *Procerovum varium* as cause of ocular inflammation in children, South India. *Emerg Infect Dis*. 2016;22:192–200.

7. Jordan P, Webbe G, Sturrock RF. *Human Schistosomiasis*. Wallingford, UK: CAB International; 1993:1–465.

8. McManus DP, Dunne DW, Sacko M, et al. Schistosomiasis. *Nat Rev Dis Primers*. 2018;4:13.

9. Gryssels B. Schistosomiasis. *Infect Dis Clin North Am*. 2012;26:383–397.

10. Keiser J, Utzinger J. Food-borne trematodiases. *Clin Microbiol Rev*. 2009;22:466–483.

11. Sturrock RF. The schistosomes and their intermediate hosts. In: Mahmoud AAF, ed. *Schistosomiasis*. London: Imperial College Press; 2001:7–83.

11a. Horák P, Mikeš L, Lichtenbergová L, et al. Avian schistosomes and outbreaks of cercarial dermatitis. *Clin Microbiol Rev*. 2015;28:165–190.

12. Ross AG, Vickers D, Olds GR, et al. Katayama syndrome. *Lancet Infect Dis*. 2007;7:218–224.

13. Protasio AV, Dunne DW, Berriman M. Comparative study of transcriptome profiles of mechanical- and skin-transformed *Schistosoma mansoni* schistosomula. *PLoS Negl Trop Dis*. 2013;7:e2091.

13a. Catalano S, Sène M, Diouf ND, et al. Rodents as natural hosts of zoonotic *Schistosoma* species and hybrids: an epidemiological and evolutionary perspective from West Africa. *J Infect Dis*. 2018;218:429–433.

13b. Zoni AC, Catalá L, Ault SK. Schistosomiasis prevalence and intensity of infection in Latin America and the Caribbean countries, 1942–2014: a systematic review in the context of a regional elimination goal. *PLoS Negl Trop Dis*. 2016;10:e0004493.

13c. Bergquist R, Zhou XN, Rollinson D, et al. Elimination of schistosomiasis: the tools required. *Infect Dis Poverty*. 2017;6:158.

13d. Soe HZ, Oo CC, Myat TO, et al. Detection of *Schistosoma* antibodies and exploration of associated factors among local residents around Inlay Lake, Southern Shan State, Myanmar. *Infect Dis Poverty*. 2017;6:3.

13e. Yang GJ, Bergquist R. Potential impact of climate change on schistosomiasis: a global assessment attempt. *Trop Med Infect Dis*. 2018;3:E117.

14. Colley DG, Secor WE. Immunology of human schistosomiasis. *Parasite Immunol*. 2014;36:347–357.

15. Kurtis JD, Friedman JF, Leenstra T, et al. Pubertal development predicts resistance to infection and reinfection with *Schistosoma japonicum*. *Clin Infect Dis*. 2006;42:1692–1698.

16. Lingscheid T, Kurth F, Clerinx J, et al. Schistosomiasis in European travelers and migrants: analysis of 14 years TropNet Surveillance data. *Am J Trop Med Hyg*. 2017;97:567–574.

17. Nicolls DJ, Weld LH, Schwartz E, et al. Characteristics of schistosomiasis in travelers reported to the Geosentinel Surveillance Network 1997-2008. *Am J Trop Med Hyg*. 2008;79:729–734.

18. Leshem E, Meltzer E, Marva E, et al. Travel-related schistosomiasis acquired in Laos. *Emerg Infect Dis*. 2009;15:1823–1826.

19. Clerinx J, Van Gompel A. Schistosomiasis in travelers and migrants. *Travel Med Infect Dis*. 2011;9:6–24.

20. Wilson RA. Virulence factors of schistosomiasis. *Microbes Infect*. 2012;14:1442–1450.

21. Wilson MS, Mentink-Kane MM, Pesce JT, et al. Immunopathology of schistosomiasis. *Immunol Cell Biol*. 2007;85:148–154.

22. Skelly PJ, Alan WR. Making sense of the schistosome surface. *Adv Parasitol*. 2006;63:185–284.

23. Doherty JF, Moody AH, Wright SG. Katayama fever: an acute manifestation of schistosomiasis. *BMJ*. 1996;313:1071–1072.

24. De Jesus AR, Silva A, Santana LB, et al. Clinical and immunological evaluation of 31 patients with acute schistosomiasis mansoni. *J Infect Dis*. 2002;185:98–105.

25. Warren KS, Domingo EO, Cowan RBT. Granuloma formation around schistosome eggs as a manifestation of delayed hypersensitivity. *Am J Pathol*. 1967;51:735–756.

26. Kassis AI, Warren KS, Mahmoud AAF. The *Schistosoma haematobium* egg granuloma. *Cell Immunol*. 1978;38:310–318.

27. Fairfax K, Nascimento M, Huang SC, et al. Th2 responses in schistosomiasis. *Semin Immunopathol*. 2012;34:863–871.

28. Larkin BM, Smith PM, Ponichtera HE, et al. Induction and regulation of pathogenic Th17 cell responses in schistosomiasis. *Semin Immunopathol*. 2012;34:873–888.

29. Johnston MJG, MacDonald JA, McKay DM. Parasitic helminths: a pharmacopeia of anti-inflammatory molecules. *Parasitology*. 2009;136:125–147.

