Gastrointestinal nematodes and their management: a review

Shikha Malik

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Abstract

Nematode parasites in humans are more prevalent in geographical areas where environmental factors and poor sanitary conditions favour the parasitism. Lesions in the intestine can be due to damage directly caused by the infectious pathogen, indirect pathology caused by toxic products, or the immune response incited by infections or ectopic parasitism. The majority of the clinically important species of parasites involved in intestinal infection are reviewed in this paper. Parasites are discussed by the disease or infection they cause. Gastrointestinal (GI) nematode infections affect 50% of the human population worldwide, and cause great morbidity as well as hundreds of thousands of deaths. Despite modern medical practices, the proportion of the population infected with GI nematodes is not falling. This is due to a number of factors, the most important being the lack of good healthcare, sanitation and health education in many developing countries. A relatively new problem is the development of resistance to the small number of drugs available to treat GI nematode infections.

Keywords: Ancylostoma duodenale, Ascaris lumbricoides, Enterobius vermicularis, Necator americanus, Strongyloides stercoralis, Trichuris trichiura, intestinal roundworm, pinworm hookworm, threadworm, whipworm, nematodes, life cycle)

Introduction

Nematodes (roundworms) have elongated, bilaterally long cylindrical bodies which contain an intestinal system and a large body cavity. Parasitic nematodes vary in length from several millimetres to approximately 2 metres and have larval stages and adult worms of both sexes. Approximately 60 species of roundworms are parasites of humans (Wharton, 1986). Some nematode infections can be transmitted directly from person to person but, in others, the nematode eggs must mature outside the host. The parasites may spend a part of their life cycle in the soil before becoming infective to humans. Parasites are always present in any community (plants and animals) and usually infect hosts species that dominate the higher trophic levels in any food chain (Maclnnis, 1976; Edem et al., 2008). Parasitic infections are a major medical problem throughout the world, especially in developing countries where they cause more morbidity and mortality than other infectious diseases and are the primary cause of death. There are two main groups of parasites: (a) the protozoa, which are unicellular organisms and include the malaria parasite, Plasmodium; and (b) the helminths, which are metazoan organisms and include the cestodes, trematodes and nematodes (khuroo, 1996). The protozoa are responsible for the majority of the mortality associated with parasitic infections, while the helminths generally produce long-term (or chronic), debilitating diseases: one of the reasons why there is more public awareness of parasitic protozoan infections than of infections with helminths. In this paper, we attempt to review major human gastrointestinal nematodes, the problems associated with the control of these parasites and a potential new therapeutic approach.

Adaptation of Nematodes

Nematodes have successfully adapted to nearly every ecological niche from marine to fresh water, from the Polar Regions to the tropics, as well as the highest to the lowest of elevations (Lee et al., 1960). They are ubiquitous in freshwater, marine, and terrestrial environments, where they often outnumber other animals in both individual and species counts, and are found in the locations as diverse as Antarctica and oceanic trenches (Bird et al., 1971). They represent, for example, 90% of all life on the seafloor of the Earth. The many parasitic forms include pathogens in most plants and animals.

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Some nematodes can undergo cryptobiosis (Lima, 1998).

**Location of Nematodes**
Parasitic nematodes are either located in the intestine or tissues of their hosts and are referred to as intestinal and tissue nematodes, (Rafiaa, 2009).

**Intestinal nematodes**
Small intestine: *Ascaris, Ancylostoma, Strongyloides* etc.
Large intestine: *Enterobius, Trichuris* etc.

**Tissue nematodes**
Lymphatic system: *W. bancrofti*
Subcutaneous tissue: *O. volvulus, Loa loa, D. medinesis*
Muscles/lungs/brain: *Trichinella (larva)*
Toxocara canis non human species larva carried in blood to liver, lung, brain, and eye.

**Epidemiology**
It is safe to say that everyone, at one time or another, has pinworms. It is a cosmopolitan parasite found most often in families and in institutionalized children (Benthony et al., 2006). The parasite is transmitted hand-to-mouth after scratching the perianal region, by handling contaminated bedding and night clothing, or by inhaling eggs in airborne dust. Eggs will not embryonate at temperatures below 23°C, but embryonated eggs remain viable for several weeks under moist and cool conditions. A report by the World Health Organization (WHO) in 2005 stated that approximately 0.807-1.221 billion humans have ascariasis, 604-795 million have trichuriasis, and 576-740 million have hookworm infections worldwide (Hokeyek et al., 2011). The bowel of a child living in poverty in a developing country is likely to be parasitised with at least one nematode and, in many cases, multiple infection (eg, whipworms, ascaris, and hookworms), with resultant impairments in physical, intellectual, and cognitive development (Stepek et al., 2006). The prevalence of nematode infections throughout the world is generally increasing but varies according to levels of poverty, natural disasters and human conflicts (Beyrer et al., 2007). The spread of infection is also increasing in line with increased travel and mobility (eg, angiostrongyliasis and anisakiasis). However, some eradication programmes (notably for guinea worm disease) have been effective in reducing the burden of infection (Moyo et al., 1996). The pattern of intestinal parasitic infection is summarized in table 1.

