pyrimethamine (75 mg/day) together with folinic acid (10 to 25 mg/day).[50] Other drugs, including nitazoxanide, diclazuril, roxithromycin, a combination of albendazole and ornidazole, metronidazole, quinacrine, and furazolidone, may also be effective.

Sarcocystis Species

Sarcocystis species, previously known as *Sarcosporidia,* are zoonotic protozoan parasites. Since the first report of sarcocystosis in mice in 1843, more than 130 species of *Sarcocystis* have been reported from a wide range of domestic and wild animals. Unlike many other coccidian parasites, *Sarcocystis* has an obligatory two-host cycle. Definitive and intermediate hosts are generally species specific but have been identified for only half of all *Sarcocystis* species. Human intestinal sarcocystosis, in which humans are the definitive hosts, is caused by one of two species, *Sarcocystis hominis* or *Sarcocystis suihominis.* Humans may also be accidental intermediate hosts for other *Sarcocystis* species, leading to human muscular sarcocystosis.

Life Cycle

Through the ingestion of poorly cooked or raw meat containing tissue cysts, humans may serve as definitive hosts for *Sarcocystis* in pigs (*S. suihominis*) and cattle (*S. hominis*). Humans may also be incidental intermediate hosts when food or water contaminated with fecal sporocysts is ingested.

After consumption of tissue cysts by the definitive host (usually a carnivore), motile bradyzoites emerge from sarcocysts and enter the intestinal lamina propria. Bradyzoites mature into male and female forms, and sexual reproduction follows in the intestinal mucosa; mature oocysts, each of which contains two sporocysts, are formed. The thin walls of oocysts are readily disrupted, leading to shedding of both oocysts and infectious sporocysts in the feces. In contrast, sporocysts are hardy, resisting treatment with bleach, chlorhexidine, and iodophors. Each sporocyst measures approximately 10 by 15 μm and contains four sporozoites.

After ingestion of sporocysts by the intermediate host (usually an herbivore), sporozoites are released, penetrate the intestinal epithelium, and migrate to vascular endothelium, where they undergo cycles of asexual multiplication. The resulting merozoites are then hematogenously disseminated and invade cardiac or striated muscle cells. Within muscle, the characteristic septate cysts (sarcocysts) containing bradyzoites develop. Sarcocysts become infectious only after they have matured, a process that may take 2 months or more depending on the species. The cycle is complete when mature muscle cysts are eaten by an appropriate definitive host.

Epidemiology

Although worldwide in distribution, most human cases of *Sarcocystis* infection have been reported from tropical and subtropical climes, mainly Southeast Asia and, in particular, Malaysia. Cases have been less commonly reported from other continents. Identification of *Sarcocystis* in stool or muscle, or of antibodies in serum, is most often an incidental finding. As many as 20% of residents in some endemic areas are seropositive, reflecting the sanitary conditions and dietary habits in these regions.[51] In 2011, an outbreak of suspected symptomatic muscular sarcocystosis was first reported among travelers to Tioman Island, Malaysia,[52] with the outbreak continuing into 2012.[53] To date, over 100 travelers are infected, and no definite source has been identified. Studies after an outbreak of 89 cases associated with a trip to Pangkor Island, Malaysia,[54] demonstrated molecular identity of the disease isolates with *Sarcocystis nesbitti* found in the stool of snakes (*Naja naja*), with the route of transmission presumably being the consumption of water or food contaminated with snake feces.[55]

Sarcocystis infections are common in many other animals, including nonhuman primates, cattle, dogs, cats, rodents, and reptiles, among others.

Clinical Manifestations

Most individuals with either intestinal or muscular sarcocystosis have mild symptoms or are asymptomatic. Development of symptoms may depend in part on the species of sarcocysts that are ingested.[56] In human volunteers who have ingested pork or beef containing *Sarcocystis* species, a mild self-limited gastrointestinal illness developed in some, whereas others passed sarcocysts but remained asymptomatic. Symptoms induced by experimental challenge with infected meat include nausea, abdominal discomfort, and self-limited nonbloody diarrhea, with symptom severity dependent on the amount of meat consumed.[56] Onset of diarrhea is generally rapid, within 48 hours of ingestion, and illness is typically brief and self-limited. Segmental eosinophilic and necrotizing enteritis attributed to sexual forms of *Sarcocystis* has been reported; however, causation in these cases was not definitely established.[57]

Muscular sarcocystosis is thought to be typically asymptomatic. Muscle cysts vary greatly in size, ranging from 50 μm to 5 cm. Eosinophilic myositis has been reported, occurring in association with other symptoms, including fever, bronchospasm, transient pruritic rashes, lymphadenopathy, subcutaneous nodules, and arthralgias.[58] In the first Malaysian outbreak, travelers had myalgias and most had fever, in conjunction with eosinophilia. The hallmark of the illness was clinically significant myositis that occurred 30 days or more after travel.[53] A second outbreak in persons attending a retreat on Pangkor Island was attributed to *S. nesbitti.*[54] The onset of symptoms occurred between days 1 and 26 after the retreat, with the majority (70.7%) beginning between days 9 and 11. The median duration of symptoms was 17 days. The disease was characterized as an acute, febrile, relapsing myositis. Myocarditis seems to be rare. Other reports include systemic disease in one patient with AIDS, with organisms recovered from the stool, small bowel, liver, and blood[59]; acalculous cholecystitis requiring cholecystectomy in a second patient with AIDS[60]; and laryngeal sarcocystosis.[61]

Diagnosis

Sarcocystosis can be suspected when compatible symptoms are present in conjunction with a history of recent consumption of raw or undercooked meat in an endemic area. Sporocysts may be identified in the stool of symptomatic (and asymptomatic) individuals with intestinal sarcocystosis. Oocysts (Fig. 283.3) are less commonly visualized in stool samples owing to the fragility of their cell walls. Brightfield microscopy and fecal flotation wet mounts are optimal, using density gradient media rather than other sedimentation methods.[56] The Kato thick smear technique also has excellent sensitivity for diagnosis.[62] Speciation cannot be determined by microscopy.

For patients with symptoms suggestive of acute muscular disease, muscle biopsy using conventional histologic staining can demonstrate sarcocysts, although staining may be variable. Myositis and myonecrosis associated with mixed inflammatory infiltrates and sometimes tissue eosinophilia may be seen in cases of acute muscular sarcocystosis.[58]

Serology using Western blot assay is highly suggestive of previous exposure but is not diagnostic for acute disease and is not believed to be able to distinguish between intestinal and muscular disease.

Therapy

No specific treatment for *Sarcocystis* infection is known. Infection, if symptomatic, is generally self-limited. Albendazole suppressed symptoms in one human case but was not curative.[58] TMP-SMX has been used

FIG. 283.3 Mature oocyst of *Sarcocystis,* containing two readily visualized sporocysts. *(From DPDx Image Library, Centers for Disease Control and Prevention, Atlanta, GA.)*

with apparent clinical effect in several cases.[63] The efficacy of other antiparasitic agents in treating human disease is unknown. Corticosteroids may provide symptomatic relief in cases of acute myositis.

Prevention

Intestinal sarcocystosis can be prevented by ensuring meat is cooked or frozen such that bradyzoites are killed. Muscular sarcocystosis can be prevented by reducing individual exposures to sporocyst ingestion. This may be challenging given potential environmental seeding and contamination of food and water; however, drinking filtered, boiled, or bottled water and thorough cooking of food that may be contaminated with sporocysts can mitigate the risk of infection.

BALANTIDIUM COLI

Balantidium coli was identified in 1857. It is the largest protozoan and the only ciliate pathogen of humans.

Life Cycle

After ingestion of cysts via contaminated food or water, trophozoites are released in the small intestine. The oval trophozoite usually measures 30 to 150 µm in length and 25 to 120 µm in width but may reach 200 µm in length. Its surface is covered with tiny cilia that propel it through the intestinal lumen. Trophozoites migrate to the large intestine, where they multiply in the colon wall and formation of cysts occurs. Cysts, which measure 40 to 60 µm in diameter, are the infective forms of the organism and survive well in the external environment.

Epidemiology

B. coli has a worldwide distribution but is most frequently reported from Latin America, Southeast Asia, Papua New Guinea, and parts of the Middle East. Although *B. coli* is found in many mammals, domestic and wild pigs are considered to be the main reservoir for human infection, with prevalence rates of 40% to 100%.[64] In humans, the prevalence is usually less than 1%; higher rates have been reported among individuals in hyperendemic areas and residential institutions. Human infection most often results from the ingestion of produce or water contaminated with pig excrement or from handling of the animal. An increase in the population of feral pigs in Australia was associated with the first reported case of balantidiasis on that continent.[65] Person-to-person transmission can also occur. However, humans are generally resistant to infection, and poor nutrition and underlying debility seem to be risk factors for disease.[64]

Clinical Manifestations

Most infections are asymptomatic. Clinical manifestations may include a chronic course characterized by intermittent diarrhea, abdominal pain, and weight loss. Rarely, a more fulminant colitis with blood and mucus in stools may occur; this may lead to intestinal perforation with subsequent peritonitis or extraintestinal disease.[66–68] Rare presentations include a fatal case of pneumonia in a patient with cancer, pulmonary hemorrhage, symptomatic (hematuria) and asymptomatic urinary infection, vertebral osteomyelitis, liver abscess, and keratitis.[69–75]

Diagnosis and Therapy

Balantidiasis can be diagnosed by finding rapidly motile trophozoites (Fig. 283.4A) in fresh or preserved stool; cysts (Fig. 283.4B) are infrequently detected. In invasive intestinal disease, endoscopic findings include necrosis and ulceration similar to those found in invasive amebiasis, bacterial dysentery, and inflammatory bowel disease; trophozoites may be recovered from scrapings of the periphery of ulcers detected on endoscopic examination. Pulmonary disease may be diagnosed by the identification of trophozoites in bronchoalveolar lavage specimens.

Tetracycline is the treatment of choice; metronidazole and iodoquinol are alternatives (Table 283.3).[47] Nitazoxanide has also been used effectively. Courses of therapy for as long as 20 days may be required for cure in persons with HIV infection.[76]

BLASTOCYSTIS SPECIES

Despite its high prevalence throughout the world, major issues about *Blastocystis* remain unresolved, including its taxonomy and pathogenicity.[77,78] Uncertainties about the role of *Blastocystis* in causing human disease are due to challenges in diagnosis and increasing recognition of varying pathogenicities of different *Blastocystis* subtypes.

TABLE 283.3 Therapy (Adult) for Balantidiasis

DRUG[a]	DOSAGE
Tetracycline	500 mg PO qid for 10 days
Metronidazole	750 mg PO tid for 5 days
Iodoquinol	650 mg PO tid for 20 days

[a]Drugs are listed in order of preference.
PO, Orally.