30. Karanja DMS, Boyer AE, Strand M, et al. Studies on schistosomiasis in western Kenya, I. Evidence for immune-facilitated excretion of schistosome eggs from patients with *Schistosoma mansoni* and human immunodeficiency virus coinfections. *Am J Trop Med Hyg*. 1997;56:515–521.

31. Andrade ZA. Schistosomiasis and liver fibrosis. *Parasite Immunol*. 2009;31:656–663.

31a. Carson JP, Ramm GA, Robinson MW, et al. Schistosome-induced fibrotic disease: the role of hepatic stellate cells. *Trends Parasitol*. 2018;34:524–540.

32. Cheever AW. A quantitative post-mortem study of schistosomiasis mansoni in man. *Am J Trop Med Hyg*. 1968;17:38–64.

33. Abdel Salam E, Abdel Fattah M. Prevalence and morbidity of *Schistosoma haematobium* in Egyptian children: a controlled study. *Am J Trop Med Hyg*. 1977;26:463–469.

34. Siongok TKA, Mahmoud AAF, Ouma JH, et al. Morbidity in schistosomiasis mansoni in relation to intensity of infection: study of a community in Machakos, Kenya. *Am J Trop Med Hyg*. 1976;25:273–284.

35. Ellis MK, Zhao ZZ, Chen HG, et al. Analysis of the 5q31-33 locus shows an association between single nucleotide polymorphism variants in the IL-5 gene and symptomatic infection with the human blood fluke, *Schistosoma japonicum*. *J Immunol*. 2007;179:8366–8371.

36. Karanja DMS, Hightower AW, Colley DG, et al. Resistance to reinfection with *Schistosoma mansoni* in occupationally exposed adults and effect of HIV-1 co-infection on susceptibility to schistosomiasis: a longitudinal study. *Lancet*. 2002;360:592–596.

37. Brooker S, Akhwale W, Pullan R, et al. Epidemiology of *Plasmodium*-helminth co-infection in Africa: populations at risk, potential impact on anemia and prospects for combining control. *Am J Trop Med Hyg*. 2007;77(suppl 6):88–98.

38. Secor WE. Immunology of human schistosomiasis: off the beaten path. *Parasite Immunol*. 2005;27:309–316.

39. Corachan M. Schistosomiasis and international travel. *Clin Infect Dis*. 2002;35:446.

40. Boggild AK, Yohanna S, Keystone JS, et al. Prospective analysis of parasitic infections in Canadian travelers and immigrants. *J Travel Med*. 2006;13:138.

41. Gordy MA, Cobb TP, Hanington PC. Swimmer's itch in Canada: a look at the past and a survey of the present to plan for the future. *Environ Health*. 2018;17:73.

42. Pavlin BI, Kozarsky P, Cetron MS. Acute pulmonary schistosomiasis in travelers: case report and review of the literature. *Travel Med Infect Dis*. 2012;10:209–219.

43. Coron N, Le Govic Y, Kettani S, et al. Early detection of *Schistosoma* egg-induced pulmonary granulomas in a returning traveler. *Am J Trop Med Hyg*. 2016;94:611–614.

44. Jaureguiberry S, Ansart S, Perez L, et al. Acute neuroschistosomiasis: two cases associated with cerebral vasculitis. *Am J Trop Med Hyg*. 2007;76:964–966.

45. Ferrari TSA, Moreira PR. Neuroschistosomiasis: clinical symptoms and pathogenesis. *Lancet Neurol*. 2011;10:853–864.

46. King CH, Dickman K, Tisch DJ. Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet*. 2005;365:1561–1569.

46a. Ezeamama AE, Bustinduy AL, Nkwata AK, et al. Cognitive deficits and educational loss in children with schistosome infection—a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2018;12:e0005524.

47. Friedman JF, Mital P, Kanzaria HK, et al. Schistosomiasis and pregnancy. *Trends Parasitol*. 2007;23:159–164.

48. King CH, Dangerfield-Cha M. The unacknowledged impact of chronic schistosomiasis. *Chronic Illn*. 2008;4:65–79.

49. Prata A. Disease in *Schistosomiasis mansoni* in Brazil. In: Mahmoud AAF, ed. *Schistosomiasis*. London: Imperial College Press; 2001:297–332.

50. Olveda RM. Disease in *Schistosomiasis japonica*. In: Mahmoud AAF, ed. *Schistosomiasis*. London: Imperial College Press; 2001:361–390.

51. Lamyman MJ, Noble DJ, Narang S, et al. Small bowel obstruction secondary to intestinal schistosomiasis. *Trans R Soc Trop Med Hyg*. 2006;100:885–887.

52. Salim OEH, Hamid HK, Mekki SO, et al. Colorectal carcinoma associated with schistosomiasis: a possible causal relationship. *World J Surg Oncol*. 2010;8:68.

52a. Hamid HKS. *Schistosoma japonicum*-associated colorectal cancer: a review. *Am J Trop Med Hyg*. 2019;100:501–505.

53. Mies S, Neto OB, Beear A Jr. Systemic and hepatic hemodynamics in hepatosplenic Manson's schistosomiasis with and without propranolol. *Dig Dis Sci*. 1997;42:751–761.

