Treatment Options and Considerations for Intestinal Helminthic Infections

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Abstract

Objective: To review the literature regarding the epidemiology and treatment of intestinal helminthic infections. **Data Sources:** A literature search of MEDLINE (1946-January 2014), EMBASE (1980-January 2014), International Pharmaceutical Abstracts (1970-January 2014), and the Cochrane Library (1996-January 2014) was performed using the following terms: intestinal, helminthic, humans, United States, and individual drug names (albendazole, ivermectin, mebendazole, nitazoxanide, praziquantel, pyrantel pamoate). Secondary and tertiary references were obtained by reviewing related articles. **Study Selection and Data Extraction:** All English-language articles identified from the data sources and clinical studies using anthelmintic agents were included. **Data Synthesis:** The 2011 removal and continued absence of mebendazole from the market has left limited options for helminth infections. For hookworm, albendazole has a 72% cure rate compared to 32% for pyrantel pamoate. Albendazole, ivermectin, and nitazoxanide appear to be effective for *Ascaris* with cure rates of 88%, 100%, and 91%, respectively. Both albendazole and pyrantel pamoate have been evaluated for pinworm with cure rates of 94.1% and 96.3%, respectively. Combination therapy with ivermectin and albendazole produces cure rates of 38% to 80% for whipworm. For *Strongyloides stercoralis*, ivermectin cure rates are 93.1% to 96.8% compared with 63.3% for albendazole. Praziquantel is effective for intestinal trematode infections with cure rates of 97% to 100% while its efficacy against tapeworm ranges from 75% to 85%. **Conclusions:** Albendazole is the drug of choice for hookworm, *Ascaris lumbricoides*, and pinworm. In combination with ivermectin, it is the first-line agent for whipworm. Ivermectin is preferred for *Strongyloides* stercoralis, and praziquantel is effective against most nematodes and trematodes.

Keywords

anthelmintic, adult, children, flukes, hookworm, intestinal helminthic infections, pinworm, roundworm, tapeworm, treatment, whipworm

The helminths are multicellular organisms that are among the most common causes of infections worldwide. The highest prevalence of these occurs in warm, developing areas where poverty, climate, and environmental factors contribute to an abundance of vectors and increased exposure. Intestinal worms that infest humans include nematodes (pinworm, whipworm, hookworm), trematodes (flukes), and cestodes (tapeworm). Determining treatment can be challenging due to variability in preferred drug of choice and dose for specific worm infestations, as well as formulation and acquisition concerns. Mebendazole, once a mainstay in the treatment of helminth infections, has been discontinued in the United States without explanation by the sole manufacturer of the product.[1] The remaining treatment options include albendazole, ivermectin, nitazoxanide, praziquantel, and pyrantel pamoate (Table 1). These less commonly used agents may be unfamiliar to providers treating patients with helminth infestations, and consideration should be given to consultation with an infectious diseases expert when treating less common helminths. This review article discusses common human intestinal helminthic infections, treatment options, and pharmacological considerations with a focus on treating these infections in the United States.

A literature search of MEDLINE (1946-January 2014), EMBASE (1980-January 2014), International Pharmaceutical Abstracts (1970-January 2014), and the Cochrane Library (1996-January 2014) was performed using the following terms: intestinal, helminthic, humans, United States, and individual drug names (albendazole, ivermectin,

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Table 1. Treatment Options for Intestinal Worms[a,2-7].

