An Update on the Geohelminths: *Ascaris lumbricoides*, Hookworms, *Trichuris trichiura*, and *Strongyloides stercoralis*

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Geohelminths remain prevalent throughout the developing world where levels of sanitation, personal hygiene, and maternal education are low. The five species of nematodes responsible for the bulk of disease are *Ascaris lumbricoides*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, *Trichuris trichiura*, and *Strongyloides stercoralis*. Geohelminths are acquired through ingestion of fecally contaminated food or water or through contact with infected soil. In developing countries, infection with more than one nematode species and high worm burdens are common. The morbidity is substantial, particularly among children, and deaths occur. Geohelminthic infections are encountered in industrialized countries among immigrants and long-term travelers who have lived in endemic regions where sanitation is poor, and occasionally following autochthonous transmission.

Introduction

Intestinal nematodes or roundworms that inhabit the human gastrointestinal tract have been known since antiquity, but only in the past few decades have their full impact on health and the beneficial effects of mass treatment programs been appreciated. These geohelminths are prevalent throughout the developing world in areas where sanitation, personal hygiene, and maternal education are low. Geohelminthic infections result from ingestion of fecally contaminated food or water or through skin contact with contaminated soil. It is estimated that more than 3 billion people are infected worldwide [1••]. Intestinal helminths remain important causes of morbidity, and occasionally morality, among residents of impoverished areas.

The five nematodes accounting for the major burden of disease are *Ascaris lumbricoides*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, *Trichuris trichiura* and *Strongyloides stercoralis*. *A. lumbricoides* is the most prevalent. It is followed in frequency by the hookworms, *T. trichiura* and *S. stercoralis*. In developing areas, the majority of the population is often infected with more than one geohelminthic species, and worm burdens are frequently heavy, particularly in children.

In the United States and Canada, intestinal nematodes are most likely to be encountered among immigrants, those seeking asylum, and travelers who have lived for prolonged periods of time under conditions of poor sanitation. However, not all geohelminthic infections are acquired abroad. *S. stercoralis* is endemic in focal areas of the southeastern United States. On rare occasions *A. lumbricoides* and *T. trichiur*a are diagnosed among residents of the United States who have not traveled.

The past decade has witnessed substantial advances in understanding the epidemiology, immunology, and impact of the geohelminths, along with the introduction of effective broad-spectrum anthelmintic drugs [2]. Targeted mass treatment programs with albendazole in populations with a high prevalence of *A. lumbricoides*, hookworms, and *T. trichiura* have been shown to enhance growth and performance in school-aged children. Ivermectin has emerged as the treatment of choice for *S. stercoralis*. Recent developments associated with the geohelminths and their treatment are discussed below.

Ascaris lumbricoides

Ascaris lumbricoides is the only intestinal nematode, or roundworm, that resembles an earthworm in size and shape. Female *A. lumbricoides* attain lengths up to 40 cm, while the males can reach 35 cm. Each female produces as many as 200,000 eggs a day. They are excreted in the stool. One of the factors that accounts for the high prevalence of infection worldwide is the ability of the eggs to survive under a variety of environmental conditions. Eggs take 2 to 4 weeks to become infective after reaching the soil. After

ingestion, they excyst in the gut. Larvae invade the wall of the intestine, travel to the lungs, enter the alveolae, migrate to the larynx, are swallowed, and then develop to adulthood in the gastrointestinal tract.

An estimated 1.3 billion people globally are infected with *A. lumbricoides,* with approximately 12 million cases of acute illness and 10,000 deaths each year [3•]. Most morbidity is in children. Epidemiologic studies suggest that susceptibility to the parasite frequently aggregates in families. An analysis of a single large pedigree in Nepal indicated that the genetic component accounted for between 30% and 50% of the variation in worm burden, while shared environmental factors accounted for only 3% to 13% of the phenotypic variance [4]. The mechanism of immunity to *A. lumbricoides* is not fully understood, but there appears to be a highly polarized Th2-type response during infection, and there is a correlation between the titer of parasite-specific IgE and resistance [5,6]. In a study in Venezuela, children with a strong atopic history demonstrated higher specific IgE responses against the parasite and had significantly lower intensities of infection than their nonatopic counterparts [6].

Ascaris lumbricoides produces several forms of disease. Migrating larvae in the lungs can elicit fever, cough, chest pain, dyspnea, and wheezing [7]. Eosinophilia is common and chest radiographs may reveal opacities. But most of the pathology in *A. lumbricoides* infection is due to adult worms. When the worm burden is high, adult worms can form a bolus in the intestinal tract causing obstruction [8•,9•]. On occasion, single worms migrate into the hepatobiliary tract producing biliary colic or occasionally cholangitis [10,11] or pancreatitis [12]. Adult *A. lumbricoides* have also been found in the appendix of persons presenting with symptoms of acute appendicitis [13]. Finally, heavy infections with *A. lumbricoides* and other intestinal helminths in children have been associated with malnutrition and growth retardation.