54. Abruzzi A, Fried B, Alikhan SB. Coinfection of *Schistosoma* species with hepatitis B or hepatitis C viruses. *Adv Parasitol*. 2016;91:111–231.

55. King CH. Disease due to *Schistosoma mekongi, S. intercalatum* and other schistosome species. In: Mahmoud AAF, ed. *Schistosomiasis*. London: Imperial College Press; 2001:391–412.

56. Muth S, Sayasone S, Odermatt-Biays S. *Schistosoma mekongi* in Cambodia and Lao People's Democratic Republic. *Adv Parasitol*. 2010;72:179–203.

57. King CH. Disease in *Schistosomiasis haematobia*. In: Mahmoud AAF, ed. *Schistosomiasis*. London: Imperial College Press; 2001:265–295.

58. Khalaf I, Shokeir A, Shalaby M. Urologic complications of genitourinary schistosomiasis. *World J Urol*. 2012;30:31–38.

59. Christinet V, Lazdins-Helds JK, Stothard JR, et al. Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease. *Int J Parasitol*. 2016;46:395–404.

60. Miller-Fellows SC, Howard L, Kramer R, et al. Cross-sectional interview study of fertility, pregnancy, and urogenital schistosomiasis in coastal Kenya: documented treatment in childhood is associated with reduced odds of subfertility among adult women. *PLoS Negl Trop Dis*. 2017;11:e0006101.

61. Kjetland EF, Hegertun IE, Baay MF, et al. Genital schistosomiasis and its unacknowledged role on HIV transmission in the STD intervention studies. *Int J STD AIDS*. 2014;25:705–715.

62. Schwartz E, Pick N, Shazberg G, et al. Hematospermia due to schistosome infection in travelers: diagnostic and treatment challenges. *Clin Infect Dis*. 2002;35:1420–1424.

63. Abdel-Naser MB, Altenburg A, Zouboulis CC, et al. Schistosomiasis (bilharziasis) and male infertility. *Andrologia*. 2018;51:e13165.

64. Ishida K, Hsieh MH. Understanding urogenital schistosomiasis-related bladder cancer: an update. *Front Med (Lausanne)*. 2018;5:223.

65. Gavilanes F, Fernandes CJ, Souza R. Pulmonary arterial hypertension in schistosomiasis. *Curr Opin Pulm Med*. 2016;22:408–414.

66. Papamatheakis DG, Mocumbi AO, Kim NH, et al. Schistosomiasis-associated pulmonary hypertension. *Pulm Circ*. 2014;4:596–611.

67. Barsoum R. The changing face of schistosomal glomerulopathy. *Kidney Int*. 2004;66:2472–2484.

68. dos-Santos WL, Sweet GM, Bahiense-Oliveira M, et al. Schistosomal glomerulopathy and changes in the distribution of histological patterns of glomerular diseases in Bahia, Brazil. *Mem Inst Oswaldo Cruz*. 2011;106:901–904.

69. Ross AG, McManus DP, Farrar J, et al. Neuroschistosomiasis. *J Neurol*. 2012;259:22–32.

70. Young SW, Higashi G, Kamel R, et al. Interaction of salmonellae and schistosomes in host parasite relations. *Trans R Soc Trop Med Hyg*. 1973;67:797–802.

71. Hsiao A, Toy T, Seo HJ, et al. Interaction between *Salmonella* and schistosomiasis: a review. *PLoS Pathog*. 2016;12:e1005928.

72. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet*. 2000;355:887–891.

73. Secor WE. The effects of schistosomiasis on HIV/AIDS infection, progression and transmission. *Curr Opin HIV AIDS*. 2012;7:254–259.

