8.11.4 Intestinal trematode infections 1562

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infections Alastair McGregor ESSENTIALS It is notoriously difficult to estimate the prevalence of intestinal trematode infection. The most widely accepted figures suggest that 40–50 million people worldwide are infected with at least one of these organisms. The great majority of infections are found in trop- ical South and East Asia, mostly as a result of local culinary prac- tice. The incidence of trematode infections is probably changing as a result of migration, increased transportation, altered dietary habits, and other factors. The most important intestinal flukes are Fasciolopsis buski and members of the families Echinostomatidae and Heterophyidae. As with all the flukes, these parasites have com- plicated lifecycles with a definitive host (which can be human) and two intermediate hosts. The first intermediate host is generally a snail. Infection is acquired through the ingestion of the second intermediate host—undercooked freshwater fish, molluscs, frogs, or vegetation contaminated with live metacercariae. Fasciolopsis buski, one of the largest (at 20–77 mm) and most important flukes, is acquired by ingestion of contaminated water plants.

Heavy in- fections may cause abdominal discomfort and diarrhoea, but most infections are entirely asymptomatic. Diagnosis of intestinal trematodiasis is with microscopy of faecal concentrates for ova, but it is extremely difficult to distinguish the eggs of organisms within the same family. Praziquantel is the drug of choice for all of these infections, which can be prevented by thoroughly cooking poten- tially infected foodstuffs. Introduction Parasitic trematodes are divided according to their target organ into blood, liver, lung, and intestinal flukes. With the exception of blood flukes (Schistosoma spp.), infections with these para- sites are together classed as the food-borne trematodiases and are recognized as a neglected tropical disease by the World Health Organization. Approximately 76 species of intestinal fluke belonging to 14 fam- ilies have been recorded as parasites of humans, making intestinal flukes the largest and most diverse group within the food-borne trematodes. In clinical terms, however, they are probably the least important members given the often benign nature of infection and the association of other flukes (Clonorchis, Opisthorcis, and Schistosoma spp.) with cancers. Intestinal trematode infections are widespread but are most common in Asia. The lifecycles of these organisms are complex and fascinating. The definitive host acquires infection through the in- gestion of food containing metacercariae, a stage in which the larva is dormant and encysted. The vector is most commonly a fresh- water fish, mollusc, or amphibian, although some species encyst on aquatic plants. Infections occur when these metacercariae are not killed during food preparation, which may be because the food is eaten raw or undercooked, or because processing (smoking, drying, pickling) does not kill the encysted parasites. Metacerceriae mature into adult flukes in the definitive host. Ova from these flukes ma- ture into miracidia if they find themselves in water once excreted in the faeces of the definitive host. The parasite passes through the first intermediate host (a snail) and then encysts in the second, awaiting ingestion by the definitive host. In general, the severity of symptoms relates to the parasite burden, which is entirely the product of the numbers of ingested metacercariae. Symptoms are nonspecific and include abdominal discomfort and diarrhoea. Most infected individuals are asymptom- atic and might only be identified when screened. Diagnosis The diagnosis of intestinal fluke infections is usually based on recovery of eggs from stools. Unfortunately, ova from species within a given family often look very similar and it may only be possible when using routine laboratory methods to identify an in- fection to family level such as a heterophyid or echinostomatid egg. Definitive identification requires recovery of adult worms expelled after anthelmintic treatment. Identifying characteristics are provided in parasitology texts although taxonomy is confusing and many of these trematodes have been named on more than one occasion.

8.11.4 Intestinal trematode infections 1563 Treatment Praziquantel has been shown to be effective with several of these in- fections and is the drug of first choice. It is given in a dose of 20 mg/ kg orally after a meal, perhaps repeated once or twice. Flukes are usu- ally expelled the following day. The role of triclabendazole, which is the drug of choice for Fasciola spp. is not yet clear. Other alternatives which are less likely to be effective include niclosamide 150 mg/kg orally for 1 or 2 days and albendazole 200 mg orally for 2 days. Prevention These fluke infections can be prevented by thoroughly cooking po- tentially infected foodstuffs. Echinostomiasis This term covers infections with flukes of the family Echinostomatidae. There are more than 30 genera in this family and nearly 20 species have been reported to infect humans (Table 8.11.4.1). These spe- cies vary in size from 1 to 20 mm in length. Echinostomes live in the intestines of various birds and mammals. Eggs are passed in the stools and the miracidium develops, hatches and enters a snail (the first intermediate host) when these eggs reach water. Within the snail, the parasite then develops