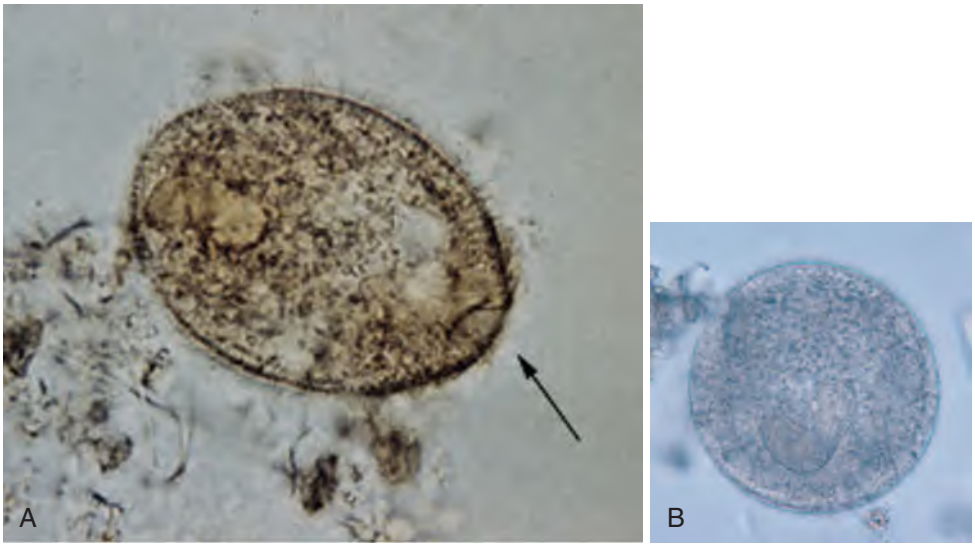

FIG. 283.4 *Balantidium coli* trophozoite and cyst. (A) *B. coli* trophozoite demonstrating cilia on the cell surface *(arrow).* A bean-shaped macronucleus is visible toward the left of the trophozoite. (B) Wet mount of an unstained *B. coli* cyst. Cysts are infrequently visualized in stool. *(From DPDx Image Library, Centers for Disease Control and Prevention, Atlanta, GA.)*

Sequences of the small subunit ribosomal RNA gene place *Blastocystis* in the stramenopiles, a diverse group of protist organisms that includes brown algae and diatoms[79]; under the six-kingdom classification, it is placed in the kingdom Chromista. Analysis of the elongation factor-1α gene, however, has indicated relatedness to *Entamoeba histolytica.*[80] *Blastocystis* lacks a cell wall, contains organelles with features of a protozoan, and reproduces asexually, usually by binary fission. The organism exhibits considerable morphologic variability and karyotype diversity. At least 17 species from humans and animals have been identified, 9 of which have been identified in humans.[81] As a result, *Blastocystis* in humans is referred to as *Blastocystis* spp. rather than *Blastocystis hominis.* Subtypes 1 to 4, and particularly subtype 3, are most frequently found in humans. Humans may also be infected by *Blastocystis* species of other primates, mammals, rodents, and birds.[82]

Life Cycle

Four major forms of *Blastocystis* predominate: vacuolar, granular, ameboid, and cystic forms. All four forms contain cytoplasm and organelles. The vacuolar form, with a large central vacuole, usually measures between 4 and 15 µm but is highly variable in size and is the most frequently detected form in fecal specimens. The granular form is similar to the vacuolar form but is characterized by intracytoplasmic or intravacuolar granules. The ameboid form, rarely visualized, has been considered to be important in pathogenesis.[83] More recently, cysts measuring 2 to 5 µm have been identified; they may be readily misidentified as fecal debris owing to their small size. Multivacuolar and avacuolar forms have also been described.

Various life cycles have been proposed for *B. hominis.* Currently, it is believed that after ingestion of infective cysts, excystation occurs in the large intestine. Cysts then develop into vacuolar forms and undergo encystation before being excreted in stool.[82]

Epidemiology

Whereas *Blastocystis* is found worldwide, differences in the geographic distribution of specific subtypes have been reported, although definitive conclusions may be difficult to make given the varying diagnostic techniques used in different studies. For example, subtype 3 appears to be present globally and is the most commonly identified subtype among human isolates,[84] whereas subtype 4 is prevalent in Europe[85] but is uncommon in Asia.[86] The significance of these observations is unclear. Regardless, the prevalence of blastocystosis in humans seems to be higher in developing countries (30%–50%) than in developed countries (1.5%–10%).[87] However, even within a given country, reported prevalence rates vary greatly; in China, for example, the prevalence in four communities ranged from 1.9% to 32.6%.[78] With the advent of PCR, previous epidemiologic study results may be found to be significantly underestimated, as noted by a recent study from Senegal showing a 100% infection rate.[88] Such variability may reflect differences not only in socioeconomic status or hygienic conditions but also in local customs and living conditions.

Risk factors associated with infection include immune compromise, travel to and immigration from developing countries, and exposure to contaminated food and water.[82] Among Polish soldiers involved in peacekeeping missions to Iraq and Afghanistan, *B. hominis* was identified in 15.3%.[89]

Pathogenicity

The role of *Blastocystis* in causing disease remains controversial. It has been hypothesized that there may be virulent and avirulent strains of *Blastocystis,* which could account for the variability in symptoms. However, most studies fail to show a definite correlation between pathogenicity and subtypes or genotypes.[90,91] Evidence that *Blastocystis* is causally linked to intestinal disease is based on numerous case reports and uncontrolled or retrospective series in which infection was associated with nonspecific gastrointestinal symptoms. In many studies that have included asymptomatic controls, neither the identification of *Blastocystis* in stool samples nor the concentration of organisms in stool has correlated with the presence of gastrointestinal symptoms. However, observational studies of TMP-SMX therapy[92] and small placebo-controlled studies with metronidazole[93] and nitazoxanide[94] have demonstrated symptomatic improvement coincident with reduction or elimination of the organism in stool and suggest that *Blastocystis* may be pathogenic. The pathogenicity of the organism remains unclear because of the uncertainty that other causes of symptoms, including other pathogens, have been eliminated in case series and treatment trials, and the inability of case-control studies to determine the association of a low-grade pathogen with disease.

Although some authors have suggested that *Blastocystis* is most likely to be pathogenic when large numbers of organisms are present (>5/oil immersion field), no association has been noted between number of organisms and symptoms.[95] In addition, since the parasite is intermittently excreted, there is often no consistency in organism count.

Clinical Manifestations

Clinical signs and symptoms attributed to *Blastocystis* typically include acute or chronic diarrhea, bloating, flatulence, abdominal cramps, and fatigue. Irritable bowel syndrome (IBS) has been associated with *Blastocystis* in some studies. A meta-analysis of epidemiologic studies of *Blastocystis* species showed that there was a 2.34-fold relative risk of *Blastocystis* infection in those with IBS.[96] Cases of refractory ulcerative colitis[97] recurrent megacolon,[98] and invasive colonic disease[99] caused by *Blastocystis* have been reported. Extraintestinal manifestations attributed to *Blastocystis* infection, including generalized urticaria and iron-deficiency anemia during pregnancy, have also been described.

Diagnosis

Until the recent availability of PCR assays, diagnosis relied primarily on the demonstration of parasites in stool. Microscopic diagnosis is challenging owing to the variable forms and sizes of *Blastocystis,* and sensitivity is poor compared with PCR assay.[100,101] *Blastocystis* may be visualized in wet mounts (Fig. 283.5A), but permanent smears are preferred for microscopic diagnosis. The trichrome stain (see Fig. 283.5B) seems to be the most sensitive stain for detection. Concentration methods may be less sensitive than other microscopic techniques. Use of electron microscopy or immunofluorescence assay for diagnosis is neither practical nor readily available. In vitro cell cultivation requires 48 to 72 hours for incubation but is more sensitive than microscopy and concentration methods,[100] especially if small numbers of organisms are present. PCR assay is not only highly sensitive and specific but also facilitates subtyping[100–102]; this technique is becoming widely available for routine diagnosis. Serology is not useful in diagnosing infection.

Therapy

Treatment of asymptomatic infections is unnecessary.[103] Symptoms attributed to *Blastocystis* infection are often self-limited, and therapy for "symptomatic" infections should be withheld until other causes of intestinal symptoms have been ruled out. Treatment of blastocystosis is often unsatisfactory; metronidazole, TMP-SMX, iodoquinol, and paromomycin are the most commonly recommended therapies[47] (Table 283.4) but are variably successful.[92,93,104] Nitazoxanide[94] and *Saccharomyces boulardii*[105] have been used with good effect in limited clinical studies. In one small study of 12 isolates, in vitro susceptibility tests did not support the efficacy of many commonly used agents, such as metronidazole, paromomycin, or triple therapy with furazolidone,

TABLE 283.4 Therapy (Adult) for Blastocystosis

DRUG[a]	DOSAGE
Metronidazole	750 mg PO tid or 1.5 g daily, for 10 days
Trimethoprim-sulfamethoxazole	1 DS tablet[b] bid or 2 DS tablets daily for 7 days
Iodoquinol	650 mg PO tid for 20 days
Nitazoxanide	500 mg bid for 3 days
Paromomycin	25–35 mg/kg divided tid for 7 days

[a]Drugs are listed in order of preference.
[b]One DS tablet contains 160 mg trimethoprim/800 mg sulfamethoxazole.
DS, Double strength; *PO,* orally.

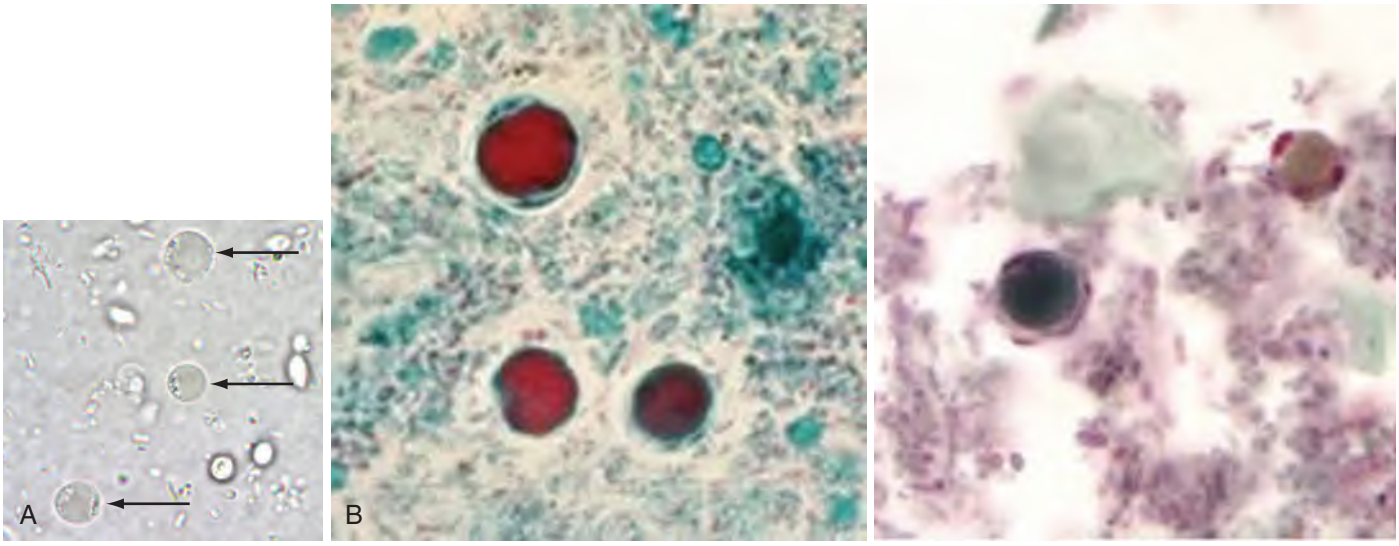

FIG. 283.5 *Blastocystis hominis* cysts. (A) Unstained wet mount. Arrows indicate cysts. (B) Stained with trichrome. Vacuoles vary from red to blue. *(From DPDx Image Library, Centers for Disease Control and Prevention, Atlanta, GA.)*

nitazoxanide, and secnidazole, but consideration was offered on the possible utility of TMP-SMX or ivermectin.[106] However, in vitro data do not always correlate with clinical studies that do show therapeutic efficacy, for example, in studies of metronidazole, paromomycin, and nitazoxanide.[93,94,107] It is important to remember that symptomatic improvement in those who are successfully treated for blastocystosis may be due to other drug effects on the microbiome or on organisms that were not detected prior to treatment.

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Diseases Due to Toxic Algae

284 Human Illness Associated With Harmful Algal Blooms

J. Glenn Morris, Jr.

SHORT VIEW SUMMARY

Definition
- Illnesses of primary clinical concern related to preformed toxins produced by algal species include ciguatera fish poisoning, paralytic shellfish poisoning, and amnesic shellfish poisoning.

Epidemiology and Microbiology
- Depending on the agent, illness is caused by ingestion of toxins in seafood or by inhalation or skin contact.
- Occurrence of illness is usually linked with blooms of specific toxic algal species (see Table 284.1). Harmful algal bloom–related illnesses in the United States have been reported from the Atlantic, Pacific, and Gulf Coasts; Hawaii; Alaska; and the Caribbean (see Fig. 284.1).

Diagnosis
- Diagnosis is based on clinical presentation (see Table 284.1).

Therapy
- Therapy is supportive. The syndrome of hypotension/bradycardia seen in severe cases of ciguatera fish poisoning may require atropine; respiratory support may be necessary in severe cases of paralytic shellfish poisoning.