73a. Wall KM, Kilembe W, Vwalika B, et al. Schistosomiasis is associated with incident HIV transmission and death in Zambia. *PLoS Negl Trop Dis*. 2018;12:e0006902.
74. Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV in rural Zimbabwe: effect of treatment of schistosomiasis on CD4 cell count and plasma HIV-1 RNA load. *J Infect Dis*. 2005;192:1956–1961.
75. Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV in rural Zimbabwe: efficacy of treatment of schistosomiasis in individuals with HIV co-infection. *Clin Infect Dis*. 2006;42:1781–1789.
76. Goovaerts O, Mwinzi PNM, Muok EMO, et al. Aberrant plasma MMP and TIMP dynamics in *Schistosoma*-immune reconstitution inflammatory syndrome (IRIS). *PLoS Negl Trop Dis*. 2018;12:e0006710.
77. Weerakoon KGAD, Gobert GN, Cai P, et al. Advances in the diagnosis of human schistosomiasis. *Clin Microbiol Rev*. 2015;28:939–967.
78. Sousa-Figueiredo JC, Betson M, Kabatereine NB, et al. The urine circulating cathodic antigen (CCA) dipstick: a valid substitute for microscopy for mapping and point-of-care diagnosis of intestinal schistosomiasis. *PLoS Negl Trop Dis*. 2013;7:e2008.
79. He P, Gordon CA, Williams GM, et al. Real-time PCR diagnosis of *Schistosoma japonicum* in low transmission areas of China. *Infect Dis Poverty*. 2018;7:8.
80. Al-Shehri H, Koukounari A, Stanton MC, et al. Surveillance of intestinal schistosomiasis during control: a comparison of four diagnostic tests across five Ugandan primary schools in the Lake Albert region. *Parasitology*. 2018;145:1715–1722.
81. Wichmann D, Poppert S, Von Thien H, et al. Prospective European-wide multicentre study on a blood-based real-time PCR for the diagnosis of acute schistosomiasis. *BMC Infect Dis*. 2013;13:55.
82. Tsang VC, Wilkins PP. Immunodiagnosis of schistosomiasis. *Immunol Invest*. 1997;26:175–186.
82a. Röser D, Bjerrum S, Helleberg M, et al. Adventure tourism and schistosomiasis: serology and clinical findings in a group of Danish students after white-water rafting in Uganda. *JMM Case Rep*. 2018;5:e005141.
83. Medhat A, Zarzoura A, Nafeh M, et al. Evaluation of an ultrasonographic score for urinary bladder morbidity in *Schistosoma hematobium* infection. *Am J Trop Med Hyg*. 1997;57:16–19.
84. Richter J, Botelho MC, Holtfreter MC, et al. Ultrasound assessment of schistosomiasis. *Z Gastroenterol*. 2016;54:653–660.
85. Olveda DU, Inobaya M, Olveda RM, et al. Diagnosing schistosomiasis-induced liver morbidity: implications for global control. *Int J Infect Dis*. 2017;54:138–144.
86. Berhe N, Myrvang B, Gundersen SG. Reversibility of schistosomal periportal thickening/fibrosis after praziquantel therapy: a twenty month follow-up study in Ethiopia. *Am J Trop Med Hyg*. 2008;78:228–234.
87. Richter J. The impact of chemotherapy on morbidity due to schistosomiasis. *Acta Trop*. 2003;86:161–183.
88. Kjetland EF, Ndhlovu PD, Kurewa EN, et al. Prevention of gynecologic contact bleeding and genital sandy patches by childhood anti-schistosomal treatment. *Am J Trop Med Hyg*. 2008;79:79–83.
89. King CH, Olbrych S, Soon M, et al. Utility of repeated praziquantel dosing in the treatment of schistosomiasis in high-risk communities in Africa: a systematic review. *PLoS Negl Trop Dis*. 2011;5:e1321.
89a. Secor WE, Colley DG. When should the emphasis on schistosomiasis control move to elimination? *Trop Med Infect Dis*. 2018;3:85.
90. Vale N, Gouveia MJ, Rinaldi G, et al. Praziquantel for schistosomiasis: single-drug metabolism revisited, mode of action, and resistance. *Antimicrob Agents Chemother*. 2017;61:e02582-16.
91. Zwang J, Olliaro P. Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: a meta-analysis. *Parasit Vectors*. 2017;10:47.
92. Wu W, Wang W, Huang Y. New insights into praziquantel against various developmental stages of schistosomes. *Parasitol Res*. 2011;109:1501–1507.
92a. Mutapi F, Maizels R, Fenwick A, et al. Human schistosomiasis in the post mass drug administration era. *Lancet Infect Dis*. 2017;17:e42–e48.
93. Grandiere-Perez L, Ansart S, Paris L, et al. Efficacy of praziquantel during the incubation and invasive phase of *Schistosoma haematobium* schistosomiasis in 18 travellers. *Am J Trop Med Hyg*. 2006;74:814–818.
94. Ismail M, Botros S, Metwally A, et al. Resistance to praziquantel: direct evidence from *Schistosoma mansoni* isolated from Egyptian villagers. *Am J Trop Med Hyg*. 1999;60:932–935.
