
277 Tissue Nematodes

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Parasitic roundworms capable of invasion of human tissues are classified as tissue nematodes. They are found in a variety of ecologic niches that allow for human exposure. Many are present in outdoor environments and are transmitted to children through the ingestion of nonfood substances. The infectious stages of many of these tissue parasites often involve an animal host and can be classified as zoonotic infections. Many of these zoonotic parasitic tissue nematodes can permanently affect the cognitive ability, development, and vision of an infected child. This chapter focuses on some of the most medically relevant tissue nematodes.

VISCERAL LARVA MIGRANS AND OCULAR LARVA MIGRANS CAUSED BY *TOXOCARA CANIS*, *TOXOCARA CATI*, AND *BAYLISASCARIS PROCYONIS*

Besides *Enterobius vermicularis* (pinworm), toxocariasis may be the most common helminth infection in the United States, with seroprevalence in many areas exceeding 10%; however, the true burden of disease resulting from this large number of infections is poorly characterized.¹ Several clinical manifestations can follow exposure to the infectious

larval forms of these tissue nematodes. Infected people can develop covert toxocarasis, which is a clinical manifestation of toxocarasis involving wheezing and eosinophilia that can manifest similar to and be misdiagnosed as asthma. Covert toxocarasis is believed to be caused by chronic exposure.² Perhaps the most commonly recognized clinical syndrome is visceral larva migrans, which manifests as a febrile illness characterized by multisystem involvement and eosinophilia.¹ Patients can also present with devastating neurologic manifestations (neurologic toxocarasis) or ocular larva migrans, which can be severe with irreversible visual loss resulting from scarring of the retina and in some cases retinal detachment secondary to larval migration to the eye.³ *Toxocara* spp. infections identified through serologic testing may be associated with longterm cognitive consequences. Measurable reductions in scores on cognitive tests have been demonstrated when comparing children with serologic evidence of *Toxocara* spp. infection with children without such evidence.⁴ Longitudinal studies to confirm these findings are still needed, but concern has been raised that the impact of this disease goes far beyond the cases brought to medical attention by symptoms.

Human infection with these tissue nematodes was first described in the 1950s, when a larva was detected in the eye of a child, and a series of children presenting with eosinophilia and severe multisystem disease was reported to be infected with *Toxocara canis* and *Toxocara cati* larva.^{5,6} *T. canis* and *T. cati* are common causes of infections of dogs and cats, respectively, whereas *Baylisascaris procyonis*, a third important nematode in this group, commonly infects raccoons.⁷ The life cycles and morphologic features of these tissue nematodes share similarities with *Ascaris lumbricoides* in humans, yet the adults of these 3 species have a shorter length than the adult *Ascaris* (Fig. 277.1).

Life Cycle

Human infection with *T. canis*, *T. cati*, or *B. procyonis* is initiated after embryonated eggs are ingested by humans. Humans come into contact with these eggs accidentally when their environment is contaminated by fecal material from dogs, cats, or raccoons that harbor the adult worms (Fig. 277.2).^{8,9} After ingestion, the eggs are triggered to hatch, thereby releasing larvae that penetrate the wall of the small intestine and enter the circulation. In humans, the larvae migrate through various tissues, unable to complete their life cycle, and end up dying in the tissues they invade (Fig. 277.3).

When these embryonated eggs are ingested by their definitive host, they undergo the classic ascarid life cycle, including hatching, penetrating the intestinal, and entering the circulation. In the definitive zoonotic host,



FIGURE 277.1 Adults of *Toxocara canis*. The male measures 6 cm and the female measures 9 cm in length.



FIGURE 277.2 Embryonated egg of *Toxocara* species (65 μ m).

they migrate to the lungs and are coughed up and swallowed. Then they return to the intestinal tract, where they mature into adult worms after a period of 60 to 90 days from time of egg ingestion.¹⁰ The adult worms produce eggs that are released into the environment and become infective after 2 to 4 weeks of maturation in the soil.¹¹ Infection can occur through ingestion of eggs, transplacentally, or through breast milk.¹² Although adult worms live for only 4 to 6 months, embryonated eggs can survive for several years in warm, moist soils.

Clinical Features

Toxocarasis is a disease that consistently affects the young, with visceral larva migrans occurring mainly in children <7 years of age and ocular larva migrans in children 8 to 16 years of age.¹³ Although these diseases disproportionately affect the young, these helminths also are a recognized and perhaps underdiagnosed cause of disease in travelers.³ The clustering of infection in children is believed to reflect their frequent exposure to fecally contaminated play environments (e.g., playgrounds, yards, and sandboxes). In addition to young age, risk factors for infection include