Parasite/Disease	Drug	First line or Alternative	Adult Dose	Pediatric Dose
Intestinal nematodes				
Hookworm	Albendazole	First line	400 mg single dose	1-2 years: 200 mg single dose ≥2 years: 400 mg single dose
	Pyrantel pamoate	Alternative	11 mg/kg of pyrantel base (up to 1 g) daily for 3 days	
Ascaris lumbricoides	Albendazole	First line	400 mg single dose	
	Ivermectin	Alternative	150-200 µg/kg single dose	
	Nitazoxanide	Alternative	500 mg twice daily for 3 days	1-3 years[b]: 100 mg twice daily for 3 days 4-11 years[b]: 200 mg twice daily for 3 days
	Pyrantel pamoate	Alternative	11 mg/kg of pyrantel base (up to 1 g)	
Pinworm	Albendazole	First line	400 mg once and repeat dose in 2 weeks	
	Pyrantel pamoate	Alternative	11 mg/kg of pyrantel base (up to 1 g); repeat in 2 weeks	
Whipworm	Albendazole	First line	400 mg for 3 days (7 days for high worm burden)	
	Ivermectin and albendazole	Alternative for high worm burden	Ivermectin 200 µg/kg single dose and albendazole 400 mg single dose	
	Ivermectin	Alternative	200 µg/kg every day for 3 days	
	Nitazoxanide	Alternative	500 mg for 3 days	1-3 years[b]: 100 mg twice daily for 3 days 4-11 years[b]: 200 mg twice daily for 3 days
Intestinal trematodes				
Fasciolopsis buski; Heterophyes heterophyes; Metagonimus yokogawai; Nanophyteus salmincola	Praziquantel	First line	25 mg/kg 3 times daily for 1 day	
Intestinal cestodes (tapeworm)				
Taenia saginata (beef), *Taenia solium* (pork), *Diphyllobothrium latum* (fish), *Dipylidium canium* (dog)	Praziquantel	First line	5-10 mg/kg single dose	≥4 years[c]: 5-10 mg/kg single dose
	Nitazoxanide	Alternative	500 mg twice a day for 3 days	1-11 years[b]: 7.5 mg/kg (100 or 200 mg) twice a day for 3 days ≥12 years: 500 mg twice a day for 3 days
Hymenolepis nana (dwarf tapeworm)	Praziquantel	First line	25 mg/kg single dose	
	Nitazoxanide	Alternative	500 mg twice a day for 3 days	1-11 years[b]: 7.5 mg/kg (100 or 200 mg) twice a day for 3 days ≥12 years: 500 mg twice a day for 3 days

[a]Table only includes agents commercially available in the United States.
[b]Dosage varies depending on indication and reference; oral suspension only for <12 years.
[c]Case reports exist with safe and efficacious use as young as 2 weeks of age.[8]

mebendazole, nitazoxanide, praziquantel, pyrantel pamoate). Secondary and tertiary references were obtained by reviewing related articles. All English-language articles identified from the data sources and clinical studies using anthelmintic agents were included.

Nematodes

Nematodes or roundworms are the most common human parasites in the world. The intestinal nematodes that most commonly infect humans are *Necator americanus* (hookworm), *Ancylostoma duodenale* (hookworm), *Ascaris lumbricoides, Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), and *Strongyloides stercoralis*.[9] Although all are members of the phylum Nematoda, they have varying disease processes that are manifested and treated uniquely in humans.

Hookworm

Nematodes in the Ancylostomatidae family are commonly known as hookworms. The species that generally affect humans are *Necator americanus* and *Ancylostoma duodenale. Ancylostoma braziliense* is the causative species for a specific type of infection called cutaneous larva migrans (CLM).

Together Asia and sub-Saharan Africa have the largest number of cases of hookworm annually.[10] Since there is no reporting or surveillance in North America for hookworm, the prevalence is unknown. The risk of infection and overall worm burden rises with increasing age, with the highest prevalence in middle-aged persons.[10]

Hookworm infections are acquired by humans through soil penetration of the skin or through ingestion. The larvae are most commonly transmitted to those working in agricultural settings and on exposure of bare feet to soil. Larval hookworms can live in the soil for weeks and will resume development once in contact with human serum and tissues. After 5 to 8 weeks of entering the human host, the hookworm is sexually mature and will begin producing thousands of eggs each day. *A duodenale* can live in the human intestine for 1 to 3 years and *N americanus* for 3 to 10 years.[10]

Clinical presentation of *A duodenale* and *N americanus* may include pruritis of the skin typically in the hands and feet accompanied by a papulovesicular rash.[10] Acute infection with *A braziliense* results in CLM presenting as folliculitis or burrows in the feet, buttocks, and abdomen. CLM is more common among travelers to the Caribbean and residents of the Atlantic and Gulf coasts of the United States.[11] Hookworm larvae migrate through the pulmonary vasculature and lung parenchyma resulting in cough, sore throat, and fever, which may be accompanied by eosinophilic infiltrates. Once the larvae leave the lungs through coughing and enter the gastrointestinal tract, epigastric pain may occur. The gastrointestinal symptoms seen, including pain, flatulence, and nausea, peak between 30 and 45 days after infection. Blood eosinophils peak at the onset of gastrointestinal symptoms. Diagnosis is made by identifying hookworm eggs in a stool sample.