through the stages of sporo- cyst, mother rediae, and daughter rediae, and eventually cercariae. The cercariae leave the snail and in turn infect second intermediate hosts to become encysted metacercariae. Suitable hosts vary with the species of fluke but include various species of gastropod snails, bivalves, frogs and fish, or they encyst on vegetation. Humans are infected after ingestion of inadequately cooked food containing these metacercariae. In humans, mature worms live in the small bowel, particularly the jejunum, where they may cause a variable amount of mucosal damage. Heavy worm loads may cause abdominal discomfort, flatu- lence, and diarrhoea. Eggs (80–150 × 50–75 µm in size) are passed in the stools (Fig. 8.11.4.1). They are yellow-brown, ellipsoidal, thin-shelled, and operculate and contain an immature embryo; they cannot be reliably differentiated from each other or from those of the intestinal fluke Fasciolopsis buski or the liver flukes Fasciola hepatica and F. gigantica. Table 8.11.4.1 Intestinal trematodes belonging to the family Echinostomatidae that infect humans Species Geographical distribution Definitive hosts other than humans Source of infection Size of adults (mm) Size of eggs (µm) Acanthoparyphium tyosenense Korea Birds Freshwater molluscs 2–4 × 0.5–0.7 84–110 × 60–69 Artyfechinostomum (Paryphostomum) malayanum India, South East Asia Rats, pigs Freshwater snails 4.8–8.4 × - 96 × 64 Echinochasmus fujianensis (= liliputanus) East Asia Dogs, cats, foxes, pigs Water, raw freshwater fish 1.5–2.1 × 0.47–0.56 Echinochasmus japonicus East Asia Cats, dogs, rodents, chickens Freshwater fish 0.6–0.9 × 0.16–0.18 77–90 × 51–57 Echinochasmus liliputanus China, Middle East Dogs, cats Freshwater fish 1.5–2 × 0.5 66–80 × 43–46 Echinochasmus perfoliatus Asia, Egypt Cats, dogs, foxes,
rats, pigs Freshwater fish 4.0–5.5 0.85–1.1 99–125 × 58–74 Echinochasmus (Echinoparyphium) recurvatum Egypt, East Asia Birds, mammals Amphibians, freshwater molluscs 1.9–7.3 × 0.4–0.9 88–111 × 54–75 Echinostoma cinetorchis East Asia Rats Amphibians, freshwater snails 5.6–21.2 × 1.3–3.7 96–100 × 61–70 Echinostoma echinatum Indonesia, Brazil Rats, birds Freshwater molluscs 13–22 × 2.5–3.0 92–124 × 65–76 Echinostoma hortense East Asia Dogs, rats Freshwater fish, amphibians 8.2–14 × 0.9–1.6 110–126 × 61–70 Echinostoma ilocanum Southeast Asia, China Dogs, rats, mice Freshwater snails 4–8 × 0.55–1.0 86–116 × 52–72 Echinostoma macrorchis Japan Rats Freshwater snails 3.3–4.2 × 0.68–0.86 81–89 × 54–58 Echinostoma malayanum Southeast Asia, China Rats Freshwater snails, tadpoles, fish 5–10 × 2.5 137 × 75.5 Echinostoma revolutum Asia Ducks, geese, chickens, rats Amphibians, freshwater molluscs 21–26 × 2.0–3.5 104–112 × 64–72 Episthmium caninum Thailand Dogs Fish 1.0–1.5 × 0.40–0.75 84 × 50–60 Himasthla muehlensi USA Birds Molluscs 11–18 × 0.41–0.67 114–149 × 62–85 Hypoderaeum conoideum Thailand Ducks, fowl Amphibians, freshwater molluscs 6–12 × 1.3–2.0 95–108 × 61–68 Isthmiophora melis Romania, China, USA Rodents and carnivores Tadpoles, fish 5.5–7.5 × 1.20 132–154 × 75–85

section 8 Infectious diseases 1564 Fasciolopsiasis This infection, caused by Fasciolopsis buski, is endemic in Asia. The adult fluke (20–70 × 8–20 mm in size; Fig. 8.11.4.2) is found in the small intestine of humans and pigs. When eggs are passed in the stools and reach water, the miracidium develops, hatches, and enters the first intermediate host, a freshwater snail of the species Segmentina, Hippeutis, and Gyraulis, among others. In the snail, the miracidium then develops through the stages of sporocyst and rediae and, after 8 weeks or so, cercariae escape from the snail. The cercariae encyst on water plants and develop into metacercariae over 4 weeks. Infection is acquired by ingestion of infected uncooked edible plants such as water caltrop (Trapa species), water chestnut Eliocharis tuberosa, water bamboo Zizania aquatica, and watercress Neptunia oleracea. Fifty years ago, it was estimated that 10 million people were in- fected with this parasite. The current prevalence is entirely unknown. Fasciolopsiasis occurs most commonly in areas where