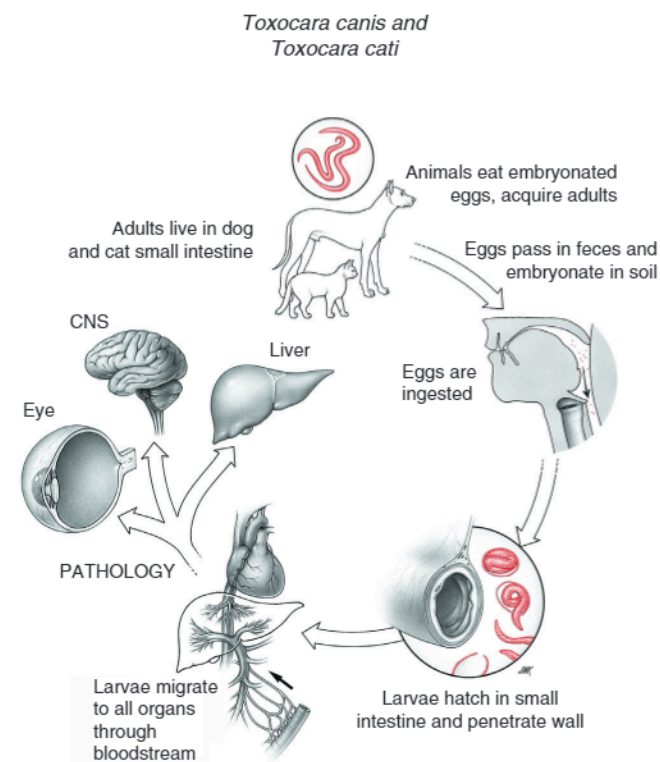


FIGURE 277.3 Life cycle of *Toxocara canis* and *T. cati*. CNS, central nervous system. (Redrawn from Despommier DD, Gwadz RW, Hotez PJ, Knirsch CA [eds]. *Parasitic Diseases*, 5th ed. New York, Apple Trees Productions, 2005.)

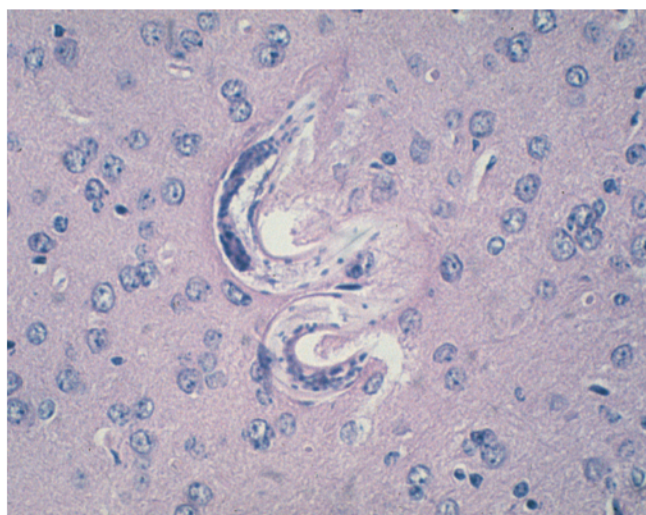


FIGURE 277.4 The third-stage larva of *Toxocara canis* in the brain of an experimentally infected mouse.

male sex, pet ownership, low level of education, psychiatric disease, foreign birth, and play in public parks.¹

With the introduction of larval forms into humans after ingestion of embryonated eggs, a range of pathologic features can occur that largely depends on which tissues are invaded. The clinical presentation appears to vary based on host factors such as the age of the person infected and whether the person is immunologically naïve, as well as pathogen-related aspects such as inoculum size, number of exposures, and tropism of particular strains.^{11,14} The pathologic findings are believed to be caused by the host's immune response to dead and dying larvae in the viscera (Fig. 277.4). Patients with visceral larva migrans may present with a febrile illness including eosinophilia, hepatosplenomegaly, bronchospasm, and a myriad of other symptoms depending on localization of the nematode larva. The spectrum of disease that can result includes subclinical infections, less severe covert toxocariasis, and fully symptomatic visceral larva migrans with inflammation and disease in multiple organs. Before liver biopsy was replaced by serologic testing, the liver was a common site for isolating nematode larvae in eosinophilic granulomas.⁶ Pulmonary symptoms, potentially confused with asthma, may be accompanied by infiltrates apparent on chest imaging.² Myocarditis as well as nephritis can develop. If larvae invade the central nervous system (CNS), then encephalopathy, seizures, and functional intestinal disorders can develop in infected patients.¹⁵⁻¹⁹

Ocular larva migrans is a devastating manifestation that tends to occur in people at a slightly older age; it generally manifests in adolescents as visual impairment isolated to a single eye. Larvae that have invaded the retina trigger an immune response as the larvae start to die. This immune response leads to granuloma formation that can result in deformation of the retina and detachment of the macula. In some cases these lesions have been visualized on ophthalmic examination, and because of their visual similarities to retinoblastoma, the risk of unnecessary enucleation of the infected eye exists.²⁰⁻²³

Although *Toxocara* spp. infections can be fatal in puppies, death is rare in human infection. When death occurs in humans, it is attributed to involvement of the myocardium or CNS, along with an overly exuberant immune response when infection is with *T. canis* and *T. cati*. In contrast, infection with *B. procyonis*, a common infection of raccoons, can have high mortality rates.