The major manifestation of hookworm infection is iron deficiency anemia and protein energy malnutrition from blood loss. Blood loss from the gastrointestinal tract is secondary to hookworm attachment to the intestinal mucosa, which ruptures capillaries and arterioles. The risk for anemia is highest in pregnant women and children. If there is an unusually high worm burden, protein loss can lead to malnutrition.

Two anthelmintics currently available in the United States have been studied for the treatment of hookworm: albendazole and pyrantel pamoate. A systematic review and meta-analysis assessing the efficacy of albendazole single-dose regimens evaluated 14 randomized placebo-controlled trials including 742 patients. The effect of albendazole on *A duodenale* and *N americanus* was evaluated. The mean cure rate was 72%, while the egg reduction rate ranged from 64.2% to 100%.[12] Pyrantel pamoate was evaluated in the same systematic review and meta-analysis. Four randomized, placebo-controlled trials of 152 patients were included. The mean cure rate was 32%, and the egg reduction rate ranged from 56.4% to 75%.[12,13] Praziquantel may be effective for reducing hookworm burden but cure rates have not been established. Mebendazole (cure rate of 15%) and levamisole (cure rate of 10% to 11.9%) are modestly effective but not available in the United States.[12]

Ascaris lumbricoides

Ascaris lumbricoides is the most common infectious intestinal worm worldwide.[14] Some estimates put infection globally at over 1 billion people annually. The high prevalence of infection may be due in part to the pervasiveness of the organism and the ability of the female to lay up to 200 000 eggs per day.[14] Adult worms appear pink in color with tapered ends, and infection typically occurs by ingestion of the eggs from soiled hands, food products, or other fomites.[15-17] Eggs hatch in the intestine within 1 to 2 days after ingestion, molt into second stage larvae, and travel through the blood to the liver and lungs. Once in the lungs the larvae penetrate the aveoli and gain access to the capillary beds at which point they again molt, this time to third stage larvae. The larvae ascend the endobronchial tree and are swallowed and return to the intestine. The mature females begin producing eggs 2 to 3 months after the initial infection.[18]

Symptoms can be seen 5 to 6 days after the initial ingestion.[18] After the larvae travel to the lungs 14 days after ingestion, the patient may experience wheezing, dyspnea, cough, and fever lasting 10 days or more (Loeffler's syndrome). Infiltrates in the lungs can be observed on X-ray,

and the patient may also have an increase in eosinophils.[18] This is seen in more severe infections, whereas mild to moderate infections may be asymptomatic. Other common symptoms are abdominal pain, nausea, anorexia, diarrhea, and/or constipation. Heavy infection or chronic disease may rarely cause intestinal or biliary obstruction, appendicitis, and intestinal perforation necessitating surgical intervention. Diagnosis is made through identification of the eggs, larvae, or adult worms.

Several anthelmintics can be used for treatment of *A lumbricoides* infection. In the absence of mebendazole, albendazole is the treatment of choice. A meta-analysis of 10 placebo controlled trials of albendazole found egg reduction rates of 86.5% to 100% and a cure rate of 88% compared to placebo.[12] In contrast, cure rates for mebendazole in the same meta-analysis were 95% with egg reduction rates of 96.1% to 99%. Ivermectin, nitazoxanide, and pyrantel pamoate are alternative agents (Table 1) available in the United States. A randomized, double-blind study of ivermectin compared to albendazole for the treatment of intestinal nematode infections was conducted in China. The study evaluated 816 patients infected with nematode infections. The cure rates for *Ascaris* were similar, with ivermectin (100%) and albendazole (99%) demonstrating the efficacy of ivermectin against this nematode.[19] Nitazoxanide has been evaluated in a study of 70 children with *Ascaris* who were randomized to treatment with either albendazole or nitazoxanide. Nitazoxanide produced a cure rate of 89% and an egg reduction rate of 99.9% while albendazole had similar cure rate of 91% and an identical egg reduction rate.[20] Pyrantel pamoate has been evaluated in a meta-analysis of 3 randomized placebo-controlled trials that included 131 patients. The mean cure rate was 88%, and 1 of the 3 trials reported an egg reduction rate of 87.9%.[12]

Pinworm

Enterobius vermicularis, or pinworm, is a white threadlike worm primarily infecting the cecum and adjacent bowel. Worldwide estimates of infection are nearly 30%, while prevalence rates may be as high as 100%.[21] Humans are believed to be the only known carriers; however, common household pets may transfer eggs on their fur.[22]

