Chapter

Soil-Transmitted Helminths

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Abstract

Helminths currently affect over 2 billion people worldwide with a quarter of the world's population infected at some time in their lives. Sobering statistics from the WHO March 2008 report that 80% of the "Bottom Billion" impoverished population of the world have *Ascaris*, 60% have *Trichuris*, and 57% have hookworms. This would only be a problem of pharmacologic distribution if not for an additional report demonstrating that several new studies reported to the WHO claim a 50% failure rate clearing *Trichuris* and 90% failure rate clearing hookworm. These parasitic infections pose a challenge to tropical physicians who have considered mebendazole and albendazole as adequate treatments for children. This is even more of a challenge for physicians in temperate climates who may be less familiar with these medications. This article presents the recent data and the approach to treatment failure and new therapeutic approaches.

Keywords: helminths, *Ascaris*, *Trichuris*, hookworm

1. Introduction

Intestinal parasites cause substantial morbidity and mortality, particularly in children in whom they have detrimental effects on growth and cognitive performance. Parasitic infestation leads to deformity and long-term disabilities and often stigmatizes the child. Parasitized pregnant women are anemic, have increased fetal wastage, and have low birth weight newborns. Though tropical diseases affect a large proportion of the world's population, less than 1% of new drug development over the past 30 years focused on tropical diseases. Recent philanthropic interest has resulted in research, long tardy, for these diseases.

2. Epidemiology

There are three soil-transmitted helminth infections, *Ascaris lumbricoides*, hookworm (*Ancylostoma duodenale* and *Necator americanus*), and *Trichuris trichiura*, labeled by the WHO as the "Unholy Trinity." They are ubiquitous in tropical climates and even temperate rural areas in poverty-stricken communities with poor sanitation (see **Table 1**). *Ascaris* and *Trichuris* increase in prevalence from infancy to puberty and then decrease in adulthood. In contrast, hookworm, the leading cause of anemia throughout the world, continues to increase through life, not reaching a plateau until age 40. This characteristic has a profound effect on women of childbearing age and is associated with small-for-gestation newborns as well as increasing fetal loss.

Disease	Global prevalence (millions) [1]	Population at risk (billions)	Estimated global disease burden (disability-adjusted life years in millions)	Vulnerable population
Ascariasis	807	4.2	1.8–10.5	School-age children
Trichuriasis	604	3.2	1.8–6.4	School-age children
Hookworm	576	3.2	1.5–22.1	School-age children, women of reproductive age

Table 1.
Impact of soil-transmitted helminths [2].

3. Management

The WHO has classified parasitic infestation by egg intensity to clarify symptomatic and asymptomatic infestations (see **Table 2**). Children with light worm loads are often asymptomatic, but children form the greatest population of the heavy intensity group. Even children considered asymptomatic may have subtle differences in learning and intellectual achievement [1].

The clinical presentation relates to parasite migration in the skin, viscera, and gastrointestinal tract. *Trichuris* and *Ascaris* are a result of fecal-oral ingestion. Wheezing, dyspnea, nonproductive cough, fever, bloody sputum, chest x-ray infiltrates, and systemic eosinophilia result during pulmonary vascular migration. Once swallowed the larvae mature, and their migration in the gut causes abdominal pain, distention, and malabsorption.

If adult *Ascaris* migrate into the biliary tree, then pancreatitis, cholangitis, and cholecystitis result. Hepatic abscesses and appendicitis may result from *Ascaris* migration. In younger children, heavy loads of worms can cause partial or complete bowel obstruction in the ileum. Swelling of Peyer's patches leads to an increased risk of intussusception and volvulus. Unrecognized obstruction may eventually cause bowel infarction and perforation with resulting peritonitis.

Trichuris may infect any part of the colon, but the parasite prefers the cecum. Eggs release the larvae in the small intestine, and the worms mature in the colon where they tunnel into the mucosa, causing inflammation. Heavy infestation causes a dysentery syndrome severe enough that it may result in rectal prolapse. Impaired growth and anemia are the consequences of chronic infestation.

Hookworm infects through skin penetration. Itching erythematous rash from multiple skin penetrations causes severe pruritus of the skin, usually on the feet or hands. The larvae use the pulmonary vasculature to access the bronchial secretions and then, when swallowed, mature into adults in the gastrointestinal tract. Bronchial migration presents as clinical pneumonitis but may be mistaken for asthma. Pulmonary symptoms are seldom as dramatic as with *Ascaris*. The significant sequelae of infection relate to intestinal blood loss. As few as 40 worms can reduce the hemoglobin below 11 g/dl. Heavy infestations lead to loss of protein with resulting loss of plasma osmotic pressure and anasarca.

Helminth infestations cause anemia and malnutrition, growth stunting, and cognitive deficits, associated with poor school attendance and performance. Since this occurs in an impoverished area where the diet has limited resource to protein, the consequences of the poor child's limited diet magnifies the malnutrition. If this occurs in a malaria area, the anemia caused by helminths exaggerates the anemia of malaria.