people keep pigs and raise and eat freshwater plants. The adult worms attach themselves to the mucosa of the upper small bowel where they may cause inflammation and erosion and provoke a mucous intestinal discharge. Light infections are gener- ally asymptomatic but heavy worm burdens can be associated with anorexia, nausea, abdominal discomfort and diarrhoea, or even intestinal obstruction. Rarely, heavy infections may cause small bower perforation. Stools may be foul-smelling and contain undigested food. In severe cases, a protein-losing enteropathy is associated with ascites, generalized oedema, and prostration. Eggs (130–140 × 80–85 µm in size) are passed in the stools (Fig. 8.11.4.3). These are yellow-brown, ellipsoid, thin-shelled, and operculate and contain an immature embryo; they cannot be reli- ably differentiated from those of the intestinal echinostomes or of the liver flukes F. hepatica and F. gigantica. Heterophyiasis This term may be conveniently used to include all infections with flukes of the family Heterophyidae, although some infections are more precisely known by the generic name of the infecting organism (e.g. metagonimiasis). These are small flukes, generally less than 1 to 2 mm in length. Almost 30 species in this family have been reported to infect humans (Table 8.11.4.2). These infections are found in many places but are most common in Asia and Fig. 8.11.4.1 Egg of Echinostoma ilocanum. All echinostome eggs look similar, as do those of Fasciolopsis and Fasciola species. Courtesy of P Radomyos. Fig. 8.11.4.2 Adult Fasciolopsis buski, 6.5 cm in length. Courtesy of P Radomyos. Fig. 8.11.4.3 Egg of Fasciolopsis buski. Note its similarity to ova of Fasciola species and echinostomes. Courtesy of AR Butcher.

8.11.4 Intestinal trematode infections 1565 Egypt. Metagonimus yokogawai is believed to be the most common heterophyid infection. Heterophyids live in the intestines of various mammals and birds. When eggs are passed in the stools, they contain a ciliated mira- cidium which hatches when ingested by a freshwater or brackish- water snail, the first intermediate host. Snails susceptible to Heterophyes include Pirenella conica, Cerithidea cingulata, and Tympanotonus micropterus. Semisulcospira libertina and Thiara granifera are host to Metagonimus spp. In the snail, the miracidium then develops through the stages of sporocyst and one or two gen- erations of rediae until leaving the snail as cercariae. The cercariae in turn invade tissues of the second intermediate host, various spe- cies of freshwater or coastal salmonoid and cyprinoid fish. These include mullet (e.g. Mugil cephalus) and minnow (Gambusia spe- cies) for Heterophyes species, and carp (e.g. Carassius carrasius) and sweet fish Plecoglossus altivelis in the case of Metagonimus species. Humans are infected after ingestion of inadequately cooked fish containing metacercariae, which mature in the flesh or scales of the fish. The adult worms attach to or invade the mucosa of the upper small bowel where they may cause granulomatous inflammation and erosion. Light infections are generally asymptomatic but heavy worm burdens may be associated with anorexia, nausea, abdominal discomfort, and mucous diarrhoea. Occasionally ova deposited in the bowel wall enter blood vessels and embolize to other tissues. Eggs have been found in the heart and central ner- vous system and rarely in the blood. In cases of heterophyiasis described in the Philippines, cardiac failure was associated with subepicardial haemorrhages, myocardial damage caused by occlusion of vessels by ova, and eggs stuck to a thickened, calcified mitral valve. Neurological features include focal cerebral disturb- ances and transverse myelitis. Table 8.11.4.2 Intestinal trematodes belonging to the family Heterophyidae that infect humans Species Geographical distribution Definitive hosts other than humans Source of infection Size of adults (mm) Size of eggs (µm) Apophallus donicus USA Dogs, cats, rats, foxes, rabbits Fish 1.1–1.3 × 0.58–0.72 35 × 25 Acanthotrema felis Korea Cats Fish 0.43–0.46 × 0.27–0.29 13–15 × 25–28 Acanthotrema (Stictodora) tridactyla Arabia Cats Fish Centrocestus armatus East Asia Cats, dogs, rodents, herons