Transmission of *E vermicularis* usually occurs through the fecal–oral route, and eggs are typically deposited by the female in the perianal region prior to death of the organism. However, autoinfection through ingestion of eggs commonly occurs, causing the host to remain infectious. One female pinworm can lay up to 10 000 eggs, and the eggs can remain infective for up to a month. Incubation periods for pinworm vary from 2 to 6 weeks. Once the eggs are in the small intestine, they hatch, mature, and travel to the colon.[21,23] Reports of migrating pinworms infecting the vagina and urinary tract have also been published.[24-26]

Symptoms of infection vary from asymptomatic to anal pruritus, restlessness, and fitful sleep. Diagnosis of infection with *E vermicularis* is made when adult worms are visualized in the perianal region. This can be observed 2 to 3 hours after the patient is asleep, with use of cellophane tape to collect the specimens.

Due to the lack of significant effects of pinworm infection, treatment must be carefully weighed, and prevention is emphasized. Prevention of pinworm infection is largely focused on hand hygiene and routine cleaning of objects. Proper laundering of clothes, bed linens, and other objects is strongly recommended.[24]

Mebendazole was previously the primary agent used in the treatment of pinworm. Cure rates ranged from 60% to 81.5%.[21] In the absence of mebendazole, the treatment of choice for pinworm infection is albendazole or pyrantel pamoate, given as a single dose and repeated in 2 weeks.[24,27] This allows for activity against both the active worm infection and eggs. A randomized double-blind multicenter trial comparing ivermectin and albendazole demonstrated a cure rate 94.1% for albendazole compared to 52.9% for ivermectin ($P < .0001$) when treating *E vermicularis.*[19] Older data have revealed similar cure rates of 96.3% with pyrantel pamoate.[28] However, there is a lack of recent data on the comparative efficacy of albendazole and pyrantel pamoate.

Whipworm

Whipworm (*Trichuris trichiura*) is found largely in tropical climates. Some estimates put infection rates as high as 800 million people worldwide.[16] It is a thin worm with a broad posterior end and a whip-like anterior end. The eggs are yellowish-brown in color and barrel shaped with translucent plugs at the top and bottom of the barrel. Transmission of infection occurs by ingestion of eggs found in food contaminated by human feces. The eggs hatch in the intestine and migrate to the cecum. Once in the cecum the worms mature, mate, and lay eggs—taking up to 12 weeks. A mature female can live for up to 3 years.[16]

Similar to hookworm infections, most of those infected do not display symptoms. The host typically does not become symptomatic until they begin to harbor hundreds to thousands of worms. Rectal prolapse has been reported in children with severe infestations of *T trichiura*. Mucoid diarrhea, bleeding, weight loss, and vague abdominal discomfort have also been described in infected patients. Diagnosis is made through identification of eggs in stool specimen through identification of the characteristic plug at the end of each egg.[16,29]

Treatment of *T trichiura* has historically been with mebendazole, which is no longer available. Cure rates with mebendazole were reported as 36% with an egg reduction rate of 81% to 92.8%.[12] Albendazole and ivermectin have both been recommended as alternative treatment options.

A meta-analysis of 9 randomized placebo-controlled trials of single-dose albendazole against *T trichiura* demonstrated a cure rate of 28% (range 0% to 83.9%), and an egg reduction rate of 0% to 89.7%.[12] Due to the low efficacy rates of mebendazole and albendazole, ivermectin has been studied in the treatment of this nematode. The cure rates of ivermectin against *Trichuris* were compared to those of albendazole during a study conducted in China. The cure rates of the 2 agents were similar versus this organism with 66.7% for ivermectin and 67.7% for albendazole.[19] The egg reduction rates were also comparable between the 2 groups with 86.2% for ivermectin and 87.3% for albendazole.