Prevention
- Prevention is based on avoidance of fish or shellfish that contain toxins. Environmental monitoring of shellfish for toxins responsible for paralytic, amnesic, and neurotoxic shellfish poisoning is conducted by state and local health departments.

During the past several decades, the association of human health and environmental problems with harmful and toxic algae has been increasingly recognized,[1,2] as has awareness of the complex range of natural toxins (and toxin congeners) that can be produced by these microorganisms. Toxic species constitute a small percentage of the thousands of species of microscopic algae at the base of the marine food chain. However, when these species proliferate, they may cause massive killing of fish and shellfish, the death of marine mammals and seabirds, alterations in marine habitats, and, with specific exposure, human illness and death. Although blooms of certain species such as *Karenia brevis* (formerly known as *Gymnodinium breve*) may be manifested as red tides, adverse events often occur in the absence of visible discoloration of water.

Harmful algal blooms appear to be increasing in frequency; in the United States, problems that in the past were confined to a few geographic locations are now being seen at multiple sites along the US coastline (Fig. 284.1). The factors leading to this apparent increase in incidence are not well understood, although it has been postulated that human-related phenomena such as nutrient enrichment of waterways, climatic change, and disruption of ecosystems play a role.[1,3–9] These are, however, complex systems, and there may be wide variability in incidence rates, with a number of factors influencing risk for disease.[10]

Eight clinical syndromes or illnesses are currently linked with harmful algal blooms (Table 284.1).[1] As more research is done in this area, it is possible that other syndromes will be identified. Ciguatera fish poisoning, paralytic shellfish poisoning, and neurotoxic shellfish poisoning are also described in Chapter 101.

CIGUATERA FISH POISONING

Worldwide, ciguatera fish poisoning is the most clinical syndrome associated with marine biotoxins, with estimates that global case numbers range from 50,000 to 500,000 per year. It is a major public health problem in the Caribbean and South Pacific regions, particularly in areas with tropical reefs.[8,10–14] Illness is caused by ciguatoxins that are passed up the marine food chain, with large predatory reef fish (e.g., barracuda, jacks, snappers, moray eels) posing the greatest risk for toxicity.[14,15] A 2013 study in the US Virgin Islands found that 12% of lionfish (a highly invasive species being found with increasing frequency on tropical reefs in Florida and the Caribbean) had potentially toxic levels of ciguatoxin,[16] suggesting that recommendations to "eat more lionfish" to save reefs may be ill-advised.

Toxins are produced by dinoflagellates within at least eight species in the genera *Gambierdiscus* and *Fukuyoa,*[14,17,18] with toxicity varying by species. Increases in numbers of these toxic dinoflagellates have been associated with disruption of normal reef ecology and reef communities, including disruption by storms, human activity, and climate change.[3,14] Multiple ciguatoxin conjoiners have been identified, with ciguatoxins from the Pacific having slight structural differences from ciguatoxins found in the Caribbean. The toxin acts by stimulation of mucosal ion transport in the gastrointestinal tract and interaction with voltage-gated sodium channels along the peripheral nerves; in animal studies, it has been shown to cross the blood-brain barrier.

Among patients with ciguatera fish poisoning, gastrointestinal symptoms—nausea, vomiting, and diarrhea—are usually the presenting symptoms, occurring within 6 to 24 hours of eating a toxic fish. Patients typically present to emergency departments in the early hours of the morning after unknowingly eating a toxic fish for dinner. Within 12 to 48 hours of onset of illness, most patients also begin to experience neurologic symptoms, including headache; pain and weakness in the legs; and dysesthesias such as tingling sensations in the extremities and around the mouth, cold allodynia (cold objects feeling burning hot), burning sensation in the mouth, and aching pain around the teeth. These neurologic symptoms may persist for weeks to months[13,19] and may be linked with clinical depression. In a small percentage of cases, this can lead to a chronic/recurring syndrome that has many of the manifestations of chronic fatigue syndrome.

In severe cases, patients may be acutely bradycardic and hypotensive; in the Pacific, respiratory difficulties have also been reported. Restlessness and confusion may occur, and seizures and coma have rarely been reported. Deaths are exceedingly rare and are generally associated with high toxin exposure (consumption of viscera of a highly toxic fish), often in the setting of underlying cardiac or respiratory illness.[15] The diagnosis of ciguatera fish poisoning is clinical, based on the combination

TABLE 284.1 Human Illness Associated With Harmful Algal Blooms

SYNDROME	CAUSATIVE ORGANISMS	TOXIN PRODUCED	CLINICAL MANIFESTATIONS
Ciguatera fish poisoning	*Gambierdiscus* spp. and others	Ciguatoxin	Acute gastroenteritis followed by paresthesias and other neurologic symptoms
Paralytic shellfish poisoning	*Alexandrium* spp. and others	Saxitoxins	Acute paresthesias and other neurologic manifestations; may progress rapidly to respiratory paralysis
Neurotoxic shellfish poisoning	*Karenia brevis*	Brevetoxins	Gastrointestinal and neurologic symptoms; formation of toxic aerosols by wave action can produce respiratory irritation and asthma-like symptoms
Diarrhetic shellfish poisoning	*Dinophysis* spp.	Okadaic acid and others	Acute gastroenteritis, abdominal pain
Amnesic shellfish poisoning	*Pseudo-nitzschia* spp.	Domoic acid	In acute cases, gastroenteritis followed by memory loss, neurologic manifestations; may progress to amnesia, coma, and death; chronic, low-level exposure may result in mild memory loss
Azaspiracid shellfish poisoning	*Azadinium* spp. and others	Azaspiracid	Acute gastroenteritis, abdominal pain
Cyanobacteria exposure syndromes, *Lyngbya*	*Lyngbya* spp. *Microcystis* spp.	Lyngbyatoxin A, debromaplysiatoxin Microcystins ? BMAA	Swimmers' itch, particularly in inguinal area; sore eyes, ears; headache; possibly gastrointestinal symptoms Possible hepatotoxicity, neurotoxicity
Pfiesteria-associated syndrome	*Pfiesteria* spp. (?)	Unidentified to date	Deficiencies in learning and memory; acute respiratory and eye irritation; acute confusional syndrome

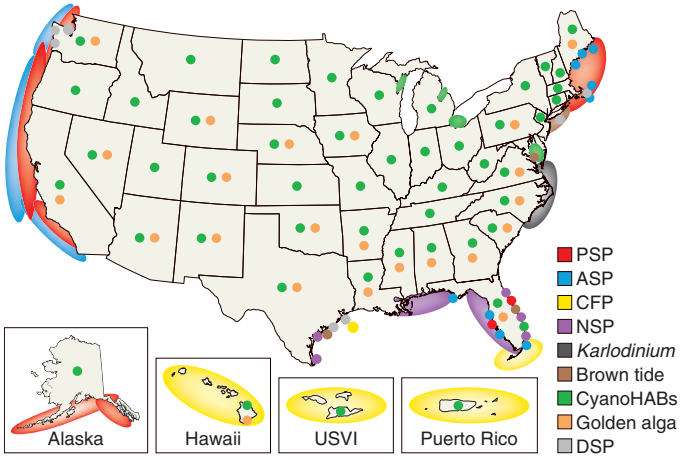

FIG. 284.1 US map depicting the various harmful algal bloom poisoning syndromes and other impacts that occur in specific areas. Colored dots or ovals indicate locations where the incidence of a particular syndrome has been reported or where toxins have been detected in tissue extracts or plankton. Ovals are used to indicate regional phenomena that occur at multiple locations along a coastline. All 50 states are impacted by cyanobacterial harmful algal blooms *(cyanoHABs)*, typically in many different rivers, streams, reservoirs, and so forth. The same is true for 23 states impacted by golden algal blooms caused by *Prymnesium parvum*. It is not practical to indicate the location of each cyanoHAB or golden algal bloom, so each state experiencing these blooms is indicated using a single green or gold dot. Larger green ovals denote widespread cyanoHAB problems in those areas. *ASP,* Amnesic shellfish poisoning; *CFP,* ciguatera fish poisoning; *DSP,* diarrhetic shellfish poisoning; *NSP,* neurotoxic shellfish poisoning; *PSP,* paralytic shellfish poisoning; *USVI,* US Virgin Islands. *(From National Office for Harmful Algal Blooms at Woods Hole Oceanographic Institution. Distributions of HABs in the U.S. Updated 2016.* http://www.whoi.edu/redtide/regions/us-distribution.*)*

of gastrointestinal and characteristic neurologic symptoms occurring after eating a reef fish that carries a risk for toxicity. Other individuals who have eaten the same fish may also be ill, although not everyone who eats a toxic fish will manifest symptoms. Individuals who have had prior episodes of ciguatera fish poisoning are more likely to be symptomatic, and there is a suggestion that alcohol consumption increases symptom risk. There are no confirmatory laboratory tests for illness. Identification of toxin in fish is possible but technically difficult. In the United States, testing is available only through the US Food and Drug Administration laboratories as part of an outbreak investigation.

Treatment is symptomatic and includes maintenance of adequate hydration, use of atropine for bradycardia/hypotension, and administration of analgesics and antidepressants as appropriate. For severe cases in the Pacific, monitoring of respiratory status is indicated. Some literature suggests that intravenous mannitol alleviates acute symptoms, and use of mannitol is common in emergency departments in endemic areas; however, no benefit with use of mannitol was seen in one double-blind randomized clinical trial.[20] At an anecdotal level, case reports suggest that neurologic manifestations, including pain syndromes, can be reduced by drugs such as amitriptyline, nifedipine, gabapentin, or pregabalin.[21]

Prevention is difficult because the toxin is not inactivated by cooking, and toxic fish have a normal appearance and taste. For native populations in endemic areas, prevention requires avoidance of high-risk fish from reef areas known to be toxic. Families concerned about the toxicity of a specific fish often report the use of crude bioassays, including feeding of suspect fish to the family cat.

In endemic areas in the Pacific and Caribbean, ciguatera fish poisoning can have major economic and nutritional impact, as local populations are often reluctant to eat locally caught fish because of the risk for illness. Reflecting these concerns, tourist hotels and restaurants in endemic areas such as the Caribbean tend to import all of their seafood from nonendemic regions. Cases are common in local populations in Puerto Rico and the US Virgin Islands, where the annual incidence in one study was estimated at 1200 cases per 100,000 population.[10] Cases seen in South Florida and Hawaii are generally associated with recreational fishing in reef areas. In Florida, data from a population survey are consistent with an incidence of between 5 and 6 cases per 100,000 population per year; rates are highest in Hispanic populations (relative risk, 3.4), possibly due to differences in patterns of fish consumption, including increased consumption of high-risk fish such as barracuda.[22]

PARALYTIC SHELLFISH POISONING

Based on reported cases, paralytic shellfish poisoning is one of the most common causes of marine biotoxin–associated illness in the continental United States and Alaska.[23,24] Illness has traditionally been associated with eating clams and mussels that contain saxitoxins produced by *Alexandrium* spp. and related dinoflagellates, although a variety of other vehicles have been reported.[25] Saxitoxins exert their effect by binding directly to the voltage-dependent sodium channels in nerve and muscle cell membranes, interrupting nerve signal transmission and leading to paralysis.

In contrast to ciguatera poisoning, gastrointestinal symptoms are less prominent than neurologic manifestations. Circumoral paresthesias and paresthesias of the extremities usually appear within 1 hour of

ingesting toxic shellfish, and they may be accompanied by ataxia, dysphagia, and changes in mental status. Hypertension may occur and corresponds to the extent of the ingested dose; in the most severe cases, patients may proceed to respiratory paralysis, usually within the first 24 hours of illness. Assays are available for identification of saxitoxins in serum and urine samples from affected patients, albeit at an experimental level.[26,27] Treatment is symptomatic; respiratory support may be necessary in the most severe cases.

Prevention is achieved through regular monitoring of shellfish populations for saxitoxin by public health authorities, with sampling data available on state health department web pages (e.g., the biotoxin web page of the Washington State Department of Health, www.doh.wa.gov/CommunityandEnvironment/Shellfish.aspx). Blooms of toxic *Alexandrium* spp. occur primarily between April and October along cold water marine coasts. In North America, this includes Alaska, the Pacific Northwest, and the St. Lawrence Seaway region of Canada. Toxic shellfish have also been found in cold water regions of southern Chile, England, Japan, and the North Sea. Most shellfish remain toxic for several weeks after a bloom subsides, although some shellfish species including butter clams may retain toxicity for more than a year.

