Giardiasis: Modern Concepts in Control and Management

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Abstract
Giardia is the most common enteric protozoan pathogen of humans, domestic animals and wildlife. Children are at the most risk from the clinical consequences of Giardia infection, particularly those in developing countries and living in disadvantaged community settings. Molecular epidemiological studies have helped to elucidate sources of infection and the public health significance of animal reservoirs. Although aspects of the pathogenesis of Giardia infection are now understood, we are still a long way from understanding the factors that predispose to clinical disease. Effective drugs are available to treat giardial infections but can serve only as an adjunct to traditional public health approaches in endemic settings where children are commonly infected.

Introduction
Intestinal protozoan infections are common in humans worldwide [1]. Infections in childhood, in pregnancy, and those related to AIDS, are of major importance. Associated morbidity and mortality are high, with more than 58 million cases of childhood protozoal diarrhea per year, where the direct costs of management alone are estimated to be in the region of USD 150 million [1]. The flagellate protozoan Giardia is globally the most common enteric protozoan parasite of humans, and is also the most common enteric parasite of domestic animals, including livestock, dogs and cats [1–4].

In developed countries, infections with Giardia are most common in children, especially in daycare centers and travelers, and a rising incidence in such settings has led to the designation of giardiasis as a reemerging infectious disease in the developed world [2–5]. In developing countries, particularly in Asia, Africa and Latin America, about 200 million people have symptomatic giardiasis with some 500,000 new cases reported each year [6]. Children living in communities are most commonly infected in developing countries and among disadvantaged groups living in isolated communities such as Australian Aborigines [1, 2, 7]. These children are most at risk from the chronic consequences of Giardia infection.

The WHO has given consideration to intestinal protozoa for many years but because of their very different disease dynamics they did not initially form part of the Neglected Diseases Initiative. However, since all have a common link with poverty, the current view is to take a comprehensive approach to all these diseases. In Septem-
ber 2004, *Giardia* was included in the WHO’s Neglected Diseases Initiative [1].

The protozoa that collectively comprise the genus *Giardia* have intrigued biologists and clinicians for over 300 years, ever since Antony van Leeuwenhoek first discovered the organisms [8]. Despite its long history, *Giardia*’s taxonomy, pathogenicity and relationship with its hosts are still poorly understood, even though it is the most ubiquitous of all the enteric protozoa of mammals.

**Taxonomy**

Members of the genus *Giardia* are flagellated protozoans belonging to the class Zoomastigophorea and order Diplomonadida. They commonly affect the intestinal tracts of numerous vertebrate species [4]. The phylogenetic affinities of *Giardia* have been a matter of controversy for many years. *Giardia* has a very simple intracellular organization and has been proposed to represent an early branching eukaryote lineage that diverged before the acquisition of mitochondria [9]. *Giardia* has therefore become a key organism in attempts to understand the evolution of eukaryotic cells [4].

The recent application of molecular, PCR-based tools has enabled the genetic relationships of a range of morphologically identical ‘strains’ of *Giardia* to be determined [4, 10–12]. As a consequence, a large number of species and genotypes of *Giardia* are now recognized that differ principally in their host range. The current taxonomy of *Giardia* is summarized in table 1 and has been extensively reviewed [4, 11, 13]. The nomenclature most widely accepted at the present time for the genotypes that have been characterized is ‘assemblage’, although a revised taxonomy has been proposed [4, 11]. Some species and genotypes/assemblages appear to be restricted to particular species or types of hosts (e.g., *Giardia* assemblages C/D [G. canis] and E [G. bovis] in dogs and livestock, respectively; table 1) whereas others have broad host ranges including humans (e.g. *G. duodenalis* assemblages A and B; table 1) and are therefore of zoonotic significance. *G. duodenalis* (syn *G. intestinalis*; *G. lamblia*) is the only species found in humans.