Humans are exposed to *B. procyonis* through ingestion of embryonated eggs deposited in the environment by raccoons. The increased severity of disease and high mortality rate are attributed to unique features of this tissue nematode. *B. procyonis* larvae are larger, up to 2 mm compared with 0.5 mm for *T. canis* and *T. cati*, and have the unique ability to continue to grow inside the infected human.²⁴ *B. procyonis* is known as a pathogen to include in the differential diagnosis of eosinophilic meningitis and presents a public health problem because raccoons often enter human environments.²⁵

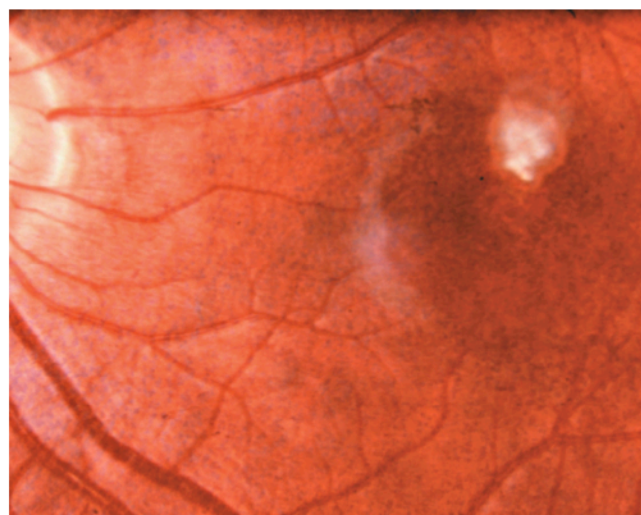


FIGURE 277.5 Larva of *Toxocara* in retina that manifests as a granuloma.

Diagnosis

T. canis, *T. cati*, and *B. procyonis* infection should be included in the differential diagnosis in a child, adolescent, or returning traveler presenting with an unexplained febrile illness with eosinophilia and a compatible history. A combination of clinical presentation, appropriate risk factors, and a positive serologic test result supports the diagnosis. The recommended test for toxocariasis detects immunoglobulin G against excretory-secretory antigens derived from *Toxocara* spp. larvae. This *Toxocara* enzyme immunoassay is available through the US Centers for Disease Control and Prevention and is estimated to be 78% sensitive and 92% sensitive when the appropriate cutoff is used.²⁶ One of the challenges of using serologic testing in the diagnosis is that the test detects an immune response to the larval form of the nematode and does not necessarily confirm current active infection. Although a biopsy demonstrating larvae is definitive, this is rarely indicated. The diagnosis of ocular larva migrans also incorporates a consistent ophthalmologic examination (Fig. 277.5). Stool examination of infected people is not helpful because these tissue nematodes are unable to complete their life cycle in humans, and thus adult egg-producing worms are never present in the human gastrointestinal tract. Although a serologic test has been developed for *B. procyonis* that has high sensitivity and specificity, many human cases are not diagnosed until autopsy (Fig. 277.6).

Treatment

Although evidence-based guidance with regard to treatment is limited, patients with *T. canis* and *T. cati* infections can be treated with oral albendazole, 400 mg twice daily for 5 days.²⁷ In the case of active ocular inflammation, topical and systemic corticosteroids can be used, whereas the role of anthelmintic therapy is unclear because of the lack of knowledge regarding the intraocular pharmacokinetics and pharmacodynamics. The best treatment for *B. procyonis* infection is unclear, but good outcomes have been reported with high-dose albendazole, 25 mg to 50 mg/kg/day in divided doses started promptly and continued for 10 to 20 days, with concomitant corticosteroids.^{25,28}

Prevention and Medical Ecology

Limiting human exposure to infective embryonated eggs in the environment is a critical aspect of decreasing the disease burden of these tissue nematodes. Once introduced into the environment, the infective ascarid eggs can remain viable for months to years because of their resistant acellular outer shell that allows them to withstand extreme temperature changes, various degrees of desiccation, and even harsh chemicals.^{29,30} Any strategies to rid contaminated soil of these hardy eggs must overcome this barrier.

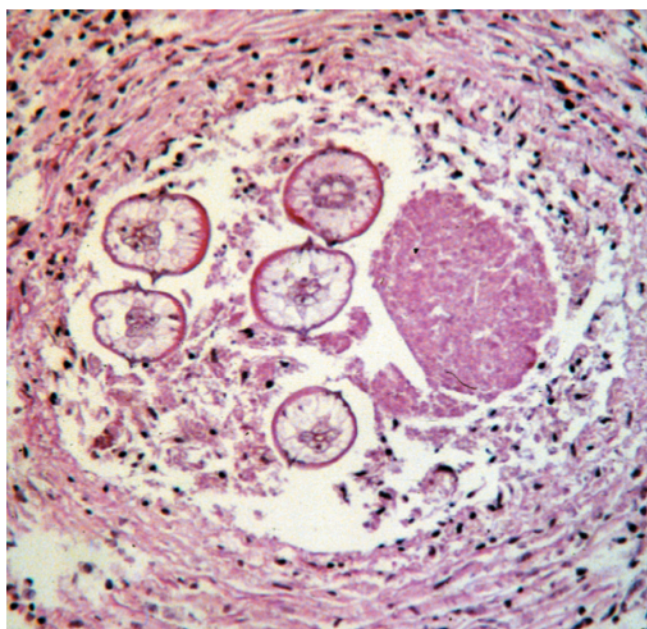


FIGURE 277.6 Larvae of *Baylisascaris procyonis* in brain of a child who died of the infection.

Once introduced into the soil by the indiscriminate deposition of fecal material by dogs, cats, or raccoons, eggs can be distributed through the environment. The common earthworm is efficient at redistributing fecal material back up to the surface even with eggs initially buried up to 2 feet below the surface.²⁹ Various domestic animals distribute contaminated soil on their paws, whereas ground-feeding birds such as pigeons, starlings, and sparrows can carry eggs farther afield on their feet and beaks.^{10,31}

Eggs also can enter municipal drinking water supplies and end up in waters used for recreational purposes, where inadvertent water ingestion can infect a swimmer.¹⁰ When infected animals deposit these eggs in an environment that allows for their maturation into an embryonated and infective state, the opportunity for continued transmission exists. In this particular public health challenge, veterinarians can have the most striking impact by encouraging pet owners to maintain dewormed pets.