95. Alonso D, Munoz J, Gascon J, et al. Failure of standard treatment with praziquantel in two returned travelers with *Schistosoma haematobium* infection. *Am J Trop Med Hyg*. 2006;74:342–344.
96. Osakunor DNM, Woolhouse MEJ, Mutapi F. Paediatric schistosomiasis: what we know and what we need to know. *PLoS Negl Trop Dis*. 2018;12:e00061444.
97. Friedman JF, Olveda RM, Mirochnick MH, et al. Praziquantel for the treatment of schistosomiasis during human pregnancy. *Bull World Health Organ*. 2018;96:59–65.
98. Ndibazza J, Muhangi L, Akishule D, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: a randomized controlled trial. *Clin Infect Dis*. 2010;50:531–540.
99. Olveda RM, Acosta LP, Tallo V, et al. Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2016;16:199–208.
100. Danso-Appiah A, Olliaro PL, Donegan S, et al. Drugs for treating *Schistosoma mansoni* infection. *Cochrane Database Syst Rev*. 2013;(2):CD000528.
101. Utzinger J, Keiser J, Shuhua X, et al. Combination chemotherapy of schistosomiasis in laboratory studies and clinical trials. *Antimicrob Agents Chemother*. 2003;47:1487–1495.
102. Pérez del Villar L, Burguillo FJ, López-Abán J. Systematic review and meta-analysis of artemisinin based therapies for the treatment and prevention of schistosomiasis. *PLoS ONE*. 2012;7:e45867.
103. Bergquist R, Elmorshedy H. Artemether and praziquantel: origin, mode of action, impact, and suggested application for effective control of human schistosomiasis. *Trop Med Infect Dis*. 2018;3:125.
104. Keiser J, N'Guessan NA, Adoubryn KD, et al. Efficacy of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium*; randomized, exploratory open-label trial. *Clin Infect Dis*. 2010;50:1205–1213.
105. Hou X-Y, McManus DP, Gray DJ, et al. A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute *Schistosomiasis japonica* in China. *Bull World Health Organ*. 2008;86:788–795.
106. Jaureguiberry S, Caumes E. Neurological involvement during Katayama syndrome. *Lancet Infect Dis*. 2008;8:9–10.
107. Bergquist R, Utzinger J, Keiser J. Controlling schistosomiasis with praziquantel: how much longer without a viable alternative? *Infect Dis Poverty*. 2017;6:74.
108. Grimes JET, Croll D, Harrison WE, et al. The roles of water, sanitation and hygiene in reducing schistosomiasis: a review. *Parasit Vectors*. 2015;8:156.
109. Campbell SJ, Biritwum NK, Woods G, et al. Tailoring water, sanitation, and hygiene (WASH) targets for soil-transmitted helminthiasis and schistosomiasis control. *Trends Parasitol*. 2018;34:53–63.
110. Andrade G, Bertsch DJ, Andrea Gazzinelli A, et al. Decline in infection-related morbidities following drug-mediated reductions in the intensity of *Schistosoma* infection: a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2017;11:e0005372.
111. Wang LD, Chen HG, Guo JG, et al. A strategy to control transmission of *Schistosoma japonicum* in China. *N Engl J Med*. 2009;360:121–128.
112. Sun LP, Wang W, Hong QB, et al. Approaches being used in the national schistosomiasis elimination programme in China: a review. *Infect Dis Poverty*. 2017;6:55.
112a. Sokolow SH, Huttinger E, Jouanard N, et al. Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host. *Proc Natl Acad Sci U S A*. 2015;112:9650–9655.
112b. Lo NC, Gurarie D, Yoon N, et al. Impact and cost-effectiveness of snail control to achieve disease control targets for schistosomiasis. *Proc Natl Acad Sci U S A*. 2018;115:e584–e591.
113. Tebeje BM, Harvie M, You H, et al. Schistosomiasis vaccines: where do we stand? *Parasit Vectors*. 2016;9:528.
114. Siddiqui AA, Siddiqui SZ. Sm-p80-Based schistosomiasis vaccine: preparation for human clinical trials. *Trends Parasitol*. 2017;33:194–201.
115. Fürst T, Duthaler U, Sripa B, et al. Trematode infections: liver and lung flukes. *Infect Dis Clin North Am*. 2012;26:399–419.
116. Toledo R, Esteban JG, Fried B. Current status of food-borne trematode infections. *Eur J Clin Microbiol Infect Dis*. 2012;31:1705–1718.
116a. Harrington D, Lamberton PHL, McGregor A. Human liver flukes. *Lancet Gastroenterol Hepatol*. 2017;2:680–689.
117. Mordvinov VA, Yurlova NI, Ogorodova LM, et al. *Opisthorchis felineus* and *Metorchis bilis* are the main agents of liver fluke infection of humans in Russia. *Parasitol Int*. 2012;61:25–31.
118. Azmoudeh-Ardalan F, Soleimani V, Jahanbin B. *Dicrocoelium dentriticum* in explanted liver: report of an unusual finding. *Exp Clin Transplant*. 2017;15(suppl 1):178–181.