Fish 0.35–0.63 × 0.18–0.29 28–32 × 16–17 Centrocestus caninus Taiwan Dogs, cats, rats Fish 0.4–0.45 × 0.21–0.25 32–35 × 17–20 Centrocestus cuspidatus Egypt, Taiwan Chickens, rats Fish 0.5–0.8 × 0.25–0.35 30–35 × 15–20 Centrocestus formosanus East Asia Rats, cats, dogs, chickens, ducks Fish, frogs 0.42–0.47 × 0.21–0.25 0.24–0.42 × 0.21–0.25 Centrocestus kurokawai Japan Dogs, rodents (experimental) Fish 0.35–0.51 × 0.18–0.23 33–40 × 17–21 Centrocestus longus Taiwan Dogs, cats (experimental) Fish 0.6 × 0.15 41 × 22 Cryptocotyle lingua Greenland Cats, dogs, rats Fish 1.2–2.0 × 0.4–0.9 42–48 × 20–22 Haplorchis pleurolophocerca Egypt Cats Fish 0.32–0.42 × 0.14–0.17 29–32 × 15–18 Haplorchis pumilio Southeast Asia, Egypt Dogs, cats, birds Fish 0.45–0.89 × 0.2–0.4 24–28 × 12–15 Haplorchis taichui Asia Dogs, cats Fish 0.47–0.64 × 0.18–0.22 20–33 × 11–17 Haplorchis vanissimus Philippines Fish 0.38–0.51 × 0.25–0.31 25–30 × 18–21 Haplorchis yokogawai Asia Dogs, cats Fish 0.47–0.64 × 0.18–0.22 20–33 × 10–17 Heterophyes heterophyes Egypt, Asia Cats, dogs, rats, foxes, weasels, birds Fish 1.0–1.7 × 0.3–0.4 28–30 × 15–17 Heterophyes nocens East Asia Dogs, cats, rats Fish 0.9–1.1 × 0.4–0.5 28 × 15.5 Heterophyopsis continua East Asia Dogs Fish 2.0–2.1 × 0.24–0.28 25–26 × 14–16 Metagonimus minutus Taiwan Cats, mice Fish 0.43–0.50 × 0.25–0.40 21–24 × 12–15 Metagonimus miyatai Korea Fish 0.9–1.3 ×.04–0.6 28–32 × 16–19 Metagonimus takahashii Korea Dogs, cats, rats, birds Fish 0.84–1.48 × 0.42–0.72 28–34 × 17–21 Metagonimus yokogawai Asia, Europe Dogs, cats, pigs, pelicans Fish 1.0–2.5 × 0.40–0.75 26–28 × 15–17 Phagicola sp. Brazil Dogs Fish Procerovum calderoni Philippines Cats, dogs Fish 0.47–0.55 × 0.25–0.26 21–25 × 11–15 Procerovum varium Japan Cats, birds Fish 0.26–0.38 × 0.13–0.16 25–29 × 12–18 Pygidiopsis summa Korea Birds, cats, dogs, rats Fish 0.49–0.76 × 0.25–0.44 21–23 × 11–14 Stellantchasmus falcatus Asia, Hawaii Dogs, cats Fish 0.59 × 0.23 21–23 × 12–13 Stellantchasmus formosanus Taiwan Cats, rats Fish 0.32–0.56 × 0.13–0.21 18–24 × 20–22 Stellantchasmus pseudocirratus Hawaii, Philippines Dogs, cats Fish 0.3–0.6 × 0.2–0.3 18–21 × 9–12 Stictodora fuscata East Asia Cats, birds Fish 0.59 × 0.23 36–38 × 22–23 Stictodora lari Korea Seagulls Fish 0.70–0.86 × 0.27–0.36 28–37 × 17–20