NEUROTOXIC SHELLFISH POISONING

Illness is caused by brevetoxins produced by *Karenia brevis,* a major cause of red tides along the Florida coast; other *Karenia* spp. have been implicated in illness in other parts of the world. Ingestion of shellfish containing the toxin causes nausea and vomiting and circumoral paresthesias and paresthesias of the extremities. In more severe cases, patients may report ataxia, slurred speech, dizziness, and, in rare cases, mild respiratory distress.[28] Aerosolization of toxins by heavy wave action on the Atlantic coast of Florida can result in respiratory irritation and asthma-like symptoms in people walking along affected beaches.[29] Brevetoxin metabolites have been identified in urine samples from affected patients.[30] Treatment is symptomatic. The Florida Department of Health and other health authorities regularly monitor coastal areas for the presence of *K. brevis,* and they notify consumers accordingly. Data on occurrence of the organism in Florida waters are posted on the website of the Florida Department of Health (http://www.floridahealth.gov/environmental-health/aquatic-toxins/red-tide.html).

DIARRHETIC SHELLFISH POISONING

Diarrhetic shellfish poisoning results from eating mussels, scallops, or clams that have been feeding on toxic *Dinophysis* spp. or *Prorocentrum* spp. Symptoms include diarrhea, nausea, vomiting, and abdominal pain (which may be quite severe). Although okadaic acid appears to be the primary toxin responsible for the observed clinical syndrome, other toxic compounds have been isolated from these species. Although case reports came initially from Japan, diarrhetic shellfish poisoning has now been reported from multiple locations in Europe, Asia, South America, South Africa, and North America.

AMNESIC SHELLFISH POISONING

Amnesic shellfish poisoning results from the ingestion of shellfish containing domoic acid, which is produced by the diatom *Pseudo-nitzschia.*[1] An outbreak of illnesses caused by this toxin was reported in the Atlantic provinces of Canada in 1987.[31] Symptoms included vomiting, abdominal cramps, diarrhea, headache, and loss of short-term memory. On neuropsychological testing several months after the acute intoxication, patients were found to have severe antegrade memory deficits with relative preservation of other cognitive functions; patients also had clinical and electromyographic evidence of pure motor or sensorimotor neuropathy or axonopathy. In four patients who died, neuropathologic studies demonstrated neuronal necrosis and loss, predominantly in the hippocampus and amygdala.[32] Canadian authorities now analyze mussels and clams for domoic acid, and they close shellfish beds to harvesting when levels in shellfish exceed 20 mg/g.

Domoic acid has been identified in the marine food web in multiple locations in the United States including the Monterey Bay and Puget Sound areas. Elevated levels of domoic acid have been linked to neurologic illness and death in seabirds and sea lions[33] in these areas, possibly in relation to consumption of shellfish or anchovies; the toxin itself has been identified in 13 species of marine mammals in Alaska, in both adult and fetal tissue.[25] No cases of acute, severe amnesic shellfish poisoning comparable to the cases initially reported from Canada in 1987 have been confirmed in humans in the United States. However, a study of subsistence shellfish eating in Native American tribes in the Puget Sound area found that during years when high domoic acid levels were present in shellfish, infants born to shellfish-eating mothers had a significantly lower score on the Mental Developmental Index compared with infants born in other years.[34] An analysis of 4 years of data from this same cohort demonstrated a slight, albeit statistically significant, reduction in memory functioning in adults who consumed 15 or more razor clams per month (razor clams are a major source of domoic acid exposure in this population).[35] These data suggest that exposure to elevated domoic acid levels represents a health risk to infants and children and raise questions about the effect of chronic, low-level exposure to the toxin. In response to these data, the Washington State Department of Health in 2017 released an advisory recommending that people limit razor clam consumption to fewer than 15 clams per month. Further studies are needed to define the levels of domoic acid that may represent a risk in the setting of chronic exposure; it is likely that this level will be substantially below the current 20 mg/g limit currently used as the basis for closure of shellfish harvesting areas.

AZASPIRACID SHELLFISH POISONING

In 1995 an outbreak of shellfish-associated illness that very closely resembled diarrhetic shellfish poisoning was reported in The Netherlands. Subsequent studies demonstrated that the implicated shellfish were contaminated not with okadaic acid (the cause of diarrhetic shellfish poisoning) but with what is now known as azaspiracid, a class of toxins linked with dinoflagellates in the genus *Azadinium* (and possibly other related dinoflagellates in Amphidomataceae).[36] Toxic shellfish have subsequently been identified in multiple outbreaks of azaspiracid shellfish poisoning in western Europe and in Morocco.[37] Although no cases of azaspiracid shellfish poisoning have been reported to date in the United States, *Azadinium* spp. producing a new azaspiracid toxin have been identified in Puget Sound.[38]

CYANOBACTERIA EXPOSURE SYNDROMES, INCLUDING *LYNGBYA*

Cyanobacterial species can produce thick, foul-smelling, high-biomass blooms (triggered in many instances by increasing nutrient flows) that have been linked to human illness, animal mortality, and adverse ecosystem and economic effects in the United States and worldwide. Cyanobacterial species can produce microcystins, which are well recognized as hepatotoxins. While their role in causing liver disease in human populations remains controversial, there are increasing data that suggest a link between exposure to blooms and occurrence of illness.[39] There has also been recent interest in the cyanobacterial toxin beta-N-methylamino-L-alanine (BMAA), which has been implicated as a possible cause of neurodegenerative disease, including amyotrophic lateral sclerosis (AML).[39a] *Lyngbya* spp. have been implicated in a series of studies as a cause of skin itching (swimmers' itch), particularly in the inguinal region; sore eyes and ears; headache; and, in a small percentage of patients, abdominal pain and vomiting.[40,41]

PFIESTERIA-ASSOCIATED SYNDROME

Pfiesteria was first isolated during the early 1990s as a suspected cause of massive fish killings in the New River and Albemarle-Pamlico estuarine system of North Carolina, with respiratory symptoms, rashes, and problems with cognition being reported among laboratory personnel working with the microorganism. In subsequent studies conducted in the Chesapeake Bay region,[42] a significant association was found between the degree of exposure to waterways where *Pfiesteria* was known to be present and short-term deficiencies (<6 months' duration) in learning, memory, and higher-order cognitive function. No further outbreaks or cases have been reported, and, in the absence of identification of a toxin or other laboratory confirmation, questions remain about the role of *Pfiesteria* in the observed symptoms.

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J Diseases Due to Helminths

285 Introduction to Helminth Infections

James H. Maguire[a]

The helminthiases are among the most prevalent infections in the world and a leading cause of morbidity, particularly in low-income and resource-constrained regions. An estimated 1.5 billion persons harbor at least one species of parasitic worm.[1–3] The helminths that parasitize humans include the nematodes (roundworms) and platyhelminths (flatworms); the latter group consists of cestodes (tapeworms) and trematodes (schistosomes and other flukes). Leeches, ectoparasites belonging to the phylum Annelida (segmented worms), are not discussed here (see Chapter 291). Some helminths are exclusively or primarily human parasites, whereas others parasitize both humans and various other mammals, and others are parasites of lower mammals and infect human beings incidentally.

BIOLOGY OF HELMINTHS

Helminths are multicellular organisms that range from less than 1 cm to more than 10 m in length. They are covered by a cuticle or tegument that protects them from digestion and environmental stresses. Reproductive organs take up a large part of the body regardless of whether the sexes are separate or the species is hermaphroditic, as is the case with cestodes and nonschistosomal trematodes. Neuromuscular, digestive, excretory, and secretory systems typically are smaller and less complex, in keeping with the parasitic state.

The life cycle of all worms includes an egg, one or more larval stages, and the adult. Transmission to humans occurs by ingestion of helminth eggs or larvae, penetration of intact skin by larvae, or inoculation of larvae by biting insects. Depending on the species, humans are the only host; the intermediate host, in which asexual reproduction takes place; or, when there are one or two intermediate hosts, the definitive host in which sexual reproduction occurs.

Most helminths are unable to complete their life cycle within the human host, and development of eggs or larvae on soil, in water, within a plant, arthropod, or other animal intermediate host is necessary. Hence the geographic distribution of these parasites reflects the environmental conditions necessary for development of eggs or larvae or for survival of intermediate hosts and vectors. The only way for the intensity of infection in a person to increase is by further exposure to the infective stage; in the absence of continued exposure the infection lasts only as long as the life span of the adult worm.

In contrast, a few species, most notably *Strongyloides stercoralis*, are able to reproduce and multiply in numbers within the definitive human host.[4] In the case of *Strongyloides*, infectious larvae can be passed directly from one person to another, and transmission is possible in all geographic areas. Infection can persist for the life span of the host, and in the setting of immunosuppression, accelerated autoinfection can lead to overwhelming numbers of organisms even after a distant and light exposure.

[a]This chapter is based in part on the chapter by Adel A.F. Mahmoud in the fifth edition. All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

EPIDEMIOLOGY

The prevalence of helminth disease is highest in warm, developing areas, where climate, environment, and an abundance of vectors favor completion of the life cycle and where poverty leads to increased exposure to parasites because of poor sanitation, lack of clean water, and inadequate housing. Human activity can facilitate transmission, as seen in the huge numbers of new cases of schistosomiasis and foodborne trematode infections resulting from water resource development projects for hydroelectric power, irrigation, and aquaculture.[5,6] Conversely, in some endemic areas, large-scale control programs have led to interruption or dramatically decreased transmission of dracunculiasis (guinea worm disease), filariasis, onchocerciasis, and other parasitic worms.[7] Helminth infections are less common in temperate and industrialized areas, where they have been imported after travel or residence in tropical areas or acquired locally from domestic or wild animals via improperly prepared meat, fish, or vegetables, or from close personal contact, as in the case of pinworm infections.

Helminths produce large numbers of eggs or larvae and have a high reproductive capacity, which can lead to an extremely high prevalence of human infection when conditions are conducive to transmission, such as in rural areas in the tropics. Helminths are not uniformly distributed in human populations but are overdispersed, with most infected individuals harboring low worm burdens and only a small number harboring heavy infections.[8] The basis for aggregation of helminths in human populations may be related to the intrinsic biology of the parasites and density-dependent constraints on parasites, such as competition for nutrients, parasite-induced pathology, and host factors, including genetic susceptibility to infection, immunity, nutrition, and behavioral factors.

PATHOGENESIS AND HOST-PARASITE RELATIONSHIP

Most infected persons harbor few worms and have few or no signs or symptoms of disease, whereas a small proportion of persons with large numbers of worms are at risk of severe disease. Children with even moderate numbers of worms appear to be at risk of malnutrition, impaired growth, and impaired intellectual development.[9,10] Polyparasitism is widespread throughout the tropics and subtropics, and infection with multiple species of helminths seems to have an additive or multiplicative effect on nutrition and pathology.[11] Although mortality rates attributable to helminth infections are low, rates of chronic morbidity and debilitation are substantial.

Helminths produce disease by a variety of mechanisms, including mechanical effects such as intestinal obstruction (e.g., ascariasis), invasion of host cells or tissues with damage or loss of function (e.g., trichinellosis), or competition for nutrients (e.g., vitamin B_{12} deficiency from fish tapeworm infection). The host responses may lead to immunopathologic lesions, such as schistosome egg granulomas, which contribute significantly to disease. Interactions with other pathogens or potential carcinogens may contribute to chronic sequelae, such as advanced liver disease associated with coinfection of hepatitis B or C with *Schistosoma mansoni* or bladder cancer associated with *Schistosoma haematobium*.[12]

Basic to understanding the pathogenesis of helminthiasis is an appreciation of the size of the organisms, the multiplicity of their antigens, and the chronicity of the infection. Host responses are composed of myriad immunologic and nonimmunologic factors, some of which contribute to disease. Sterilizing immunity to helminth infections does not develop, and the extent to which previous infections with helminths lead to resistance to subsequent reinfection is not well defined. A degree of acquired immunity has been shown in infected individuals who were cured chemotherapeutically and then continued to live under the same conditions of exposure to infection.[13] These findings suggest that induction of resistance by vaccines may be a viable control strategy.