**Life Cycle**

*Giardia* has a very simple two-stage life cycle [14]. The organism produces environmentally resistant cysts which are voided in the feces and will initiate infection if ingested by another host. Exposure first to an acidic environment in the stomach and then to bile salts in the proximal small intestine stimulates release of trophozoites from the cysts which then attach to and colonize the mucosal surface of the small intestine on which they multiply rapidly by asexual binary fission. As trophozoites pass through the small intestine they encyst and are passed in the feces. Cysts voided in the feces are the infective stage and are immediately infective if ingested. The cysts may be transmitted directly from one individual to another under circumstances that are conducive to fecal-oral transfer such as in daycare centers or in environments where hygiene levels are compromised. The cysts are capable of prolonged survival in the environment, particularly if moisture levels are sufficient to prevent desiccation.

<table>
<thead>
<tr>
<th>Species/assemblage</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>G. duodenalis</em>/assemblage A</td>
<td>Humans and other primates, dogs, cats, livestock, rodents and other wild mammals</td>
</tr>
<tr>
<td><em>G. duodenalis</em>/assemblage B (G. enterica)</td>
<td>Humans and other primates, dogs</td>
</tr>
<tr>
<td><em>G. agilis</em></td>
<td>Amphibians</td>
</tr>
<tr>
<td><em>G. muris</em></td>
<td>Rodents</td>
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<tr>
<td><em>G. psittaci</em></td>
<td>Birds</td>
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<tr>
<td><em>G. ardea</em></td>
<td>Birds</td>
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<tr>
<td><em>G. duodenalis</em>/assemblage C/D (G. canis)</td>
<td>Dogs</td>
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<td><em>G. duodenalis</em>/assemblage F (G. cati)</td>
<td>Cats</td>
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<tr>
<td><em>G. duodenalis</em>/assemblage E (G. bovis)</td>
<td>Cattle and other hoofed livestock</td>
</tr>
<tr>
<td><em>G. duodenalis</em>/assemblage G (G. simondi)</td>
<td>Rats</td>
</tr>
</tbody>
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1 See Thompson and Monis [4].
tion. As such, *Giardia* may be transmitted mechanically via contaminated food, flies, or by drinking contaminated water [12].

**Diagnosis**

Light microscopy remains the most practical approach for the diagnosis of *Giardia* in a clinical setting, using concentration techniques such as zinc sulfate centrifugation for concentration of cysts in fecal specimens [15, 16]. Because cyst excretion is sporadic, several fecal samples should be examined over 4–5 days. There are a number of ELISA-based methods available that detect coproantigens and these work well but are relatively expensive. Indirect immunofluorescence and PCR are principally epidemiological and research tools due to their cost.

The big advantage of microscopy is that it is not specific and therefore other parasites can be detected, which may be important in determining the cause of nonspecific symptoms such as diarrhea.

**Epidemiology and Transmission**

An important aspect of the epidemiology of infections with *Giardia* is understanding the host range of different species and genotypes/assemblages, how they are maintained in nature, and the potential for cross-transmission [3, 11]. This is particularly important in determining the zoonotic potential of *Giardia* infections in domestic animals [3, 11]. *Giardia* is maintained in a variety of transmission cycles that can operate independently, for example between humans, livestock, dogs, or wildlife. However, the circumstances under which such cycles may interact are not understood, particularly when this may result in zoonotic transfer. In this respect, establishing a correct taxonomy has provided the basis for a better understanding of the links between infections in domestic animals and humans [4, 11, 17] (table 1).

Giardiasis is the most frequently diagnosed waterborne disease and, along with cryptosporidiosis, is the major public health concern of water utilities in developing nations [3, 18, 19]. Infected livestock have long been incriminated as sources for the waterborne transmission of giardiasis [3, 10, 20]. However, there is little evidence from molecular epidemiological studies that domestic animals were the original source of waterborne outbreaks, and thus contamination with human effluent in sewage is the most likely source [3, 17].