119. Khalil G, Haddad C, Otrock ZK, et al. Halzoun, an allergic pharyngitis syndrome in Lebanon: the trematode *Dicrocoelium dendriticum* as an additional cause. *Acta Trop*. 2013;125:115–118.
120. Moure Z, Zarzuela F, Espasa M, et al. *Dicrocoelium dendriticum*: an unusual parasitological diagnosis in a reference international health unit. *Am J Trop Med Hyg*. 2017;96:355–357.
121. Sripa B, Tesana S, Yurlova N, et al. A historical review of small liver fluke infections in humans. *Parasitol Int*. 2017;66:337–340.
122. Qian MB, Utzinger J, Keiser J, et al. Clonorchiasis. *Lancet*. 2016;387:800–810.
123. Hung NM, Madsen H, Fried B. Global status of fish-borne zoonotic trematodiasis in humans. *Acta Parasitol*. 2013;58:231–258.
124. Pakharukovaa MY, Mordvinov VA. The liver fluke *Opisthorchis felineus*: biology, epidemiology and carcinogenic potential. *Trans R Soc Trop Med Hyg*. 2016;110:28–36.
125. Tang ZL, Huang Y, Yu XB. Current status and perspectives of *Clonorchis sinensis* and clonorchiasis: epidemiology, pathogenesis, omics, prevention and control. *Infect Dis Poverty*. 2016;5:71.
126. Chan HH, Lai KH, Lo GH, et al. The clinical and cholangiographic picture of hepatic clonorchiasis. *J Clin Gastroenterol*. 2002;34:183–186.
127. Xia J, Jiang SC, Peng HJ. Association between liver fluke infection and hepatobiliary pathological changes: a systematic review and meta-analysis. *PLoS ONE*. 2015;10:e0132673.
128. Saichua P, Sithithaworn P, Jariwala AR, et al. Microproteinuria during *Opisthorchis viverrini* infection: a biomarker for advanced renal and hepatobiliary pathologies from chronic opisthorchiasis. *PLoS Negl Trop Dis*. 2013;7:e2228.
129. Zheng S, Zhu Y, Zhao Z, et al. Liver fluke infection and cholangiocarcinoma: a review. *Parasitol Res*. 2017;116:11–19.
130. Sripa B, Brindley PJ, Mulvenna J, et al. The tumorigenic liver fluke *Opisthorchis viverrini*-multiple pathways to cancer. *Trends Parasitol*. 2012;28:395–407.
131. Lim JH, Kim SY, Park CM. Parasitic diseases of the biliary tract. *AJR Am J Roentgenol*. 2007;188:1596–1603.
131a. Worasith C, Kamamia C, Yakovleva A, et al. Advances in the diagnosis of human opisthorchiasis: development of *Opisthorchis viverrini* antigen detection in urine. *PLoS Negl Trop Dis*. 2015;9:e0004157.
131b. Li HM, Qian MB, Yang YC, et al. Performance evaluation of existing immunoassays for *Clonorchis sinensis* infection in China. *Parasit Vectors*. 2018;11:35.
132. Keiser J, Duthaler U, Utzinger J. Update on the diagnosis and treatment of food-borne trematode infections. *Curr Opin Infect Dis*. 2010;23:513–520.
133. Buathong S, Leelayoova S, Mungthin M, et al. Molecular discrimination of Opisthorchis-like eggs from residents in a rural community of central Thailand. *PLoS Negl Trop Dis*. 2017;11:e0006030.
134. Sayasone S, Meister I, Andrews JR, et al. Efficacy and safety of praziquantel against light infections of *Opisthorchis viverrini*: a randomized parallel single-blind dose-ranging trial. *Clin Infect Dis*. 2017;64:451–458.
135. Qian MB, Yap P, Yang YC, et al. Efficacy and safety of tribendimidine against *Clonorchis sinensis*. *Clin Infect Dis*. 2013;56:e76–e82.
136. Viravan C, Bunnag D, Harinasuta T, et al. Clinical field trial of praziquantel in opisthorchiasis in Nong Rangya Village, Khon Kaen Province, Thailand. *Southeast Asian J Trop Med Public Health*. 1986;17:63.
137. Vivatanasesth P, Sornmani S, Schelp FP, et al. Mass treatment of opisthorchiasis in Northeast Thailand. *Southeast Asian J Trop Med Public Health*. 1982;13:609.
138. Cwiklinski K, O'Neill SM, Donnelly S, et al. A prospective view of animal and human fasciolosis. *Parasite Immunol*. 2016;38:558–568.
139. Esteban JG, Flores A, Angles R, et al. High endemicity of human fascioliasis between Lake Titicaca and La Paz Valley, Bolivia. *Trans R Soc Trop Med Hyg*. 1999;93:151–156.
140. Estaban JG, Gonzalez C, Curtale F, et al. Hyperendemic fascioliasis associated with schistosomiasis in villages in the Nile Delta of Egypt. *Am J Trop Med Hyg*. 2003;69:429–437.
141. Fried BF, Abruzzi A. Food-borne trematode infections of humans in the United States of America. *Parasitol Res*. 2010;106:1263–1280.
142. Ashrafi K, Bargues MD, O'Neill S, et al. Fascioliasis: a worldwide parasitic disease of importance in travel medicine. *Travel Med Infect Dis*. 2014;12:636–649.