Eosinophilia is a characteristic of many helminth infections.[14] Peripheral blood, bone marrow, and tissue eosinophilia is associated with the migration or presence of worms in tissues. Eosinophilia is not observed in infections with helminths that reside in the lumen of the human gut (e.g., tapeworms) or are contained in cystic structures (e.g., echinococcal cysts). Eosinophils seem to play a significant role in the killing of helminths and host resistance to helminth infections and are responsible for a considerable amount of inflammatory pathology.[15] Chronic infection with worms typically leads to a constant state of immune activation characterized by a dominant Th2 type of cytokine profile, high immunoglobulin E levels, and proliferation and activation of eosinophils that acts to reduce parasite burden and reduce host tissue damage.[16]

Worms have successfully developed multiple strategies to evade host protective responses. Mechanisms include encapsulation within a host fibrous reaction (hydatid cyst), intraluminal location (e.g., *Ascaris*), acquisition of host antigens (schistosomes), and inhibition and downregulation of the host's immune response (filariae, cysticerci). Immune modulation by helminths can dampen the host response to other pathogens, allergens, and autoantigens and may have an adverse impact on the efficacy of vaccines against other organisms, promote progression of infections, such as tuberculosis and human immunodeficiency virus/acquired immunodeficiency syndrome, or affect the expression of allergic and autoimmune disease.[17–21] Helminth infections have been associated with modulation of inflammatory bowel disease, arthritis and diabetes, and, in different studies, increased or decreased risk of asthma and other atopic conditions.[17,22]

DIAGNOSIS OF HELMINTH INFECTIONS

Recognition of helminth infections requires knowledge of their clinical presentation, geographic distribution, and epidemiologic risk factors. Persons with light infections may be asymptomatic, and the only clues to diagnosis may be a history of travel and potential exposure to the parasite, as well as peripheral blood eosinophilia. It should be kept in mind, however, that eosinophilia may be absent, even in persons with invasive infections. The diagnosis of helminth infections rests heavily on microscopic examination of stool, urine, blood, other body fluids, and tissue (Table 285.1).[23,24] When eggs or larvae are produced in abundance, microscopy can be extremely sensitive, but multiple examinations or concentration procedures may be necessary to detect light infections or infections with organisms such as *Strongyloides*, which often shed low numbers of larvae in the stool. Serologic tests offer greater sensitivity than microscopic examination and may be the only way to avoid invasive diagnostic procedures for infections with tissue-invading helminths. Some serologic tests for helminths are available only from reference laboratories, and they may lack sensitivity or specificity and not distinguish between past and present infections. Assays to detect helminth antigens and molecular diagnostic techniques have been used mostly for research purposes and monitoring and evaluating control programs rather than diagnosis and management of individual patients.[25] Detailed information on laboratory procedures for diagnosis of parasitic infections, an image library, and instructions for obtaining prompt assistance in diagnosis is available on *DPDx*, the parasitology diagnostic website of the Centers for Disease Control and Prevention (http://dpd.cdc.gov/dpdx).

TREATMENT OF HELMINTH INFECTIONS

Excellent drugs are available for treating most helminth infections. Because agents such as albendazole, mebendazole, praziquantel, and ivermectin are highly effective in single or a few orally administered doses, as well as being safe and inexpensive, they are suitable for mass drug administration as well as individual treatment.[26,27] Heavy use of these drugs in control programs raises concerns for the emergence of resistance and the need for new drugs. A novel approach to treatment of individual persons with onchocerciasis and filariasis is the use of doxycycline to eliminate the endosymbiotic bacteria *Wolbachia* and thereby sterilize or kill the adult worms.[28,29] For infections such as cysticercosis, toxocariasis, and trichinellosis, antiinflammatory agents are used to minimize tissue damage and symptoms caused by the host's response to the parasite.

PREVENTION AND CONTROL

Helminth infections are prevented by (1) avoiding ingestion of infective eggs, larvae, or intermediate hosts infected with larvae; (2) preventing contact of bare skin with infective larvae; and (3) avoiding bites of infected vectors. At the personal level, these measures entail drinking safe water; properly cleaning, cooking, and otherwise preparing food; adequate hand washing and general hygiene; and using measures to avoid insect bites, among others. Communities can be protected by interventions such as provision of clean water and sanitation; enforcement of appropriate food-producing practices to prevent infection of fish, meat, and vegetables; vector control; and prevention or treatment of infections in domestic animals. Chemoprophylaxis with diethylcarbamazine can prevent infection with *Loa loa,* and artemisinin derivatives have prophylactic activity against *Schistosoma japonicum.*[30,31]

Global efforts to eradicate, eliminate, or reduce transmission of helminth diseases are advancing as a result of partnerships among governments, international agencies, nongovernmental organizations, philanthropic institutions, and industry.[27,32] The guinea worm eradication program, which relies on community education and participation, provision of filters for drinking water, clean water sources, and case containment, is nearing its goal of zero cases globally.[33] The cornerstone of global programs to eliminate onchocerciasis and lymphatic filariasis and reduce disease caused by schistosomiasis and intestinal helminths is periodic mass administration of anthelmintic drugs to populations at risk.[34] Pharmaceutical companies have donated and will continue to donate hundreds of millions of tablets of anthelmintic medications in support of these programs, and integration of different large-scale programs is lowering costs and improving efficiency.[34,35] The World Health Organization has set ambitious but realistic targets for the year 2020 as part of its Neglected Tropical Diseases program: global eradication of dracunculiasis, global elimination of lymphatic filariasis; elimination of onchocerciasis from the Americas and elimination as a public health problem elsewhere; and elimination of schistosomiasis from the Americas, Western Pacific region, and selected countries in Africa.[7,35] Ongoing research in support of these programs and to expand efforts to include other helminth diseases focuses on the development of new drugs, diagnostic methods, control strategies, and novel tools such as anthelmintic vaccines.[36,37]

TABLE 285.1 Diagnosis of Major Helminth Infections

PARASITE	STAGE	MICROSCOPIC DIAGNOSIS: SPECIMEN	OTHER METHODS
Roundworms (Nematodes)			
Intestinal Roundworms			
Ascaris lumbricoides (large intestinal roundworm)	Eggs	Feces	Identification of passed worm
Trichuris trichiura (whipworm)	Eggs	Feces	
Ancylostoma duodenale, Necator americanus (hookworm)	Eggs, larvae	Feces	
Strongyloides stercoralis (threadworm)	Larvae	Feces, duodenal fluid, sputum	Serology[a]
Enterobius vermicularis (pinworm)	Eggs	Swab of perianal skin; occasionally in feces	Cellophane tape test; identification of adult worms on skin
Tissue Roundworms			
Trichinella spiralis (trichinellosis)	Larvae	Muscle biopsy	Serology[a]
Dracunculus medinensis (guinea worm)			Identification of emergent adult worm
Wuchereria bancrofti, Brugia malayi (lymphatic filariasis)	Microfilariae	Blood, urine (in setting of chyluria)	Serology,[a] antigen test (blood)
Loa loa (African eye worm)	Microfilariae	Blood	Identification of adult worm in eye, serology
Onchocerca volvulus (river blindness)	Microfilariae	Skin snip	Identification of adult worm in resected nodules
Ancylostoma braziliense, other species (cutaneous larva migrans, creeping eruption)			Inspection of rash
Toxocara canis, Toxocara cati (visceral larva migrans), *Baylisascaris procyonis*	Larvae	Biopsy of liver, other tissues (usually not necessary)	Serology[a] (preferred)
Flukes (Trematodes)			
Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum, Schistosoma mekongi	Eggs	Feces, rectal snips, urine (S. haematobium)	Serology,[a] antigen test (serum and urine)
Fasciolopsis buski (intestinal fluke)	Eggs	Feces	
Heterophyes heterophyes (intestinal fluke)	Eggs	Feces	
Metagonimus yokogawai (intestinal fluke)	Eggs	Feces	
Clonorchis sinensis, Opisthorchis spp. (liver fluke)	Eggs	Feces, bile	Serology
Fasciola hepatica (liver fluke)	Eggs	Feces, bile	Serology[a]
Paragonimus spp. (lung fluke)	Eggs	Sputum, feces	Serology[a]
Tapeworms (Cestodes)			
Intestinal Tapeworms			
Taenia saginata (beef tapeworm)	Eggs	Stool	Identification of passed proglottid (segment)
Hymenolepis nana (dwarf tapeworm)	Eggs	Stool	
Diphyllobothrium latum (fish tapeworm)	Eggs	Stool	Identification of passed proglottid
Taenia solium (pork tapeworm)	Eggs	Stool	Identification of passed proglottid; stool antigen test; serology
Larval Tapeworms			
Echinococcus granulosus (cystic hydatid disease)	Protoscolices, hooklets	Fluid from cyst	Serology,[a] CT, MRI, or ultrasonography can be diagnostic
Echinococcus multilocularis (alveolar hydatid disease)	Larvae	Liver biopsy	Serology
Cysticercus (larval *Taenia solium*)	Larvae	Brain biopsy	Serology,[a] CT, or MRI of head can be diagnostic

[a]Serologic test is available through Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, GA.
CT, Computed tomography; *MRI,* magnetic resonance imaging.

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The complete reference list is available online at Expert Consult.

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286 Intestinal Nematodes (Roundworms)

Rojelio Mejia, Jill Weatherhead, and Peter J. Hotez

SHORT VIEW SUMMARY

Definition
- Soil-transmitted helminths (STHs) are parasitic worms of the human gastrointestinal tract (see Table 286.1).
- *Ascaris, Ancylostoma duodenale,* and *Trichuris* have a fecal-oral route in the consumption of contaminated soil.
- *Strongyloides* and the hookworms have dermal penetration when human are exposed to soil.
- *Enterobius* can be transmitted person to person via consumption of eggs.

Epidemiology
- More than 1 billion persons are infected with an intestinal parasite. Poverty and poor sanitation are associated with STH infections.
- Some resource-rich countries also have disparate populations in poverty and are at risk for parasite infections.

Microbiology
- Intestinal parasites have a limited life span inside the host, and their life cycle requires development in soil.
- *Strongyloides* is the exception and can continuously reinfect the host via autoinfection. This can last for decades and can lead to hyperinfection or dissemination if the host is treated with immunosuppressants including corticosteroids.
- *Ascaris,* hookworms, and *Strongyloides* all migrate through the vasculature and have a lung stage before residing in the gastrointestinal tract.
- *Trichuris* and *Enterobius* have only a fecal-oral route and do not migrate internally to other organ systems.

Diagnosis
- The majority of symptoms are subclinical (especially for light infections), but symptoms can include abdominal pain and diarrhea for some species, and malnutrition and physical growth and cognitive deficits when they occur in children and adolescents. In addition to these effects, each of the STHs can cause unique symptoms (especially during moderate and heavy infections):
  - *Ascaris:* intestinal obstruction
  - Hookworms: anemia
  - *Strongyloides:* hyperinfection and disseminated infection
  - *Trichuris:* colitis, rectal prolapse
  - *Enterobius:* anal itching
- Eosinophilia occurs during tissue migration and is persistent only in strongyloidiasis.
- All STHs can be diagnosed by looking for eggs or through larvae stool microscopy.
- Only *Strongyloides* infections can reliably be detected with serologic assessment.
- Pinworm can be detected with the cellophane or paddle method.

Therapy (see Table 286.1)
- Albendazole or mebendazole in a single dose is used for *Ascaris* and pinworm.
- Albendazole in a single dose (although sometimes additional doses are required) or mebendazole in multiple doses is used for hookworm
- Albendazole is given in three doses or in combination with oxantel pamoate or ivermectin for *Trichuris.*
- Daily ivermectin is given for *Strongyloides,* in an extended course for hyperinfection or dissemination.

Prevention
- Proper sanitation and waste management, including hand washing, are important.
- Mass drug administration may be used in schools or community-level programs.
- Empirical therapy for strongyloidiasis is administered to avoid dissemination before the patient receives immunosuppressants.