Although studies on the occurrence of the different genotypes of *Giardia* serve to emphasize the potential public health risk from domestic dogs and cats, data on the frequency of zoonotic *Giardia* transmission are lacking [3, 21]. Such information can be obtained from molecular epidemiological studies that genotype isolates of the parasites from susceptible hosts in localized endemic foci of transmission, or as a result of longitudinal surveillance and genotyping of positive cases. In the former, recent research in localized endemic foci of transmission has provided evidence in support of the role of dogs in cycles of zoonotic *Giardia* transmission involving humans and domestic dogs from communities in tea-growing areas of Assam, India, and in temple communities in Bangkok, Thailand [22, 23]. In both these studies, some dogs and their owners sharing the same living area were shown to harbor isolates of *G. duodenalia* from the same assemblage. Other studies have shown that zoonotic genotypes of *Giardia* may occur frequently in individual pet dogs living in urban areas [for review, see 21].

Although animals may serve as reservoirs of *Giardia* infection that under certain circumstances may spill over to humans, from a clinical viewpoint, direct human-to-human transmission is of most significance, particularly in situations where the frequency of transmission is high. Human-to-human transmission of *Giardia* can occur indirectly through the accidental ingestion of cysts in contaminated water or food, or directly in environments where hygiene levels may be compromised, such as daycare centers or disadvantaged community settings, where the frequency of transmission is high and/or conditions are conducive to direct person-to-person transfer [2, 7]. Under such circumstances, children may be at constant risk of infection, even though chemotherapeutic interventions may be instituted [1, 24]. If children are constantly exposed they will be re-infected rapidly since antigiardial agents have no residual activity. The fact that children in such endemic settings do not appear to develop resistance to *Giardia* infection may be due to sub-optimal immunological competence and/or infection with different strains/sub-genotypes of *Giardia* [25]. It would be expected that competitive interactions might result in the predominance of particular genotypes of *Giardia* and the exclusion of others, but this does not appear to be the case.

Humans may be infected with *Giardia* genotypes belonging to assemblage A or assemblage B [11, 13]. There is considerable evidence of phenotypic differences between these two assemblages in characters such as metabolism and growth rate [4]. It has, therefore, been pro-
posed that there may be differences in the nature of infection between these two assemblages in humans, which may be reflected in the duration of infection, drug sensitivity and virulence [4]. There is growing evidence to support these suggestions but there is a need for more focused molecular epidemiological studies. For example, in tea-growing communities in Assam, India, the proportion of assemblage B and A infections in 18 infected people was 61 and 39%, respectively [22]. Another study in the United Kingdom that examined 35 human clinical samples found that 64% were assemblage B, 27% were assemblage A genetic sub-group II, and the remainder were a mixture of assemblage B and assemblage A genetic group II [26]. Similarly, an institutional survey in Australia found that infections with assemblage B were more prevalent (70%) than assemblage A (30%) [27]. The assemblage B genotype was also found to be responsible for an outbreak in a nursery in the UK where 21 of 24 (88%) cases were infected with this genotype [26]. The longitudinal study, which was undertaken in daycare centers in Perth, Western Australia, found that children infected with isolates of Giardia belonging to assemblage A were 26 times more likely to have diarrhea than children infected with assemblage B isolates [27]. Thus, children infected with isolates of Giardia from assemblage B will not be excluded from such daycare centers since exclusion is dependent on the occurrence of diarrhea. This would explain why infections with assemblage B are more common in such environments. Children with such infections are likely not to be treated which also raises questions about the long-term consequences of such chronic infections if they persist and there is no ‘self cure’. This is thought to be significant in situations where infected children are disadvantaged in terms of nutrition and/or exposure to concurrent enteric infections with other parasites such as Hymenolepis and Ancylostoma. This is the situation in isolated Aboriginal communities in northern Australia, where Giardia infections are recognized as contributing to nutritional disorders and poor growth. In such communities, infections with isolates of Giardia from assemblage B are more common than those with assemblage A [25, 28, 29].