Albendazole and ivermectin used individually have not been shown to be overwhelmingly successful in clearing *T trichiura* infection. A randomized controlled trial published in 2009 was conducted to evaluate the efficacy and safety of albendazole and mebendazole combined with ivermectin against *T trichiura* as previous studies had shown cure rates of 65% and 80% while a third study showed no effect of the combination.[30] In this study, 548 children from Zanzibar Island, Tanzania, were randomized to 1 of 4 treatment arms: albendazole plus placebo, albendazole plus ivermectin, mebendazole plus placebo, or mebendazole plus ivermectin. The cure rates were highest for the combination therapies, 55% for mebendazole plus ivermectin and 38% for albendazole plus ivermectin. The cure rate for albendazole alone was 10%, while the cure rate for mebendazole alone was 19%. Ivermectin had an additive effect on both albendazole and mebendazole. When adjusted for sex, age, and days to last follow-up, the addition of ivermectin improved the cure rate from 14% to 47% compared to placebo. Egg reduction rates were 97% for mebendazole–ivermectin, 91% for albendazole–ivermectin, 67% for mebendazole, and 40% for albendazole. Combination therapy with albendazole and ivermectin has been reported as effective, with cure rates of up to 80% and egg reduction rates of approximately 94%. Due to the high environmental prevalence of *T trichiura*, reinfection often occurs.[27,31]

Strongyloides

Strongyloides stercoralis is a roundworm that exists on all continents except for Antarctica. It is most commonly found in tropical and subtropical regions but may also be seen in warm temperate locations. While the global prevalence is unknown, it is estimated that 3 to 100 million people are infected worldwide.[32]

Infection occurs by contact with soil contaminated with *Strongyloides* larvae. Persons at highest risk for this are those walking with bare feet or those who have contact with human waste or sewage. There also appears to be an association between infection with Human T-Cell Lymphotropic Virus-1 (HTLV-1) and *Strongyloides*. Once infected, these patients are more likely to develop severe cases of strongyloidiasis.[32]

Strongyloides has a complex life cycle due to an alternation between free-living and parasitic cycles as well as the potential to both autoinfect and multiply in the host. The larvae penetrate the human skin and are transported to the lungs entering the alveolar spaces and traveling to the pharynx. They are swallowed and then reach the small intestine where they molt and become adult female worms. The females produce eggs that become the larvae that can either be passed in the stool or cause autoinfection leading to persistent infections for many years.[32]

Most infections go unnoticed as immunocompetent patients are typically asymptomatic. The most common symptoms include abdominal symptoms (nausea and diarrhea), respiratory symptoms (cough and throat irritation), and a rash on the skin. Up to 75% of patients with chronic disease may have a mild peripheral eosinophilia.[32] Immunocompromised patients, such as those on corticosteroids or chemotherapy, or those with HTLV-1 may have hyperinfection syndrome, a severe, life-threatening form of the disease that may result in sepsis and organ failure.[32,33] Hyperinfection syndrome may cause gastrointestinal, pulmonary, neurologic, systemic, and cutaneous symptoms.[32] In 2012, a Puerto Rican–born organ donor transmitted *S stercoralis* to the patients who received a kidney/pancreas transplant, a kidney transplant, and a heart transplant in Pennsylvania.[34]

The treatment of *S stercoralis* may be accomplished with either ivermectin or albendazole although ivermectin is preferred.[33] For patients with hyperinfection syndrome, immunosuppressive therapy should be stopped if possible, and ivermectin 200 μg/kg should be given daily until stool and/or sputum examinations are negative for 2 weeks.[32] For the management of acute or chronic disease, ivermectin is typically given as a single dose of 200 μg/kg repeated at 2- to 3-week intervals to eliminate larvae generated by autoinfection. A study conducted from July 2008 to April 2010 in Thailand evaluated the safety and efficacy of a single dose of ivermectin compared to 2 doses of ivermectin given 2 weeks apart and a 7-day course of high-dose albendazole (400 mg twice daily) in uncomplicated disease.[35] Ninety patients were divided among the 3 treatment groups. Parasite elimination was documented in 63.3% of albendazole-treated patients compared to 96.8% of single-dose ivermectin patients and 93.1% of 2-dose ivermectin patients. The albendazole-treated group had a higher rate of relapse than either ivermectin-treated group. This study demonstrates why ivermectin is considered first-line while albendazole should be reserved for those who cannot tolerate ivermectin.

Trematodes

The trematodes, or flatworms, include the schistosomes (blood flukes) and the liver, lung, and intestinal flukes.