INTESTINAL NEMATODES

More than 1 billion people are infected with intestinal nematodes worldwide.[1] Also referred to as soil-transmitted helminths (STHs), intestinal nematodes are complex, nonsegmented, multicellular worms. Each organism is surrounded by a species-specific acellular cuticle composed of structural proteins, enzymes, and lipids that permit tissue migration through the host and evasion of the host immune response. Under the cuticle lies a muscular ring of tissue and entire gastrointestinal and reproductive tracts. There are more than a dozen species of intestinal nematodes that cause human disease, led by the roundworm *(Ascaris lumbricoides),* whipworm *(Trichuris trichiura),* hookworms (*Necator americanus, Ancylostoma duodenale,* and *Ancylostoma ceylanicum*) and threadworm *(Strongyloides stercoralis).*[2] Intestinal nematode infections are found commonly in people living in extreme poverty in tropic and subtropic regions of the Americas, sub-Saharan Africa, and Asia. Although these infections most commonly occur in low- and middle-income countries, vulnerable populations living in high-income countries are also at risk, with evidence showing that hookworm and other STH infections are present among the poor in the southern United States.[3,4] Persons living in conditions with poor sanitation, overcrowding, unsafe water supply, poor health care infrastructure, and low income potential (earning less than $2 per day) are at the highest risk of repetitive exposure and infection.[3] In addition, because these organisms have overlapping geographic endemicity and affect similar at-risk groups, polyparasitism is common (e.g., a single individual may be simultaneously infected with *Ascaris* roundworms, *Trichuris* whipworms, and hookworms),[5] as are STH coinfections with malaria and other tropical diseases.[6]

Intestinal nematodes infect all age groups from neonates to adults; however, only a small proportion of the community will harbor the greatest disease intensity.[2] The age of peak prevalence and peak worm intensity varies based on the specific organism, development of partial immunity after repeated infection, and changes in behavior-associated risk factors.[7] Intestinal nematodes are not a major cause of death, but instead result in severe chronic disability, causing more than 3 million disability-adjusted life years (DALYs) worldwide.[5] However, alternative estimates indicate that the global disability from STH infections may be much higher than previously realized.[8] Malnutrition; weight loss; gastrointestinal symptoms; increased bacterial, viral, and parasitic infections such as human immunodeficiency virus (HIV), malaria, and tuberculosis; and cognitive and growth stunting are well-recognized features of intestinal nematode infection.[7] These organisms impair physical and mental growth, impede educational advancement, decrease workforce productivity, and suppress economic development, creating a sustained cycle of poverty in endemic regions.[8]

High prevalence and heavy worm burden can be devastating to a community. Annual or biannual mass preventive chemotherapy programs have been established in endemic areas worldwide.[9] Administration of a single dose of albendazole or mebendazole is recommended for all

TABLE 286.1 Features of Intestinal Nematodes

MAJOR HUMAN SPECIES	COMMON NAME	ESTIMATED NO. OF CASES (MILLIONS)	DURATION OF INFECTION	MAJOR CLINICAL SYNDROME	TREATMENT
Ascaris lumbricoides	Roundworm	800	1–2 years	Vitamin A malabsorption Intestinal obstruction Asthma	Albendazole 400 mg PO once or mebendazole 500 mg PO once
Trichuris trichiura	Whipworm	435	1–3 years	Colitis Trichuris dysentery syndrome Rectal prolapse	Albendazole 400 mg PO × 3–7 days or mebendazole 500 mg daily or 100 mg PO twice × 3–7 days Also combined with ivermectin (200 µg/kg daily)
Necator americanus *Ancylostoma duodenale/ ceylanicum*	Hookworm	450	3–5 years 1 year	Anemia Ground itch Abdominal pain	Albendazole 400 mg PO once or mebendazole 100 mg twice daily x 3 days
Strongyloides stercoralis	Threadworm	100	Lifelong	Larva currens Eosinophilia Abdominal pain Dissemination to other organs including skin and brain	Ivermectin (200 µg/kg daily ×2) Disseminated: ivermectin (200 µg/kg daily ×14)
Enterobius vermicularis	Pinworm	Estimated at 30% world population	1 month	Pruritus ani Vulvovaginitis	Pyrantel pamoate (11 mg/kg ×1) Albendazole (400 mg ×1)

preschool and school-aged children, nonpregnant adolescent girls (10–19 years old), and nonpregnant women of reproductive age (15–49 years old) living in areas with disease prevalence >20% to reduce worm burden and to reduce morbidity. In addition, pregnant women in their second or third trimester living in areas with hookworm or *Trichuris* prevalence >20% and in areas where >40% of pregnant women have anemia should also be routinely treated.[5] The major goal of these programs is improvements in STH-associated morbidities including growth stunting, cognitive disabilities, and pregnancy outcome, although some investigators have questioned the actual and sustainable benefits of global deworming programs.[10] Interruption of intestinal nematode transmission within a community using mass preventive chemotherapy programs is also feasible in some areas with low worm prevalence, a robust health system, and in-country financial support to maintain control programs.[10] However, global elimination of these diseases will not be feasible without prioritizing reduction in poverty, making changes in infrastructure, investing in health education, and improving hygiene and sanitation, alongside the expansion of preventive chemotherapy programs across broader age classes[11] (Table 286.1). There is also a need for improvements in the efficacy of single-dose anthelmintic drugs, especially for trichuriasis and hookworm, prompting the search for new-generation anthelmintic drugs and vaccines.[12,13]

ASCARIS LUMBRICOIDES

Epidemiology

A. lumbricoides, human roundworm, is the most common helminthic infection in the world, chronically infecting 800 million individuals.[14] Year-round transmission is standard in humid tropical and subtropical regions of the Americas, sub-Saharan Africa, and Asia.[3] In more arid environments, where eggs can remain viable in the soil for months, seasonal transmission occurs. *Ascaris* prevalence and worm intensity increase from infancy to preschool and school-aged children. Young children disproportionately harbor the highest amount of worms within a community, leading to the most significant morbidity.[3] Mortality secondary to ascariasis is low, accounting for only 2700 deaths per year, but ascariasis is a significant cause of severe morbidity, causing 1.27 million DALYs owing to the effects of intestinal parasitism on child growth and development.[15] In addition, the larval stages of *Ascaris* worms migrating through the lungs have been shown to cause asthma and other lung disorders.[16]

Ascaris suum, swine roundworm, is morphologically indistinguishable from *A. lumbricoides* and can cause human disease.[17] *A. suum* and *A. lumbricoides* have minimal genetic differences, with greater than 98% similarity of the mitochondrial genome, with known nucleotide differences commonly resulting in synonymous mutations.[18] In addition, the life cycles of both species are identical and can be completed in both humans and pigs, causing similar clinical manifestations.[19] As with *A. lumbricoides, A. suum* infection has a high prevalence in pigs worldwide, including in the United States, with few farms free of infection.[20] Humans become infected by ingesting pig manure or soil contaminated with *A. suum* eggs.[17]

Life Cycle

Adult *Ascaris* worms live in the small intestine of the host and can survive in the presence of host digestive hydrolases owing to the presence of a resistant outer cuticle. Adult worms are large and can grow up to 30 cm in length and live up to 1 to 2 years within the host.[3] Female adult worms release over 200,000 eggs per day, or 3540 eggs per gram of stool[21] (Table 268.2). *Ascaris* eggs are durable; they are resistant to extreme environmental conditions and survive up to 10 years in ideal soil conditions and up to 2 months without soil. The ability to survive in extreme conditions promotes transmission of ascariasis in both moist and arid environments and in rural and urban communities. Infection occurs by fecal-oral transmission when embryonated eggs from the environment are ingested.[3] After ingestion, stage 2 larvae (L2) hatch in the host small intestines, penetrate the intestinal wall, and are carried by the portal vasculature system to the liver. From the liver, the L2 larvae are transported in the blood to the lung parenchyma, where the larvae molt from stage L2 to L3 larvae. The L3 larvae migrate up the bronchotracheal tree, across the epiglottis, and are swallowed back into the intestinal lumen of the small intestine, where they develop into adult worms (Fig. 286.1). Adult worms generally live from 12 to 24 months. During the migratory process, *Ascaris* larvae release excretory/secretory products (ES) that elicit a strong host inflammatory response represented by visceral eosinophilic infiltrates, peripheral eosinophilia, and high levels of immunoglobulin E (IgE).[22] Egg production can be detected in the host stool for 2 to 3 months after embryonated eggs are ingested[3] (Fig. 286.2).

Clinical Syndromes

The symptoms of ascariasis vary based on the phase of the disease—that is, acute migratory phase versus chronic intestinal phase. Symptoms associated with the acute migratory phase are a result of the intense host type 2 immune response, with very high levels of IgE and eosinophilia, that occurs as the larvae migrate through visceral organs.[22] Infected people may have abdominal pain, nausea, and vomiting as the larvae migrate through the intestines and liver, and symptoms of acute lung inflammation known as Loeffler syndrome, dyspnea, bronchohyperreactivity, and eosinophilic infiltrate as the larvae migrate through the lung parenchyma.[23] Chronic intestinal infection is commonly asymptomatic or associated with mild symptoms of abdominal distention, pain, and nausea.[20] However, people harboring a moderate-to-heavy

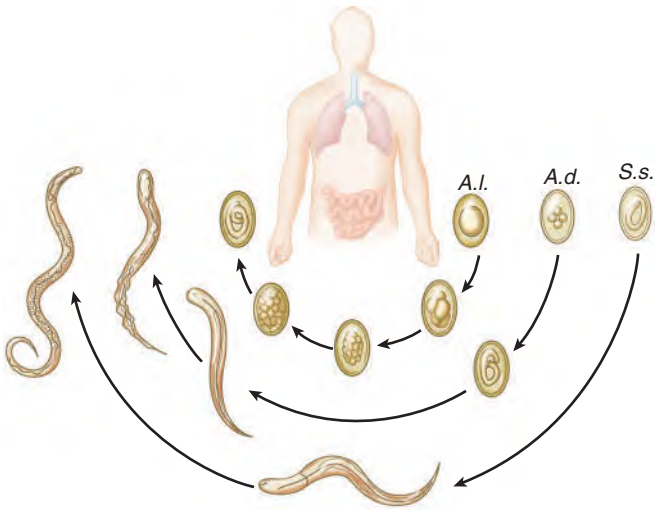

FIG. 286.1 Life cycle of intestinal nematodes that travel through the lungs. Eggs of *Ascaris lumbricoides (A.l.), Ancylostoma duodenale (A.d.),* and *Strongyloides stercoralis (S.s.)* are consumed and migrate from the gut to the lungs, undergoing maturation. *Necator americanus, A. duodenale,* and *S. stercoralis* penetrate the dermis and migrate to the lungs. These worms migrate from the trachea down the esophagus and mature in the gastrointestinal tract, releasing eggs to compete the cycle.

worm burden can have significant morbidity. Ascariasis can have a severe impact on the host nutritional status, specifically protein loss and vitamin A deficiency, leading to impairments in physical and cognitive development. Reduction in cognitive abilities leads to decreased school participation and future economic productivity.[20] Because of the large size of the adult *Ascaris* worm, small bowel obstruction, typically in the terminal ileum, is common in hosts (especially young children) with high worm burden and may necessitate surgical removal. Less commonly, volvulus, intussusception, perforation, and peritonitis can occur. Chronic *Ascaris* infection can also increase the risk of developing wheezing and bronchohyperreactivity, possibly because of the high levels of IgE and cross-reactivity with aeroantigens or because of parenchymal lung damage during acute larvae migration.[23] This syndrome produces a Loeffler pneumonitis, which clinically resembles asthma.