VISCERAL LARVA MIGRANS CAUSED BY *ANGIOSTRONGYLUS* SPP.

The 2 major *Angiostrongylus* spp. of medical importance are *Angiostrongylus cantonensis* and *A. costaricensis*. *A. cantonensis* is the major cause of visceral larva migrans throughout China, Southeast Asia, and many areas of the Pacific and South Pacific, including Hawaii. *A. costaricensis* is found in Central and South America.

Life Cycle. Rats are the definitive hosts for *Angiostrongylus* spp. The worms infect several rat species and live and lay eggs in the pulmonary arteries of rats. The released eggs move through the capillaries in the lung and then penetrate the alveolar spaces. From the alveolar spaces, the larvae migrate up the respiratory tree and are swallowed down into gastrointestinal tract ultimately to pass out of the rat in feces.³² *A. cantonensis* larvae incubate in the soil before being consumed by a variety of mollusks and crustaceans.^{33–36} Humans are infected when they inadvertently consume the larval stages of *A. cantonensis* present in uncooked snails, slugs, or raw vegetables contaminated with secretions of these invertebrates.

A. costaricensis larvae generally are restricted to infecting only 1 invertebrate host, the slug, and in most cases the specific slug known as *Vaginulus plebeius*. Human infection results when humans accidentally ingest these slugs or food contaminated with its secretions.

Clinical Features. In most cases, human infection with *Angiostrongylus* spp. results in failure of the worm to complete its life cycle. Once in a human host the larvae often migrate to the brain or, rarely, to the lungs

as has been observed in infants and small children. Then, the larvae die surrounded by an eosinophil-rich inflammatory infiltrate.³⁷ The pattern of clinical presentation varies with each species of this nematode. *A. cantonensis* third-stage larvae usually migrate to the meningeal capillaries, where the dying larvae trigger eosinophilic inflammation and resulting eosinophilic meningoencephalitis. Part of the disease can involve vascular thrombosis and aneurysms. *A. cantonensis* is the most common cause of eosinophilic meningitis outside the developed world and should be considered in the differential diagnosis in travelers returning from endemic areas.³⁷

Patients infected with *A. costaricensis* present with fever, bitemporal or frontal headache, and meningismus. Vomiting is reported in most cases, as are migrating painful paresthesias.³⁸ Investigators have suggested that migrating painful paresthesias often persist for weeks to months along with headaches. Although eosinophilic meningitis is characteristic on cerebral spinal fluid examination, focal lesions are usually not present on head computed tomography or magnetic resonance imaging, and this can finding be useful in distinguishing the disease from other disorders such as *Gnathostoma spinigerum* infection and neurocysticercosis.³⁹ The natural course of the disease without treatment is for resolution of symptoms in 1 to 2 weeks. Unfortunately, in children disease duration may be longer and severity may be worse.

Diagnosis. The diagnosis of *Angiostrongylus* spp. is usually based on clinical presentation because serologic testing is not widely available. Confirmation of suspected cases has been achieved using posttreatment serologic testing in concert with research laboratories.³⁸

Treatment. With the self-limiting nature of this disease, treatment options often have focused on symptomatic features rather than on anthelmintic medications. Although animal models have supported the use of anthelmintic therapy trials, efficacy in human infection has not been demonstrated, and reports have noted that anthelmintic therapy may lead to disease exacerbation.^{40–42} Serial lumbar punctures and analgesics are the usual approaches to therapy.

VISCERAL LARVA MIGRANS CAUSED BY *GNATHOSTOMA SPINIGERUM*

G. spinigerum is a parasite that infects a variety of mammals including cats, dogs, and mongooses; its intermediate hosts are copepods, snakes, fish, and birds. The disease is endemic in Southeast Asia and is increasingly recognized in Mexico and Central and South America.⁴³

Life Cycle. *G. spinigerum* adults live coiled in the wall of the small intestine of their definitive hosts. Eggs are passed out into the environment in the feces and hatch in freshwater. Larvae are released and are ingested by copepods of the genus *Cyclops*. Snakes, fish, and birds then ingest these infected crustaceans. In these intermediate hosts, the larvae mature into a stage infective for humans. When humans ingest infected crustaceans, the larvae are able to exit the gastrointestinal tract and then invade various tissues.^{44–46}

Clinical Features. The clinical features of *G. spinigerum* infection, or gnathostomiasis, are caused by the invasion of deep tissue by these larvae. Although these larvae fail to mature in the human host, they are aggressive migrators and cause direct destruction as well as the host inflammatory reaction.⁴⁷ Skin manifestations can include cutaneous larva migrans, panniculitis, and subcutaneous swellings. Invasion of the CNS can occur with peripheral eosinophilia, as well as eosinophilic meningitis with radicular pain and paresthesias caused by larval migration. *G. spinigerum* also can invade the eye and result in intraocular disease.⁴⁸

Diagnosis. Although previously the diagnosis of gnathostomiasis was limited to an appropriate travel history, clinical presentation, and eosinophilia, diagnostic tests have become available. Enzyme-linked immunosorbent assay and Western blot are now aiding diagnosis, but these tests are not available in the US, and definitive diagnosis is often not possible.⁴⁹