143. Weisenberg SA, Perlada DE. Case report: domestically acquired fascioliasis in northern California. *Am J Trop Med Hyg*. 2013;89:588–591.
144. Chen J-X, Chen M-X, Ai L, et al. An outbreak of human fascioliasis gigantica in Southwest China. *PLoS ONE*. 2013;8:e71520.
144a. Cabada MM, Goodrich MR, Graham B, et al. Fascioliasis and eosinophilia in the highlands of Cuzco, Peru and their association with water and socioeconomic factors. *Am J Trop Med Hyg*. 2014;91:989–993.
145. Pulpeiro JR, Armesto V, Varela J, et al. Fascioliasis: findings in 15 patients. *Br J Radiol*. 1991;64:798–801.
146. Patel NU, Bang TJ, Dodd GD III. CT findings of human *Fasciola hepatica* infection: case reports and review of the literature. *Clin Imaging*. 2016;40:251–255.
147. Han JK, Han D, Choi BL, et al. MR findings in human fascioliasis. *Trop Med Int Health*. 1996;1:367–372.
148. Cosme A, Ojeda E, Poch M, et al. Sonographic findings of hepatic lesions in human fascioliasis. *J Clin Ultrasound*. 2003;31:358–363.
149. Cevikol C, Karaali K, Senol U, et al. Human fascioliasis: MR imaging findings of hepatic lesions. *Eur Radiol*. 2003;13:141–148.
150. Lopez M, White AC Jr, Cabada MM. Burden of *Fasciola hepatica* infection among children from Paucartambo in Cusco, Peru. *Am J Trop Med Hyg*. 2012;86:481–485.
151. Ishikawa T, Stephenson VM, Heitman SJ. Biliary obstruction caused by the liver fluke, *Fasciola hepatica*. *CMAJ*. 2016;188:524–526.
152. Dolay K, Hasbahçeci M, Hatipoğlu E, et al. Endoscopic diagnosis and treatment of biliary obstruction due to acute cholangitis and acute pancreatitis secondary to *Fasciola hepatica* infection. *Ulus Travma Acil Cerrahi Derg*. 2018;24:71–73.
153. Kaya M, Bestas R, Cetin S. Clinical presentation and management of *Fasciola hepatica* infection: single-center experience. *World J Gastroenterol*. 2011;17:4899.
154. Xuan le T, Hung NT, Waikagul J. Cutaneous fascioliasis: a case report in Vietnam. *Am J Trop Med Hyg*. 2005; 72:508.
155. Dalimi A, Jabarvand M. *Fasciola hepatica* in the human eye. *Trans R Soc Trop Med Hyg*. 2005;99:798.
156. Hillyer GV, De Galanes MS, Rodriguez Perez J, et al. Use of the Falcon assay screening test enzyme-linked immunosorbent assay (FAST-ELISA) and the enzyme-linked immunoelectro-transfer blot (ElTB) to determine the prevalence of human fascioliasis in the Bolivian Altiplano. *Am J Trop Med Hyg*. 1992;46:603–609.
157. Shin SH, Hsu A, Chastain HM. Development of two FhSAP2 recombinant–based assays for immunodiagnosis of human chronic fascioliasis. *Am J Trop Med Hyg*. 2016;95:852–855.
158. Le TH, Nguyen KT, Nguyen NT, et al. Development and evaluation of a single-step duplex PCR for simultaneous detection of *Fasciola hepatica* and *Fasciola gigantica* (family Fasciolidae, class Trematoda, phylum Platyhelminthes). *J Clin Microbiol*. 2012;50:2720–2726.
159. Cabada MM, Malaga JL, Castellanos-Gonzalez A, et al. Recombinase polymerase amplification compared to real-time polymerase chain reaction test for the detection of *Fasciola hepatica* in human stool. *Am J Trop Med Hyg*. 2017;96:341–346.
160. Millan JC, Mull R, Freise S, et al. The efficacy and tolerability of triclabendazole in Cuban patients with latent and chronic *Fasciola hepatica* infection. *Am J Trop Med Hyg*. 2000;63:264–269.
161. Richter J, Freise S, Mull R, et al. Fascioliasis: sonographic abnormalities of the biliary tract and evolution after treatment with triclabendazole. *Trop Med Int Health*. 1999;4:774–781.
161a. Kelley JM, Elliott TP, Beddoe T, et al. Current threat of triclabendazole resistance in *Fasciola hepatica*. *Trends Parasitol*. 2016;32:458–469.
161b. Cabada MM, Lopez M, Cruz M, et al. Treatment failure after multiple courses of triclabendazole among patients with fascioliasis in Cusco, Peru: a case series. *PLoS Negl Trop Dis*. 2016;10:e0004361.
162. Zumaquero-Rios JL, Sarracent-Pérez J, Rojas-Garcia R, et al. Fascioliasis and intestinal parasitoses affecting schoolchildren in Atlixco, Puebla State, Mexico: epidemiology and treatment with nitazoxanide. *PLoS Negl Trop Dis*. 2013;7:e2553.
163. Favennec L, Jave Ortiz J, Gargala G, et al. Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of fascioliasis in adults and children from northern Peru. *Aliment Pharmacol Ther*. 2003;17:265–270.
164. Lama NS, Longa X, Sub XZ, et al. Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis. *Pharmacol Res*. 2018;133:77–100.
165. Keiser J, Sayed H, el-Ghanam M, et al. Efficacy and safety of artemether in the treatment of chronic fascioliasis in Egypt: exploratory phase-2 trials. *PLoS Negl Trop Dis*. 2011;5:e1285.
166. Fürst T, Sayasone S, Odermatt P, et al. Manifestation, diagnosis, and management of foodborne trematodiasis. *BMJ*. 2012;314:e4093.
167. Chai J-Y, Shin E-H, Lee S-H, et al. Foodborne intestinal flukes in Southeast Asia. *Korean J Parasitol*. 2009;47(suppl):S69–S102.
168. Graczyk TK, Gilman RH, Fried B. Fasciolopsiasis: is it a controllable food-borne disease? *Parasitol Res*. 2001;87:80–83.