Despite living in the small intestines, adult worms are motile. Under stress, adult worms will migrate into the appendix, stomach, oropharynx, or biliary and pancreatic ducts, causing mechanical obstruction, appendicitis, cholecystitis, cholangitis, pancreatitis, and biliary strictures. Surgical intervention through an endoscopic removal of common bile duct worms or open surgery may be required in circumstances of worsening intestinal obstruction, persistent biliary impaction, or hepatic disease with an abscess.[24] Dead adult *Ascaris* worms within the hepatobiliary system can become a nidus of pigmented hepatic stone formation within the common bile duct. Biliary migration of adult *Ascaris* worms is enhanced in patients with previous sphincterotomy or sphincter ablation, cholecystectomy, or bilioenteric anastomosis. Infected pregnant

FIG. 286.2 Eggs and larvae of intestinal nematodes. (A) *Ascaris lumbricoides,* (B) *Enterobius vermicularis,* (C) hookworm egg, (D) *Strongyloides stercoralis* larvae, and (E) *Trichuris trichiura*. *(Courtesy Rojelio Mejia.)*

women are also at high risk of *Ascaris* migration into the hepatobiliary system secondary to relaxation of the sphincter of Oddi due to high progesterone levels.[25]

Diagnosis

Detection of *Ascaris* eggs in stool through use of the Kato-Katz thick smear method is the gold standard for diagnosis of *Ascaris* infection[26] (see Fig. 286.2). Kato-Katz is a standardized microscopy technique that measures worm burden by quantitating the number of eggs per gram of stool in two separate stool samples.[26] The technique is cheap and has few false-positive test results but is labor-intensive. Daily fluctuation in egg excretion and dependence on trained microscopists can cause highly variable results, particularly in areas of low disease burden, leading to a false-negative test result.[26] To overcome the variability in areas with low worm burden, concentration techniques such as FLOTAC can increase the sensitivity by using larger volumes of stool. Use of concentration techniques in combination with Kato-Katz is critical for increasing the diagnostic accuracy in epidemiologic mapping and for monitoring mass preventive chemotherapy programs. However, the use of concentration techniques remains labor-intensive and increases the cost of the test by requiring additional equipment.[26]

Highly sensitive, specific, and rapid diagnostic methods are required for eradication efforts.[27] Polymerase chain reaction (PCR) methods using multiplex, multiparallel real-time technology improve accuracy in estimating *Ascaris* egg burden and increase sensitivity to detect infection in areas with low worm burden. Although more expensive in terms of upfront costs, PCR methods are less labor-intensive, use a single stool sample, and can be used to identify a higher distribution of polyparasitism compared with standard microscopy, making such methods ideal for monitoring both organism elimination and organism resurgence.[27] False-negative and false-positive results can occur with PCR owing to variation in DNA extraction and target amplification.[28]

Management

Use of an oral benzimidazole, albendazole 400 mg daily or mebendazole 500 mg daily, is efficient to treat *Ascaris* infection and reduce morbidity in persons with high worm intensity. Single-dose oral albendazole, mebendazole, and pyrantel pamoate, used in mass preventive chemotherapy programs, have cure rates of 88%, 95%, and 88%, respectively.[29] However, mass preventive chemotherapy programs targeting high-risk groups are not sufficient to lead to elimination because rapid reinfection is common.[29] More frequent anthelmintic therapy applied to a broader age group within a community is required to overcome high reinfection rates.[9] Improvements in water, sanitation, and hygiene (WASH), including proper disposal of human and animal feces, and increased access to potable water and health infrastructure will be essential to interrupt transmission and prevent reinfection.[20]

ENTEROBIUS VERMICULARIS

Epidemiology

Also known as pinworm, *E. vermicularis* is endemic in Western countries, including the United States. Updated studies in the United States are lacking; the last prevalence study estimated 40 million infections in the 1980s.[30] Worldwide, the prevalence can be as high as 30%.[31] Pinworm infections are not limited to lower socioeconomic groups and can affect families and people living in close quarters.[32]

Life Cycle

The gravid female measures approximately 1 cm; the organism is limited to fecal-oral transmission, and the main gastrointestinal location is the cecum and appendix.[33] The lifespan of a worm is less than 3 months; it spends 1 month as an adult and releases over 10,000 eggs (see Fig. 286.2). The females migrate to the perianal area at night, where they release their eggs and die (Fig. 286.3). Eggs will embryonate and become infectious at 6 hours. These activities create a nidus of pruritus, leading to scratching and contamination, especially underneath the fingernails. The infectious eggs can then be transferred via the fecal-oral route to other individuals or through autoinfection to the host. Bedding, clothing, or surrounding surfaces can be contaminated with eggs. Eggs will become noninfectious after a few days unless ingested, continuing the life cycle. Sexual transmission can occur between partners engaging in oral-anal sex.

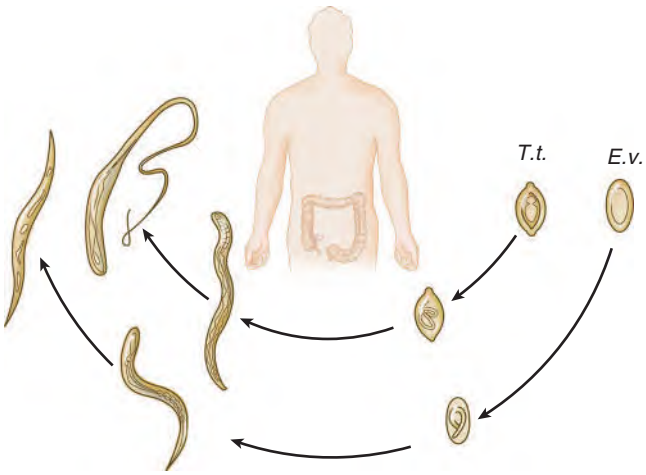

FIG. 286.3 Fecal-oral life cycle of intestinal nematodes. *Trichuris trichiura (T.t.)* and *Enterobius vermicularis (E.v.)* eggs are ingested and mature into larvae in the intestines. *T. trichiura* releases eggs in the stool, and *E. vermicularis* releases at the perianal site.

Clinical Syndromes

The majority of pinworm infections cause only pruritus ani. This perianal itching is due to inflammation caused by the larvae and eggs during the night. Pruritus ani, if severe, can lead to secondary bacterial infections resulting from aggressive scratching, and also difficulty sleeping.[34] Ectopic diseases are rare but have been reported in vulvovaginal regions.[31] Such disease occurs via direct migration of worms to the perineal region and has been associated with vulvovaginitis and urinary tract infections in women.[35] Because the worms are found in the appendix, there are controversial debates regarding whether pinworm can cause appendicitis, with inflamed appendixes containing *E. vermicularis* worms.[36] Although eosinophilic enterocolitis has been reported, there is generally no peripheral eosinophilia and likely no hematogenous spread to other occult body sites.[37]

Diagnosis

Adult worms can be seen, especially at night at the perianal site. The standard of diagnosis involves use of a clear paddle or adhesive tape that is pressed on the anus early in the morning to capture eggs for visualization with a microscope.[33] Stool should not contain eggs, and there are currently no PCR or serologic assays for pinworms.

Management

Pyrantel pamoate (11 mg/kg, maximum of 1 g) is available without a prescription in many locations. Albendazole (400 mg once) also has high efficacy. Both medications should be given 2 weeks apart and have almost 100% posttreatment cure rates.[38] Treatment includes washing all bedding and clothes to remove eggs. Hand washing will also decrease household contact exposure. All household contacts should be treated, given that transmission is so high between family members.[39]

HOOKWORMS

Epidemiology

Hookworm is a major cause of anemia in the world's resource-poor nations.[40,41] Three main hookworm species infect humans and have complete life cycles. These include *N. americanus, A. duodenale,* and *A. ceylanicum*. Although other hookworm species can cause cutaneous larva migrans (especially the dog and cat hookworm, *Ancylostoma braziliense*), they do not complete their life cycle in the human host and do not typically induce intestinal or pulmonary pathologic conditions. There are approximately 450 million people chronically infected with hookworm worldwide.[8] *N. americanus* is the predominant species globally, and the major species found in sub-Saharan Africa, Southeast Asia, and the

Americas, whereas *A. duodenale* is more focally endemic in parts of Africa, India, China, and elsewhere.[3,40,42] *N. americanus* also still occurs in areas of extreme poverty in the southern United States.[4] *A. ceylanicum*, previously considered a nonhuman parasite, has been identified as a zoonotic infection in East Asia, the South Pacific, and Australia.[43,44] There is considerable overlap of these species throughout the world.[45]

Life Cycle

The eggs of all three species are thinly shelled ova with multinucleated centers, and they are indistinguishable via microscopy (see Fig. 286.2). The worm will bind to the small intestinal mucosal lining, using cutting plates to consume host blood. The hookworm larvae range in length from 7 to 13 mm, with *Ancylostoma* being generally larger; the size allows it to take in up to 10 times more human blood than *Necator* (0.30 mL/day vs. 0.03 mL/day per worm).[46] *Necator* can survive 3 to 5 years in the host, while *Ancylostoma* live about a year. The initial infection is through dermal penetration by the hookworm, although *A. duodenale* infection has been shown to occur through oral consumption of contaminated foods or soil. After dermal penetration, the larvae will produce a local pruritic maculopapular rash that will track as the worm begins deeper tissue invasion. The larvae will travel via vasculature to the lungs. The majority of people will be asymptomatic, but some may exhibit a transient pneumonitis.[47] As with *Ascaris* and *Strongyloides,* the hookworms migrate up the trachea and are swallowed, then enter the gastrointestinal tract and reside in the small intestine (see Fig. 286.1).

Clinical Syndromes

Clinical symptoms are based on the location of the larvae in the host. The rash can form a serpiginous or vermicular pattern, usually on the feet (known as "ground itch"), but also on the ankles because the infectious larvae can elevate on blades of grass and ground vegetation. Typical gastrointestinal symptoms include abdominal pain and diarrhea; these symptoms are most severe with initial infections and decrease with chronic exposures.[48] Symptom severity is dependent on worm burden, with massive infections producing increased morbidity[49] (see Table 286.2).

The term *hookworm* comes from the attachment of the buccal cutting plates to the intestinal mucosa in the small intestine. This unique pathophysiologic feature of the hookworms enables its consumption of red blood cells from the intestinal vasculature. The worms produce anticoagulants at the biting site, which allow continuation of bleeding after detachment.[50,51] After hookworms digest blood, they use parasite-derived hemolysins to open the red blood cells, and then digest host hemoglobin through a cascade of hemoglobin-digesting proteases, after which the released heme is detoxified through a modified glutathione *S*-transferase.[52,53] The resulting blood loss leads to both iron and protein deficiencies. Iron-deficiency anemia is a chronic problem and correlates with worm burden, duration, and recurrence of infection.[54] Symptoms include fatigue, weakness, and edema due to hypoproteinemia. Growth and cognitive delays are associated in children with moderate and heavy infections (see Table 286.2).[55] In severe infections, the chronic blood loss can lead to congestive heart failure and eventually death of the host.[7] Today, hookworm infection is a leading global cause of iron deficiency anemia.[41,55]

Increasingly it is recognized that hookworm anemia represents a major complication of pregnancy,[56] especially in resource-poor areas of Africa, Asia, and Latin America, where it leads to increased maternal morbidity and mortality and decreased neonatal survival. Hookworm and malaria coinfections in pregnancy can lead to especially profound anemia.[6,57]

Diagnosis

Fecal microscopy is the standard of diagnosis throughout the world. Direct smears and concentration techniques such as Kato-Katz and McMaster's are semiquantitative.[58] Hookworm egg morphologic features are indistinguishable with microscopy (see Fig. 286.2), and quantitative PCR-based methods are species specific and can correlate with the burden of infection[27,45] (see Table 286.2).