The diagnosis of *A. lumbricoides* is typically made by identifying ova in stool. On occasion, migrating adult worms may be seen in feces or may be expectorated or emerge from the nose. Adult worms can be identified in the small bowel, biliary tree, pancreas, or appendix by ultrasound [10,12,13]. They appear as ecogenic, nonshadowing images, either as single or multiple strips. The digestive tract of the worm appears as an anechoic inner tube. Adult worms can also be visualized by CT scan. In the lumen of the bowel, they appear as cylindrical filling defects when contrast is used. The intestinal tract of the worm may be seen as a thin thread of oral contrast material within the tubular filling defect [14].

Among the intestinal nematodes, *A. lumbricoides* is the most sensitive to treatment with benzimidazoles. A single dose of albendazole, 400 mg, which is commonly used in mass treatment programs, is highly effective. Although mebendazole, 100 mg twice a day for 3 days, is typically recommended, a single dose of as little as 25 mg may be effective [15]. Pyrantal pamoate and ivermectin are alternatives.

Mass treatment programs with albendazole have generally targeted school children infected with *A. lumbricoides* and other intestinal nematodes. In areas of high endemicity where reinfection is common, treatment at 3- to 4-month intervals is more effective than at 6- to 12-month intervals. Endoscopic extraction and sphincteroplasty have been used successfully to remove adults from the biliary tract [12], but noninvasive treatment with an anthelminthic is also effective in most cases [16].

Hookworms: *Ancylostoma duodenale* and *Necator americanus*

The hookworms, *A. duodenale* and *N. americanus*, are major causes of iron loss and iron deficiency anemia among residents of developing countries [17,18•]. They are estimated to infect approximately 1 billion people worldwide. The prevalence of hookworm infection increases with age in children, typically plateauing in late adolescence. Infection occurs when people come in contact with fecally contaminated soil, and infectious filariform larvae invade through their skin. Hookworm larvae produce an aspartyl proteinase that degrades a number of cutaneous macromolecules allowing penetration [19]. After entering the skin, larvae migrate to the lung, enter alveolae, migrate up the bronchial tree, are swallowed, and reach adulthood in the gastrointestinal tract.

Adult hookworms attach to the mucosa of the small intestine and live on the host's blood, which flows through their intestine. They have a number of complementary strategies that allow them to inhibit the host's hemostatic processes [20–22]. Hookworms inhibit platelet aggregation and adhesion through functional blockade of integrins GPIIb/IIIa and GPIa/IIa [21]; secrete anticoagulant peptide, a specific and potent inhibitor of factor Xa [22]; and release fibrinogenolytic enzymes [20].

Penetration of the skin by filariform larvae can produce a local vesicular rash with pruritus and edema known as "ground itch." Cough, chest pain, wheezing, dyspnea and pulmonary infiltrates with eosinophilia can result as larvae migrate through the lung [7]. Chest radiographs may reveal opacities. Humans experimentally infected with *N. americanus* developed abdominal pain and other gastrointestinal symptoms approximately 5 weeks after infection when adult worms attached in the intestine. Ova first appeared in the stool beginning at approximately week 6. Thus, travelers who are infected with hookworm may present with eosinophilia and abdominal symptoms before ova appear in their stools. On rare occasions, heavy primary hookworm infections are associated with gross gastrointestinal bleeding.

The hallmark of chronic hookworm infection is iron deficiency anemia. The development of anemia depends on the hookworm species and the number of adult worms, as well as the amount of iron in the diet and its bioavailability. Anemia is greater per worm with *A. duodenale*

than *N. americanus*. In a recent study in Tanzania, the prevalence of anemia among children with *A. duodenale* was 80.6%, and in children with *N. americanus* the prevalence of anemia was 60.5% [23]. Hookworms are also an important cause of anemia in pregnant women, who may be overlooked in current helminthic control programs that target school-aged children.

Albendazole 400 mg once or mebendazole 100 mg twice a day for 3 days are the treatments of choice. Both drugs are teratogenic and should not be used during pregnancy. Hookworms are also susceptible to pyrantal pamoate, but not to ivermectin [24]. The anemia associated with hookworm infection responds to iron replacement.

