Review

A Systematic Overview of Zoonotic Helminth Infections in North America

Blaine A. Mathison, BS, M(ASCP),[1,] Bobbi S. Pritt, MD, MS, DTM&H[2]*

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ABSTRACT

Zoonotic helminths are frequent human parasites that generally complete their natural life cycle in the absence of humans. This review encompasses 30 common or clinically relevant zoonotic helminth infections that are endemic to North America. For each organism or disease, the following information is briefly reviewed: taxonomy, biology, and life cycle, epidemiology, route of transmission for the human host, clinical manifestations, pathologic features, treatment, and laboratory diagnosis. Illustrations are provided for select parasites.

Keywords: zoonotic, helminth, parasite, North America, vector, host

Most parasitic helminth (worm) infections of humans originate among animals, whether by coevolution between humans and parasites after centuries of exposure or by new and emerging relationships due to increased human activity into areas and habitats that allow for exposures to novel etiologies. Zoonotic infections, in the broad sense, are those that cycle between humans and nonhuman animals.

In this review, we apply the term *zoonotic* to those parasites that usually complete their natural cycle in the absence of a human host. There is no discrimination as to whether humans can serve as adequate definitive hosts; often, they can. The geographic scope of this review is North America; Hawaii is included as part of United States in the political sense, although it should be noted that Hawaii is not considered part of North America in terms of biogeography.

Abbreviations:

O&P, ova and parasite; NAATs, nucleic-acid amplification tests; CDC, United States Centers for Disease Control and Prevention; PCR, polymerase chain reaction; PMNs, polymorphonuclear leukocytes; CNS, central nervous system; ELISA, enzyme-linked immuosorbent assay; VLM, visceral larval migrans; OLM, ocular larval migrans; NIP, neglected parasitic infection; CSF, cerebrospinal fluid; Ig, immunoglobulin; CLM, cutaneous larval migrans; PAIR, Percutaneous Aspiration of cyst contents, Injection of a scolicidal agent, and Reaspiration; TB, tuberculosis; H&E, hematoxylin/eosin; OM, original magnification

[1]Parasitology and Fecal Testing Laboratory, ARUP Laboratories, Salt Lake City, UT [2]Division of Clinical Microbiology, Department of Laboratory Medicine & Pathology, Mayo Clinic, Rochester, MN

*To whom correspondence should be addressed.

blaine.mathison@aruplab.com

In the medical and clinical realms, *helminths* are members of 1 of 4 broadly unrelated groups of animals: nematodes (roundworms), cestodes (tapeworms), trematodes (flukes), and acanthocephalans (thorny-headed worms; see also the Glossary). Members of these groups are all multicellular animals. Most parasitic species have multihost life cycles, involving a vertebrate definitive host and 1 or more invertebrate or vertebrate intermediate hosts. Nuances defining and separating the various groups, as well as the zoonotic helminths in each group, will be discussed systematically in detail later in this article and are outlined in **Table 1**.

Helminth infections can involve nearly all sites in the human body and can be associated with a broad range of clinical manifestations.[1,2] Although this is also true for zoonotic helminths, it is important to note that the site(s) of infection and clinical manifestations may differ from what is observed in the natural animal host. Some zoonotic helminth infections cause minimal to no symptoms in humans (eg, *Dipylidium caninum*, *Hymenolepis nana*), whereas others, particularly those that migrate throughout the body, can cause serious, life-threatening disease (eg, *Baylisascaris procyonis*, *Trichinella* spp, *Toxocara* spp).[1,2]

Means of diagnosing helminth infections in the clinical laboratory can vary greatly depending on the species and specimen type. Most helminths that colonize the human intestinal tract are identified by the gross morphology of adult worms or proglottids in stool specimens, or the identification of eggs and larvae in ova and parasite (O&P) examinations of stool. Filarial

Glossary*

accidental host—a host that is not usually part of the parasite's natural life cycle

arthropod—the phylum of animals that includes insects, arachnids, crustaceans, centipedes, and millipedes, characterized by a hardened exoskeleton and joined appendages; arthropods often serve as vectors of parasitic agents of disease

cestode—a parasitic flatworm of the class Cestoda, which includes tapeworms

dead-end host—a host from which the parasite is not capable of completing its life cycle and is not transmitted to other susceptible hosts

definitive host—the host in which the parasite reaches sexual maturity

fecundity—ability to produce many offspring

gravid—pregnant; carrying eggs or larvae

helminth—a parasitic worm; includes flukes (*trematodes*), tapeworms (*cestodes*), roundworms (*nematodes*), and thorny-headed worms (*acanthocephalans*)

intermediate host—the host in which larval development of the parasite takes place

nematode—roundworm of the phylum Nematoda

oncosphere—a motile, 6-hooked tapeworm embryo seen within eggs of certain (cyclophyllidean) tapeworms. It is the earliest differentiated stage of these tapeworms and is also called a *hexacanth embryo*

operculum—a lid-like structure found on eggs of certain cestodes and trematodes

paratenic host—a host in which no development of the parasite occurs; a substitute or potential intermediate host that harbors the parasite until it reaches the appropriate definite host. Paratenic hosts are not always necessary to the completion of the parasite's life cycle

proglottid—a segment of a tapeworm body. Each proglottid contains male and female reproductive units

protoscolex—immature form of a cestode scolex found within the larval stage (eg, coenurus or hydatid cyst)

sanguinivorous—feeding on blood

scolex—the anterior end of a tapeworm, equipped for attachment to the intestinal lining of the definitive host (eg, via suckers, hooklets, or sucking grooves)

stichosome—a multicellular organ that is prominent in some nematodes such as the trichuroids. It is comprised of a longitudinal row of individual cells (*stichocytes*) that encompass the esophagus and serve as a useful identifying morphologic feature

strobila—the segmented body of a tapeworm, made up of multiple connected proglottids

trematode—parasitic flatworm (phylum Platyhelminthes) of the class Trematoda; commonly referred to as a *fluke*

vector—an organism such as a biting tick or insect that transmits an infectious microorganism (eg, parasite) from one animal to another

*Terms are defined as they relate to parasitic infections of humans and animals

nematodes that use humans as the definitive host are usually identified by the finding of microfilariae in blood or skin snips. Most helminth infections can be identified at some point in their development by the histological examination of tissue specimens. Serologic and molecular (nucleic-acid amplification tests [NAATs]) assays are also available for select etiologies. Still, morphologic analysis remains the criterion standard for the identification of most parasitic infections.

Diagnosis of zoonotic helminths presents several inherent challenges. First, many species are not common and therefore may not be familiar to most bench technologists or microbiologists. Secondly, if the parasites do not mature to adults or reproduce in the human host, traditional diagnostic methodologies, such as O&P examinations of stool or examination of blood films, may not be appropriate. Many zoonotic helminthiases are best diagnosed by the examination of histopathologic preparations of biopsy specimens and require the expertise of a pathologist or experienced parasitologist.

This review encompasses the 30 most common and/or clinically relevant zoonotic helminth infections that are endemic to North America (**Table 1**). It also provides a brief description

Table 1. Characteristics of the 30 Most Common and/or Clinically Relevant Zoonotic Helminth Infections Endemic to North America

Genus/Species	Primary Natural/ Reservoir Hosts (Secondary Hosts)	Route of Infection for Human Host	Location in Human Host (Secondary/Ectopic Locations)	Primary Method of Diagnosis (Secondary Methods)
Nematodes				
Capillaria hepatica	Rodents	Ingestion of embryonated eggs	Liver	Histopathology
Anatrichosoma buccalis	Opossums	Unknown	Oral cavity; subcutaneous	Histopathology
Trichinella spiralis, *T. pseudospiralis*, *T. nativa*, *T. murrelli*, *Trichinella* T6	Domestic and wild pigs, bears, walruses	Ingestion of infectious larvae in infected animal meat	Adults: small intestine Larvae: skeletal muscle	Serology (histopathology)
Ascaris lumbricoides (syn. *A. suum*)	Pigs	Ingestion of embryonated eggs	Adults: small intestine (liver, gall bladder) L3 larvae: lungs	Detection of eggs and/or adults in stool specimens (histopathology: L3 larvae)
Baylisascaris procyonis	Raccoons (dogs)	Ingestion of embryonated eggs	CNS, eyes, (liver, lungs, heart)	Serology(histopathology)
Toxocara cati, *T. canis*	Cats, dogs	Ingestion of embryonated eggs (ingestion of L3 larvae)	Liver, heart, brain, lungs, eyes, other body parts	Serology (histopathology)
Anisakis spp, *Pseudoterranova* spp, *Contracaecum* spp	Fish-eating birds and marine mammals	Ingestion of infective larvae in fish and shellfish	Stomach, intestinal tract (pancreas, mesocolic lymph nodes, perimetrium, mesenteries, peritoneum)	Detection of expelled larvae or larvae removed via endoscopy (histopathology, serology)
Dirofilaria immitis	Dogs, other carnivores	Vectorborne (mosquitoes)	Pulmonary vessels	Radiography
Dirofilaria tenuis, *D. ursi*, *D. striata*, *D. subdermata*	Raccoons (*D. tenuis*), bears (*D. ursi*), wild felids (*D. striata*), porcupines (*D. subdermata*)	Vectorborne (black flies for *D. ursi*; mosquitoes for others)	Subcutaneous nodules (conjunctiva)	Histopathology (extraction of adult worms from the eye)
Onchocerca lupi	Wild canids, felids	Vectorborne (black flies)	Subcutaneous, cervical nodules	Histopathology
Molinema spp	Rodents	Vectorborne (mosquitoes)	Eyes	Extraction of worms from the eye
Brugia spp	Rodents, carnivores	Vectorborne (mosquitoes)	Lymphatic tissue	Histopathology
Gnathostoma spinigerum	Cats	Ingestion of L3 larvae in copepods or paratenic hosts	Skin, liver, eyes, CNS, mesenteries, others.	Histopathology (serology)
Thelazia californiensis, *T. gulosa*	Dogs, cats, sheep, deer (*T. californiensis*), cattle (*T. gulosa*)	Vectorborne (muscoid flies)	Eyes	Extraction of adult worms from the eye
Gongylonema pulchrum	Various mammals	Ingestion of infected insect intermediate host	Oral cavity	Extraction of adult worms from oral lesions (detection of eggs in stool specimens)
Ancylostoma caninum, *A. braziliense*	Dogs, cats	Penetration of skin by L3 larvae	Skin	Clinical presentation
Angiostrongylus cantonensis	Rats	Ingestion of L3 larvae in raw mollusks or produce contaminated with mollusk parts	CNS	PCR (serology; detection of L4 larvae in CSF; histopathology)
Cestodes				
Dibothriocephalus latus *D. nihonkaiense*	Fish-eating carnivores	Ingestion of pleurocercoid larvae in undercooked fish	Small intestine	Detection of eggs and/or proglottids in stool specimens
Spirometra mansonoides	Dogs, cats	Ingestion of procercoid (microcrustaceans) or pleurocercoid (fish, reptiles, amphibians) larvae	Subcutaneous, soft tissues (eyes)	Histopathology (extraction of spargana from eye)
Dipylidium caninum	Dogs, cats	Ingestion of cysticercoid larvae in infected fleas	Small intestine	Detection of proglottids or egg packets in stool specimens

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Table 1. continued

Genus/Species	Primary Natural/ Reservoir Hosts (Secondary Hosts)	Route of Infection for Human Host	Location in Human Host (Secondary/Ectopic Locations)	Primary Method of Diagnosis (Secondary Methods)
Hymenolepis nana, *H. diminuta*	Rodents	Ingestion of cysticercoid larvae in infected insects (*H. nana* eggs directly infectious)	Small intestine	Detection of eggs in stool specimens
Mesocestoides spp	Cats, dogs	Ingestion of tetrathyridium larvae in intermediate hosts	Small intestine	Detection of proglottids in stool specimens
Taenia serialis	Dogs, foxes	Ingestion of infectious eggs	Subcutaneous tissue	Histopathology
Echinococcus granulosus, *E. multilocularis*	Dogs, wild canids (cats, wild felids)	Ingestion of infectious eggs	Liver, lung (brain, heart, gall bladder, bone, others)	Serology; histopathology
Trematodes				
Fasciola hepatica	Cattle, sheep, buffalo	Ingestion of metacercariae on contaminated plant material	Liver	Observation of eggs in stool specimens; serology(histopathology)
Paragonimus kellicotti	Cats, dogs, raccoons, foxes, minks, muskrats	Ingestion of metacercariae in undercooked crayfish	Lungs	Observation of eggs in stool or respiratory specimens (serology; histopathology)
Nanophyetus salmincola	Raccoons, minks, skunks, otter, foxes, herons, mergansers (dogs)	Ingestion of metacercariae in undercooked fish	Small intestine	Observation of eggs in stool specimens
Metorchis conjunctus	Bears, foxes, wolves, raccoons, minks, fishers (dogs, cats)	Ingestion of metacercariae in undercooked fish	Liver	Observation of eggs in stool specimens
Acanthocephalans				
Macracanthorhynchus hirudinaceous, *M. ingens*	Pigs (*M. hirudinaceous*), raccoons (*M. ingens*)	Ingestion of cystacanths in infected arthropod intermediate hosts	Intestinal tract	Observation of adults in stool specimens
Moniliformis moniliformis	Rats	Ingestion of cystacanths in infected arthropod intermediate hosts	Intestinal tract	Observation of adults and/or eggs in stool specimens
Corynosoma strumosa	Seals, sea lions, fish-eating birds	Ingestion of cystacanths in fish paratenic hosts	Intestinal tract	Observation of adults

CNS, central nervous system; PCR, polymerase chain reaction; CSF, cerebrospinal fluid.

of the taxonomy, biology and life cycle, epidemiology, route of transmission for the human host, clinical manifestations, pathologic features, treatment, and laboratory diagnosis for these organisms. Illustrations are provided for select parasites (**Figures 1–4**). The reader is directed to several comprehensive publications to assist in the identification of helminth and other parasitic infections.[1-8] The DPDx website, managed by the United States Centers for Disease Control and Prevention (CDC),[2] contains illustrations of life cycles and an extensive image library showing the morphologic features of many parasites in a variety of clinical specimens. Also, the DPDx Team at the CDC offers a free telediagnostic/online diagnostic service (https://www.cdc.gov/dpdx/contact.html) for rapid diagnosis of parasitic infections.[9] The website for the CDC's National Center for Emerging and Zoonotic Infectious Diseases (https://www.cdc.gov/ncezid/) is a useful source for up-to-date information regarding zoonotic infections in the United States.

Nematodes

Nematodes (roundworms) constitute one of the largest animal taxa. Many species have evolved to be parasitic in humans and nonhuman animals. Most parasitic nematodes of humans are *dioecious* (ie, having separate male and female individuals) and have 5 developmental stages after the egg: 4 larval stages (L1 through L4) and adult (L5) (a notable exception to

the dioecious life cycle is *Strongyloides stercoralis*, which only has parasitic females that reproduce parthenogenetically in the human host). For most parasitic nematodes, the infectious stage is the L3 larva (commonly referred to as a *filariform larva*).