Management

There is a high degree of variability in the efficacy of oral albendazole (400 mg orally) and mebendazole (500 mg orally). For example, a systematic review found that single-dose mebendazole results in only 15% cure rates, and although single-dose albendazole appears to be a better drug for hookworm, there are highly variable effects of single-dose albendazole when used in deworming programs.[29,59] Whether these low cure rates result from emerging drug resistance is under investigation. In some cases, repeat treatment may improve cure rates, although it has been noted that efficacy can also decrease with repetition.[60] Although benzimidazole anthelmintics such as albendazole and mebendazole are embryotoxic in laboratory animals, it is increasingly recognized that pregnant women are at high risk of complications due to severe hookworm anemia, so in resource-poor settings the benefits of deworming with mebendazole or albendazole during the second and third trimesters may outweigh the risks.[55] According to the World Health Organization, "in endemic areas preventive anthelminthic treatment is recommended for pregnant women after the first trimester as part of worm infection reduction programmes."[61] Alternatively, pregnant women can be treated with pyrantel pamoate, an intraluminal drug with little systemic absorption, orally at a dosage of 11 mg/kg daily for 3 days. As with the other STHs, reinfection is common in high-prevalence areas.[62] Retreatment at 6 months is acceptable if the risk of reinfection is high, especially in areas with greater than 50% percent prevalence.[63] A vaccine that targets hookworm hemoglobin degrading and detoxifying enzymes is in development.[64–66]

STRONGYLOIDES STERCORALIS

Epidemiology

The epidemiology of *S. stercoralis* infection differs from that of most other helminth infections in large part because of the parasite's ability to reinfect its human host, a process known as autoinfection.[67] *S. stercoralis* is a parasitic nematode that can infect humans. It is found throughout most tropical and temperate climate zones of the world including North America and parts of Europe. Approximately 100 million people are infected with *S. stercoralis* worldwide,[68] with billions at risk. The incidence is dependent on poor sanitation, often seen in resource-limited regions of the world. The improper management of human waste and runoff from sewage systems allow for continued transmission.[69]

Life Cycle

Whereas most other STH infections are self-limited, *Strongyloides* larvae in the stool can penetrate the perianal skin or the intestinal wall and continue the life cycle. The majority of primary infections occur through contact with soil in which filariform larvae (derived from the eggs of free-living adult worms) (see Fig. 286.2) can penetrate the skin. These larvae then migrate through the venous system to the lungs. In the lungs, the larvae continue to mature in the alveoli and are eventually coughed up and swallowed. The parasitic females lodge into the small intestine surface (lamina propria) and release eggs that hatch into the rhabditiform larvae. These larvae either are excreted during defecation or can mature into the infectious filariform larvae that pass through

TABLE 286.2 World Health Organization Intensity of Infection for Soil-Transmitted Helminths

ORGANISM	LIGHT-INTENSITY INFECTIONS	MODERATE-INTENSITY INFECTIONS	HEAVY-INTENSITY INFECTIONS
Ascaris lumbricoides	1–4999 epg	5000–49,999 epg	>50,000 epg
Trichuris trichiura	1–999 epg	1000–9999 epg	>10,000 epg
Hookworms	1–1999 epg	2000–3999 epg	>4000 epg

epg, Eggs per gram of feces.
From World Health Organization. Eliminating Soil-Transmitted Helminthiases as a Public Health Problem in Children: Progress Report 2001–2010 and Strategic Plan 2011–2020. *Geneva, Switzerland: World Health Organization Press; 2012.*

the colonic walls or perianal skin, again entering the venous system and restarting the cycle.[70] Because of this unique autoinfection capability, a host can remain infected lifelong[71] (see Fig. 286.1). Another mode of infection is the fecal-oral route, in which unwashed fruits or vegetables exposed to night soil (human feces used as a fertilizer) that contain the eggs or larvae are consumed.[72]

Clinical Syndromes

Strongyloidiasis can manifest in many forms. The majority of infections are clinically asymptomatic, although some can manifest with gastrointestinal symptoms including bloating and abdominal discomfort after eating. A prevalent symptom is a new onset of heartburn that is not related to being supine. Often patients are diagnosed with gastroesophageal reflux disease (GERD) and prescribed a proton pump inhibitor with little resolution of symptoms. Episodic diarrhea is common, although this may alternate with constipation and can mimic irritable bowel syndrome.[73] Surprisingly, there are very few symptoms during the pulmonary migration of the *Strongyloides* parasite. It has been postulated that the worms are sufficiently small that despite their migration through lung tissue, there is no significant tissue damage or inflammatory response.[74] Skin manifestations are seen quite commonly. Early in the infection as the worms travel through the skin, they may leave a serpiginous trail of dermatitis known as *larva currens*. In chronic infections, urticaria (hives) or pustular eruptions may occur, which is a sign presumably related to allergic sensitization to parasite antigens. These occur most commonly on the extremities and over the abdomen.

Because chronic infections are often clinically asymptomatic, it is not uncommon for the infection to be uncovered after an incidental finding of peripheral blood eosinophilia.[75] Because *S. stercoralis* is an invasive tissue parasite, it is felt that the organisms induce a Th2-type $CD4^+$ T-cell response dominated by interleukin (IL)-4 and IL-5, (the latter cytokine being responsible for eosinophilia[76]).

Accelerated autoinfection leading to hyperinfection syndrome with an accumulation in the numbers of larvae penetrating the gut and an increase in adult worms in the gut, or even disseminated infection, in which adult worms are found at ectopic extraintestinal sites, is the most dangerous and often fatal condition associated with *S. stercoralis* infection. With respect to hyperinfection, for reasons that are not entirely clear, although often related to corticosteroid administration or underlying human T-cell leukemia virus 1 (HTLV-1) infection, larvae are present in the gastrointestinal tract in large numbers. Some of these invade the gastrointestinal mucosa, often carrying enteric bacteria into the bloodstream. The gram-negative (or polymicrobial) bacteremia can lead to meningitis and septic shock. The parasites can cause devastating pulmonary inflammation with widespread pneumonitis and bleeding. Periumbilical purpura is also common. Untreated, this process can lead to almost certain death, with mortality estimates ranging from 35% to 100% depending on the study. Hyperinfection rarely occurs in the healthy host, but does occur when the patient is immunosuppressed. Oral corticosteroids have been associated with *Strongyloides* hyperinfection most commonly.[77] Although other immunosuppressive agents—chemotherapeutics, biologics—have also been associated with disseminated strongyloidiasis,[77] steroids remain the common link, and dissemination can occur within as few as 6 days of therapy.[78] Surprisingly, HIV/AIDS does not show a significant risk for hyperinfection and dissemination, but HTLV-1 has a substantial risk of dissemination.[76]

Diagnosis

It can take several weeks after infection for larvae to be detected in the stool.[79] Stool microscopy techniques such as Baermann concentration and the agar plate method have improved sensitivity to standard stool examination, but because *Strongyloides* has intermittent egg excretion, almost seven different stool examinations are needed to diagnose strongyloidiasis[80] (see Fig. 286.2). Serologic assays are useful for diagnosing chronic strongyloidiasis; these include crude-antigen enzyme-linked immunosorbent assays (ELISAs) that cross-react with other IgG antibodies against helminths and give a false-positive result.[81,82] Recombinant *Strongyloides* antigens (NIE and SsIR) ELISA and newer bead-based assays approach 100% sensitivity and specificity.[81,83,84] Real-time PCR has been used to detect small amounts of parasite DNA without cross-reactivity to other helminths.[45,85] Hyperinfection and dissemination syndromes are diagnosed by means of finding larvae in body fluids outside the gastrointestinal tract.[77]

Management

Ivermectin (200 µg/kg daily) is the cornerstone of treatment; a 2-day dose has been shown to cure 93% of patients[86] (see Table 286.1). For disseminated strongyloidiasis, daily ivermectin for 14 (or more) days is the standard treatment. In those unable to take oral medication, there are rectal and injectable routes of administration, including subcutaneous routes, that have been used successfully.[87–90] Parenteral ivermectin is a veterinary formulation that has not been approved by the US Food and Drug Administration (FDA), and requires approval under a compassionate use protocol to be administered to severely ill patients.

Although cure is commonplace in acute and chronic strongyloidiasis, treated patients are still at risk for reinfection, because immunity to *S. stercoralis* infection has not been formally demonstrated. As for other parasitic infections, there is active research to develop vaccines and prevent reinfection,[91] and for *S. stercoralis,* there have been some vaccine candidates that have undergone preclinical testing.[92]

Thus, infection with *S. stercoralis,* a parasitic nematode (worm) with a relatively cosmopolitan global distribution, can lead to lifelong infection because of its unique life cycle. Its ability to cause hyperinfection or disseminated infection in the face of immunosuppression makes its diagnosis, treatment, and ultimate prevention through public health measures or vaccines of paramount importance.

TRICHURIS TRICHIURA

Epidemiology

Over 430 million people are infected with *T. trichiura,* human whipworm, worldwide.[16] Similar to other intestinal nematodes, trichuriasis is most common in poverty-stricken areas of the Americas, sub-Saharan Africa, and Asia,[3] where it is a major cause of colitis and inflammatory bowel disease. Disease prevalence and worm intensity are highest in preschool- and school-aged children, with a decline in disease intensity as children age into early adulthood.[3] Coinfection with other intestinal nematodes is common.

Life Cycle

Adult whipworms live and mature for approximately 1 to 2 years in the colon, preferentially residing in the cecum.[3] Female worms can grow up to 30 to 50 mm and male worms up to 30 to 56 mm in length.[3] After male and female copulation in the colon, female worms excrete 3000 to 5000 eggs per day in host feces, which are released into the soil. *Trichuris* eggs require high humidity, sandy soil, and warm temperatures to embryonate.[3] After 3 weeks in the environment, the eggs are infective.[1] Infection occurs by fecal-oral transmission as the host ingests embryonated eggs from contaminated soil. L1 larvae hatch in the small intestines, penetrate the columnar epithelium, molt, and emerge as immature adult worms. The immature adult worms are then carried to the colon, where they develop into adults. Adult worms secrete natural products, including parasite macromolecules, that reduce the barrier function of the intestinal epithelium, leading to increased mucosal permeability.[3] The adult worm can embed the anterior portion, the stichosome, into the mucosal epithelium of the colon, while the posterior portion protrudes into the lumen (see Fig. 286.3). Adults worms generally live 1 to 3 years in the host. Egg production can be detected in the stool 3 months after ingestion of embryonated eggs by the host.[3]

Clinical Syndromes

Heavy-intensity infection can be associated with severe gastrointestinal disease (see Table 286.2). Colitis extending from the ileum to the rectum can resemble inflammatory bowel disease with chronic abdominal pain and diarrhea.[7] *Trichuris*-induced dysentery is a clinical syndrome consisting of mucoid diarrhea and rectal bleeding. Severe chronic colitis and *Trichuris*-induced dysentery have been associated with significant weight loss, iron deficiency anemia, and tenesmus leading to rectal prolapse. Chronic infection in children has also been shown to cause severe malnutrition, growth stunting, and cognitive suppression.[10]

Low-intensity trichuriasis may be asymptomatic or associated with mild symptoms. Despite the lack of symptoms, low-intensity trichuriasis

is associated with chronic growth restriction and should be treated to prevent long-term morbidity.[93] Mild *Trichuris* infection may also have immunomodulatory effects that suppress colonic inflammation.[3] Infection with nonhuman whipworm species, including *Trichuris suis,* has been evaluated as potential immunomodulatory therapy for the treatment of human allergic and autoimmune diseases.[94] However, iatrogenic treatment with *T. suis* eggs has not shown essential effects over placebo for treatment of allergic rhinitis or inflammatory bowel disease.[95] Not only does *T. suis* lack efficacy, but infection is also associated with increased risk of adverse gastrointestinal reactions including moderate-to-severe flatulence, diarrhea, and upper abdominal pain.[96] Ultimately, human trichuriasis represents a major global cause of, and not a cure for, human colitis and inflammatory bowel disease.

Diagnosis

Similar to other STHs, microscopy is the primary form of diagnosis, with the characteristic taper ends and terminal plugs of the ova making visualization easier. There are several molecular methods used for detection in research, but none are available commercially.[27,97]

Management

Unlike ascariasis, trichuriasis can be a challenge to treat with single-dose anthelmintic therapy. A single dose of oral albendazole or mebendazole leads to a 25% to 33% cure rate.[29] Prolonged therapy with albendazole 400 mg for 3 to 7 days or mebendazole 500 mg daily or 100 mg twice a day by mouth for 3 to 7 days[98] may be more successful[29] in heavy infections of at least 1000 eggs per gram of stool (see Table 286.1). For preventive chemotherapy programs, the use of albendazole plus oxantel pamoate in combination has shown higher cure rates and egg reduction against *T. trichiura* compared with a single dose of benzimidazoles.[9] Albendazole can also be combined with ivermectin for improved treatment compared with monotherapy.[9] People living in highly endemic regions are also at high risk for reinfection and benefit from regular mass drug administration programs to reduce morbidity.

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The complete reference list is available online at Expert Consult.

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