Of the 65 intestinal flukes known to infect humans, the most common are *Fasciolopsis buski* (large intestinal fluke), *Heterophyes heterophyes*, and *Metagonimus yokogawai*.[36] Trematodes vary in distribution worldwide with an estimated 56 million people globally suffering from one or more food-borne trematode infections.[37] Most cases occur in South-East Asia and South America.[37] An exception is *Nanophyetus salmincola*, which has been identified in the Pacific Northwest of the United States, and *H heterophyes* and *M yokogawai*, which can be found in Hawaii.[38,39]

The life cycle of most trematodes is similar. The eggs hatch on reaching fresh water where they penetrate into the snail intermediate host.[38] After multiplication, free-living larvae develop and may survive on aquatic plants for up to 1 year. These plants may be ingested by humans where the parasites develop into mature worms that can survive 6 months or more living in the upper portion of the small intestine.[38]

While most intestinal fluke infections are asymptomatic, some may cause local inflammation, ulceration, abscesses, epigastric pain, and diarrhea.[38] Eosinophilia, transient obstruction, and ileus may occur with heavy infections.[38] Infection with *N salmincola* may produce influenza-like symptoms and diarrhea.[40] The diagnosis of fluke infection is difficult as the morphology and size of the eggs of different species are similar, so species diagnosis is best made on examination of the expelled adult worms after treatment is completed.[38]

The preferred treatment for all intestinal trematodes is praziquantel. It is highly effective in treating intestinal, liver, and lung fluke infections.[40] Efficacy rates vary depending on number of doses given per day and the dose used, but can be as high 97% to 100% when at least 3 doses are given.[39] Several cases of *N salmincola* successfully treated with praziquantel have been reported in the United States.[41,42] The largest report includes 9 patients infected with *N salmincola* from west-central Oregon who were treated with praziquantel in 3 divided doses for a total 1-day dose of 60 mg/kg.[41] In all cases follow-up stool examinations were negative for eggs, and of the 4 patients who were symptomatic, 2 achieved symptom resolution after treatment with praziquantel.

Treatment durations and doses vary depending on the type of trematode involved.[36] Praziquantel primarily has activity against the adult worm and little activity against the eggs. For the treatment of most intestinal flukes, praziquantel is given in a dose of 25 mg/kg 3 times daily for 1 to 2 days. Triclabendazole may also be used in the treatment of intestinal flukes.[43] However, the availability of this agent in the United States is restricted to an investigational protocol through the Centers for Disease Control and Prevention.[44]

Cestodes

In the gastrointestinal tract, cestodes cause disease as segmented, ribbon-like adult tapeworms. The adult tapeworm lives only in the gastrointestinal tract; however, larvae can be located in any organ. Tapeworm infections can be found worldwide, with the highest prevalence in areas of poor sanitation and/or locations where cattle graze or swine are fed. The epidemiology of tapeworm infections, either globally or within the United States, is unknown.

The 4 species of cestodes that are responsible for the majority of human intestinal tapeworm infections are (*a*) *Taenia saginata* (beef tapeworm), (*b*) *Taenia solium* (pork tapeworm), (*c*) *Diphyllobothrium latum* (fish tapeworm), and (*d*) *Hymenolepis nana* (dwarf tapeworm). *T saginata, T solium*, and *D latum* infections occur from eating raw or undercooked beef, pork, and fish, respectively.

Taenia solium can lead to cysticercosis, an infection of the brain, muscle, or other tissues caused by larval cysts.[45] In low-income countries, this infection is a major cause of adult onset seizures. While this is more common in Latin America, Asia, and Africa, it can occur in those who have never traveled outside the United States. It is considered one of the neglected parasitic infections that have been targeted by the Centers for Disease Control and Prevention for public action. Occasionally, fecally contaminated food containing tapeworm eggs may be eaten in the United States, and cysticercosis may be seen in those who have immigrated to the country.

Hymenolepis nana is the most prevalent tapeworm worldwide and is the only tapeworm that can be transmitted directly from human to human. Transmission is usually fecal–oral from contaminated food or fomites. Additionally, a number of other species can affect humans. For example, humans can have an accidental zoonotic exposure with tapeworms that are common in mammals. One seen in the United States is *Dipylidium canium* (dog tapeworm), which results from the common domestic dog. Infection is easily transferred to the human host via an ingested flea from an infected canine. A common picture of transmission could occur when a dog licks a child's face after it has crushed a flea in its mouth.

The cestode incubation period is 2 to 3 months, and gastrointestinal infections are often asymptomatic.[2] Mild abdominal discomfort, nausea, weakness, change in appetite, or weight loss may occur with infection. Patients typically become aware of the infection by finding segments of the worm in the stool. Actual diagnosis is made by the detection of eggs or worm segments in the stool or perianal region. As with pinworm infection, cellophane-tape can be used to swab for examination. To distinguish among the various tapeworm species, evaluation of the mature proglottids (worm segments) is required. Serologic tests are not beneficial diagnostically.