section 8 Infectious diseases 1566 Eggs (20–40 × 10–20 µm in size) are passed in the stools (Fig. 8.11.4.4). They are yellow-brown, elongated, opercu- late, and contain a miracidium. Eggs of members of the family Heterophyidae cannot be reliably differentiated from each other. Furthermore, they are extremely difficult to differentiate from eggs of Clonorchis sinensis and Opisthorchis species although heterophyids tend to have a smoother egg shell and a less prom- inent shoulder at the operculum, and the abopercular knob may be absent. Other intestinal fluke infections There are another dozen or so species of intestinal flukes be- longing to various families that have been reported to infect hu- mans (Table 8.11.4.3). All appear to be very uncommon and little is known about their epidemiology, although some probably exist in pockets of hyperinfestation, exploiting peculiarities in local behavioural, culinary, and animal husbandry practices. As with other fluke infections, definitive identification depends upon recovery of adult worms, as excreted ova lack discriminatory features (Fig. 8.11.4.5). This is most commonly achieved by treat- ment with praziquantel. Fig. 8.11.4.4 Egg of Metagonimus yokogawai. All heterophyid eggs look similar, as do those of Clonorchis sinensis and Opisthorchis viverrini. Courtesy of P Radomyos. Table 8.11.4.3 Families of intestinal trematodes containing species that are uncommon human pathogens Species Geographical distribution Definitive hosts other than humans Source of infection Size of adults (mm) Size of eggs (µm) Brachylaimidae Brachylaima cribbi South Australia Mice, birds Land snails 6–12 × 0.3–0.5 28–30 × 16–17 Gastrodiscidae Gastrodiscoides hominis Asia, Nigeria Pigs, rats, monkeys, deer Water plants 4–8 × 3–4 150 × 72 Gastrothylacidae Fischoederius elongatus China Ruminants Aquatic plants 9–20 × 3–6 110–140 ×

60–80 Gymnophallidae Gymnophalloides seoi Korea Birds Oysters 0.4–0.5 × 0.2–0.3 20–25 × 11–15 Lecithodendriidae Phaneropsulus bonnei Thailand, Indonesia Bats, monkeys Dragonflies 0.48–0.78 × 0.22–0.35 27–29 × 10–12 Phaneropsulus spinicirrus Thailand 0.55–0.76 × 0.43–0.63 27–33 × 13–16 Prosthodendrium molenkampi Thailand, Indonesia Bats, monkeys, rats Dragonflies, damselflies 30 × 15 Microphallidae Gynaecotya squataroloe Korea Birds Crabs 560–690 × 285–361 21 × 17 Spelotrema (= Carneophallus) brevicaeca Philippines Birds Crabs 0.5–0.7 × 0.3–0.4 15–16 × 9–10 Nanophyetidae (= Troglotrematidae) Nanophyetus salmincola Russia, North America Dogs, foxes, birds Fish 1–2 × 0.3–0.5 80 × 40 Neodiplostomidae Neodiplostomum seoulens Korea Freshwater snails Frogs, snakes 0.8–1.2 × 0.4–0.5 86–99 × 55–63 Paramphistomatidae Watsonius watsoni Southern Africa Monkeys Water plants? 8–10 × 4–5 120–130 × 75–80 Plagiorchidae Plagiorchis harinasutai Thailand Insect larvae 1.75–1.87 × 0.60–0.65 32–34 × 16–18 (continued)

8.11.4 Intestinal trematode infections 1567 FURTHER READING Chai JY (2007). Intestinal flukes. In: Murrell KD, Fried B (eds). Food-borne parasitic zoonoses, p. 429. Springer, New York, NY. Chai JY, et al. (2009). Foodborne intestinal flukes in Southeast Asia. Korean J Parasitol, 47, Suppl, S69–S102. Keiser J, Utzinger J (2009). Food-borne trematodiases. Clin Microbial Rev, 22, 466–83. Sripa B, et al. (2010). Foodborne trematodiases in Southeast Asia: epidemiology, pathology, clinical manifestation and control. Adv Parasitol, 72, 305–50. Toledo R, Fried B (eds) (2014). Digenetic trematodes: advances in experi- mental medicine and biology, Vol. 766. Springer, New York, NY. Photographs of various stages of these parasites
and diagrams of life cycles may be found at several excellent websites: Centers for Disease Control and Prevention. http://www.dpd.cdc.gov/ DPDx/HTML/Image_Library.htm Korean Society for Parasitology. http://www.atlas.or.kr Fig. 8.11.4.5 Egg of Brachylaima cribbi. Courtesy of AR Butcher. Species Geographical distribution Definitive hosts other than humans Source of infection Size of adults (mm) Size of eggs (µm) Plagiorchis javensis Indonesia Birds, bats Insect larvae 1.8 × 0.7 36 × 22–24 Plagiorchis muris Japan Birds, dogs, rats Snails, aquatic insects 0.8–2.0 × 0.24–0.84 36 × 21 Plagiorchis philippinensis Philippines Birds, rats Insect larvae 1.5–2.0 × 0.39–0.44 28–30 × 19–21 Strigeidae Cotylurus japonicus China Birds Snails Table 8.11.4.3 Continued

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