<table>
<thead>
<tr>
<th>Defects in sanitation, water supply, and food hygiene</th>
<th>Most likely infection pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faeces disposal</td>
<td>High endemicity of</td>
</tr>
<tr>
<td>Indiscriminate defication</td>
<td>ascariasis in children</td>
</tr>
<tr>
<td>-around the houses</td>
<td>under 5 year</td>
</tr>
<tr>
<td>-around the villages</td>
<td>hookworm infection and ascariasis in all age Groups</td>
</tr>
</tbody>
</table>

**Monitoring change of intestinal nematode in the global situation**
Today, estimates of infection in different regions in the world are calculated by extrapolating from prevalence surveys several estimates of global and regional prevalence and of numbers of infection have been made in recent years (Crumpton, 1986) and all give a similar picture. The most recent estimates are 1273 million infection (24% prevalence) with *A. lumbricoides*, 902 million (17%) with *T. trichiura* and 1277 million (24%) with hook worms. Taking into account the likely margin of error in all these estimates, it is clear that the proportions of the world population infected with each of these parasites remain virtually unchanged over the past 50 years, despite enormous advances in technology and medicine. The large increase in the global population over this period means that the actual numbers infected have increased greatly. In the industrialized countries, including many of those recently industrialized, widespread infection with intestinal nematode has disappeared, but reported significant levels of infection with intestinal worms even in north America and Europe (Stoll,1947) but this is clearly no longer the case. Furthermore some countries in Asia (including Japan and Korea) have experienced dramatic decreases in the prevalence of infection as a result of both specific control efforts and economic development (Seo, 1990). However, these countries form a relatively small proportion of the world population; the established market economies (USA, Canada, western Europe, Japan,
Australia and New Zealand) and the European former socialist economies together now constitute 23% of the world population (World Bank 1996). Very little information has been published in the literature on current levels of infection in the former Soviet Union and Eastern Europe. Prevalence of intestinal nematode infections can be extremely high in urban slum areas, where sanitation is poor and infection is essentially universal (Hall et al., 1992). A number of people infected does not translate directly into the disease burden suffered by the population, ways to translate the estimates of disease burden and the possible impact of interventions on this disease burden are here considered, together with the currently available tools for intervention programmes.

**Gastrointestinal nematode infections in Humans**

According to Chan (1997), the prevalence of GI nematode infections has remained unchanged in over 50 years, with 39 million disability-adjusted life years (DALYs) lost due to these parasites when compared with 35.7 million lost to malaria or 34.1 million lost to measles. How can this be the case with modern medical practices? The majority of infections with GI nematodes remain asymptomatic, and those cases which do cause morbidity are not directly fatal, in contrast to malaria. This may be one reason why GI nematode infections have been neglected diseases in terms of public recognition and research funding (Hendrix, 1995).

Of the 342 helminth species that infect humans (Crompton, 1999) the species of greatest medical importance are *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms), *Trichuris trichiura* (whipworm), *Enterobius vermicularis* (pinworm) and *Strongyloides stercoralis* (threadworm) (Table 2). For more than 50 years, the number of cases of GI nematode infections has increased with the global population, such that over 50% of the world's population are affected by the six major GI nematode species (Chan, 1997; Horton, 2003). The majority of these people live in the developing countries, with those living in rural and urban slums most at risk. This is probably due to the poor housing, overcrowded living conditions, lack of adequate sanitation and hygiene and poor education and health care in these areas, all of which are associated with poverty. In the case of *S. stercoralis* in urban slums, one risk factor for transmission of infection is believed to be close contact between individuals, linked with poor personal hygiene (Conway et al., 1995). In addition, warm and humid climatic conditions appear to favour the survival of free-living larval stages of species such as *N. americanus, A. duodenale* and *S. stercoralis* (Kappus et al., 1994), with the latter parasite endemic in tropical and subtropical countries, including South East Asia, the Far East, West Africa, Italy and Australia. Although GI nematodes are largely restricted to the tropics and sub-tropics, infections can occur in the Northern hemisphere when ambient conditions are favourable. For example, hookworms caused anaemia in tin miners in Cornwall at the start of the 20th century and also caused problems among engineers in the Alps (Boycott & Haldane 1903; Boycott, 1911; Foster, 1965). In both cases, the poor hygiene standards of the workers, in warm, moist conditions, favoured transmission.