Externally, many nematodes have a similar morphology, being long and slender and lacking true segmentation. However, nematodes vary considerably in the form of their internal organs and organ systems; the form and arrangement of internal structures are taxonomically and diagnostically important. Some of the important internal diagnostic structures include the form of the musculature, lateral nerve chords, intestine, and reproductive structures.[5]

There are many laboratory methods for diagnosing nematode infections, depending on the species and stage involved. For those nematodes that colonize the human intestinal tract, diagnosis is typically made by finding eggs or larvae in O&P examinations of stool or adult worms in stool specimens. Filarial nematodes are usually diagnosed by finding microfilariae (early L1 larvae) in blood or skin snips, or adults in biopsy specimens. For many zoonotic species for which humans are not part of the natural life cycle, or for those nematodes that colonize nonintestinal sites, diagnosis is often achieved by examining sections of worms in biopsy specimens. Serologic tests and NAATs, such as polymerase chain reaction (PCR), are available for other nematode infections.

Trichuroid Nematodes

The *trichuroid* (capillarid) nematodes (order Trichocephalida) are a specialized group of nematodes whose members are all parasites of vertebrates in the adult stage. Morphologically, they are distinguished by having a specialized glandular structure called a *stichosome* (which is made up of individual cells called stichocytes) that encases the esophagus, as well as a cellular hypodermis with specialized gland cells and modified regions of the cuticle forming bacillary bands (**Figure 4B**).[5] The most familiar members of this group are *Trichuris trichiura* (the human whipworm) and *Trichinella* spp; however, 2 other genera can cause zoonotic infections in the human host: *Capillaria* and *Anatrichosoma*.

Capillaria hepatica (hepatic capillariasis)

General considerations

Capillaria hepatica is a cosmopolitan parasite of rodents. The entire life cycle, including maturation, mating, and oviposition, takes place in the liver of the host. Eggs are not shed in the feces of the host and are only liberated into the environment by death and decomposition of the host, or after being spuriously passed by a predator after predation of the rodent host. Eggs embryonate in the environment (or while being passed by a predator), and infection occurs from the ingestion of embryonated eggs containing infectious larvae. Humans infection also occurs from ingestion of embryonated eggs, usually in food or on *fomites* (objects or materials likely to carry infection) contaminated with soil containing such eggs, and also causes hepatic disease.[10]

Clinical manifestations and pathologic features

Although hepatic capillariasis can be a serious, life-threatening condition, clinical manifestations are usually nonspecific. The worms and their eggs cause focal chronic inflammation in the liver, resulting in granuloma formation made up of macrophages, eosinophils, and multinucleate giant cells and, eventually, the encapsulation or calcification of dead worms and their eggs. Septal fibrosis usually follows. Although infection with a single worm may be asymptomatic, patients with a heavy worm burden may experience severe, even fatal, disease. When present, clinical manifestations are similar to those in patients with visceral larva migrans, including fever, hepatomegaly, and hypereosinophilia.[8,11]

Laboratory Diagnosis

Diagnosis of hepatic capillariasis is made almost exclusively by the finding of adult worms or eggs in histopathologic sections of liver biopsy specimens (**Figure 4A**). Eggs are 51–67 µm long by 30–35 µm wide and have a thick, striated shell and bipolar prominences.[1] Because the entire life cycle takes places within the liver, eggs are not shed in the feces of the host. If eggs of *C. hepatica* are observed in O&P examinations of stool, they probably represent spurious passage after the consumption of infected animal liver, and further specimens should be collected to rule out true infection.[11] When observed in stool, *C. hepatica* eggs must also be differentiated from the similar-appearing eggs of *T. trichiura*; this differentiation is easily accomplished by recognition of the striated shell that is not a feature of *T. trichiura* eggs.[1]

Anatrichosoma species (anatrichosomiasis)

General considerations

Anatrichosoma is a genus of nematodes that parasitize the oral mucosa of various mammals. *Anatrichosoma buccalis*, a parasite of the Virginia opossum, is the only species

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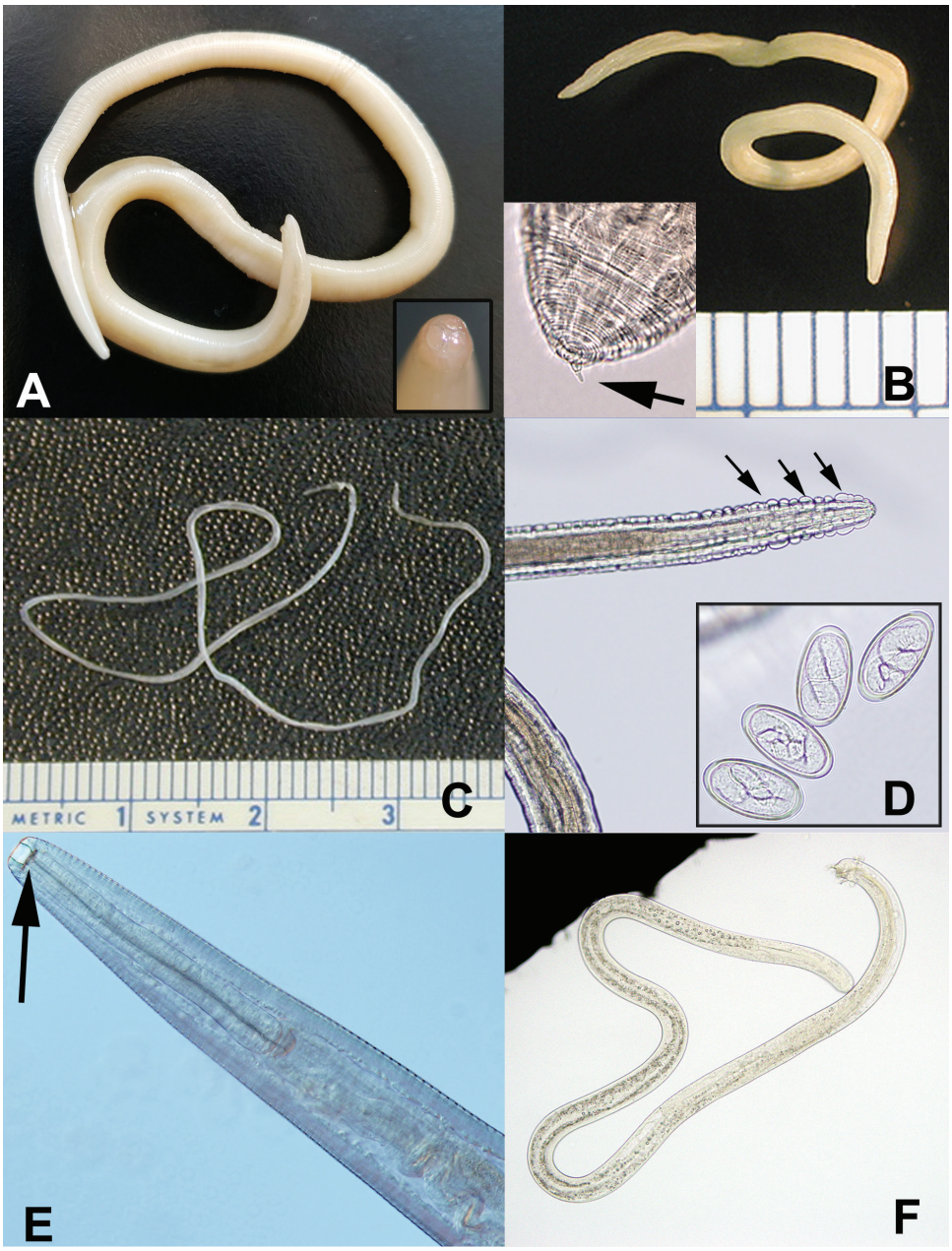

Figure 1

Gross and microscopic images of nematodes. A, *Ascaris lumbricoides* (inset shows a close-up of the ascarid "lips"). B, *Pseudoterranova* sp, (note the mucron [arrow, inset]). C, *Dirofilaria tenuis*. D, *Gongylonema pulchrum* (note the presence of cuticular *bosses*, or rounded swellings [arrows] [eggs, inset]). E, *Thelazia gulosa* (note the cup-shaped buccal cavity [arrow]). F, *Angiostrongylus cantonensis*, L4 larva in cerebrospinal fluid (CSF). Images B, C, and E courtesy of the Centers for Disease Control (CDC)–DPDx website; Image D courtesy of D. Jane Hata, PhD; Image F from Pritt BS.[8] Reproduced with permission.

currently known to be from North America. Until recently, the few documented cases of human anatrichosomiasis were from incidental findings in biopsy specimens of skin and soft tissue. However, 2 recent cases[12,13] document *Anatrichosoma* in the oral cavity of patients from the Midwest with travel to Mexico. It was not possible in either

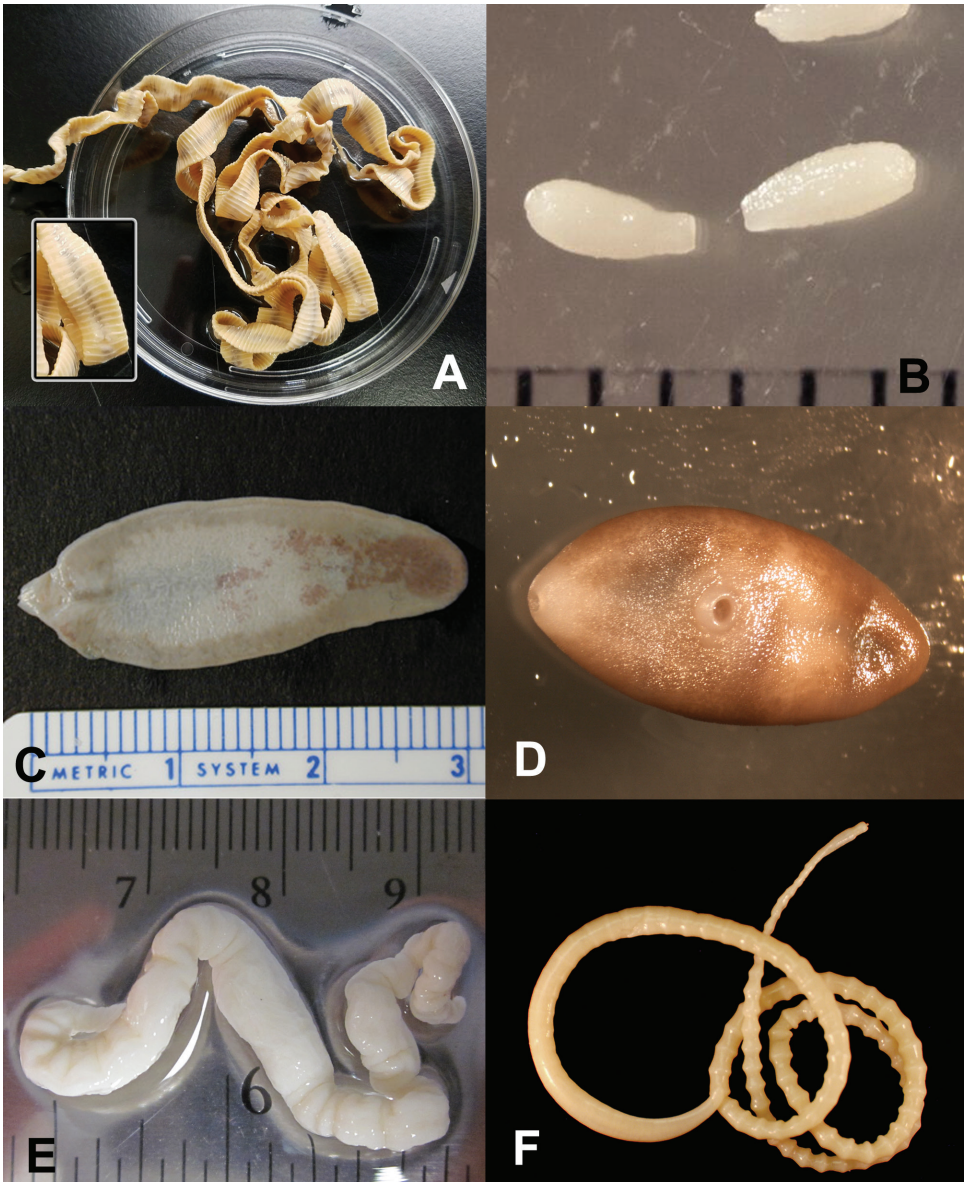

Figure 2

Gross cestodes, trematodes, and acanthocephalans. A, *Dibothriocephalus* spp, proglottids (inset, close-up of centrally-located uteri). B, *Dipylidium caninum*, proglottids (scale = 1 mm). C, *Fasciola hepatica*. D, *Paragonimus kellicotti*. E, *Macracanthorhynchus* sp. F, *Moniliformis moniliformis*. Image C courtesy of the Centers for Disease Control and Prevention (CDC)–DPDx. Image E courtesy of Marc Couturier, PhD, D(ABMM).

of those cases to confirm the identity of the worm to the species level. However, the geographic distribution and clinical presentation suggest *A. buccalis* as the causal agent.

The life cycle of *Anatrichosoma* species is not fully understood. Embryonated eggs are shed directly into the environment in the respiratory secretions of, or swallowed and passed in the feces of, the definitive host, yet laboratory experiments have failed to infect new hosts by feeding them embryonated eggs. Several related nematodes require an insect intermediate host; that might be required for *Anatrichosoma* species too. The 2 patients from the second

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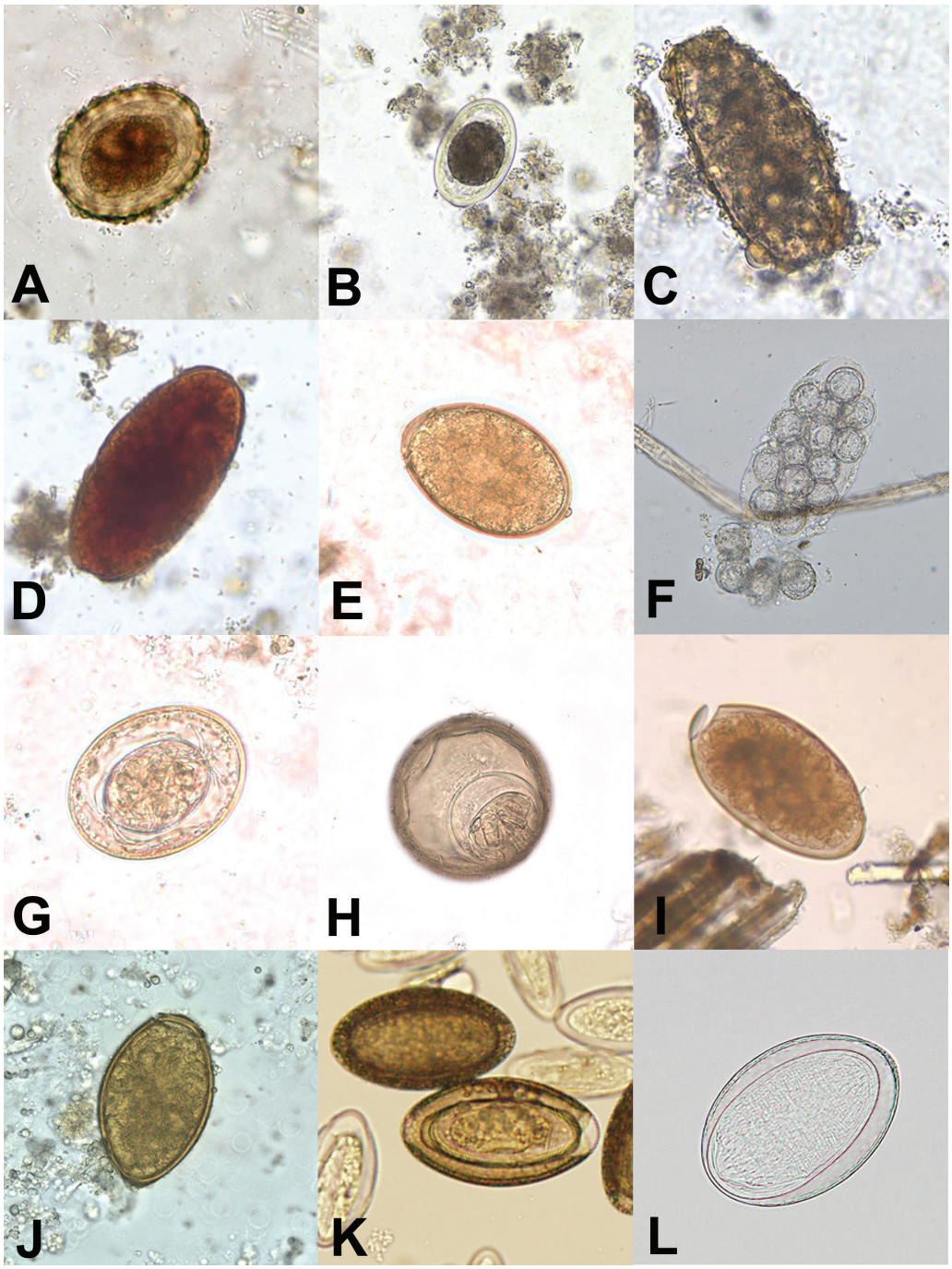

Figure 3

Helminth eggs. A, *Ascaris lumbricoides* (fertile, mamillated). B, *A. lumbricoides* (fertile, decorticated). C, *A. lumbricoides* (infertile, mamillated). D, *A. lumbricoides* (infertile, decorticated). E, *Dibothriocephalus* sp F, *Dipylidium caninum*. G, *Hymenolepis nana*. H, *Hymenolepis diminuta*. I, *Fasciola hepatica*. J, *Paragonimus* species. K, *Macracanthorhynchus ingens*. L, *Moniliformis moniliformis*. All images captured at ×400 magnification. All images courtesy of the Centers for Disease Control and Prevention (CDC)–DPDx.