Intensity	*Ascaris*	*Hookworms*	*Trichuris*
Light	1–4999 epg	1–1999 epg	1–999 epg
Moderate	5000–49,999 epg	2000–3999 epg	1000–9999 epg
Heavy	≥50,000 epg	≥4000 epg	≥10,000 epg

Epg: eggs per gram of feces.

Table 2.
Soil-transmitted helminth infection intensity [3].

This is especially crucial for women of childbearing age, since infected women were 2.6 times more likely to have preterm deliveries and 3.5 times more likely to have small-for-gestational age infants. If the woman lives in a malaria-endemic area, the risks of malaria increase the infant mortality.

4. Treatment

There are four medications currently available to treat soil-transmitted helminth infections (see **Table 3**). Benzimidazoles impede the microtubular system, in particular β-tubulin, in the worm. Since this is not a host system, patients tolerate these drugs with minimal side effects. Very few patients report nausea, vomiting, and headache, but allergic reactions with fever are rare. Levamisole and pyrantel pamoate are nicotinic acetylcholine receptor agonists, which paralyze the worms and precipitate their expulsion. Gastrointestinal symptoms, headache, dizziness, fever, and rash are usually mild and self-limited. However, a bulk of paralyzed worms increases the risk of a bowel obstruction.

The most important aspect of treatment is efficacy. Cure rates and egg reduction rates are high for all four drugs when treating *Ascaris* (see **Table 4**). Nevertheless, recent studies have documented ineffective and inconsistent treatment of *Trichuris* and hookworm, whether *Ancylostoma duodenale* or *Necator americanus*. The concern is drug resistance, despite lack of previous investigation. Researchers presumed that the drugs were effective in the past because they were effective with the other

Infection	Drug	Dose
Ascariasis	Albendazole*	400 mg once
	Mebendazole	100 mg twice daily × 3 days or 500 mg once
	Pyrantel pamoate	11 mg/kg (max 1 g) × 3 days
	Levamisole	2.5 mg/kg once
Hookworm	Albendazole*	400 mg once
	Mebendazole	100 mg twice daily × 3 days
	Pyrantel pamoate	11 mg/kg (max 1 g) × 3 days
	Levamisole	2.5 mg/kg once, repeat after 7 days for heavy infection
Trichuris	Mebendazole	100 mg twice daily × 3 days or 500 mg once
	Albendazole*	400 mg × 3 days

**In children 1–2 years old, use 200 mg.*

Table 3.
Treatment of soil-transmitted helminth infections [6].

Parasite	Drug	Dose	Cure rate (%)	Egg reduction rate (%)
A. lumbricoides	Albendazole	400 mg once	88[a,b]	87–100[a]
	Mebendazole	500 mg once	95[a,b]	96–100[a]
		100 mg twice a day for 3 days	92[c]	91–100[c]
	Pyrantel pamoate	10 mg/kg once	88[a,b]	88[a]
		10 mg/kg for 3 days	92[d]	99[d]
	Levamisole	2.5 mg/kg once	92[a]	92–100[a]
Hookworm	Albendazole	400 mg once	72[a,b]	64–100[a]
	Mebendazole	500 mg once	15[a,b]	0–98[a]
		100 mg twice a day for 3 days	80[e]	41–100[e]
	Pyrantel pamoate	10 mg/kg once	31[a,b]	56–75[a]
		10 mg/kg for 3 days	68[d]	77–99[d]
	Levamisole	2.5 mg/kg once	38[a]	68–100[a]
T. trichiura	Albendazole	400 mg once	28[a,b]	0–90[a]
	Albendazole	400 mg for 3 days	53[f]	81–100[f]
	Mebendazole	500 mg once	36[a,b]	81–93[a]
		100 mg twice a day for 3 days	63[g]/ 80[h]	38–99[g]
	Pyrantel pamoate	10 mg/kg once	31[a]	52[a]
		10 mg/kg for 3 days	27[d]	77[d]
	Levamisole	2.5 mg/kg once	10[a]	42[a]
S. stercoralis	Ivermectin	200 μg/kg once	88[i]	N/A
	Ivermectin	200 μg/kg for 2 days	96[j]	N/A
	Albendazole	400 mg once	69[k]	N/A
	Albendazole	400 mg twice daily for 3 days	62[k]	N/A

N/A, not applicable.
[a] Data derived from recent systematic review and meta-analysis (Keiser and Utzinger, 2008).
[b] Data from randomised controlled trials.
[c] Overall cure rate and egg reduction rates based on 29 trials.
[d] Overall cure rate and egg reduction rates based on three trials (Botero and Castano, 1973; Kale et al., 1982; Seah, 1973).
[e] Overall cure rate and egg reduction rates based on 27 trials.
[f] Overall cure rate and egg reduction rates based on five trials (Adams et al., 2004; Marti et al., 1996; Okelo, 1984; Sirivichayakul et al., 2001; Zhang et al., 1990).
[g] Overall cure rate and egg reduction rates based on 33 trials.
[h] Combined pooled relative risk of four randomised controlled trials (Davison, 1979; Sargent et al., 1975; Vandepitte et al., 1973; Wesche and Barnish, 1994).
[i] Overall cure rate based on six trials (Datry et al., 1994; Gann et al., 1994; Igual-Adell et al., 2004; Marti et al., 1996; Shikiya et al., 1991b, 1992).
[j] Overall cure rate based on three trials (Gann et al., 1994; Igual-Adell et al., 2004; Ordonez and Angulo, 2004).
[k] Based on literature review by Horton (2000).