In general, however, infections with GI nematodes, with the exception of *E. vermicularis*, are less frequent in temperate climates and technologically developed societies, such as the USA and Western Europe; nevertheless, a proportion of these populations still become infected, despite the higher standards of hygiene and sanitation (Kappus et al., 1994). In particular, *E. vermicularis* infections, whilst being present throughout the tropics, are also widespread in the Northern hemisphere, such as in the UK, unlike infections with the other major GI nematodes; this is possibly due to the low temperatures and high humidities which favour egg development. Infections with this nematode are the least harmful, and are considered more of a nuisance than a serious disease. Nevertheless, they are most common in crowded residences, particularly in school children 5–10 years old, and are spread easily between all family members, with frequent reinfection (Gonzalez & Javier de la Cabada, 1987; Cook, 1994; Kucik et al., 2004).
Table 2-The major gastrointestinal (GI) nematode parasites of humans

<table>
<thead>
<tr>
<th>GI Nematode (species name)</th>
<th>GI Nematode (group name)</th>
<th>Number Infected</th>
<th>Distribution</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancylostoma duodenale</td>
<td>Hookworm</td>
<td>1.3 billion</td>
<td>World wide, especially tropical region</td>
<td>Skin contact with contaminated soil</td>
</tr>
<tr>
<td>Ascaris lumbricoides</td>
<td>Round worm</td>
<td>1.3 billion</td>
<td>World wide especially tropical region</td>
<td>Ingestion of eggs</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>Whipworm</td>
<td>1.05 billion</td>
<td>World wide especially tropical region</td>
<td>Ingestion of eggs</td>
</tr>
<tr>
<td>Enterobius vermicularis</td>
<td>Pin worm</td>
<td>209 million</td>
<td>World wide</td>
<td>Ingestion of eggs, occasional inhaled</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Thread worm</td>
<td>30 million</td>
<td>World wide</td>
<td>Skin contact with contaminated soil; auto Infection</td>
</tr>
</tbody>
</table>

Transmission and life-cycle of human GI nematodes

Six GI nematode species are of major importance, *A. duodenale*, *N. americanus*, *A. lumbricoides*, *T. trichiura*, *E. vermicularis* and *S. stercoralis* have direct life-cycles, i.e. only one host is involved. These six nematode species are all highly specific to humans, with no animal reservoirs of infection for any species. Although some animal species, such as pigs, can become infected with the human GI nematodes, the life-cycle cannot reach completion in these foreign hosts. The eggs or larvae of all the major nematodes, with the exception of *E. vermicularis* require a period of development in the soil to become infective before transmission to the human host. This requirement, combined with a similar geographical distribution, generates a high frequency of concurrent multiple species infections usually *A. lumbricoides* and *T. Trichiura* (Booth & Bundy, 1992), especially in areas where several species are sympatric. In these endemic regions, multiple worm infections are more common than infections with a single species, but are still largely asymptomatic when the worm burden is low. However, multiple infections can exacerbate the pathology (Booth et al., 1998). Infections with *A. lumbricoides* and *T. trichiura* are more likely to be transmitted within the domestic situation where eggs may persist in household dust, whereas hookworm infections are more often transmitted in the field, where shoes are worn infrequently. Whereas *Ascaris* and *Trichuris* can only infect via oral ingestion, hookworms can also infect the host by skin penetration (see below). This is why the wearing of shoes is a major factor in the prevention of hookworm transmission (Killewo et al., 1991).

The life-cycles of the major GI nematodes of humans are essentially similar (Figure 1), but they do have specific differences. In all, the adult worms reproduce sexually and the mature female worms produce and release eggs into their immediate environment of the human intestine. In most species, these eggs pass into development within the soil to become infective before transmission to the human host. This requirement, combined with a similar geographical distribution, generates a high frequency of concurrent multiple species infections usually *A. lumbricoides* and *T. Trichiura* (Booth & Bundy, 1992), especially in areas where several species are sympatric. In these endemic regions, multiple worm infections are more common than infections with a single species, but are still largely asymptomatic when the worm burden is low. However, multiple infections can exacerbate the pathology (Booth et al., 1998). Infections with *A. lumbricoides* and *T. trichiura* are more likely to be transmitted within the domestic situation where eggs may persist in household dust, whereas hookworm infections are more often transmitted in the field, where shoes are worn infrequently. Whereas *Ascaris* and *Trichuris* can only infect via oral ingestion, hookworms can also infect the host by skin penetration (see below). This is why the wearing of shoes is a major factor in the prevention of hookworm transmission (Killewo et al., 1991).