Eighty-five to 98% of human intestinal tapeworm infections can be successfully treated with commercially available anthelmintics.[46] However, the treatment of neurocysticercosis typically requires control of seizures, edema, and other

neurological complications prior to the use of anthelmintic therapy.[45] The use of anthelmintics can acutely increase symptoms as viable cysts are killed and the inflammatory response is provoked. Dexamethasone is often used to decrease these symptoms. Albendazole 15 mg/kg/day given in 2 divided doses for 15 days may be superior to praziquantel at 50 mg/kg/day for 15 days.[2] Albendazole was equivalent to or superior to praziquantel in reducing the number of live cysticerci, and albendazole has been shown to significantly decrease generalized seizures.[2]

The treatment of choice for most gastrointestinal cestodes is praziquantel with the second-line agent being niclosamide (Table 1).[36,46-48] Both are well-tolerated oral agents that have direct parasiticidal effects on the worm. However, niclosamide is not commercially available in the United States. More recently, the antimicrobial agent nitazoxanide has been added as an alternative agent for various tapeworm species showing a 75% to 85% efficacy rate.[3,36,47] This agent has been especially helpful in praziquantel and/or niclosamide treatment failure, likely secondary to resistance.

Treatment Options and Pharmacological Considerations

Albendazole

Albendazole causes selective degeneration of cytoplasmic microtubules in intestinal and tegmental cells of intestinal helminthes. This results in impairment and depletion of several sources of glucose and impairment of cholinesterase inhibition, which causes immobilization of the worm and ultimately death. Its use has been described in several different types of helminthic infections—primarily nematodes. Please refer to Table 1 for dosing recommendations and Table 2 for general drug information. Albendazole is available as a 200 mg tablet with poor oral absorption, which can be increased by administering with a high-fat meal. For short courses (eg, 1-2 doses) laboratory monitoring is not required. However, for longer courses monitoring hepatic transaminases and complete blood count at the start of each cycle and every 2 weeks during chronic therapy is recommended. Dizziness, fever, and headache all have been reported as possible side effects with albendazole. Albendazole levels may be increased by grapefruit juice and decreased by aminoquinoline antimalarial agents. It is currently listed as a pregnancy category C, while excretion in breast milk is unknown.

Ivermectin

Ivermectin works by binding to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells resulting in paralysis of peripheral motor function and death of the parasite.[49] It is relatively well-tolerated in humans, and the most common adverse effects include gastrointestinal upset, dizziness, and pruritus.

There are 2 clinically relevant drug interactions that require monitoring of therapy. Azithromycin may increase the serum concentration of ivermectin, and ivermectin may enhance the anticoagulant effects of warfarin. Ivermectin is not labeled for use in children less than 15 kg, but there are reports of use in this population.[49] Studies in animals have shown teratogenic effects, though use in mass treatment programs has not shown an increased risk of adverse effects during the first and second trimesters of pregnancy in humans.

Mebendazole

Mebendazole is an anthelmintic that was widely used as the treatment of choice for many infections caused by nematodes. Mebendazole works in the same manner as albendazole and has similar pharmacokinetic parameters. It was discontinued by its sole manufacturer in December 2011. At the time that this article was written there are currently no other manufacturers in the United States making mebendazole.

Nitazoxanide

Nitazoxanide activity may be due to the interference with the pyruvate: ferredoxin/flavodoxin oxidoreductase enzyme-dependent electron transfer reaction, which is essential to anaerobic metabolism. At various dosages, nitazoxanide is well tolerated with the majority of adverse events being gastrointestinal related. Administration should be with food and no known drug interactions or monitoring parameters accompany its use.

Pediatric dosage recommendations (<12 years) are based on the oral suspension, as the bioavailability of the suspension compared with the tablet formulation is 70%.[50] Nitazoxanide is not approved for treatment of helminthes in the United States; however, dosage recommendations are available from its approvals in Central and South America.[3]

Praziquantel

Praziquantel is rapidly and reversibly taken up, yet not metabolized by flukes and tapeworms. The mechanism of action of praziquantel appears to interfere with calcium homeostasis and cause flaccid paralysis. Due to extensive first-pass metabolism to inactive metabolites, most of the active drug does not reach the systemic circulation. While praziquantel is generally well tolerated, mild side effects such as transient dizziness, headache, malaise, abdominal pain, and nausea may occur in up to 50% of patients treated. The frequency and intensity of these adverse events seem to

Table 2. Medication Considerations[7,8].