Treatment. Although this disease can be self-limited, therapy includes a 21-day oral course of albendazole at a dose of 400 mg once daily.⁵⁰ Ivermectin has also been shown to be effective in several trials and can serve as an alternate agent. The role of anthelmintic therapy remains unclear for ocular and neurologic disease, in which this therapy can worsen symptoms. In some cases, corticosteroids have been used in the

treatment of patients with CNS manifestations. Unfortunately, relapses have been reported with either therapy.³⁸

CUTANEOUS LARVA MIGRANS CAUSED BY *ANCYLOSTOMA BRAZILIENSE*

Cutaneous larva migrans is a zoonotic hookworm infection with worldwide distribution that is most often caused by larvae of a dog or cat hookworm, such as *Ancylostoma braziliense*, *Ancylostoma caninum* (Fig. 277.7), or *Uncinaria stenocephala*. *A. braziliense* is the most common causative organism. These larvae are unable to mature, but on occasion *A. caninum* larvae can migrate to the small intestines in humans and cause eosinophilic enteritis or, rarely, subacute neuroretinitis, rather than cutaneous larva migrans. Other less common nematodes also can cause cutaneous larva migrans, including raccoon-transmitted *Strongyloides procyonis*, which results in “duck hunter’s itch.”

Life Cycle. The filariform larvae of these zoonotic hookworms survive in sandy, moist soils for several days. Larvae of zoonotic hookworms are especially common in India and Southeast Asia, Brazil, the Caribbean, and Puerto Rico, where dogs and cats are permitted to defecate.⁵¹ In the human host, infection begins when the filariform larvae penetrate unbroken skin but then fail to receive the proper environmental cues. Instead of going farther in the life cycle, larvae migrate laterally through the deeper layers of the epidermis and can survive there for approximately 10 days.⁵² An intense inflammatory reaction, associated with itching in the affected areas, develops within days after larvae enter the dermis and is provoked by hydrolytic enzymes secreted by the larvae.

Clinical Features. The serpiginous lesions known as “creeping eruption” are evident after an incubation period of 1 week (Fig. 277.8). Secondary bacterial infection caused by scratching is common. In a review of 98 patients with cutaneous larva migrans seen at a travelers’ clinic in Munich, 73% of the lesions were found on the lower extremities, with the buttocks and anogenital region (13%) and trunk and upper extremities (7% each) affected less frequently.⁵³

Diagnosis. The diagnosis is almost always purely clinical unless one surgically extracts the worm. Some patients have peripheral blood eosinophilia or an elevated serum immunoglobulin E level, but laboratory findings generally play little or no role in establishing a diagnosis.⁵³

Treatment. The treatment of choice is oral therapy with anthelmintic medication. A single dose of ivermectin (200 µg/kg once, sometimes repeated) is considered more effective than a single dose of albendazole, but repeated treatments of albendazole (400 mg daily for 5–7 days) are comparable. Some investigators recommend a 3-day course of albendazole (400 mg daily). Topical thiabendazole in a concentration of 10% to 15% applied 3 times daily for 5 to 7 days is an alternative treatment, but patients’ compliance is an issue. Cryotherapy with liquid nitrogen can cause blistering and ulceration of the skin and should not be performed.⁵⁴



FIGURE 277.7 Third-stage larva of *Ancylostoma caninum*. (Courtesy of E. Gravé.)

VISCERAL LARVA MIGRANS CAUSED BY ASCARIDS OF MARINE MAMMALS

Anisakiasis in humans is caused by various species of nematodes belonging to the genera *Anisakis*, *Phocanema*, *Terranova*, and *Contracoecum*. The adults of these parasites live in the lumen of the intestinal tract and infect sea mammals, particularly dolphins, whales, sea lions, and seals. Anisakid first-stage larvae infect several crustacean species. Second-, third-, or fourth-stage larvae infect a wide variety of teleosts (bony fish).⁵⁵

Life Cycle. The adult worms of marine mammal ascarids embed in the gastric mucosa and pass unembryonated eggs out into the environment in the feces. The eggs embryonate, and larvae mature inside the eggs until free-swimming larvae are released. Free-swimming larvae are ingested by crustaceans, and in this host they mature into the stage infective for fish as well as squid. Rather than staying in the intestine of the cold-blooded vertebrate host, larvae migrate to the peritoneal cavity, where they grow up to 3 cm in length. On the death of the vertebrate host, larvae migrate to muscles where they can be ingested by marine predators and develop into adult worms. After embedding into the mucosa, adult female worms begin laying eggs, and the life cycle is complete.⁵⁶

Humans are accidental and dead end hosts for marine ascarids. Humans can become infected when they ingest raw or undercooked marine fish. In humans, the ingested larvae mature and quickly attempt to penetrate the gastric or intestinal mucosa.⁵⁷

Clinical Features. Infected people often present with abdominal pain that can be severe. The time from ingestion of parasites to the onset of symptoms is usually a matter of minutes to hours. Nausea, vomiting, abdominal distention, mild fever, and diarrhea with blood and mucus in the stool can be part of the presentation.⁵⁸ If larvae are able to penetrate the mucosa, then angioedema, urticarial, and allergic symptoms can dominate the clinical presentation.⁵⁹

Diagnosis. Definitive diagnosis and treatment are accomplished by removal of the parasite. Sometimes the worms are expelled through coughing or vomiting, but at other times endoscopic removal or surgical intervention for extraintestinal manifestations is necessary. Serologic tests using an antigen capture enzyme-linked immunosorbent assay are available in some countries and have a sensitivity reported to be nearly



FIGURE 277.8 “Creeping eruption” caused by a larva of *Ancylostoma caninum*. (Courtesy of G. Zalar.)