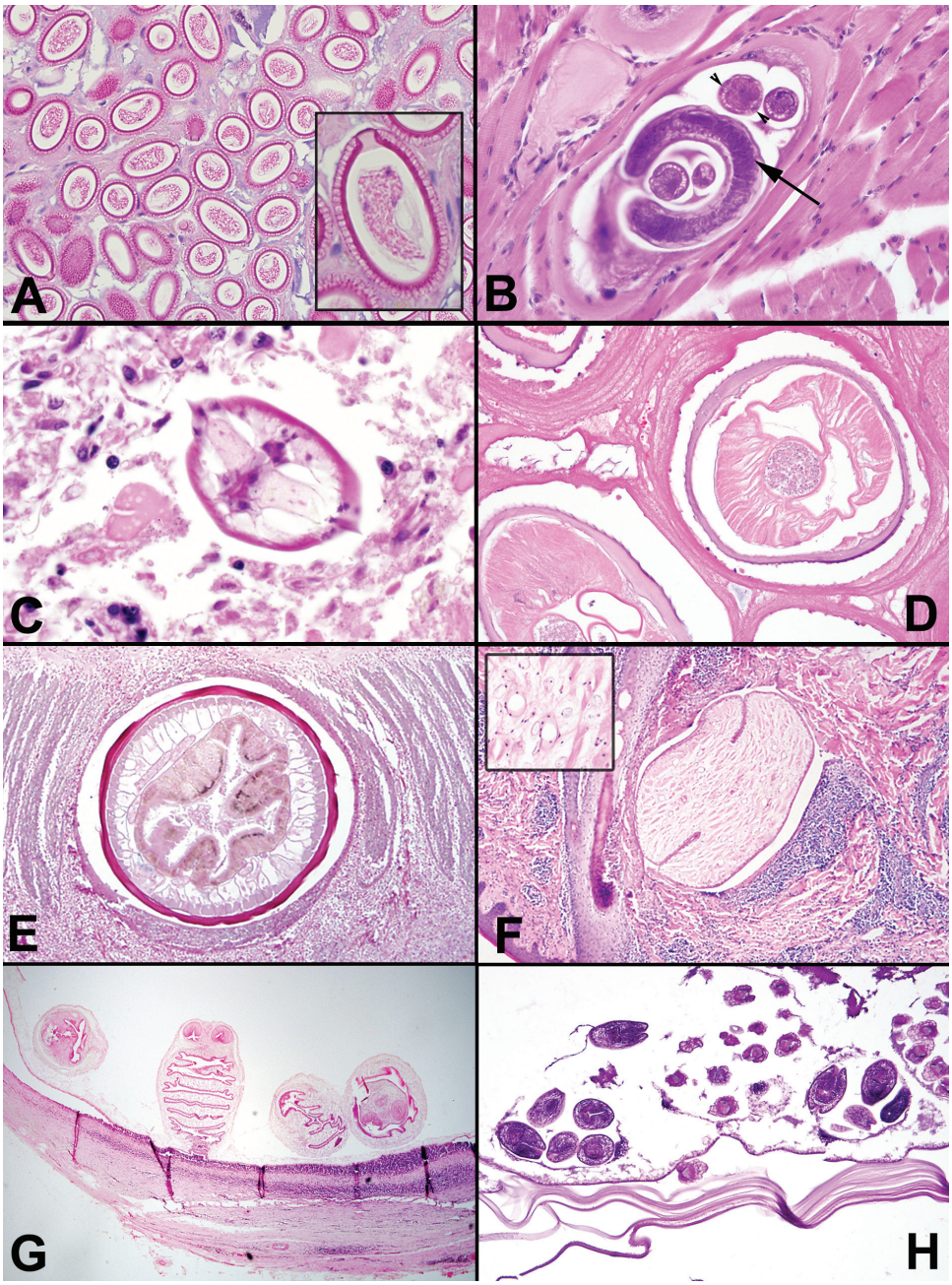

Figure 4

Helminths in histological preparations of tissue specimens. A, *Capillaria hepatica* in liver (hematoxylin/eosin [H&E] staining, original magnification [OM] ×400; inset at ×1000). B, *Trichinella spiralis* in muscle—note the presence of stichocytes (arrow) and bacillary bands (arrowheads) (H&E, OM ×400). C, *Baylisascaris procyonis* in brain (H&E, OM ×400). D, *Dirofilaria* species in subcutaneous nodule (OM ×200). E, *Gnathostoma* species in colon (OM ×100). F, *Spirometra* sp in soft tissue (H&E, OM ×40); inset shows a close-up (OM ×1000) of the calcareous corpuscles. G, *Taenia* sp coenurus from the chest wall (H&E, OM ×40). H, *Echinococcus granulosus* (H&E, OM ×100). All images except E are from Pritt BS.[8] Reproduced with permission.

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case report[13] participated in "snail facials" in Mexico, in which live snails were allowed to crawl on their faces. This detail could suggest the possible role of terrestrial mollusks as an intermediate host.

Clinical manifestations and pathologic features

The 2 case individuals who presented with oral lesions had ulcers and track-like lesions on the soft palate, tongue, inner lip, buccal mucosa, and palatal gingiva.[13] The microscopic pathologic response is undescribed in the literature, to our knowledge, for oral anatrichosomiasis.

Laboratory Diagnosis

Anatrichosomiasis has been diagnosed by the finding of adult worms in biopsy specimens. Adult worms possess typical trichuroid features, such as stichocytes and bacillary bands.

Trichinella species (trichinellosis, trichinosis)

General considerations

Trichinella species are parasites of carnivorous and omnivorous mammals, birds, and reptiles. Approximately 8 species or strains have been implicated in human disease, 5 of which are endemic to North America: *T. spiralis*, *T. pseudospiralis*, *T. nativa*, *T. murrelli*, and strain *Trichinella* T6. *Trichinella* species have an unusual life cycle in which a host serves as a definitive host, then an intermediate host, and, if not consumed, a dead-end host. Perpetuation of the life cycle is dependent on continuous cycles of predation or scavenging.

There are 2 natural cycles; in the domestic cycle, *Trichinella* worms typically cycle between domestic pigs and anthropophilic rodents, whereas in the sylvatic cycle, the worms cycle between various wild carnivores or omnivores, including rodents, wild pigs, and bears. Because of improved animal husbandry practices in the United States, infection caused by eating domestic pigs is rare, except in cases of home-raised swine. Most cases acquired in the United States are observed in hunters; sources of infection include wild boars and pigs, bears, walruses, and mountain lions. *Trichinella nativa* and *Trichinella* T6, which are usually acquired from bear meat, are freeze-resistant, so freezing game meat does not eliminate the chances of infection.[14]

Infection is initiated when infective L1 larvae are ingested in infected meat or meat products. The larvae are liberated in the stomach and upper small intestine and invade the small intestinal mucosa, where they molt 4 times and develop into adult worms. Adults mate, and after approximately 1 week, gravid females release larvae that migrate to striated muscle, where they become dormant until the muscle is consumed by a predator or human. All North American species except *T. pseudospiralis* form encapsulated cysts that contain a single, coiled larva. Larvae remain viable and infectious for years; however, if the host is not eventually consumed, the worms will die and calcify in the tissues.[14]

Clinical manifestations and pathologic features

Although mild cases are often asymptomatic, there are 3 clinical phases of trichinellosis: enteric, invasive, and encystment. The enteric phase occurs while adult worms are mating in the small intestine. Symptoms vary based on species/strain and worm burden; in contrast, the enteric phase is usually accompanied by nausea, vomiting, abdominal pain, and alternating bouts of diarrhea and constipation. Adult worms elicit chronic inflammation and edema, characterized by lymphocytes, polymorphonuclear leukocytes (PMNs), and eosinophils.[5,6,8]

The invasive phase is initiated when larvae are migrating from the intestinal tract to the striated muscle. During the peak of the migration, larvae will elicit high fever, myalgia, facial and palpebral edema, and elevated eosinophilia. Site-specific manifestations may occur if larvae migrate through specific organs or organ systems. Larvae migrating through the central nervous system (CNS) may cause dizziness, meningitis, and psychosis, whereas larvae migrating through the eye can cause conjunctivitis. Colonization of the heart can cause cardiac arrhythmia or myocarditis and may result in death.[5,6,8]

The encystment phase is initiated as larvae are settling in striated muscle. Manifestations may include muscle pain and weakness, tenderness, dyspnea, and peripheral or facial edema. Pathologically, encapsulated species are surrounded by a hyaline membrane with an infiltrate made up primarily of eosinophils.[5,6,8]

Trichinellosis is treated with mebendazole or albendazole.[15]

Laboratory Diagnosis

Diagnosis of trichinellosis is not always easy and should be based on 3 criteria: clinical manifestations, positive laboratory test results, and epidemiologic data. The primary method for laboratory diagnosis is serologic testing by

enzyme-linked immuosorbent assay (ELISA).[14,16] Larvae may be observed in muscle biopsy specimens. Also, the presence of a coiled encapsulated larva in striated muscle (**Figure 4B**) is pathognomonic for trichinellosis; however, the sensitivity of microscopic analysis is lower than with serologic testing. Larvae in muscle biopsy specimens usually exhibit typical trichuroid features, such as stichocytes and bacillary bands.[5,6,8]

Ascarid Nematodes

Members of the order Ascaridida are nematodes that are characterized in the adult stage (and often the L3 and L4 larval stages) as having 3 fleshy anterior projections commonly referred to as "lips" (**Figure 1A**, inset). Many species are parasitic in humans and nonhuman animals. Medically important genera include *Ascaris*, *Toxocara*, *Baylisascaris*, *Lagaochilascaris*, and the anisakids *Anisakis*, *Pseudoterranova*, and *Contracaecum*. Human infection with *Lagaochilascaris* is endemic to South America and is not covered further herein.

Ascaris lumbricoides (ascariasis)

General considerations

Ascaris lumbricoides is the largest intestinal nematode in the human host and one of the most commonly encountered nematodes in the diagnostic laboratory. Nearly worldwide in distribution, it remains more common in warmer and humid climates. For many years, it was generally considered that there were 2 species of *Ascaris* that can infect humans: *A. lumbricoides*, which was believed to be primarily a human parasite, and *A. suum*, which was believed to be primarily a pig parasite. However, the biology, morphology, host range, and molecular data suggest that the 2 species are conspecific, and *A. suum* is now generally considered to be synonymous with *A. lumbricoides*.[17,18] *Ascaris lumbricoides* has been a burden on humans since antiquity; we include it in this zoonotic treatise because many clusters and cases acquired in the United States have been associated with pigs.[19,20]

Ascaris lumbricoides has a complex 1-host life cycle. Adults reside and mate in the small intestine of the host; adults sometime migrate to ectopic sites, including the liver, gall bladder, pancreas, abdominal cavity, and umbilicus, or may be coughed up or emerge from the nose or tear ducts. Females shed fertilized and unfertilized eggs into the environment via the feces of the host; the unfertilized eggs are a dead-end stage in the environment. Fertilized eggs are shed unembryonated, and over a period of 2–4 weeks (depending on environmental conditions), the embryo develops into an infective L3 larva. Infectious eggs can remain viable in soil for years, depending on conditions. Infection occurs when fully embryonated eggs are ingested in food, water, or fomites contaminated with soil containing the eggs. Eggs hatch in the upper small intestine, and the L3 larvae penetrate the intestinal mucosa and enter circulation, where they are carried to the lungs. After approximately 2 weeks, the larvae penetrate the alveolar walls, ascend the bronchial tree to the epiglottis, and are swallowed. After reaching the small intestine, they mature into adults. Adults can live for 1 to 2 years and then, after death, are passed in the stool of the host.[1,2]

Clinical manifestations and pathologic features

Because *A. lumbricoides* is relatively well adapted to the human host, light infections are usually asymptomatic. During the initial larval migration in the lungs, patients may exhibit an asthma-like condition called Loeffler syndrome or *Ascaris* pneumonitis. Pathologically, Loeffler syndrome is characterized by a pulmonary infiltration of eosinophils, macrophages, and epithelial cells; Charcot-Leyden crystals may also be present. This condition appears to worsen with subsequent infections.[5,6,8]

Intestinal colonization usually does not elicit a strong inflammatory response. There may be a shortening of the villous border and increased mononuclear cells in the lamina propria. Heavy worm burdens can cause generalized gastrointestinal symptoms and, in severe cases, intestinal obstruction. This may cause some worms to perforate the intestinal wall and migrate to the abdominal cavity, biliary and pancreatic ducts, and the appendix, resulting in peritonitis, liver and pancreatic abscesses, or other localized inflammatory reactions.[5,6,8] Albendazole, mebendazole, and ivermectin have been used to successfully treat ascariasis.[15]

Laboratory Diagnosis

Ascariasis is usually diagnosed by detecting eggs in routine O&P examinations of stool or by finding adult worms passed in stool specimens. *Ascaris lumbricoides* has relatively high fecundity, and there is usually not a problem detecting eggs in fecal concentrates. There are 4 morphotypes of eggs, so laboratory scientists should be familiar with all of them: eggs may be fertile or infertile, and both of those may be *mamillated* (having an outer bumpy proteinaceous layer) or *decorticated* (smooth, lacking the outer layer). Fertilized eggs (**Figures 3A**, **3B**)

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of *A. lumbricoides* are 55–75 µm long by 35–50 µm wide and have a thick shell; the embryo is in the 1-celled stage when passed in feces. Infertile eggs (**Figures 3C**, **3D**) are larger, measuring 85–95 µm long by 43–47 µm wide, and have a thin shell and disorganized internal contents. Mature adult *A. lumbricoides* (**Figure 1A**) usually are not difficult to diagnose due to their large size and characteristic ascarid-type "lips," although younger adults may be smaller and need to be distinguished from anisakid nematodes as described later in this article.[1] Ectopic ascariasis may be diagnosed by the finding of adult, often dead and degrading, worms in biopsy or endoscopy specimens. L3 larvae are also detected, in rare instances, in lung biopsy, sputum, and bronchoalveolar lavage specimens during their migratory phase.