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Life-cycle of human gastrointestinal (GI) nematodes, with the exception of *Enterobius vermicularis*

Eggs released into the external environment, except for *S. stercoralis*, which hatch in the host’s intestinal mucosa from where the L1 are released into the external environment and develop through two moults to infective L3

- Adult female worms produce eggs
- Development to mature adult worms in the intestine
- Eggs of hookworms hatch and infective larval stages (L3) develop through two moults

Transmission to humans host by:
- Ingestion of infective eggs
- Ingestion of infective larval stages, or
- Penetration of

L3, L4 or young adult worms migrate up the trachea and are then swallowed so as to enter the

- Infective L3 migrate through tissues (*A. lumbricoides, S. stercoralis*) or blood (hookworms) to the lungs L3 either donot moult (hookworms) moult to L4 (*A. lumbricoides*) or moult twice to young female adult worms (*S. stercoralis*)
The eggs of *A. lumbricoides* and *T. trichiura* require a period of external development to become infective even though the eggs do not hatch in the external environment. The L1 of *T. trichiura* develop in the eggs and it is this stage which is infective to humans. For further development, the L1 have to be ingested, and this usually occurs via contaminated food or water. On ingestion, the eggs (containing the infective L1) hatch in the small intestine, from where the L1 migrate to the colon of the large intestine and develop, through four moults, to mature adult worms. For *A. lumbricoides*, the L1 develop and undergo two moults to the infective L3 within the eggs, whilst in the external environment. As for *T. trichiura*, the eggs containing the infective L3 enter the human host by ingestion, where they hatch and release the L3 into the duodenum. This is followed by tissue migration to the lungs, via the liver, where the third moult to L4 occurs. The L4 enter the trachea and are then swallowed and enter the intestine, where final maturation to the adult worms occurs (Whitfield, 1993; Shamshi et al., 2009).

In contrast, the eggs of hookworms (*A. duodenale* and *N. americanus*) hatch externally and release the L1, which develop as free-living stages through two moults to the infective L3. Infection of humans by these L3 is largely by active skin penetration (Brenner et al., 2003). The L3 migrate to the lungs and the trachea, from where they are swallowed, and enter the small intestine to complete their development through the two remaining moults and final maturation to adult worms. Whereas *N. americanus* can only infect humans via skin penetration, *A. duodenale* can infect both by skin penetration and by ingestion of the infective L3. Following ingestion, these L3 migrate directly to the small intestine where they develop, through two moults, to mature adult worms (Whitfield, 1993; Shamshi et al., 2009).

*Strongyloides stercoralis* is the exception in that the parasitic stages are parthenogenic female worms, which release eggs that hatch internally in the host's intestine, releasing the L1. The L1 usually pass out of the host via faeces, but in some cases, their development can be accelerated whilst still in the host. In such cases, the L1 moult twice to the infective L3, which penetrate the gut or the perianal skin surface and migrate to the lungs (autoinfection). More commonly, the L1 are released in the host faeces and then follow either the free-living or parasitic developmental cycle. In the parasitic cycle, the L1 develop through two moults to the infective L3, where no further development can occur until contact with a relevant host is made. In contrast, the L1 undergo the two moults to the L3 and then continue their development to the L4 and finally to the free-living adult worms during the free-living cycle, which is the only situation where male adult worms of *S. stercoralis* exist. In this latter route of development, the nematode can cycle through several generations as free-living organisms before reverting to the parasitic form. However, this complete free-living cycle can only occur when environmental conditions are favourable. Under unfavourable conditions, the L1 develop into infective L3, which can only undergo further development as part of the parasitic life-cycle in the human host. Whether generated through the free-living or parasitic cycles, the infective L3 penetrate the skin and migrate to the lungs where they moult twice to become young parthenogenic female worms. These young adult worms migrate to the small intestine, via the trachea, and release their eggs. Therefore, not only does *S. stercoralis* infect humans by skin penetration, it is the only GI nematode that can undergo autoinfection of the human host, causing chronic infections lasting for as long as 40 years (Whitfield, 1993; Shamshi et al., 2009).