100%.⁶⁰ Polymerase chain reaction (PCR)-based tests have been developed but are not commercially available.⁶¹

Treatment and Prevention. Currently, no anthelmintic therapy is approved by the US Food and Drug Administration for the treatment of marine ascarid infection, but successful treatment has been reported with oral albendazole 400 mg twice daily for 6 to 21 days.^{62,63} Thorough cooking or freezing of seafood before ingestion can prevent infection by anisakid nematodes. Most sushi restaurants in the US and elsewhere now inspect pieces of raw fish carefully before serving them, and the Food and Drug Administration requires freezing before raw fish are served. Flash freezing in liquid nitrogen has become a popular way of processing fish destined for sushi restaurants. After a peak in the 1980s, the incidence of anisakid visceral larva migrans in Europe and North America from the consumption of raw fish has been reduced to a few sporadic cases annually.⁶⁴

TRICHINELLA SPIRALIS (TRICHINELLOSIS)

The genus *Trichinella* has undergone revision since the advent of reliable DNA probes. Eight species and 11 genotypes are now recognized, all capable of infecting humans.^{65–67} Members of the genus *Trichinella* can infect a broad spectrum of mammalian hosts, thus making these organisms the cause of one of the world's most widely distributed nematode infections. *Trichinella* spp. are genetically related to *Trichuris trichiura* and *Capillaria* spp.; all belong to the family Trichurata. These roundworms constitute an unusual group of organisms in the phylum Nematoda in that they all live their lives as intracellular parasites.

Diseases caused by *Trichinella* spp. are referred to collectively as trichinellosis. Currently, the prevalence of trichinellosis is low in the US, with infections occurring mostly as scattered outbreaks, less often involving pork consumption and more often involving poorly cooked game.^{68,69} Most human cases are caused by *Trichinella spiralis*, and the information that follows concentrates on this species.

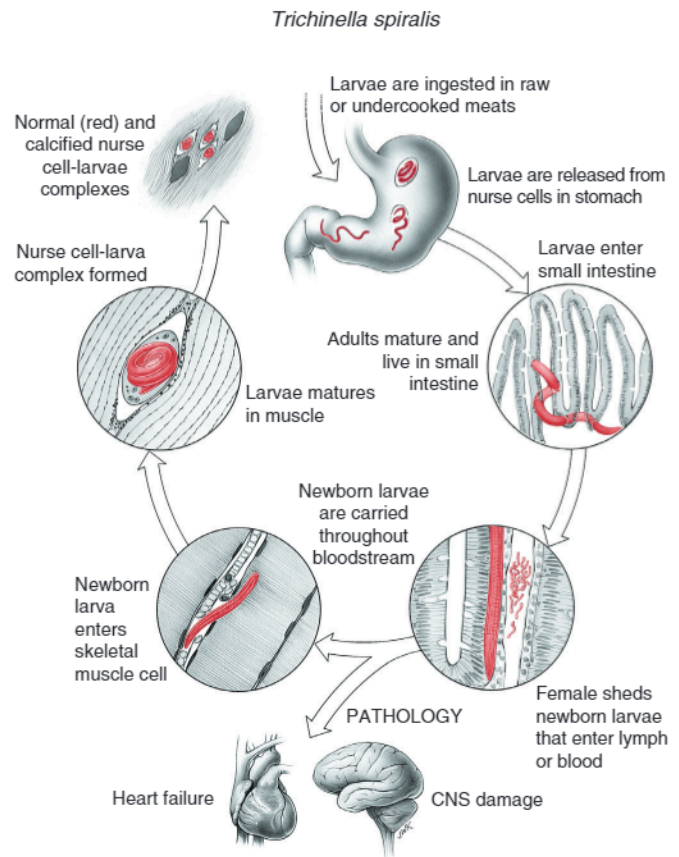
The domestic pig is the main reservoir host for *T. spiralis*. *T. spiralis* is significantly more prevalent in parts of Europe, Asia, and Southeast Asia than in the US. In Europe, and especially in Eastern Europe, the rise of trichinellosis has been associated with certain political and socioeconomic changes that resulted in a breakdown of the human and veterinary public health infrastructure.⁷⁰ Trichinellosis is considered endemic in Japan and China, and a large outbreak occurred in Lebanon in 1997 that infected more than 200 people.⁷¹ In contrast, *Trichinella* spp. infections in wildlife in the US are now thought to be caused largely by the T5 strain, tentatively designated *T. murrelli*.⁷²

Life Cycle

Infection is initiated by ingesting raw or undercooked meats harboring the nurse cell-larva complex (Figs. 277.9 and 277.10). Larvae are released from muscle tissue by digestive enzymes in the stomach and then locate to the upper two thirds of the small intestine. The outermost cuticular layer (epicuticle) becomes partially digested, thereby enabling the parasite to receive environmental cues and to select an infection site within the small intestine. Immature parasites penetrate the columnar epithelium at the base of the villus, where they live in a row and are considered intra-multicellular organisms.^{73–75}

Larvae molt 4 times in rapid succession over a 30-hour period and develop into adults. The female measures 3 mm in length by 36 μ m in diameter, whereas the male measures 1.5 mm in length by 36 μ m in diameter. Patency occurs within 5 days after mating. Adult females produce live offspring—newborn larvae, which measure 0.08 mm in length by 7 μ m in diameter (Fig. 277.11). The female produces offspring as long as host immunity does not develop. Eventually, the host acquires protective responses that interfere with the overall process of embryogenesis and create physiologic conditions in the local area of infection that force the adult parasites to egress and relocate further down the intestinal tract. Expulsion of worms from the host is the final expression of immunity and can take several weeks.