Baylisascaris procyonis (baylisascariasis, visceral larval migrans, ocular larval migrans)

General considerations

Baylisascaris procyonis is an ascarid parasite of raccoons and other members of the family Procyonidae from Canada to South America. Dogs, however, can also serve as definitive hosts for this parasite, enhancing the risk for disease in humans. In the natural cycle, raccoons acquire the parasite by 1 of 2 means. In the first, juvenile raccoons ingest fully embryonated eggs that have contaminated the fur of the mother or from soil contact in contaminated dens or *raccoon latrines* (communal defecation sites used by raccoons). The embryonated eggs hatch in the small intestine and colonize the intestinal mucosa. The worms molt 2 more times to become adults and then mate in the small intestine. Unembryonated eggs are shed by female worms approximately 50–75 days after infection. The second route of infection for the raccoon is by ingesting infective L3 larvae in paratenic hosts, such as mice, squirrels, rabbits, and chickens.

Humans become infected after the incidental ingestion of fully embryonated eggs in contaminated environmental sources, such as soil, wood chips, fireplace wood, and sandboxes. People who keep pet raccoons and children who have pica are at increased risk. The embryonation period for *B. procyonis* eggs is approximately 2–4 weeks in optimal environmental conditions, so exposure to fresh raccoon feces (for example, feces deposited overnight on a porch or deck) is not an immediate risk source, whereas exposure to feces in well-established latrines may present a substantial risk. Eggs hatch in the small intestine of the human host, and L3 larvae migrate to various body sites (liver, heart, lung, brain, eyes), resulting in a visceral larval migrans (VLM) or ocular larval migrans (OLM), similar to toxocariasis (see further information later in this article). Larvae will continue to grow, but not to develop further, in the human host; as such, humans are a dead-end host for *B. procyonis*.[21]

Clinical manifestations and pathologic features

Case individuals with a low worm burden may be asymptomatic. As larvae wander and grow, they cause severe physical damage to the affected tissue, especially the eyes and brain. *Baylisascaris procyonis* seems to have a predilection for the CNS and eyes, and in severe cases, infection can result in severe neurologic damage, permanent blindness, or death. *Baylisascaris procyonis* tends to live longer in the human host than *Toxocara* species, so there is more time for increased physical damage to surrounding tissues. Its larger size relative to *Toxocara* may also contribute to increased tissue damage. When worms eventually die, they elicit delayed-type and intermediate-type hypersensitivity reactions and, eventually, eosinophilic granulomas.[5,6,8]

The drug regimen of choice for treatment of baylisascariasis is albendazole in combination with high-dose corticosteroids. Albendazole initiated early (as many as 3 days after exposure) might prevent clinical disease and is recommended for children with known exposure history. Mebendazole, levamisole, or ivermectin could be used if albendazole is not available. Ocular infection has been treated using laser photocoagulation therapy to destroy intraretinal larvae.[15]

Laboratory Diagnosis

The primary diagnostic method for baylisascariasis is serologic testing by immunoblot, especially in conjunction with a thorough epidemiologic investigation.[22] L3 larvae may also be detected in histological preparations of biopsy or autopsy specimens (**Figure 4C**). Because *B. procyonis* does not develop to adult stage in the human host, O&P examinations of stool are not appropriate for diagnosis.

Toxocara canis, *T. cati* (toxocariasis, visceral larval migrans, ocular larval migrans)

General considerations

Toxocara species are ascarid nematode parasites of various carnivores. The 2 species usually implicated in human disease are *T. canis* and *T. cati*, which use dogs and cats, respectively, as their primary definitive hosts (although both species can be shared between both hosts). In the

natural cycle, dogs acquire *T. canis* by 1 of 4 means: direct, paratenic, transmammary, and transplacental. Puppies and younger dogs are more susceptible to direct infection, which is similar to that of *A. lumbricoides* and involves the ingestion of embryonated eggs that hatch in the small intestine, larval migration through the lungs, and eventual colonization of the small intestine by adult worms. The paratenic cycle involves the ingestion of infective L3 larvae in paratenic hosts, such as rodents and rabbits, or the ingestion of embryonated eggs in earthworms or other soil-dwelling invertebrates. In older dogs, patent infection can occur, but more commonly, larvae liberated from ingested eggs enclose themselves in cysts in the body. These larvae are reactivated in pregnant dogs, and puppies can be infected by transmammary or transplacental routes. *Toxocara cati* has a similar life cycle in cats.[23]

Humans become infected with *Toxocara* species by ingestion of fully embryonated eggs in contaminated environmental sources or L3 larvae in paratenic hosts. As with other ascarids, the embryonation period is usually 2 to 4 weeks, so fresh dog or cat feces are not a risk of infection, although the soil in the areas where dogs and cats defecate can present risks. Toxocariasis is a nationally notifiable disease in the United States and is classified by the CDC as a neglected parasitic infection (NIP) in the United States; approximately 13.9% of the United States population is seropositive for antibodies to *Toxocara*, suggesting that a greater percentage of the population is at risk of exposure.[24]

Clinical manifestations and pathologic features

Toxocara species cause VLM or OLM similar to *Baylisascaris procyonis* (as mentioned earlier herein), but the liver is the most common organ affected. The lungs, brain, and eyes also can be infected. Patients may be asymptomatic or present with hypereosinophilia, hepatomegaly, fever, cough, pulmonary infiltrates, or endophthalmitis or papillitis with secondary glaucoma. The severity of symptoms is related to worm load and organ or organ system involved. Pathologically, VLM or OLM caused by *Toxocara* species is similar to that caused by *B. procyonis*; dead and dying worms elicit delayed-type or intermediate-type hypersensitivity reactions and eventual eosinophilic granuloma formation.[5,6,8]

VLM caused by *Toxocara* species can be treated with albendazole or mebendazole. For OLM, those drugs may help for active infection, and inflammation may be controlled using corticosteroids. Surgical procedures may be required to prevent further damage due to chronic inflammation.[15]

Laboratory Diagnosis

Toxocariasis is diagnosed primarily by serologic testing, which can be performed on serum, cerebrospinal fluid (CSF), and vitreous fluid.[25] As with baylisascariasis, larvae may be observed in histological preparations of biopsy or autopsy specimens. Also, because *Toxocara* spp also do not develop to adults in the human host, O&P examination of stool is not an appropriate test.

Anisakis species, *Pseudoterranova* species, and *Contracaecum* species (anisakiasis)

General considerations

Anisakis, *Pseudoterranova*, and *Contracaecum* species (often collectively referred to as *anisakids* or *codworms*) are parasites that reside in the stomach or intestines of fish-eating birds and marine mammals. Gravid female worms shed fully embryonated eggs containing infectious L3 larvae. Eggs hatch in marine water, and the L3 larvae are ingested by a microscopic crustacean intermediate host. The infected crustaceans are eaten by fish or mollusks (squid), and the larvae become encapsulated in the host tissue and do not develop further. Because parasite development does not progress in the fish or molluscan hosts, they are considered paratenic hosts. Infected smaller fish are often eaten by larger fish, which also become infected and serve as paratenic hosts. The definitive host becomes infected after eating infected fish or squid. Encapsulated larvae are liberated and attach to the gastric or intestinal mucosa of the definitive host, where they develop into sexually mature male and female worms.[26,27]

Humans become infected after eating undercooked seafood harboring infective L3 larvae. Because anisakid nematodes have very low host specificity for the paratenic hosts, most commercial fish and squid may serve as sources of infection, including but not limited to salmon, cod, grouper, flounder, red snapper, tuna, mackerel, herring, shad, and various squid. Anisakid nematodes will not develop to adults in the human host.[26,27]

Clinical manifestations and pathologic features

The 4 main clinical presentations of anisakiasis are gastric, intestinal, ectopic, and acute allergic reactions. Most of the time, after being ingested, anisakid nematodes will leave the human body by expulsion of live worms out the nose or mouth (which, although unpleasant, is the best clinical outcome because removal is curative). However, sometimes, these nematodes will attempt to invade the gastric or

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intestinal mucosa. Gastric symptoms are acute, usually within hours after ingestion, and may include fever and epigastric pain, clinically mimicking an ulcer or angina-like chest pain. Abdominal manifestations usually take longer—as long as 1 week after consumption, and may include nausea, abdominal pain, fever, and diarrhea with blood or mucus. Eosinophilia and leukocytosis may develop.[27] If worms successfully penetrate the gastric or intestinal mucosa, they may migrate to ectopic sites, including the peritoneum, mesenteries, omental nodules, mesocolic lymph nodes, spleen, pancreas, or perimetrium.[28] Histologically, worms in tissues are usually surrounded by inflammatory cells such as eosinophils.[5,6,8]

Finally, acute and chronic allergic reactions may occur after eating seafood containing anisakid nematodes. Acute reactions may or may not be accompanied by gastric or intestinal symptoms, and the worms need not be alive. Clinical manifestations can range from urticaria or angioedema to anaphylactic shock. The severity of reactions may increase with continued exposure; thus, affected individuals should avoid ingesting potentially infected seafood. Fish handlers and food preparers may develop dermatitis or conjunctivitis from handling infected fish.[27]

Laboratory Diagnosis

Anisakiasis may be diagnosed by gross morphology of intact worms, histopathology, or serology, depending on the clinical presentation and specimen types. Most of the time, diagnosis is made by the examination of intact larvae that are expelled live or removed via endoscopy and submitted to the diagnostic laboratory. Larval anisakids (**Figure 1B**) grossly resemble young specimens of *Ascaris* and possess the typical ascarid-type "lips." Two features that may separate anisakids from young *Ascaris* are the presence of a boring tooth at the mouthparts and a terminal mucron (**Figure 1B**, inset), which is present in all species of *Pseudoterranova* but only some *Anisakis* species (and not any *Contracaecum* species). The larvae of all anisakid nematodes are superficially similar to one another externally; identification to the genus or species level is not required for patient management but may be performed for educational or epidemiologic purposes.[27] Anisakids in biopsy specimens are usually found incidentally when specimens are collected for other suspect etiologies (eg, tumors). The morphologic features of anisakid larvae in tissues are similar to, but should be differentiated from, those of ectopic *Ascaris*.[5,6,8]

Serologic diagnosis is made by observing positive skin-prick test results in conjunction with compatible clinical manifestations and an epidemiologic history of recent consumption of seafood. Positive skin-prick test results should be confirmed by specific immunoglobulin (Ig)E antibodies using additional assays, such as radioimmunoassay, and a lack of reaction to host fish proteins.[29] Because anisakid nematodes cannot develop to adults in a human host, O&P examination of stool is not an appropriate test.

Filarial Nematodes

Filarial nematodes (order: Spirurida, family: Onchocercidae) are highly specialized parasites that have a vertebrate definitive host and an arthropod vector intermediate host. The infectious stage for the vector, and the diagnostic stage for many human-adapted species, is a *microfilaria*, which is an early L1 larva. Adult worms tend to be very long and thread-like, often with marked sexual dimorphism regarding their size.[1] Some of the most debilitating parasitic diseases in the world are caused by filarial nematodes, including lymphatic filariasis caused by *Wuchereria bancrofti* and *Brugia* species and river blindness caused by *Onchocerca volvulus*. There are several zoonotic agents of disease in North America, including members of the genera *Dirofilaria*, *Onchocerca*, *Molinema*, and *Brugia*.

Dirofilaria immitis (pulmonary dirofilariasis)

General considerations

Dirofilaria immitis is a cosmopolitan parasite of dogs and wild canids and is commonly referred to as *dog heartworm*. Heartworm is the most clinically important disease of dogs in the United States. Once considered restricted to the southern United States, it now occurs in every state in the continental United States, Canada, and Alaska.[30] In 2015, at least 115,000 dogs were infected in the United States.[31] In addition to dogs, many other mammals can serve as natural definitive hosts, including seals, wild and domestic cats, horses, bears, muskrats, and nutria. Adult worms reside in the right ventricle of the heart and pulmonary artery of the canine host, resulting in blood flow obstruction and congestive heart failure. Gravid females shed microfilariae into the bloodstream, where they circulate in peripheral blood and get picked up by a mosquito vector with its blood meal. In the vector host, the worms mature to infective L3 larvae, and these are inoculated into the bite wound of a new host when the mosquito takes another blood meal.[30] The larvae undergo early development in subcutaneous tissues of the canine host for approximately 3 months before migrating to the heart.

Humans also become infected after being fed on by an infected mosquito. A wide range of species of mosquitoes

can serve as vectors, increasing the chances of canine and human infection. In humans, the L3 larvae do not undergo partial maturation in the subcutaneous tissues but instead travel through the bloodstream to the right ventricle and pulmonary artery, where they are usually destroyed by the host immune system.[30] Occasionally, dead larvae will embolize into the distal pulmonary vasculature, causing an infarct, which eventually undergoes healing via fibrosis, forming a well-defined circular lesion (ie, *coin lesion*) on chest imaging studies.[6] In most cases, *D. immitis* will not develop to an adult in the human host.[32]

Clinical manifestations and pathologic features

Patients with pulmonary dirofilariasis may be asymptomatic or may present with generalized respiratory symptoms, such as chest pain, cough, fever, hemoptysis, and malaise associated with the embolus of the dead larva into the lungs. Pathologically, dead and degenerating worms are usually observed within the lumen of a vessel surrounded by a sharply demarcated area of infarct in varying stages of organization. The necrotic area is surrounded by a narrow rim of granulomatous inflammation consisting of plasma cells, lymphocytes, and giant cells.[5,6,8]

Laboratory Diagnosis

Diagnosis of pulmonary dirofilariasis is made almost exclusively by the observation of coin lesions on radiography in conjunction with clinical symptoms.[6] If the coin lesion is biopsied (usually to evaluate for neoplasia, tuberculosis, or other infection), then the degrading and calcified worms may be observed in the histopathologic sections. The presence of a large degenerating nematode (100–350 µm in diameter) in a pulmonary infarct allows for presumptive diagnosis of *Dirofilaria immitis*, but many of the characteristic morphologic features are sometimes obscured. Because the larvae live short lives and rarely mature to adulthood, microfilariae are not produced, and therefore, examination of peripheral blood is not warranted.

Dirofilaria species, *Non-immitis* (Cutaneous Dirofilariasis, Ocular Dirofilariasis)

General considerations

In addition to *D. immitis*, several other species of *Dirofilaria* can cause human infection. In North America, these include *D. tenuis*, a raccoon parasite in the eastern and southeastern United States; *D. striata*, a parasite of bobcats and other wild felids in North and South America; *D. ursi*, a parasite of bears in northern North America; and *D. subdermata*, a porcupine parasite in the northern United States and Canada. Mosquitoes are the vectors for all of these except *D. ursi*, which is transmitted by black flies. All of these species reside in subcutaneous tissues of their natural hosts and release microfilariae into peripheral blood.[32] Humans also become infected after being fed on by an appropriate infected vector. Humans may serve as definitive hosts, but because worm burdens are low, females are rarely gravid in the human host.