The life-cycle of *E. vermicularis* differs from that of the other major human GI nematodes in that the L1 develop in the eggs on the perianal skin or under the fingernails (Morris et al., 2005). The majority of the infective eggs are ingested, or inhaled and swallowed after being coughed up, and hatch in the small intestine, where they release the L1. These L1 undergo four moults to the adult stage, usually in the large intestine and the appendix. Gravid females then migrate to the anus and deposit eggs on the perianal skin (Whitfield, 1993; Shamshi et al., 2009).

The survival of nematodes in the GI tract is favoured by the high availability of food, and an easy exit to the external environment ensures continuation of the life-cycle. Whereas most of the major GI nematodes obtain their nutrients by attaching and feeding on the mucosa of the intestinal tract, Ascaris also feeds on the contents of the intestinal lumen. Hookworms attach to the villi...
of the gut, abrading the mucosal surface and feeding on the mucosal tissues of the intestine, internalizing boluses of tissue and sucking in blood from the underlying capillaries, making anaemia a prominent symptom of the disease caused by these parasites (Shamshi et al., 2009).

**Consequences of infections with GI nematodes**

In the case of heavy infections with GI nematodes, the most common complaints are intestinal, such as diarrhoea, abdominal pain and, in the case of *A. lumbricoides* obstruction of the gut (Gilles, 1968; Gonzalez & Javier de la Cabada, 1987; Clinch & Stephens, 2000; Kucik *et al.*, 2004). However, these parasitic infections have more serious consequences, such as anaemia, malnutrition, secondary infection etc (Stepek *et al.*, 2006).

**Management of GI nematodes of humans**

Control of nematode infections is based on drug treatment, improved sanitation and health education. Now, the major means of controlling human GI nematode infections is by the administration of one of the four chemotherapeutic anthelmintic drugs recommended by the WHO for the treatment of these infections (Bowman *et al.*, 2003). These drugs are albendazole, mebendazole, levamisole and pyrantel, and there is at least one anthelmintic drug which can be used to treat each of the major GI nematodes of humans (Table 3). These drugs belong to two distinct classes: group 1, the benzimidazoles (albendazole and mebendazole), and group 2, the imidazothiazoles/tetrahydropyrimidines (levamisole and pyrantel) (Bartoloni *et al.*, 1993). There is a third class of anthelmintics, the macrocyclic lactones (group 3; e.g. ivermectin), which are used in the treatment of GI nematode infections of livestock, but which have only recently been registered for use in humans against strongyloidiasis in France, Australia and the USA, (Albonico *et al.*, 1994) although ivermectin has been available for use against filarial nematodes for several years (Albonico *et al.*, 1999).

**Table 3** - Percentage cure rates for the anthelmintics used to control infections with human gastrointestinal (GI) nematodes

<table>
<thead>
<tr>
<th>Anthelmintic</th>
<th>Hookworms</th>
<th><em>A. lumbricoides</em></th>
<th><em>T. trichiura</em></th>
<th><em>E. vermicularis</em></th>
<th><em>S. stercoralis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebendazole</td>
<td>95–100</td>
<td>95–100</td>
<td>45–100</td>
<td>96</td>
<td>44</td>
</tr>
<tr>
<td>Albendazole</td>
<td>33–95</td>
<td>67–100</td>
<td>10–77</td>
<td>40–100</td>
<td>17–95</td>
</tr>
<tr>
<td>Thiabendazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89–100*</td>
</tr>
<tr>
<td>Pyrantel</td>
<td>37–88_</td>
<td>81–100</td>
<td>0–56</td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td>66–100</td>
<td>86–100</td>
<td>16–18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>0–20</td>
<td>50–75</td>
<td>11–80</td>
<td>61–94</td>
<td>83–100</td>
</tr>
<tr>
<td>Piperazine</td>
<td>74–94</td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
</tbody>
</table>

When an infection is recognized, efforts should be made to improve personal hygiene. Fingernails should be cut short, the perianal region washed in the morning, and bedding and sleeping garments washed daily (Maipanich *et al.*, 1997). Other members of a patient’s family should be checked; the entire family may need treatment to eliminate infection. Although several anthelmintics are effective in treating enterobiasis, the drugs presently recommended are pyrvinium pamoate, pyrantel pamoate, and mebendazole (Jongsuksuntigue *et al.*, 1993). It is advisable to retreat the patient one month later.

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References


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