The newborn larva is the only stage of the parasite that possesses a sword-like stylet located in the oral cavity that is used to create an entry hole in potential host cells. Larvae enter the lamina propria in this fashion and penetrate the mesenteric lymphatics or the bloodstream. Most larvae enter the general circulation and become distributed throughout the body.



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FIGURE 277.9 Life cycle of *Trichinella spiralis*. CNS, central nervous system. (Redrawn from Despommier DD, Gwadz RW, Hotez PJ, Knirsch CA [eds]. Parasitic Diseases, 5th ed. New York, Apple Trees Productions, 2005.)

Migrating larvae leave capillaries and enter cells (Fig. 277.12). They appear to have no tropism for any particular cell type, and this cell entry is not limited to muscle cells. Once inside a cell, larvae either can remain or leave, depending on environmental cues received by the parasite. Most cell types die as the result of larval invasion. Skeletal muscle cells are the only exception. Not only do the parasites remain inside muscle cells after invasion, but also they induce a remarkable series of changes, causing the fully differentiated muscle cell to transform into one that supports the growth and development of the larva. This process is termed nurse cell formation.⁷⁶ Parasite and host cell develop in a coordinated fashion. *T. spiralis* is infective by day 14 of infection, but the worm continues to

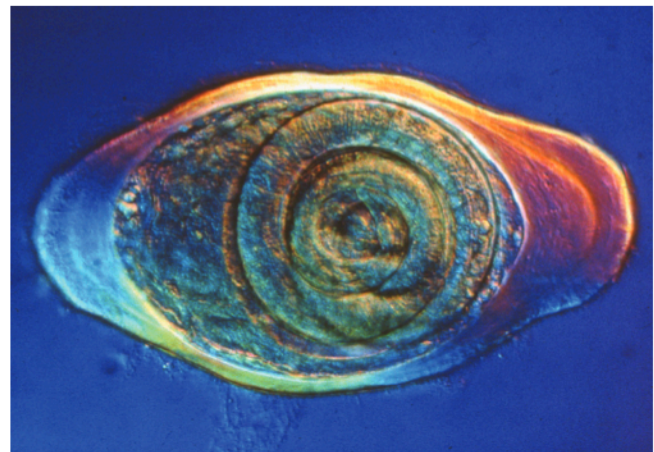


FIGURE 277.10 Nurse cell-larva complex of *Trichinella spiralis*.



FIGURE 277.11 Newborn larva of *Trichinella spiralis* (80 × 7 μm).

grow through day 20. The significance of this precocious behavior has yet to be appreciated.

Parasites inside cells other than striated muscle cells fail to induce nurse cells and either reenter the general circulation or die. Nurse cell formation results in an intimate and permanent association between the worm and its intracellular niche. At the cellular level, whorls of smooth membranes and clusters of dysfunctional mitochondria replace myofilaments and other related muscle cell components over a 14- to 16-day period. The net result is that the host cell switches from aerobic to anaerobic metabolism. Nuclei enlarge and divide, thus amplifying the host's genome within the nurse cell cytoplasm.⁷⁷ The nurse cell-parasite complex can live for as long as the host remains alive. Most do not, however, and are calcified within several months after forming. For the life cycle to continue, an infected host must die and be eaten by another mammal while the parasites are still viable. Scavenging is a common behavior among wild mammals, and this helps to ensure the maintenance of *T. spiralis* and its relatives in their respective host species.

Clinical Manifestations

The presentation of trichinellosis can vary from minimal or subclinical when a limited number of viable larvae are ingested to the distinct 2-stage presentation observed with heavy infection. Some clues, even in the early stages of the disease, can alert the physician to include trichinellosis in the differential diagnosis.

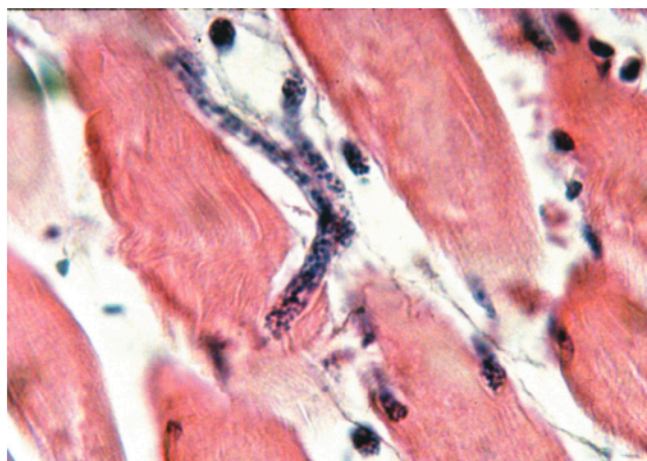


FIGURE 277.12 Migrating larva of *Trichinella spiralis* penetrating outward from a capillary.