Clinical manifestations and pathologic features

Most cases of non-*immitis* dirofilariasis present with skin nodules that may be painful or painless, and stationary or migratory. The most common sites of these nodules are the face, neck, breast, and scalp. Adult *Dirofilaria* have also been recovered from the conjunctiva.

By histopathology, skin nodules are usually seen to contain a single, coiled worm with a surrounding abscess composed of neutrophils and eosinophils. Older lesions will contain a dead, calcified worm surrounded by a granuloma composed of epithelioid cells, macrophages, eosinophils, giant cells, and lymphocytes. Parasite morphology may be obscured in older infections but is usually sufficient for making an accurate diagnosis.[5,6,8]

Laboratory Diagnosis

Cutaneous dirofilariasis is diagnosed most frequently by the observation of worms in histopathologic sections of subcutaneous nodules (**Figure 4D**). *Dirofilaria* species have several well-described morphologic features that should make a definitive diagnosis possible, including features of the cuticle, hypodermis, musculature, and lateral chords.[5,6,8] Ocular dirofilariasis is usually diagnosed by the gross morphology of adult worms removed from the conjunctiva. Few worms are recovered this way, and the presence of a long, thread-like worm in the eye of a patient who has not travelled internationally should first suggest *Dirofilaria* species (**Figure 1C**). Microscopic examination of the worm would reveal thin longitudinal ridges running lengthwise down the body of the worm.

Although *Dirofilaria* can develop to an adult in the human host, mating rarely takes place due to low worm burdens. As such, microscopic examination of peripheral blood for microfilariae is not appropriate for diagnosing dirofilariasis.

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Onchocerca lupi and *Onchocerca* species (Zoonotic Onchocerciasis)

General Considerations

Human onchocerciasis is usually attributed to infection with *Onchocerca volvulus*, found in parts of sub-Saharan Africa, Latin America, and the Middle East. However, various zoonotic *Onchocerca* species can also be occasional parasites of humans. *Onchocerca lupi* is a parasite of wild and domestic dogs and cats in Europe and North America. It was first described from the eye of a wolf in the Republic of Georgia and typically manifests as an ocular infection in its natural hosts. Before 2013, there were only 5 reported human cases, from Albania, Turkey, Tunisia, and Iran. In 2013, the first human case was reported in the United States, the patient was a 22-month-old American aboriginal female residing in Arizona.[33] From 2013 through 2016, a total of 5 more cases were recorded from the southwestern United States.[34] As with the human parasite *O. volvulus*, transmission occurs from the bite of infected black flies. It is uncertain what caused the recent surge in cases in the Southwest, but there appears to be a natural cycle present there among cats, dogs, and black flies. The life cycle of *O. lupi* in animals, and the extent to which humans are contributing to the epidemiology of the disease in this region, remains unclear.

Before the first *O. lupi* case in 2013, there had been periodic case reports of zoonotic onchocerciasis in North America with ocular involvement.[35,36] In most cases, the parasite could not been confidently identified to the species level, although in a case from Colorado, the parasite was tentatively identified as *O. cervicalis*, a parasite of veterinary importance in horses.[37]

Clinical manifestations and pathologic features

There are too few documented cases to get a concise picture of the clinical presentation associated with *O. lupi* infection. Human cases from Albania, Turkey, Tunisia, and Iran, prior to the first United States case in 2013, all had ocular infections involving the conjunctiva. The 6 cases from the southwestern United States manifested as periorbital nodule of the superior rectus muscle (n = 1), palpable nodules on the scalp or arms (n = 2), or subcutaneous cervical spinal nodules (n = 3). The patient with the periorbital nodule had presented with left upper eyelid drooping and periorbital edema. The patients with cervical nodules reported 1 or more of the following symptoms: headaches, stiff neck, sore throat, and dysphagia. With the 2 subcutaneous cases, the nodules were palpable; in 1, the nodule was tender and erythematous, but in the other case was neither tender nor erythematous.[34]

On histopathological examination, the worms were often enclosed within fibrous granulomas. Two of the cases presented with gravid female worms, which are not common in most zoonotic filarial infections.[34]

Laboratory Diagnosis

All of the current United States cases of *O. lupi* were diagnosed by the finding of adult worms in histopathologic sections of biopsy specimens. In none of the patients were microfilariae detected by skin snips or slit-lamp examinations of the eye.

Molinema species (zoonotic filariasis)

General considerations

Molinema is an enigmatic genus of filarial nematodes that primarily parasitize rodents and carnivores as definitive hosts and various sanguinivorous insects as vectors. Human cases are rare but have been documented in Canada, Oregon, and Kansas under the generic names *Dipetalonema* or *Acanthocheilonema*.[32,35] It is not usually possible to confidently identify zoonotic *Molinema* to the species level, but cases from North America have been tentatively attributed to *M. arbuta* and *M. sprenti*, which are natural parasites of porcupines and beavers, respectively. For both species, the vectors are mosquitoes.

Clinical manifestations and pathologic features

Cases of human *Molinema* infection in North America have involved a foreign-body ocular sensation in the eyes of patients. Removal of the worms proved curative.[32,35]

Laboratory Diagnosis

All cases were diagnosed by the removal and examination of intact L4 larvae from the anterior chamber of the eye. Because the worms were not sexually mature, a definitive diagnosis to the species level could not be made.

Brugia species (Zoonotic Filariasis)

General considerations

Human filariasis caused by *Brugia* species is usually attributable to *B. malayi* and *B. timori*, which cause lymphatic filariasis in Southeast Asia and the Pacific Islands. However, in the Americas, there are sporadic cases of infection with

zoonotic *Brugia* species, usually discovered on finding worms during histological examinations of excited lymphatic tissue. There have been roughly 30 cases documented from the United States, widely scattered across the continent. Most of the species in North America probably parasitize rodents or carnivores as definitive hosts and use mosquitoes as vectors. Because the internal anatomy in cross-section has not been described for most nonhuman *Brugia* species, identification to the species level is not possible in most cases diagnosed by histologic examination.[5,32]

Clinical manifestations and pathologic features

Most patients with zoonotic *Brugia* infection present with a tender mass in the cervical, axillary, or inguinal regions. Microscopic examination reveals a coiled nematode in a dilated lymphatic vessel surrounded by follicular hyperplasia and eosinophilia. Dead worms are usually encased in granulomas.[5] Excision of the nodule is considered curative.

Laboratory Diagnosis

Infections with zoonotic *Brugia* endemic to North America are diagnosed by finding adult worms during histopathologic examination of lymphatic tissue. Although in some cases female worms were gravid, microfilariae have never been detected in peripheral blood.

Miscellanaeous Spiruroid Nematodes

In addition to the filarial nematodes, several other nematodes in the order Spirurida cause zoonotic infections in humans, including members of the genera *Physaloptera*, *Gnathostoma*, *Thelazia*, *Gongylonema*, *Spirocera*, and *Rictularia*. All of these worms have multihost life cycles with at least an insect or other arthropod serving as an intermediate host or vector. The focus herein will be on members of the genera *Gnathostoma*, *Thelazia*, and *Gongylonema*, which have been reported only sporadically as agents of human infection in North America.

Gnathostoma spinigerum (gnathostomiasis)

General considerations

Four species of *Gnathostoma* have been reported to infect humans. However, *G. spinigerum* is the only species currently documented to cause human disease in Central America (Mexico).[38]

Gnathostoma spinigerum parasitizes cats as its primary definitive host, with adults residing in tumors in the stomach. Gravid females release unembryonated eggs into the stomach of the host, which are eventually passed in feces. After approximately 7 days in water, the eggs embryonate, and L1 larvae are released. The L1 larvae are ingested by freshwater microscopic crustaceans (eg, copepods or water fleas) and develop into L2 larvae. When infected crustaceans are eaten by a vertebrate intermediate host (fish, frogs, eels, birds, or reptiles), they develop into an infectious L3 larvae and encyst in the host tissues. Cats become infected after eating infected intermediate hosts. After consumption, the larvae are liberated into the stomach and migrate to the liver or abdominal cavity. After approximately a month, they return to the stomach, mature to adult stage, and mate.[39]

Human infection is usually caused by the consumption of undercooked vertebrate intermediate hosts or the incidental ingestion of infected crustaceans. Cases from Mexico have usually been attributed to the ingestion of undercooked fish in ceviche.[40,41] *Gnathostoma* species can colonize several organs and organ systems (skin, muscle, liver, mesenteries, CNS, and eyes) in humans as L3 larvae and usually do not develop further.

Clinical manifestations and pathologic features

After ingestion, larvae migrate from the intestine through the liver to muscular and subcutaneous tissues. During this larval migrans, patients may present with lack or loss of appetite for food, vomiting, abdominal pain, fever, and nausea. During the chronic phase, periodic migratory swelling might occur, made up of nodules that are well-defined, nonpitting, hard, red, and painful or pruritic. Cutaneous gnathostomiasis often manifests as a creeping eruption.

Also, *Gnathostoma* species can migrate to the CNS; eye; ear; or respiratory, gastrointestinal, or urinary tracts, resulting in localized symptoms. However, they do not migrate back to the gastric mucosa, as seen in the definitive host. Differential diagnoses include other parasitic infections such as visceral larval migrans, sparganosis, loaisis, ectopic paragonimiasis and fascioliasis, and myiasis. Histopathologic examination may show intact worms, or worms in varying stages of degradation surrounded by granulomatous inflammation, histiocytes, foreign body giant cells, and fibrosis.[5,6]

Laboratory Diagnosis

Cutaneous and visceral gnathostomiasis is usually diagnosed by observing worms in histopathologic preparations of biopsy specimens (**Figure 4E**). Ocular

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gnathostomiasis is usually diagnosed by morphologic identification of intact larvae removed from the eye of the patient. Serology is available in Mexico, Thailand, and other countries but not currently in the United States for routine clinical diagnosis. Because *Gnathostoma* species do not develop to adults in the human host, O&P examination of stool is not useful.

Thelazia californiensis, *T. gulosa* (Thelaziasis)

General considerations

There are 5 species of *Thelazia* known from North America, 2 of which have been implicated in human disease in the West: *T. californiensis* and *T. gulosa*. The latter of those was only recently recorded from humans for the first time in a patient from Oregon.[42]

Thelazia species have a 2-host life cycle involving a vertebrate definitive host and a dipteran intermediate host. Hosts for *T. californiensis* include dogs, cats, coyotes, bears, sheep, and deer; the primary hosts for *T. gulosa* are cattle, in which this parasite is of veterinary importance in North America, Central Asia, Europe, and Australia. Adult worms reside in the conjunctiva of the definitive host, and gravid females release L1 larvae into the lacrimal secretions of the host. The L1 larvae are picked up by dipteran intermediate hosts as they feed on the secretions; the primary vector for *T. californiensis* is *Fannia canalicularis*, for *T. gulosa*, it is *Musca autumnalis*. Larvae migrate to the abdomen of the fly and then to the main body cavity (the *hemocoel*), where they become infectious L3 larvae. The L3 larvae then migrate to the fly's mouthparts and are inoculated into the conjunctiva of a new host when the fly feeds on ocular secretions. The parasite develops to adulthood in the conjunctival sac and tear film of the eye.[42]

Clinical manifestations and pathologic features

Thelaziasis usually presents with conjunctival inflammation, follicular hypertrophy of the conjunctiva, and increased lacrimation. Many patients have described the sensation of something moving in their eye. In more severe infections, worms migrating across the surface of the eye have caused corneal abrasions and even blindness.[43] Because worms are usually removed intact from the conjunctiva, the associated host tissue response is not described herein. Extraction of the worms is curative; chemotherapy is not recommended.

Laboratory Diagnosis

Thelaziasis is diagnosed by the morphologic examination of adult worms removed from the conjunctiva. Adults are characterized by their cup-shaped buccal cavity and prominent transverse cuticular striations (**Figure 1E**).

Gongylonema pulchrum (gongylonemiasis)

General considerations

Gongylonema pulchrum is a spirurid nematode that causes zoonotic infections in humans, in rare instances. The parasite occurs nearly worldwide; sporadic human cases have been documented in the United States, Europe, Japan, Iraq, Morocco, China, Sri Lanka, Australia, New Zealand, and Egypt.[44]

Gongylonema pulchrum has a complex life cycle involving a mammalian definitive host and an arthropod intermediate host. The parasite can infect a broad range of hosts; definitive hosts in nature include livestock, dogs, cats, skunks, hedgehogs, and rabbits. Adult worms reside in the submucosa of the oral cavity, esophagus, and tongue and move through the skin by means of mucosal secretions, feeding on epithelial cells and inflammatory exudates. The worms form serpentine trails as they move, which are often grossly visible. Embryonated eggs are shed by gravid females and are swallowed and passed in the feces of the definitive host. Eggs containing infective L3 larvae are ingested by *coprophagous* insects (ie, those that feed on excrement), such as dung beetles and cockroaches. The definitive host becomes infected after eating insects harboring infectious L3 larvae. The larvae are released in the upper gastrointestinal tract and migrate up the esophagus and settle in the submucosa of the upper esophagus and oral cavity. Worms molt twice and become adults approximately 1 month after initial infection.[45] Human infection also occurs after ingestion of infected insects harboring L3 larvae.

Clinical manifestations and pathologic features

Clinical manifestations occur as worms burrow in the mucosa and can vary from local irritation to severe stomatitis and pharyngitis. The most common presentation is a crawling sensation in the mouth and soft palate. Serpentine trails are grossly visible. The most common sites of colonization are the lip, gums, palate, tonsils, and esophagus. Eosinophilia can occur. The pathologic response to *Gongylonema* infection is not well understood.

Histopathologic findings reveal sections of worms or eggs within the burrows.[5]

Extraction of the worm is considered curative; often, chemotherapy is not warranted. In cases of heavy parasite loads or for patients in whom reinfection is a concern, albendazole therapy may be recommended.[46]

Laboratory Diagnosis

Diagnosis of gongylonemiasis is made primarily by the identification of adult worms removed from their tracks in the mucosa or from finding worms and their eggs in histopathologic preparations of biopsy specimens. The anterior end of males and females are characterized by rounded swellings (*bosses*) (**Figure 1D**). The posterior end of the female is simple, but the posterior end of the male is asymmetric and contains 10 pairs of small *papillae* (microscopic bumps on the cuticle). On rare occasions, eggs have been detected in O&P examinations of stool. Eggs are usually shed in an embryonated state and have a thick hyaline shell, measuring 50–70 µm long by 25–37 µm wide (**Figure 1D**, inset).[1]

Strongylid Nematodes

The strongyles (order Rhabditita, suborder Strongylida) encompass a large group of nematodes that parasitize the gastrointestinal and respiratory tract of vertebrate animals. Some of the most medically important members of this group include *Strongyloides stercoralis* and the human hookworms in the genera *Ancylostoma* and *Necator*. Also, zoonotic infections are caused by animal hookworms and members of the genera *Trichostrongylus* and *Angiostrongylus*.

Ancylostoma caninum, *A. braziliense* (Cutaneous Larval Migrans, Creeping Eruption)

General considerations

Cutaneous larval migrans (CLM; also known as *creeping eruption* or *ground itch*) is a zoonotic condition caused by hookworm species that normally do not use humans as definitive hosts. The most common causes of human infestation in North America are *Ancylostoma caninum* and *A. braziliense*, which use dogs and cats, respectively, as primary definitive hosts.

Human infection is more common in the warmer and more humid regions of the Southeast and occurs when infective L3 (filariform) larvae of the hookworms directly penetrate the skin of the host while the host walks barefoot or wears sandals in regions where the soil or sand is contaminated with dog or cat feces. These worms cannot develop to adults in the human host and eventually die in the skin; on rare occasions, they may burrow deeper into the skin and migrate to other organs.