Trichuris trichiura (Wipworm)

The third major geohelminth is *T. trichiura*, the whipworm [17,25]. It is estimated to infect more than 1 billion people and is widely distributed around the world. Infection is acquired through ingestion of fecally contaminated food or water. Ova excyst and develop within the gastrointestinal tract. Adult worms insert in the wall of the colon causing local tissue damage, abdominal discomfort, diarrhea, and blood loss. A dysenteric syndrome can develop in children with heavy infections. It is associated with chronic diarrhea, anemia, malnutrition, and stunting. The effects on nutrition and growth are thought to be mediated in part by inflammatory cytokines such has tumor necrosis factor-α produced in response to infection. Rectal prolapse is a rare, but feared complication in children with heavy *T. trichiura* burdens.

Trichuris muris, a parasite of mice, has been used as a model system to study potentially protective mucosal immune responses to intestinal nematodes [26,27]. In general, inbred strains of mice that have dominant Th2-type responses expel *T. muris*. In contrast, those with dominant Th1-type responses develop chronic intestinal infections. Interleukin-9 (IL-9) is expressed early in mice with protective immune responses and is associated with enhanced intestinal mastocytosis and the production of IgE and IgG1 antibodies. IL-9 transgenic mice, which constitutively overexpress IL-9, display a rapid immune response and expel the parasite [26]. Conversely, IL-12, which is important in initiating production of interferon-γ, a Th1 cytokine, promotes chronic infection [27]. There is evidence to suggest that *T. muris* produces an interferon-γ-like homologue that may contribute to the progression of disease [28]. Finally, mice that are initially resistant to *T. muris* become susceptible when IL-4 is knocked out. IL-13 appears to play an important role in the effector mechanisms that lead to expulsion of worms in resistant animals [29]. The relevance of these findings to humans infected with *T. trichiura* and other intestinal nematodes is still conjectural.

Trichuris trichiura responds well to mebendazole 100 twice a day for 3 days. A single dose of albendazole 400 mg will reduce the worm burden, but daily doses of 400 mg for 3 days are indicated in persons with heavy infestations. Neither pyrantel pamoate nor ivermectin are effective for the treatment of trichuriasis.

Stronglyoides stercoralis

Stronglyoides stercoralis is endemic in the southeastern United States and throughout tropical and subtropical developing areas [30,31]. It is not as prevalent as *A. lumbricoides*, hookworms, or *T. trichiura* worldwide. Unlike the other intestinal nematodes discussed above, *S. stercoralis* has the capacity for autoinfection. This can result in chronic infections in immunocompetent persons and may progress to life-threatening hyperinfection in those who are immunocompromised.

Persons typically become infected when filariform larvae in the soil enter through exposed skin. Larvae migrate through the venous system to lungs, break through to alveolae, migrate to the pharynx, and are swallowed. They can produce cough, dyspnea, and wheezing while migrating through the lungs. They develop to adulthood in the gastrointestinal tract and produce ova, which hatch in the intestine releasing rhabditiform larvae, some of which convert to potentially invasive filariform larvae that can result in autoinfection.

Once established, *S. stercoralis* infections can persist for many years, as evidenced by their identification in former prisoners of war decades after they were infected in Southeast Asia during World War II. Rhabditiform larvae are excreted in a fluctuating manner in stool. After reaching soil they convert either to infectious filariform larvae or, unlike the other geohelminths, free-living adult parasites that produce ova that hatch, releasing rhabditiform larvae that mote to become infectious filariform larvae in the soil.

Persons infected with *S. stercoralis* may present with pulmonary or gastrointestinal symptoms, migrating skin larvae (larva currens), and/or eosinophilia [30,32]. In immunocompromised persons, massive numbers of filariform larvae can invade the intestine entering the lungs, central nervous system, and other organs. They can cause extensive tissue damage and are frequently associated with polymicrobial sepsis or meningitis due to enteric bacteria that are carried on their surfaces.

High prevalences of *S. stercoralis* infection and hyperinfection have been observed in persons concurrently infected with the human T-cell lymphotrophic virus-type 1 (HTLV-1) [33–35]. Peripheral blood mononuclear cells from persons with HTLV-1 spontaneously produce interferon-γ at high levels [34]. It has been postulated that interferon-γ is responsible for the down-regulation of Th2 responses and IgE production in HTLV-1-infected persons, and thereby impairs host defenses against *S. stercoralis*. Consistent with this hypothesis are observations in mice that administration of IL-12, which increases interferon-γ secretion, decreases eosinophils and parasite-specific IgG1 and thus inhibits Th2-dependent protective immune responses against *S. stercoralis* [36].