The first few days of heavy infection are known as the gastrointestinal stage. This stage begins 1 to 2 days after ingestion of infected meat and manifests with secretory diarrhea, abdominal pain, and vomiting. These symptoms usually abate within 10 days after ingestion of infected tissue. A history of eating raw or undercooked meats and reporting similar illness in others who ate the same meats are suggestive of trichinellosis.⁷⁸

The parenteral stage begins approximately 1 week after infection and can last several weeks. Typically, the patient has fever and myalgia, bilateral periorbital edema, and petechial hemorrhages, which are seen most clearly in the subungual skin but also are observed in the conjunctivae and on other mucous membranes. Muscle tenderness is detected readily. Laboratory studies reveal a moderately elevated white blood cell count (12,000–15,000 cells/mm³), with eosinophilia ranging from 5% to 50%.⁷⁸

Larvae penetrating tissues other than muscle give rise to more serious sequelae. In many cases of moderate to severe infection, cardiovascular involvement leads to myocarditis. Electrocardiographic changes are frequently noted during this stage. Parasite invasion of the diaphragm and the accessory muscles of respiration can result in dyspnea. Neurotrichinellosis may occur as a result of CNS invasion.^{79,80} A final convalescent stage follows the 2 acute stages of this illness, during which time many nurse cell-parasite complexes are destroyed.

Diagnosis

The diagnosis is established on the basis of appropriate clinical and laboratory findings. These findings include eosinophilia and increases in serum muscle enzyme levels, antibody detection or detection of larvae in muscle, and epidemiologic investigations identifying a source and origin of infection. Muscle enzymes (e.g., creatine kinase and lactic dehydrogenase) are released and cause an increase in serum levels. Results of serologic tests can be positive within 2 weeks; enzyme immunosorbent assay results can be positive as early as 12 days after infection. Definitive diagnosis depends on finding the nurse cell-parasite complex in muscle biopsy by microscopic examination or detecting *Trichinella*-specific DNA by PCR. PCR is sensitive and specific for detecting small numbers of larvae in muscle tissue, but it rarely is used in the clinical setting.⁷⁸

Muscle biopsy results can be negative, even in patients with high-density infections, because of sampling error. In addition, the larvae can be at an early stage of development, thus making them inconspicuous, even to the experienced pathologist. A rising, plateauing, and falling level of circulating eosinophils throughout the infection period is not confirmatory, but in the appropriate clinical context it could warrant empiric therapy. Bilateral periorbital edema, petechiae under the fingernails, and high fever, coupled with a history of eating raw or undercooked meats, further solidifies the diagnosis of a presumptive infection.

Treatment

An anthelmintic should be administered, with the recommended dose of albendazole (400 mg twice daily for 8–14 days). Albendazole results in higher tissue levels and therefore is preferred to mebendazole. Use of the drug in pregnancy and in children <2 years of age requires consideration of potential risks versus benefits. In addition, it is thought that anthelmintics work best in the early stages of the infection; once muscle larvae are established, the clinical effectiveness of anthelmintics is reduced, and larvae can survive for years to cause chronic myalgias. Rapidly destroying larvae with anthelmintics can exacerbate host inflammatory responses and worsen the disease. Corticosteroid therapy, particularly prednisone (30–60 mg/day) for 10 to 15 days is recommended if the diagnosis is secure and the symptoms are severe. Antipyretics and analgesics are used in the myopathic stage and can be continued until fever and allergic signs recede.

Prevention and Medical Ecology

Since 2005, outbreaks of trichinellosis in the US have become rare and sporadic. Generally, most cases have been associated with ingestion of raw or undercooked meats obtained from commercial sources or from

wild game. However, pigs raised on family farms, as compared with commercial factory farm operations, are more likely to be fed uncooked garbage and thus acquire the infection. US Department of Agriculture law, which bans feeding unprocessed garbage, is enforced only in large production facilities. Hunters and those sharing in their kills of carnivorous mammals, including bear, fox, and cougar, have sometimes become infected. Herbivores can harbor the infection because most plant eaters occasionally ingest meat when the opportunity arises. Epidemics caused by eating raw horsemeat have been reported from France, Italy, and Poland.

The scope of meat inspection in the US does not include *Trichinella* spp. In Europe, the countries in the European Union use several strategies for examining meat for muscle larvae. Most of these strategies serve to identify pools of meat sampled from given regions. If these samples consistently test negative, then a *Trichinella*-free designation is applied to that supply of meat. Nonetheless, rare outbreaks occur despite this rigorous system of inspection.

Trichinellosis caused by *T. spiralis* can be prevented by cooking meat thoroughly at 58.5°C for 10 minutes. In the case of pork with viable *T. spiralis* organisms, freezing it at –20°C for 3 days is effective. Freezing is not always effective with meat from other animals or for other species of *Trichinella*. *T. nativa* was found to survive for up to 34 months in frozen muscles of grizzly bear and for up to 5 years frozen at –18°C in the muscles of carnivores.⁶⁷ The freeze tolerance of encapsulated *Trichinella* muscle larvae appears to be largely determined by *Trichinella* spp. but also depends on host tissue.^{81–83} Hence

thorough cooking is the only way to render all meats safe from all *Trichinella* spp.

All references are available online at www.expertconsult.com.

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