Clinical manifestations and pathologic features

The feet are the most common site of infection. Initially, itching, erythema, and vesiculation usually occur at the site of skin penetration. Grossly, the skin develops linear, raised serpentine tracts that become edematous and pruritic. Scratching the lesion can result in secondary bacterial infections. If left untreated, the condition can last for weeks before the larvae eventually die in the skin. Because the clinical picture is highly suggestive of CLM, biopsies are usually not recommended; as such, the host pathologic response is not well-defined.[5] On some occasions, larvae will travel to the bowel, resulting in eosinophilic enteritis.

Because the condition is usually self-limiting, treatment is usually not required. However, treatment with albendazole or ivermectin is curative, especially with severe or relapsing cases.[15]

Laboratory Diagnosis

Diagnosis of CLM is based almost exclusively on clinical presentation in combination with a known exposure history. Biopsy specimens are rarely collected, and because these particular hookworm species cannot develop to adults in the human host, O&P examination of stool is not useful for making the diagnosis.[5]

Angiostrongylus cantonensis (Angiostrongyliasis, Eosinophilic Meningitis)

General considerations

Angiostrongylus cantonensis is a nearly worldwide parasite of rats. Historically, human disease was believed to be restricted to Southeast Asia and the Pacific Basin, but as the epidemiology became better understood, additional cases have been described from Australia, Cuba, Puerto Rico, Brazil, Ecuador, Costa Rica, Madagascar, mainland Africa, and the Unites States. In the United States, human disease is most prevalent in Hawaii, where rats and the intermediate hosts (various terrestrial and freshwater mollusks) have become serious pests. In the continental United States, sporadic human cases have been reported from

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Louisiana, Texas, and Tennessee.[47] Given the ubiquitous presence of rats and the low host specificity for the molluscan host, it is surprising that human infection is not more common on a global scale.

In the natural cycle, adults live in the pulmonary vessels of rats. After mating, gravid females release embryonated eggs into the blood that become lodged in the capillaries of the lungs. The eggs hatch, and L1 larvae migrate up the bronchial tree to the tracheae and are eventually swallowed and passed in the rodent's feces. L1 larvae are ingested by various terrestrial or freshwater mollusks, including snails, slugs, and semislugs. In the molluscan host, L1 larvae develop to infective L3 larvae. The definitive host becomes infected after eating infected mollusks or paratenic hosts (such as freshwater crustaceans, frogs, reptiles, and planarians) that have consumed infected mollusks. The L3 larvae are liberated in the stomach and migrate down to the small intestine, where they enter the bloodstream and are carried passively to the rodent's brain. In the brain, they develop to L4 larvae and then eventually adults. After maturation to adults, they leave the brain and re-enter the bloodstream, where males and females pair up and mate. The adults eventually settle in the pulmonary vessels for laying eggs.[47]

Humans can also become infected after eating undercooked mollusks, fresh produce contaminated with mollusks or parts thereof, or infected paratenic hosts. The initial part of the life cycle in humans is similar to that in rats; however, the worms typically die as L4 larvae in the brain of the human host. *Angiostrongylus cantonensis* typically cannot develop to sexual maturity in the human host.

Clinical presentation and pathologic features

The most common presentation of *A. cantonensis* infection in humans is eosinophilic meningitis due to the host response of dying larvae. Initial infection usually presents with fever, malaise, vomiting, and abdominal pain. Invasion of the meninges and brain parenchyma can result in bitemporal headache, nausea, stiff neck, and vomiting. The severity of cerebral symptoms is directly related to the parasite burden, with neurologic manifestations being initiated on the death of and inflammatory response to the larvae in the brain. In less-severe infections, patients may be asymptomatic, and the disease can be self-limiting; however, in more serious infections, patients may develop chronic neurologic issues and even die.[5]

Pathologically, worms can be found in meninges surrounding blood vessels. Dead and degrading worms are usually surrounded by eosinophilic granulomas. Trails made by wandering worms may hemorrhage and may contain host inflammatory cells. CSF examination will show an increase in eosinophils and, occasionally, L4 larvae.[5,6,8]

Treatment for eosinophilic meningitis is usually supportive, with the use of analgesics for pain and corticosteroids for inflammation. No antihelminthic drugs have proven to be effective in treatment.[15]

Laboratory Diagnosis

Eosinophilic meningitis caused by *A. cantonensis* can be difficult to diagnosis and is often made based on clinical presentation in conjunction with positive laboratory results and a detailed epidemiologic investigation after other etiologies (viruses, bacteria) have been ruled out. NAATs using PCR are available at select specialty laboratories for detecting *A. cantonensis* in CSF specimens.[48] These tests have been implemented by the Hawaii Department of Health because that state is where the disease is most prevalent within the United States. Serologic testing is available in Asia but not currently in the United States, to our knowledge.

Also, worms may be observed in biopsy or autopsy specimens of brain tissue or in CSF specimens and can be identified based on characteristic morphologic features (**Figure 1F**). Because *A. cantonensis* does not develop to adult stage in the human host, O&P examination of stool for eggs or larvae is not appropriate.

Cestodes

Cestodes (tapeworms) are segmented flatworms that have complex multihost life cycles involving a vertebrate definitive host and 1 or more invertebrate or vertebrate intermediate hosts. Adults typically reside in the small intestine of their definitive hosts. Structurally, adult cestodes are made up of 2 main sections: the *scolex*, which attaches to the intestinal mucosa of the definitive host, and the *strobila* (body), which is made up of individual segments called *proglottids*. Cestodes are *hermaphroditic*: each proglottid contains male and female sexual structures. Although self-fertilization is possible, copulation between 2

individual worms is the preferred method of reproduction. Microscopically, the parenchyma contains numerous small calcified structures of varying size and shape called *calcareous corpuscles*, the presence of which is diagnostic for cestodes (**Figure 4F**, inset).[49]

There are 2 main groups of cestodes that cause human infection: Pseudophyllidea and Cyclophyllidea. These 2 groups are probably *paraphyletic* (derived from a common ancestor but not containing all descendant groups) but still serve as convenient subcategories for clinical and medical purposes.[49]

There are several ways to diagnose cestode infections. For those species that develop to adults in the human host and colonize the human intestinal tract, diagnosis is typically made by finding eggs or proglottids in stool specimens. For invasive larval infections, diagnosis is usually made by serology or histopathologic examination of biopsy specimens.

Pseudophyllidean Cestodes

Pseudophyllidean cestodes are characterized by *bothria* (sucking grooves) on the scolex, rather than 4 suckers, and by having the genital pore on the proglottids located on the midventral surface. Typically, the eggs of pseudophyllidean cestodes are shed unembryonated and possess an operculum, which is more commonly seen on trematode eggs. Medically important genera include *Dibothriocephalus*, *Adenocephalus*, *Spirometra*, and *Diphyllobothrium*.

Dibothriocephalus latus and *D. nihonkaiensis* (Dibothriocephaliasis, Broad Fish Tapeworm Disease)

General considerations

Dibothriocephaliasis (formerly referred to in part as *diphyllobothriasis*) is a disease caused by cestodes of the genus *Dibothriocephalus*. North American members of this genus implicated in human disease were historically placed in the genus *Diphyllobothrium* until *Dibothriocephalus* was resurrected, based on molecular and morphologic data.[50] In North America, the 2 primary agents of human disease are *D. latus* and *D. nihonkaiensis*. *Dibothriocephalus latus* occurs in fish living in cool, freshwater lakes throughout much of the Northern Hemisphere; the natural definitive hosts include a variety of animals, such as bears, pigs, cats, dogs, foxes, and wolves. *Dibothriocephalus nihonkaiensis* infects several species of Pacific salmon in the Northern Pacific between Japan (where the disease is considered endemic) and the Pacific Northwest of the United States; bears are the primary natural host.

The first confirmed case of *D. nihonkaiensis* acquired in the United States was in 2015; however, earlier cases of dibothriocephaliasis from the Pacific Northwest that were previously attributed to *D. latus* may have actually been caused by *D. nihonkaiensis*.[51,52] Other North American species of *Dibothriocephalus* that have rarely been implicated in human disease include *D. dalliae* and *D. ursi*. In addition, there are 4 North American species that are still currently retained in the genus *Diphyllobothrium* that have also been rarely implicated in human disease: *D. stemmacephalum*, *D. cordatum*, *D. lanceolatum*, and *D. balaenopterae*.[50]

The natural hosts for *Dibothriocephalus* are fish-eating carnivores and omnivores. Proglottids and eggs are shed into water via feces. Eggs embryonate in the water and the first-stage larva (*coracidium*) is released into the water. Coracidia are ingested my microscopic crustaceans (eg, copepods) and develop into a procercoid larva. Infected crustaceans are eaten by small fish, and the procercoid larva migrates to the fish-host tissue and develops into a plerocercoid larva (also known as a sparganum). Larger fish may consume the smaller fish and serve as paratenic hosts. The natural definitive host becomes infected after eating fish containing plerocercoid larvae.[53,54] Humans also become infected after eating raw or undercooked fish containing plerocercoid larvae.

Clinical manifestations and pathologic features

The extent of clinical manifestations depends on the number of worms, the length of each worm, the nutrients absorbed by each worm, and the extent of the host response to infection. Most patients are infected with a single worm, but massive infections with >100 worms have been reported.[6] Mild infections are generally asymptomatic and may only come to medical attention when segments of proglottids are passed from the anus.[2,5] When present, signs and symptoms include nausea and vomiting, diarrhea, abdominal discomfort, and weight loss. In rare instances, massive infections lead to intestinal obstruction.

Free proglottids may also migrate into the biliary tree, causing pancreatitis, cholecystitis, or cholangitis. An additional complication that is unique to this cestode infection in humans is vitamin-B12 deficiency, resulting in macrocytic anemia and associated neurologic manifestations. There are no significant pathologic changes associated with the

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worm's attachment in the small intestine.[5,6] Praziquantel is the drug treatment of choice.[15]

Laboratory Diagnosis

Dibothriocephaliasis is diagnosed by finding eggs in O&P examinations of stool or chains of proglottids recovered in stool specimens. Proglottids are typically broader than long (hence the common name, *broad fish tapeworm*) and are characterized by a rosette-shaped, centrally placed uterus and a single genital pore located on the midventral surface (**Figure 2A**). Clearing proglottids in lactophenol may enhance the observation of the uterus and the eggs contained therein. Individual eggs (**Figure 3E**) are 58–75 µm long by 40–50 µm wide and are unembryonated when shed in feces. The eggs possess an operculum and therefore need to be distinguished from the similar-appearing eggs of trematodes by using size and other morphologic features. A helpful identifying feature that is usually present is a small knob at the end opposite the operculum (ie, the *abopercular end*) of the eggs. Different species of *Dibothriocephalus* and related genera cannot be reliably separated based on egg morphology.[1]

Spirometra mansonoides (Sparganosis)

General considerations

Spirometra species are pseudophyllidean cestode parasites of dogs and cats. In humans, they manifest as a larval infection called *sparganosis*. The full extent of species that can cause human disease is not well known, but sparganosis acquired in the United States is usually attributed to *S. mansonoides*.

The life cycle of *Spirometra* species is similar to that of *Dibothriocephalus* species. Unembryonated eggs and chains of proglottids are shed into the water in the feces of the canine or feline host. Eggs embryonate in the water, and the liberated coracidia are ingested by microscopic crustaceans, such as copepods, where they develop into the procercoid larva. The crustaceans are eaten by fish, reptiles, or amphibians, and the procercoid larva develops into a plerocercoid larva (*sparganum*). The definitive host becomes infected after eating infected fish, amphibians, or reptiles harboring the plerocercoid larvae. Human infection has been attributed to the consumption of not only undercooked vertebrate intermediate hosts but also the accidental ingestion of the copepod host in contaminated water. Unlike with *Dibothriocephalus*, *Spirometra* species cannot develop to adults in the human host and are found only as the larval form (sparganum) in various tissues.[55]

Clinical manifestations and pathologic features

Clinical manifestations vary by the site of the sparganum in the host. Spargana can be found nearly anywhere in the body, including the pleural and peritoneal cavities, breast, orbit of the eye, brain, abdominal viscera, and spinal cord, and can continue to migrate. Most patients have a single sparganum, but infection with multiple spargana have been described.[6] Patients with sparganosis involving the subcutaneous tissues are commonly asymptomatic but may report a painful, occasionally migrating, nodule. Lesions of the breast have a similar presentation and may be noted as an incidental nodule on screening mammography.[6,56]

CNS involvement may present with a spectrum of symptoms, including seizures, headache, and focal neurologic deficits, depending on the site of the brain affected. Finally, a particular form of sparganosis caused by the related pseudophyllidean cestode referred to as *Sparganum proliferum* manifests as an expansile lesion comprised of multiple plerocercoids.[2] If not removed, continued proliferation can result in death to the host.[57] Although a living sparganum usually escapes detection by the host's immune system, a dying sparganum elicits a marked acute immune response, with surrounding abscess formation, and eventually, a granulomatous response. Excision is the recommended therapy for sparganosis because the spargana are resistant to praziquantel.[6]

Laboratory Diagnosis

Sparganosis is diagnosed by the finding of spargana during histological examination of biopsy specimens (**Figure 4F**) or intact spargana extracted from tissues or the eye. Spargana extracted from the eye need to be differentiated from nematodes that are collected in the same manner. Intact spargana are long, thin, ribbon-like, and lack true segmentation; they often have an invagination at the anterior end. Because *Spirometra* species do not develop to adults in the human host, neither eggs nor proglottids will be found in stool specimens. Thus, O&P examinations of stool are not useful for diagnosis.

Cyclophyllidean Cestodes

Cyclophyllidean cestodes are characterized by a scolex with 4 suckers and proglottids with a single lateral or 2

bilateral genital pores. Some species have an anterior rostellum (snout-like protuberance) armed with hooklets. The eggs of cyclophyllidean cestodes are shed embryonated with an infectious oncosphere containing 6 hooklets. Several species are adapted to use humans as definitive hosts: *Taenia solium*, *T. saginata*, *T. asiatica*, *Dipylidium caninum*, *Hymenolepis nana*, and *H. diminuta*.

Several other species cause zoonotic infections as larvae, most notably canine *Taenia* species and members of the genus *Echinococcus*. A report of suspect *Raillietina* was presented by a field biologist who lives in Utah.[58,59] Although a definitive diagnosis was not possible in that case due to the presence of proglottids only (no scolex was present), the patient's clinical history, epidemiological risk factors such as aspirating insect specimens (the intermediate host) and raising chickens, and residence in Utah suggested *Raillietina rectractilis*, a parasite of rabbits and ground squirrels in Western North America, or *R. cesticillus*, a widespread parasite of chickens.[60]

Dipylidium caninum (Dipylidiasis, Dog Tapeworm Disease)

General considerations

Dipylidium caninum is a cosmopolitan parasite of dogs and cats, although humans can also serve as a definitive host. Adults reside in the small intestine of the definitive host, and gravid proglottids are shed individually or in short chains in the feces. Proglottids (or eggs liberated from them) are ingested by insects, such chewing lice or the larvae of fleas. Within the insect intermediate host, the oncosphere develops into a cysticercoid larva. The cysticercoid larvae remain viable within flea larvae even during the metamorphosis of the flea through pupation and development into an adult. The definitive host becomes infected after ingesting infected adult fleas or lice that contain infectious cysticercoids.[61] Humans infection occurs worldwide and is initiated after the incidental ingestion of infected insects in contaminated environmental sources or pet saliva. Children are particularly at risk due to their habits of putting a pet dog's or cat's tail in their mouth.