Hyperinfection can also occur in persons with suppressed immunity due to neoplasms, malnutrition, or administration of immunosuppressive drugs. Hyperinfection was once a major problem following renal transplantation in patients who received intravenous, high-dose methylprednisolone for rejection. Exogenous steroids appear to be homologues of molecules that stimulate conversion of rhabditiform to filariform larvae. No cases of hyperinfection have been observed in transplant recipients while they were taking cyclosporine [37], which has been demonstrated to have antistrongyloides activity in an animal model. Hyperinfection can occur in patients with AIDS [38–40], but the incidence has been less than initially expected [41].

Patients with hyperinfection due to *S. stercoralis* can present in a number of ways [38–47]. Some have pulmonary involvement with respiratory tract symptoms and infiltrates on chest radiograph [43]. Others develop intestinal lesions. Disseminated infection can masquerade as ulcerative colitis [44]. Eosinophilic granulomatous enterocolitis has also been reported [45], and some persons have presented with symptoms of intestinal obstruction [46,47]. Others present with polymicrobial sepsis or meningitis and multiple organ failure. The mortality rate of hyperinfection, even with therapy, is high.

The diagnosis of *S. stercoralis* is confirmed by identifying larvae in stool, tissue, or secretions. Larvae are excreted intermittently and at relatively low numbers in stool. The agar plate method appears to be the most sensitive for detection; it is positive in approximately 90% of those infected [48,49]. The detection of antistrongyloides antibodies is suggestive of prior or active infection, but it is not diagnostic. Both false-positive and false-negative results occur, and the predictive value of the test is dependent on the prevalence of *S. stercoralis* in the population.

Thiabendazole was widely used for the treatment of *S. stercoralis*, but more than half of the recipients experienced substantial side effects, and the drug is no longer produced. Ivermectin is effective for *S. stercoralis* and better tolerated than thiabendazole. In a recent large field study, a single dose of 200 µg/kg cured 83% of recipients [24]. Ivermectin has been used successfully to treat *S. stercoralis* infections that were not cured by thiabendazole [50], but some cases have been refractory to ivermectin, even after multiple doses [51]. Albendazole has activity against *S. stercoralis*, but it is less effective than thiabendazole or ivermectin. When albendazole was administered at a dose of 400 mg daily for 3 days, 45% of infected children were cured in one study [24].

Mass Treatment Programs for Geohelminths

In recent years attempts have been made to quantify the impact of intestinal nematode infections and their treatment on the nutritional status of children and adults living in endemic areas [1••,2]. A single 400-mg dose of albendazole has been widely used in mass treatment programs, many of which have been targeted at school-aged children. This dose is effective against *A. lumbricoides* and hookworms, and although not always curative for *T. trichiura*, reduces the parasite burden. Unfortunately, reinfections are common in developing areas where sanitation and hygiene are poor, and retreatment with albendazole is needed. The results are generally best if children are treated at 3- to 4-month intervals [52].

A great deal of interest followed reports from Kenya that school-aged children demonstrated improved growth and performance after treatment for hookworms, *T. trichiura*, and *A. lumbricoides* [53,54]. Four months after treatment with albendazole, school boys were found to have gained significantly more weight (1.0 kg) than untreated controls. They also had a significantly greater incremental growth in height, 0.6 cm [53]. In other studies, Kenyan children treated once or twice with albendazole during a year were 1.1 kg and 0.9 kg heavier, respectively, and had 3.3% and 2.7% greater weight-for-age than untreated controls [54]. Increased appetite and physical activity were also noted in the albendazole-treated children. Subsequently, a deworming program was shown to improve the growth of school children in Zanzibar, but the differences between treated children and controls after 1 year, although significant, were smaller, 0.20 kg in body weight and 0.30 cm in height in children younger than 10 years of age [55]. Likewise, in a study in Guatemala, a small gain was noted in weight (0.18 kg) in children 6 months after deworming [56].

It has been hypothesized that geohelminths and other enteric pathogens might also adversely affect intellectual development and cognitive function, resulting not only in physical stunting, but impaired intellectual capacity. Further studies are needed to address this in children who are infected early in life during the formative period of intellectual development.

Conclusions

The past decade has witnessed dramatic advances in the epidemiology, immunology, and understanding of the impact of geohelminthic infections, and the introduction of effective, broad-spectrum anthelmintic drugs. *A. lumbricoides*, the hookworms, *T. trichiura*, and/or *S. stercoralis* infect more than 3 billion people worldwide. They are responsible for substantial morbidity and sometimes death. Their greatest impact is on pediatric populations. Albendazole or mebendazole are the drugs of choice for *A. lumbricoides*, hookworms, and *T. trichiura*; ivermectin is indicated for *S. stercoralis*. Mass treatment programs with albendazole have resulted in enhanced growth and performance in school-aged children infected with geohelminths in developing areas. Until economic development and improved sanitation are possible, periodic targeted mass treatment appears to be the best strategy for control.

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