168a. Saurabh K, Ranjan S. Fasciolopsiasis in children: clinical, sociodemographic profile and outcome. *Indian J Med Microbiol*. 2017;35:551–554.
168b. Cao YH, Ma YM, Qiu F, et al. Rare cause of appendicitis: mechanical obstruction due to *Fasciolopsis buski* infestation. *World J Gastroenterol*. 2015;21:3146–3149.
168c. Sarma MS, Yachha SK, Srivastava A, et al. Endoscopic extraction of *Fasciolopsis buski* presenting as acute upper GI bleeding in a child. *Gastrointest Endosc*. 2015;82:743.
169. Belizario VY Jr, Bersabe MJ, de Leon WU, et al. Intestinal heterophydiasis: an emerging food-borne parasitic zoonosis in southern Philippines. *Southeast Asian J Trop Med Public Health*. 2001;32(suppl 2):36–42.
170. Wongsawad C, Phalee A, Noikong W, et al. Co-infection with *Opisthorchis viverinni* and *Haplorchis taichui* detected by human fecal examination in Chomtong district, Chiang Mai Province, Thailand. *Parasitol Int*. 2012;61:56–59.
171. Lamaningao P, Kanda S, Laimanivong S, et al. Development of a PCR assay for diagnosing trematode (*Opisthorchis* and *Haplorchis*) infections in human stools. *Am J Trop Med Hyg*. 2017;96:221–228.
172. Watthanakulpanich D, Waikagul J, Maipanich W, et al. *Haplorchis taichui* as a possible etiologic agent of irritable bowel syndrome–like symptoms. *Korean J Parasitol*. 2010;3:225–229.
173. Woon-Mok S, Chai J-Y, Yong T-S, et al. *Echinostoma revolutum* infection in children, Pursat Province, Cambodia. *Emerg Infect Dis*. 2011;17:117–119.
173a. Toledo R, Esteban JG. An update on human echinostomiasis. *Trans R Soc Trop Med Hyg*. 2016;110:37–45.
173b. Sah R, Khadka S, Hamal R, et al. Human echinostomiasis: a case report. *BMC Res Notes*. 2018;11:17.
173c. Chunge RN, Chunge CN. Infection with *Echinostoma* sp. in a group of travellers to Lake Tanganyika, Tanzania, in January 2017. *J Travel Med*. 2017;24:1–3.
174. Thaenkhaem U, Phuphisut O, Pakdee W, et al. Rapid and simple identification of human pathogenic heterophyid intestinal fluke metacercariae by PCR-RFLP. *Parasitol Int*. 2011;60:503–506.
175. Blair D, Xu ZB, Agatsuma T. Paragonimiasis and the genus *Paragonimus*. *Adv Parasitol*. 1999;42:113–222.
176. Procop GW. North American paragonimiasis (caused by *Paragonimus kellicotti*) in the context of global paragonimiasis. *Clin Microbiol Rev*. 2009;22:415–446.
177. Diaz JH. Paragonimiasis acquired in the United States: native and nonnative species. *Clin Microbiol Rev*. 2013;26:493–504.
178. Lane MA, Marcos LA, Onen NF, et al. *Paragonimus kellicotti* fluke infections in Missouri, USA. *Emerg Infect Dis*. 2012;18:1263–1267.
178a. Yoshida A, Matsuo K, Moribe J, et al. Venison, another source of *Paragonimus westermani* infection. *Parasitol Int*. 2016;65:607–612.
179. Kagawa FT. Pulmonary paragonimiasis. *Semin Respir Infect*. 1997;12:149–158.
180. Im JG, Chang KH, Reeder MM. Current diagnostic imaging of pulmonary and cerebral paragonimiasis with pathological correlation. *Semin Roentgenol*. 1997;32:301–324.
181. Henry TS, Lane MA, Weil GJ, et al. Chest CT features of North American paragonimiasis. *AJR Am J Roentgenol*. 2012;198:1076–1083.
182. Song JU, Um SW, Koh WJ, et al. Pulmonary paragonimiasis mimicking lung cancer in a tertiary referral centre in Korea. *Int J Tuberc Lung Dis*. 2011;15:674–679.
183. Chen J, Chen Z, Lin J, et al. Cerebral paragonimiasis: a retrospective analysis of 89 cases. *Clin Neurol Neurosurg*. 2013;115:546–551.
183a. Bahr NC, Trotman RL, Samman H, et al. Eosinophilic meningitis due to infection with *Paragonimus kellicotti*. *Clin Infect Dis*. 2017;64:1271–1274.
183b. Xia Y, Chen J, Ju Y, et al. Characteristic CT and MR imaging findings of cerebral paragonimiasis. *J Neuroradiol*. 2016;43:200–206.
184. Lu C, Hu Y, Chen W. Characteristic MR and CT imaging findings of hepatobiliary paragonimiasis and their pathologic correlations. *Acta Radiol*. 2012;53: 481–484.
184a. Liang T, Liang G, Du Y, et al. Scrotal paragonimiasis in adults: two case reports and review of literature. *Medicine (Baltimore)*. 2018;97:1–4.
185. Mukae O, Taniguchi H, Ashitani J, et al. Case report: paragonimiasis westermani with seroconversion from immunoglobulin (Ig) M to IgG antibody with the clinical course. *Am J Trop Med Hyg*. 2001;65:837–839.
186. Slemenda SB, Maddison SE, Jong EC, et al. Diagnosis of paragonimiasis by immunoblot. *Am J Trop Med Hyg*. 1988;39:469–471.
187. Calvopina M, Guderian RH, Paredes W, et al. Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg*. 1998;92:566–569.
188. Fischer PU, Curtis KC, Folk SM, et al. Serological diagnosis of North American paragonimiasis by Western blot using *Paragonimus kellicotti* adult worm antigen. *Am J Trop Med Hyg*. 2013;88:1035–1040.
189. Kyung SY, Cho YK, Kim YJ, et al. A paragonimiasis patient with allergic reaction to praziquantel and resistance to triclabendazole: successful treatment after desensitization to praziquantel. *Korean J Parasitol*. 2011;49:73–77.
190. World Health Organization (WHO). *Report of the WHO Expert Consultation on Foodborne Trematode Infections and Taeniasis/Cysticercosis*. Geneva: WHO; 2011.