Clinical manifestations and pathologic features

Infected individuals are often asymptomatic. When present, symptoms may include weight loss, colic, episodic vomiting, nocturnal irritability, and in severe cases, failure to thrive. In rare instances, patients have had urticarial or eosinophilia. In many cases, infection only comes to the attention of the caregiver when individual motile proglottids are noted in the child's diaper.[1,6] No specific pathologic changes are noted at the site of intestinal attachment. Treatment is with praziquantel.[15]

Laboratory Diagnosis

The diagnosis of dipylidiasis is usually made by finding characteristic double-pored proglottids in stool specimens. Individual proglottids are small and shaped like elongated/ovals; they are often described as resembling pumpkin seeds or grains of rice (**Figure 2B**). Physical "teasing" or manipulation of proglottids may reveal characteristic egg packets containing approximately 8 to 15 eggs (**Figure 3F**); individual eggs are 25–40 µm in diameter and possess a thin shell and an oncosphere with 6 hooklets. Less commonly, proglottids will rupture, and the egg packets may be observed in O&P examinations of stool.[1]

Hymenolepis nana, *H. diminuta* (Hymenolepiasis, Dwarf Tapeworm Disease)

General considerations

Hymenolepid tapeworms are primarily parasites of rodents. Two species implicated in human infection are *Hymenolepis nana* (the dwarf tapeworm) and *H. diminuta* (the rat tapeworm). Both species are nearly cosmopolitan in distribution, although *H. diminuta* is reported more sporadically than *H. nana*.[61]

Hymenolepis nana and *H. diminuta* colonize the small intestine of their rodent hosts. Because proglottids usually deteriorate while still in the host, primarily only the eggs are shed into the environment via the feces. Eggs contain a mature, infective oncosphere that when consumed by an arthropod intermediate host, such as fleas and granary beetles, invades the host insect's tissue and develops into a cysticercoid larva. The definitive host becomes infected after eating insects harboring cysticercoid larvae. *Hymenolepis nana* is unique in that it can bypass the insect intermediate host and that vertebrate hosts can become infected directly by the ingestion of eggs. Intestinal autoinfection also occurs with *H. nana*, whereby oncospheres are released from eggs while still in the intestinal tract of the definitive host. The oncospheres colonize the intestinal mucosa and develop into cysticercoid larvae. After 2 to 3 weeks, the cysticercoid larvae become adult tapeworms.[61] Humans become infected after the incidental ingestion of

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infected insects or directly from the ingestion of eggs from contaminated environmental sources. As with the rodent host, autoinfection can also occur in humans.

Clinical manifestations and pathologic features

Most infections are asymptomatic. However, massive infections produce symptoms such as abdominal pain, weight loss, nausea, vomiting, and diarrhea. Epileptiform convulsions and failure to thrive have also been reported in children.[6] Moderate peripheral eosinophilia may be present. No specific pathologic changes are noted at the site of intestinal attachment. As with infections with other adult intestinal tapeworms, praziquantel is the treatment of choice.[15]

Laboratory Diagnosis

Hymenolepiasis is diagnosed primarily by finding eggs during O&P examinations of stool. Because proglottids usually deteriorate while in the intestinal tract of the definitive host, proglottids and scoleces are rarely seen in stool specimens, although they may be detected during colonoscopy or in colonic washings. The eggs are round to oval-shaped and have an inner 6-hooked embryo (*onchosphere*) surrounded by a membrane and separated from the outer shell. *H. nana* eggs (**Figure 3G**) are 30–37 µm in diameter and have a thin, hyaline shell. The oncosphere contains 6 hooklets and 2 polar thickenings from which 4–8 filaments arise and extend towards the outer shell. *H. diminuta* eggs (**Figure 3H**) are 60–85 µm in diameter and have a thicker shell than *H. nana* eggs. The 6-hooked oncosphere, which is generally well-separated from the outer shell, lacks the polar filaments seen in *H. nana* eggs. The differences in size and presence/absence of polar filaments should readily distinguish the eggs of these 2 species.[1]

Mesocestoides species (Mesocestoidiasis)

General considerations

Mesocestoides is an enigmatic genus of cestodes for which the natural life cycle still is not completely understood. Also, the taxonomy of the genus is not well understood, but human infection acquired in North America has historically been attributed to *M. lineatus* (synonymous with *M. variabilis*).

Mesocestoides is believed to have a 3-host life cycle. Adults of *M. lineatus* parasitize the small intestine of cats, whereas other species parasitize dogs and other carnivores or birds. Proglottids are shed in the feces of the definitive host. It is believed that arthropods or other invertebrates serve as the first intermediate host, but nothing has been described definitively in nature. However, oncospheres experimentally fed directly to vertebrate intermediate hosts have not resulted in infection, suggesting there is an additional host. The presumed second-stage larva (tetrathyridium) occurs in the peritoneal cavity or musculature of a variety of mammals, including rodents, birds, reptiles, and amphibians. Cats become infected after eating small vertebrate hosts containing tetrathyridia, and the parasite develops to an adult in the cat's small intestine. On rare occasions, the tetrathyridia will migrate through the intestinal wall and colonize extraintestinal sites as tetrathyridia, never becoming adults.[62]

Human infection usually occurs after the consumption of raw or undercooked reptiles, amphibians, poultry, or wild game containing infective tetrathyridia. Because human mesocestoidiasis is usually diagnosed by the finding of proglottids in feces, humans must serve as an adequate definitive host for this parasite.[63,64]

Clinical manifestations and pathologic features

Patients are generally asymptomatic. When present, symptoms may include abdominal pain, weight loss, and irritability.[6] No specific pathologic changes are noted at the site of intestinal attachment. Treatment is with praziquantel.[15]

Laboratory Diagnosis

Human mesocestoidiasis is diagnosed by finding proglottids in stool specimens. Mature, gravid proglottids are longer than they are wide and possess a parauterine organ that contains a mass of eggs. Individual eggs are approximately 19–24 µm long and possess a membranous wall surrounding the 6-hooked oncosphere.[1]

Taenia serialis (coenurosis)

General considerations

Coenurosis is a zoonotic cestode infection caused by various canine *Taenia* species, including *T. multiceps*, *T. serialis*, and *T. brauni*. In North America, human coenurosis is usually attributed to *T. serialis*.

Adult *T. serialis* resides in the small intestine of the canine host. Proglottids and individual eggs are shed in the feces. Eggs are shed, containing a fully developed, infectious oncosphere. Intermediate hosts, such as rabbits, hares, and

rodents, become infected after ingesting infectious eggs. In the intermediate host, the liberated oncosphere penetrates the intestinal wall and is carried via the bloodstream to other organs, including the CNS, muscles, and soft tissues, where it develops into a cysticercoid larva (coenurus). The definitive host becomes infected after eating intermediate hosts harboring cysticercoid larvae.[55,65]

Humans serve as an intermediate host for *T. serialis* and are also a dead-end host. Infection is usually acquired through ingestion of infective eggs in environmental sources contaminated with dog feces and results in further infection of the subcutaneous tissues (most common) and other sites. *Taenia serialis* cannot develop to an adult in the human host.[65]

Clinical presentation and pathologic features

Like infections with other larval tapeworms, the clinical presentation can vary greatly depending on location of the larva (*coenurus*) in the body. Subcutaneous involvement (which is usually caused by *T. serialis*) commonly presents as a painless or moderately tender nodule.[6] More severe manifestations may occur with involvement of the orbit or CNS, including visual impairment, seizures, nausea, and vomiting (with increased intracranial pressure), and focal neurologic deficits (ocular and CNS involvement is more likely to be caused by *T. multiceps*). While it is alive, the coenurus is usually separated from host tissue by a host-derived fibrous wall. On its death, however, exposed parasite antigens will trigger an acute inflammatory response that will subsequently give rise to chronic inflammation, fibrosis, and calcification.[5,6] Treatment is usually via surgical excision. Praziquantel may also be used, with the caution that the host immune response to the dying coenuri may cause significant pathology.

Laboratory Diagnosis

Coenurosis is diagnosed by the finding of coenuri in biopsy specimens (**Figure 4G**). Coenuri have a morphologic appearance that is similar to some other larval cestodes. The presence of multiple protoscoleces rules out cysticercosis caused by *T. solium*. Hydatid cysts cause by *Echinococcus* may also have multiple protoscoleces, but the cysts arise from a germinal membrane along a laminated layer. Unlike cysticercosis and echinococcosis, there are no serologic assays available for coenurosis. Because *T. serialis* cannot develop to adult form in the human host, O&P examinations of stool are not useful for diagnosis human infection.

Echinococcus granulosus (cystic hydatid disease)

General Considerations

Cystic hydatid disease is caused by *Echinococcus granulosus*, a small tapeworm of dogs and wild canids that occurs nearly worldwide. Generally, life cycle patterns are described as *domestic*, in which the disease cycles between domestic dogs and livestock, or *sylvatic*, in which the disease cycles between wild canids and ungulates. Human infection in North America is most common in agricultural communities where sheep, goats, and other livestock that serve as intermediate hosts are raised, and cycles between domestic dogs and the sheep strain (G1) of *E. granulosus*.

Mature tapeworms shed eggs containing an infectious oncosphere into the feces of the definitive host. After eggs are ingested by a suitable intermediate host, the oncosphere is released in the small intestine, penetrates the intestinal wall, and is carried via the bloodstream to various organs, including the liver, lungs, and musculature. The oncosphere attaches to host tissue and develops into a hydatid cyst that enlarges over time, forming protoscoleces and daughter cysts that fill the interior of the parent cyst. The definitive host becomes infected after eating the flesh of intermediate hosts harboring hydatid cysts. In the intestinal tract of the definitive host, the protoscoleces evaginate, attach to the intestinal mucosa, and mature to adult tapeworms.[66] Humans become infected after ingesting eggs in environmental sources contaminated with dog feces. Human assume the role of the intermediate host and only harbor hydatid cysts, never adult tapeworms; the most common site of infection in humans is the liver, followed by the lungs. Less commonly, the brain, muscles, eyes, heart, bones, and spleen can be affected.

Clinical manifestations and pathologic features

The spectrum of clinical manifestations is highly dependent on the location of the hydatid cyst, its size, and whether rupture/leakage has occurred. Many cysts remain asymptomatic over many years as they slowly expand. Some anatomic locations such as the abdomen can accommodate a large (>20 cm diameter) cyst that may not be noticed for decades. However, cysts within confined spaces, such as the bones, eyes, and CNS, may quickly come to medical attention. Infection may be life-threatening when it compresses a vital organ.

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Generally, in the liver, cysts do not come to attention until they reach 10 cm in diameter.[6] Patients may note a palpable abdominal mass, and jaundice may occur with compression of the biliary tree. Patients may report chest pain, cough, dyspnea, and hemoptysis. Rupture of the cyst into the bronchial tree classically results in expectoration of ruptured cysts and fluid.

Regardless of the location, cyst rupture can cause a potentially life-threatening systemic response, due to exposure of parasite antigens to the host immune system, and may invoke urticaria, vomiting, and anaphylactic shock.[6] Intact cysts are initially surrounded by a mild inflammatory response, but this quickly subsides and is replaced with host-derived fibrous wall encapsulating the cyst. External to the cyst and fibrous wall is a surrounding rim of compressed tissue. Cyst rupture evokes a brisk granulomatous inflammatory response that will eventually destroy the parasite.[6]

Treatment is based on the location of the cyst, its amenability to surgical removal or percutaneous aspiration, and its stage (eg, unilocular, multilocular, collapsed, or calcified). When suitable, the PAIR procedure (Percutaneous Aspiration of cyst contents, Injection of a scolicidal agent, and Reaspiration), is the preferred treatment. Concomitant therapy with albendazole, antihistamines, and steroids is commonly used with the PAIR approach.[15] In other cases, chemotherapy only, surgical procedures, or even a watch-and-wait approach may be used.[2]

Laboratory Diagnosis

The diagnosis of cystic hydatid disease is made based on the findings from radiographic techniques (such as ulstrasonography and computed tomography) in conjunction with positive serologic results.[66] Cystic hydatid disease also can be identified by morphologic techniques, such as the observation of cysts in biopsy specimens (**Figure 4H**) or the presence of protoscoleces or liberated calcareous corpuscles and hooklets (*hydatid sand*) in body fluid aspirates. Because *E. granulosus* cannot develop to adult form in the human host, O&P examination of stool is not useful for diagnosis echinococcosis.

Echinococcus multilocularis (alveolar hydatid disease)

General Considerations

Alveolar hydatid disease is caused by *Echinococcus multilocularis*, which is distributed throughout the Northern Hemisphere. The life cycle is similar to that of *E. granulosus* (described earlier herein) and usually cycles between dogs, foxes, coyotes, wolves, and wild felids as definitive hosts and rodents as intermediate hosts, although domestic dogs can also host the larval stage. The site of infection in the intermediate host is almost exclusively the liver, where it forms an alveolar cyst. As with hydatid cystic disease, humans become infected with *E. multilocularis* from the incidental ingestion of eggs in environmental sources contaminated with canine or feline feces.[66]

The risk factors for alveolar hydatid disease are not well known, and human infection is relatively uncommon, given the prevalence of *E. multilocularis* in its natural definitive hosts. Occupational or behavioral factors are believed to play a role in human disease. Two groups in North America that are believed to be at increased risk are hunters or trappers that come in contact with infected definitive hosts[67] and Eskimos who live closely with their dogs in houses built directly on the tundra without a gravel or permanent foundation.[68] The most common site of infection in humans is the liver, where the larva manifests as a slow-growing destructive tumor-like cyst, occasionally with metastatic lesions in the brain, lungs, peritoneum, and other areas of the body.

Clinical manifestations and pathologic features

Alveolar hydatid disease is characterized by slow, progressive proliferation of cysts that encompass normal structures and cross tissue planes, much like a malignant neoplasm.[5,6,8] This disease is usually fatal if untreated. Given the infiltrative nature of the infection, extensive surgical debridement (with complete removal when possible) is the mainstay of treatment, accompanied by albendazole therapy for a minimum of 2 years.[15] Lifelong suppression with albendazole may be necessary when complete surgical excision is not achieved.

Laboratory Diagnosis

As with cystic hydatid disease, diagnosis of alveolar hydatid disease is made based on the findings from radiographic techniques in conjunction with positive serologic results.[66] Also, as with hydatid cyst disease, humans cannot serve as definitive hosts for *E. multilocularis*. Therefore, O&P examination of stool is not appropriate.

Trematodes

Trematodes are parasitic flatworms commonly referred to as flukes. All species have complex life cycles with 1 or more

intermediate hosts; in all species that parasitize humans, the first intermediate host is a freshwater or terrestrial snail. Most adult trematodes are hermaphroditic, the major exception being *Schistosoma* spp, in which individual adult males and females live as a coupled pair, with mature females residing in a gynecophorol canal along the male's body. Structurally, most trematodes are flat and elongated, often tapering on 1 or both ends and appearing leaf-shaped. Adults are characterized by having 2 muscular suckers: an oral sucker that surrounds the mouth and a ventral sucker (*acetabulum*) located further down the body. Both suckers function for attachment to host tissue. Although self-fertilization is possible among the hermaphroditic species, mating between 2 individual flukes is the optimal method of reproduction for genetic variation. Eggs shed by flukes may be unembryonated or embryonated, and possess an operculum (non-*Schistosoma* spp) or lack an operculum but possess a terminal or lateral spine (*Schistosoma* spp).[69]

Diagnosis of trematode infections varies by the species and location in the host, but most trematode infections can be diagnosed by finding eggs in clinical specimens (stool, urine, respiratory specimens). Trematode eggs are often shed intermittently and in low numbers, so concentration procedures and examination of multiple collections are recommended to enhance detection. Serologic examination is also available for some species.