Medication	Dosage Forms	Adverse Effects	Pregnancy and Lactation Considerations	Administration Considerations
Albendazole	200 mg tablet	Dizziness, fever, headache, vertigo, alopecia, abdominal pain, increased liver enzymes, acute liver failure	Limited human data but poor bioavailability suggests low risk—animal data suggests moderate risk Avoid use during the first trimester No data on use during lactation—is excreted in breast milk but effects on infant are unknown	Administer with a high fat content food
Ivermectin	3 mg tablet	Mazzotti-type reaction, pruritus, fever, edema, urticarial rash, lymph node tenderness and/or enlargement, arthralgia, synovitis, dizziness, gastrointestinal upset, elevation of liver enzymes, leukopenia	No teratogenicity or toxicity has been observed in limited human use during pregnancy Excreted in breast milk but use has not been reported; low drug levels expected in breast milk Compatible with breastfeeding	Administer on an empty stomach
Nitazoxanide	100 mg/5 mL suspension[a]; 500 mg tablet	Gastrointestinal disturbance, headache, yellow discoloration of sclera, allergic reactions, increased creatinine, dizziness, flatulence, malaise, salivary gland enlargement, discolored urine, anemia	No human data—animal data suggests low risk If indicated, nitazoxanide should not be withheld; consider avoiding exposure during the first trimester Effects of exposure to a nursing infant unknown but likely not significant due to extensive protein binding	Administer with food
Praziquantel	600 mg tablet	Abdominal pain, diarrhea, malaise, headache, dizziness, sedation, fever, sweating, nausea, eosinophilia, hiccups	Reserve for use when the parasite is causing clinical illness Not an animal teratogen May be mutagenic and carcinogenic in humans especially when multiple treatment courses are used Excreted into breast milk at ¼ the maternal serum concentration Hold nursing on the day of treatment and during the subsequent 72 hours	Administer tablets with water during meals. Tablets should be promptly swallowed to avoid bitter taste that may cause gagging or vomiting. Tablets may be halved or quartered. Do not chew.
Pyrantel pamoate	144 mg/mL suspension (50 mg/mL as pyrantel base) 720.5 mg chewable tablet (250 mg as pyrantel base)	Abdominal pain, diarrhea, nausea, vomiting, headache	No human data—limited animal data suggests low risk No data available for breastfeeding	May mix with milk or fruit juice

[a]Suspension only for patients <12 years; tablet for ≥12 years.

be dose dependent.[51] Praziquantel is a major substrate of CYP3A4 and therefore carries clinically relevant drug interaction potential. Medication levels are also increased when taken with food, particularly meals high in carbohydrates and fat.

In the United States, praziquantel is commercially available only as a 600 mg tablet. Liquid oral formulations are not available, which presents a challenge in pediatric populations. Although most references only provide dosing of praziquantel for patients 4 and older, a significant number of infections occur in younger children. Case reports exist with safe and efficacious use of this medication as young as 2 weeks of age.[8]

One compounding option might be to make a trituration of praziquantel with inert powder (eg, lactose) and take aliquot samples of the dose needed. This small volume of powder could then be mixed in applesauce for consumption. This would bypass any bitter tasting liquid that would have the propensity for gagging or vomiting and allow for ease of administration.

Pyrantel Pamoate

Pyrantel Pamoate is available without a prescription from community pharmacies in the United States and is considered an alternative agent to treat most nematodes. It paralyzes helminths by causing acetylcholine release and inhibiting cholinesterase. It is poorly absorbed from the gastrointestinal tract, thus decreasing the risk for systemic adverse effects. There are no clinically relevant drug interactions that would require therapy modification or patient counseling.

Summary

Intestinal helminthic infections are common, with varying types of organisms causing infections. While some infections may be asymptomatic initially, they can develop into more severe infestations and cause symptoms that require treatment. Current treatment options are varied and are specific to the species and type of helminthic infection. Identifying the treatment of choice for the specific type of infection will allow for successful infection eradication. Albendazole is currently the preferred treatment for most roundworms including hookworms, pinworms, and *Ascaris lumbricoides*. In combination with ivermectin, albendazole is effective against whipworm. Ivermectin alone is preferred against *Strongyloides stercoralis* while praziquantel is the treatment of choice for most intestinal nematodes and trematodes.

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