Table 4.
Efficacy of single- and multiple-dose anthelminthic drugs against common soil-transmitted helminth infections [4].

helminths. Recent studies by veterinarians tested efficacy in mass drug administration to animals in endemic areas. Such studies presumed human efficacy. Subsequent studies done in adults excluded children and pregnant women, the most at-risk populations.

Currently, research established benzimidazoles as safe for children greater than 1 year of age. Teratogenic potential seen in animal studies requires careful

assessment of benefit/risk ratio. The WHO does recommend treatment of hookworm in pregnancy due to the adverse effect of anemia which is greater than the risk of the medication [2]. Limited studies show no congenital anomalies or perinatal mortality with the use of albendazole, mebendazole, or ivermectin, although use in the first trimester is still discouraged. Studies have yet to focus on levamisole and pyrantel in pregnancy [2].

5. Prevention

Because of the large burden of disease, prevention needs to be the foremost consideration in improving community health. Sanitation, access to a clean source of water, and careful food preparation limit fecal-oral contamination. Careful disposal of feces decreases exposure to helminthic eggs, and footwear limits hookworm exposure.

The other approach has been to limit morbidity through periodic treatment. The school system has been the logical institution for community treatment. Many studies have employed deworming schoolchildren on an annual basis, while others have focused on women of reproductive age. One recent study focused on community versus schoolchildren treatment justified a strategy that involves the entire community [3]. Community treatment in several studies documents the requirement to reach at least 75% of the at-risk population. Governments willing to institute such programs recognize the cost of $0.02 USD. Several pharmaceutical companies made the drugs affordable. One example, a study done in Zanzibar, examined the co-administration of ivermectin, albendazole, and praziquantel in 5055 children and adults. This mass drug administration benefitted the entire community.

6. Future research and treatment

Considering the high prevalence of soil-transmitted helminths and the established resistance, there is a need for other treatment options. This has provoked enthusiasm for vaccines and drugs with novel mechanisms of action. Unfortunately, there has been little financial incentive for developing human vaccines and novel drugs for poverty-stricken areas, but veterinary medicine has the financial incentive of herd treatment.

The nicotinic acetylcholine receptor is unique to helminths and nematodes, although it appears to be a malaria parasite receptor as well. Since this receptor does not exist in humans, a medication to block this receptor should be effective and well tolerated. A vaccine with an antibody against this receptor seems a logical potential step for research. Tribendimidine is an L-type nicotinic acetylcholine receptor agonist. It is very effective in animals. Clinical trial in humans resulted in approval in China in 2004. Despite the difference in chemical structure and the hypothesized receptor agonist effect, it proved to have the same mechanism of action as benzimidazoles and showed no advantage in humans.

Monepantel is a nicotinic acetylcholine receptor agonist. It is highly effective and licensed for sheep. Researchers initiated studies in humans. It does appear to have a unique mechanism of action since in animals it has been effective in multidrug resistant nematode infections it may also be effective in humans with resistant infestations.

Developing a vaccine requires an antigen. Developers have struggled with which antigen to use that will allow a sufficient and effective antigenic response. Vaccines developed for soil-transmitted helminths are effective in newborn animals. A vaccine to the hookworm antigen, Na-ASP-2, is effective in dogs [4]. Vaccinated

while still puppies, they were resistant to hookworm infection. This success led to a limited phase 1 trial in Brazil. Unfortunately, 30% of the patients developed urticaria, and one patient developed anaphylaxis. These reactions stopped the trial. Speculation as to the cause of this intense reaction led to the hypothesis that the study patients had antibodies to the antigen because of previous exposure from residing in an endemic area. Like the puppies, the requirement must to vaccinate human subjects prior to antigenic exposure [5].

7. Conclusions

Helminth infections are a common problem. Presumed effectiveness of drugs is a deficient hypothesis. The available medications are not as effective as once thought. The trials of mass treatment of schoolchildren do not exterminate the source of infection or resolve the community exposure. New medication research is essential, especially for *Trichuris*. Novel treatments such as vaccines may be on the horizon, but safety concerns for humans with previous exposure is an important immunologic problem. Sanitation is still the most important community solution. The recent disaster in Port-au-Prince, Haiti, demonstrated that without sewer systems and potable water, we humans are indeed a vulnerable species.

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