Most trematode infections are endemic to tropical and subtropical areas of South America and the Caribbean, Mediterranean, Middle East, Africa, and Southeast Asia. Few trematode infections are naturally acquired in North America.

Fasciola hepatica (Fascioliasis)

General Considerations

Fasciola hepatica is a large trematode that resides in the large biliary ducts of its definitive hosts (**Figure 2C**). *Fasciola hepatica* has a nearly worldwide distribution: cattle, sheep, and goats are its normal definitive hosts. A second species, *F. gigantica*, causes human infection in Africa and Asia.

Gravid flukes discharge unembryonated eggs into the biliary ducts that are eventually passed via the feces of the definitive host into fresh water. Eggs embryonate in the water and release the first-stage larva, known as a *miracidium*. The miracidium infects an appropriate snail host and undergoes several asexual cycles, resulting in the formation of motile cercariae. The cercariae leave the snail host and encyst as metacercariae on aquatic vegetation, such as watercress and water parsley. The definitive host becomes infected after eating undercooked or raw vegetable matter containing infectious metacercariae. In the definitive host, metacercariae excyst in the duodenum, and the young flukes penetrate the intestinal wall and invade the peritoneal cavity. Then, they penetrate the capsule of the liver and migrate throughout the liver parenchyma, leaving inflammation and fibrosis in their wake. They eventually penetrate bile ducts, where they mature to adults. Ectopic colonization of other organs, such as the intestine, brain, skin, pharyngeal mucosa, and lungs, can also occur on rare occasions. The time between ingestion of metacercariae and maturation to an adult is approximately 3–4 weeks.[70]

Like the natural definitive host, humans also become infected after ingesting metacercariae on contaminated plants or water in which such plants are growing. Humans can also ingest eggs after eating the infected liver of herbivores and pass the eggs in stool. Such shedding of eggs is spurious and needs to be distinguished from true infection (see the Laboratory Diagnosis section later herein).

Clinical manifestations and pathologic findings

Patients generally experience symptoms such as fever and abdominal pain during the initial migration of larval flukes throughout the peritoneum and liver, as well as nausea, vomiting, lack or loss of appetite for food, and diarrhea. Eosinophilia and urticaria are also common, with dermatographism being a distinctive feature during early infection.[6] In heavy infections, significant fibrosis and even cirrhosis can occur due to the damage caused by larval migration. Additional location-specific symptoms may occur in cases of ectopic migration. Once the flukes reach the bile ducts, they cause mechanical irritation and obstruction of the biliary tree due to their large size, resulting in epigastric pain, biliary colic, fat intolerance, jaundice, right upper quadrant tenderness, hepatomegaly, ascites, and choledocalithiasis.[5,6,8] Mild to high levels of eosinophilia are common throughout all stages of infection, as well as anemia, an elevated sedimentation rate, hyperbilirubinemia, and elevated IgE levels. Unlike the other flukes, *Fasciola* does not respond to praziquantel and instead must be treated with triclabendazole. This drug is not commercially available in the United States and can only be obtained after consultation with the CDC through an investigational use protocol.[2,15]

Laboratory Diagnosis

Diagnosis of fascioliasis is made primarily by finding eggs during O&P examination of stool (**Figure 3I**). Often, eggs are

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shed intermittently and in small numbers, so concentration procedures and multiple collections are required. Eggs in fresh clinical specimens are unembryonated and measure 130–150 µm long by 63–90 µm wide and have a small, inconspicuous operculum. The eggs are morphologically indistinguishable from the trematodes *Fasciolopsis buski* and *Gastrodiscoides hominis*, which are endemic to India and Southeast Asia.[1] Adults and eggs may be detected in liver biopsy specimens. Eggs observed in biopsy specimens should be distinguished from those of *Schistosoma* spp, which are roughly the same size but possess a fully developed miracidium.[8] As mentioned previously herein, eggs may be found in the stool of patients who consumed the infected livers of cattle or other herbivores. In these cases, the passage is spurious, and additional collections should be performed to rule out true infection. Serologic examination is available for fascioliasis at the CDC in the United States.[71]

Paragonimus kellicotti (Paragonimiasis)

General Considerations

Paragonimus is a genus of trematodes that infects the lungs of its definitive hosts. There are roughly 8 to 9 species that cause clinical disease in humans, but only *P. kellicotti* (**Figure 2D**) is endemic to North America, where it is found in streams and rivers in the Mississippi River Basin, including the central United States west to the Rocky Mountains. Primary definitive hosts for *P. kellicotti* include domestic cats, bobcats, skunks, foxes, coyotes, and minks.

Sexual reproduction between 2 individuals is the norm for *Paragonimus* species. Paired adults of *P. kellicotti* reside in cysts in the pleural space of the definitive host. After mating, the cysts rupture, releasing eggs into the lungs that are coughed up and expelled in respiratory secretions or swallowed and passed in feces. Eggs embryonate fully in fresh water, followed by the release of a miracidium. The miracidium infects an appropriate snail host and undergoes several cycles of asexual reproduction, resulting in the formation of cercariae. Cercariae leave the snail host and infect the next intermediate host: crayfish. Within the crayfish host, cercariae encyst as infective metacercariae. The definitive host becomes infected after eating crayfish harboring infective metacercariae. The metacercariae excyst in the small intestine, and the young fluke penetrates the intestinal tissue and migrates to the peritoneal cavity. After about 2 to 3 weeks, the flukes migrate through the diaphragm to the pleural space, where they mature. Experiment evidence suggests that some *Paragonimus* will not develop to the adult fluke stage until they come in contact with an appropriate mate.[72-74] Like the natural definitive host, humans become infected after eating undercooked or raw crayfish infected with metacercariae. Ectopic cerebral paragonimiasis is a rare but well-described phenomenon.[6]

Clinical manifestations and pathologic features

Patients are often asymptomatic during the initial migration stage of infection, although some develop diarrhea and abdominal pain.

Once in the lung, the presence of the flukes within a cystic cavity elicits an inflammatory response associated with cough and expectoration of rusty-colored, foul-smelling sputum (described as having a fishy odor).[6] Chest pain and night sweats may also occur, which clinically mimic symptoms of tuberculosis (TB). In cases of heavy infection, complications such as pneumothorax, hydropneumothorax, and pleural effusion may occur.[6] Eosinophilia ranging from 10% to >90% is seen in most patients and is a useful differentiating feature from TB. Over time, patients will often continue to experience fever and cough, as well as fatigue, myaligia, clubbing of fingers, and rales.[6] In cases of cerebral paragonimiasis, the flukes and their eggs evoke a brisk inflammatory response with abscess and granuloma formation.[5,6,8] Symptoms include headache, vomiting, seizures, and focal neurologic deficits. Treatment is usually with praziquantel.[15]

Laboratory Diagnosis

Diagnosis of paragonimiasis is usually made by finding eggs in respiratory specimens or O&P examination of stool. Eggs in fresh clinical specimens (**Figure 3J**) are unembryonated and measure 80–120 µm long × 45–70 µm wide, with a moderately thick shell and an obvious operculum and prominent opercular shoulders. The abopercular end is often thickened, but there is not a defined abopercular knob.[1] Adults and eggs can also be found in lung biopsies. *Paragonimus* eggs are *birefringent* (having 2 different refractive indices) under polarized light in histopathology specimens.

Serologic testing is available for paragonimiasis. Also, Western blot assay has been optimized to detect infection caused by *P. kellicotti*.[75]

Nanophyetus salmincola (Nanophyetiasis)

General Considerations

Nanophyetus salmincola is an intestinal fluke that parasitizes fish-eating mammals and birds in the Pacific Northwest. Natural definitive hosts include foxes, raccoons, otters, coyotes, skunks, herons, and mergansers. The primary intermediate hosts are fish in the family Salmonidae, and the definitive hosts becomes infected after eating infected fish harboring metacercariae. Dogs can experience a fatal *rickettsial* disease called *salmon poisoning* that is carried by the flukes.[76]

Human infection also comes from the ingestion of metacercariae in infected salmon and related fish, although there is at least 1 case of a fish handler becoming infected after necropsying coho salmon without wearing protective gloves; the infection probably resulted from the incidental ingestion of metacercariae after contact with contaminating environmental sources.[76] Despite being common in naturally infected hosts, there are less than 50 documented human cases.[77,78]

Clinical manifestations and pathologic features

There are too few documented cases of human nanophyetiasis to get a complete sense of its clinical picture, but patients have presented with abdominal discomfort, diarrhea or increased number of bowel movements, fatigue, nausea, vomiting, weight-loss, and eosinophilia.[77] The pathologic response to human nanophyetiasis is undescribed in the literature, to our knowledge. *Nanophyetus salmincola* can host 2 species of *Neorickettsia* that cause salmon poisoning disease, a fatal rickettsial disease in dogs[79]; humans do not appear to be affected by the bacterium. Praziquantel is the drug of choice for nanophyetiasis.[80]

Laboratory diagnosis

Human nanophyetiasis is diagnosed by finding eggs during O&P examination of stool. Eggs are unembryonated and measure 64–97 µm long × 34–55 µm wide. The operculum is relatively inconspicuous, and the abopercular end is blunt and thickened.[1]

Metorchis conjunctus (Metorchiasis)

General considerations

Metorchis conjunctus is a liver fluke that parasitizes fish-eating mammals, such as bears, foxes, wolves, raccoons, minks, and fishers in Canada and the northeastern United States. Domestic dogs and cats can also serve as definitive hosts. The primary intermediate host and known source of human infections is the white sucker, *Catostomus commersonii*.[81,82] Human infections are rare but have been documented sporadically in Canada.[75,81,83]

Clinical manifestations and pathologic features

Althought there are only a few case reports, patients with metorchiasis have presented with abdominal pain, fever, headache, lack or loss of appetite for food, nausea, backache, elevated liver enzymes, and increased eosinophilia.[78,81] The pathologic response has not been described in the human host. Patients have responded well to praziquantel.[81]

Laboratory Diagnosis

Diagnosis of metorchiasis has been made based on the finding of eggs during O&P examination of stool. Eggs measure 30 µm long × 17 µm wide and, like other opisthorchids, are shed embryonated with a mature miracidium and have a prominent operculum.[82]

Acanthocephalans

Acanthocephalans are multicellular parasitic animals commonly referred to as *thorny-headed worms*. Although members of this group superficially resemble nematodes, they are more closely related to microscopic rotifers, or are possibly even nested within the phylum Rotifera.[84] Acanthocephalans have a complex life cycle involving a vertebrate definitive host and an arthropod intermediate host, with fish, reptiles, and amphibians serving as paratenic hosts. Human infection is rarely documented, and most cases of acanthocephaliasis have been attributed to members of the genera *Macracanthorhynchus* and *Moniliformis*. In addition to the species covered herein, there is 1 report of human infection from North America of *Corynosoma strumosa*, which is normally a parasite of seals, sea lions, and fish-eating birds, in an Eskimo in Alaska.[85]

Macracanthorhynchus hirudinaceous, *M. ingens*, *Moniliformis moniliformis* (Acanthocephaliasis)

General considerations

Most human cases of acanthocephaliasis are attributed to *Macracanthorhynchus hirudinaceous*, *M. ingens*, and *Moniliformis moniliformis*. *Macracanthorhynchus*

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hirudinaceous and *M. moniliformis* probably occur nearly worldwide in places where their primary definitive hosts (pigs and rats, respectively) live, whereas *M. ingens* is endemic to the eastern two-thirds of North America, where its primary definitive host is the raccoon. Although most human cases involving *Macracanthorhynchus* spp. have been attributed to *M. hirudinaceous*, it has been suggested[86,87] that most cases from the United States are probably caused by *M. ingens*, especially given that it is a native species, along with the anthropophilic nature of the raccoon host.

Adults reside in the small intestine of the definitive host, where they attach to the intestinal mucosa by means of an armed rostellum. This rostellum is not used for feeding; rather, nutrients taken up by the host are absorbed directly through the cuticle. Mated females release eggs that are shed in the feces of the definitive hosts. Eggs are shed containing a fully developed infective first-stage larva (*acanthor*). After eggs are ingested by an appropriate arthropod intermediate host, the acanthor molts into the second larval stage, known as an *acanthella*. Primary intermediate hosts for *M. hirudinaceous*, *M. ingens*, and *M. moniliformis* are scarabaeoid beetles, millipedes, and cockroaches, respectively.

After several weeks to several months, the acanthella becomes an infective cystacanth that remains dormant in the tissue of the arthropod host. The definitive host becomes infected after eating arthropods harboring infective cystacanths.[87] Humans also become infected after the ingestion of infected arthropods harboring cystacanth larvae. In the United States, most cases are seen in young children, who are more likely to put insects in their mouths.

Clinical manifestations and pathologic features

Patients with acanthocephalan infection may experience severe symptoms such as high fever, severe abdominal pain, lack or loss of appetite, nausea, diarrhea, frankly bloody stools, abdominal distension, intestinal perforation, intussusception, ascites, and peritonitis; they may even die.[6,87] In particular, patients with *M. hirudinaceus* are likely to present with an acute syndrome.[6] Leukocytosis and eosinophilia are common. Treatment is with albendazole or other antihelminth drugs.[2]

Laboratory diagnosis

Typically, acanthocephaliasis is diagnosed by finding adult worms in stool specimens or, less commonly, by the finding of eggs in O&P examination of stool. *Moniliformis moniliformis* seems more likely to release eggs into the feces of the human host than *Macracanthorhynchus* spp.

Adults are large pseudocoelomate worms. They may have constrictions or wrinkles but lack true segmentation. Adult female *Macracanthorhynchus* species (**Figure 2E**) are 12–32 cm long; males are smaller, at 7–8 cm long. They are often heavily wrinkled or distorted and may be mistaken for mucus strands. *Moniliformis moniliformis* (**Figure 2F**) is slightly smaller and more slender, with females measuring 10–27 cm long and males 4–10 cm long; adults have prominent annulations in the anterior two-thirds or so of the body. Adults of both genera have a retractable proboscis that contains an armed rostellum with recurved hooks.[87] In clinical specimens, the proboscis may be retracted, and the worm may require dissection for this feature to be examined.

Adult *Macracanthorhynchus* species can be separated by the length-to-width ratio of the proboscis or by performing a morphometric analysis of the hooks.[88] Eggs of *Macracanthorhynchus* species (**Figure 3K**) are 80–100 µm long × 50 µm wide and have a tick shell that is heavily textured with a lattice-like wrinkling; the eggs of *M. hirudinaceous* and *M. ingens* cannot be separated morphologically. Eggs of *M. moniliformis* (**Figure 3L**) are slightly larger, measuring 90–125 µm long × 65 µm wide and have a thinner shell. Eggs of both genera contain a fully developed acanthor when shed in feces.[1,87]

Conclusion

As described in this article, some zoonotic helminths can cause serious and even life-threatening infections in humans. Although we have covered the most clinically relevant zoonotic helminth infections endemic to North America, many other zoonotic infections can, on rare occasions, cause human infections with potentially severe consequences. For this reason, clinicians and laboratory scientists should be familiar with the main clinical and diagnostic features of common zoonotic helminths and the resources available for their identification. **LM**

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