In such community settings, children infected with Giardia are treated regularly with antigiardial agents, particularly the nitroimidazoles, yet treatment failures are common and are exacerbated by high re-infection rates as a consequence of poor hygiene and environmental contamination [4, 25]. A hypothesis that should be tested is that assemblage B isolates of Giardia are more persistent than assemblage A, have a more intimate association with the intestinal mucosa than assemblage A isolates, and are less sensitive to antigiardial agents. Longitudinal studies of the long-term effects of Giardia assemblage-related species/genotype/sub-genotype infections in endemic communities are required [1].

There is a need for additional large-scale molecular epidemiological surveys of Giardia infections in humans. With the limited data currently available it is not possible to determine the geographical distribution and prevalence of human-infective genotypes. With such data it may be possible to determine the significance of any strain-related differences in virulence.

**Pathogenesis and Clinical Impact**

The pathogenesis of Giardia infection is not clearly understood. The parasite is not invasive and lives and multiplies by asexual multiplication on the luminal surface of the small intestine of its vertebrate host. Giardia infections can cause malabsorptive diarrhea but the factors associated with this are still unclear and much of what we know about the pathogenesis is confined to experimental infections. Pathogenesis results from interaction between parasite products, such as proteinases that break the epithelial barrier, and host inflammatory and immunological responses [30–33]. Giardia induces enterocyte apoptosis, associated with disruption of cytoskeletal and tight junctional proteins in a strain-dependent manner [34]. Villous atrophy, diffuse shortening of microvilli, reduced disaccharidase activity, loss of epithelial barrier function, increased permeability and apoptosis have all been reported in Giardia infections [35]. Recent evidence shows that Giardia infection can also cause hypersecretion of chloride ions [36]. These changes are thought to be due to a combination of parasite products, possibly a toxin, and host immune factors, particularly involving CD8+ cells [35].

Symptomatic infection in humans may not be evident in a significant proportion of infected individuals [37] and represents only a fraction (20–80%) of all stool-positive Giardia infections [38–40]. Symptoms are highly variable but include continuous, usually short-term, diarrhea, epigastic pain, nausea, vomiting and weight loss [5, 14]. Symptoms typically occur 6–15 days after infection and last for 2–4 days. As such, infection is assumed to be self-limiting in >85% of cases (indicating that effective host defenses exist), although chronic cases occur occasionally in the absence of apparent immunodeficiencies [38, 39].
The risk factors for clinical giardiasis, particularly in humans, have yet to be resolved but clearly involve host and environmental factors, as well as the strain/genotype/assemblage of the parasite [36]. However, a distinction needs to be made between the effects of a single infection which may give rise to the classical short-term episode of diarrhea and the long-term effects of *Giardia* infection, particularly in children living in environments where the frequency of transmission is high. Here the picture is very different. In endemic foci where the frequency of transmission is high and often enhanced by poor hygiene and environmental contamination, children are at particular risk from the more serious and long-term consequences of *Giardia* infection that are associated with malnutrition, micronutrient deficiency and failure to thrive, iron deficiency anemia and poor cognitive function [1, 40–43]. Clearly, the impact of *Giardia* under such circumstances will be exacerbated by poor/suboptimal nutrition and concurrent infections with other enteric parasites such as *Hymenolepis nana* and *Blastocystis*. Longitudinal studies on the impact of enteric parasites on childhood growth and mental development in endemic areas is urgently required [1].

**Treatment and Control**

A variety of drugs are available to treat infections with *Giardia* in humans. These include metronidazole, tinidazole and furazolidone (which are nitroimidazoles), albendazole (a benzimidazole), and quinacrine (a substituted acridine). Paromycin has also been shown to be useful in some situations, and nitazoxanide has been proposed as an alternative to the conventional nitroimidazoles, but more studies are required to fully evaluate its efficacy [1, 14, 44, 45]. However, at the present time, the nitroimidazoles (metronidazole and tinidazole) and albendazole are the drugs of choice for treating *Giardia* infections [1]. Treatment failures have been reported with all the commonly used drugs but whether this represents resistance has yet to be convincingly demonstrated [1, 14]. The lack of patient compliance and side effects can result in treatment failures, and there is some evidence of variable sensitivity between strains of *G. duodenalis* [1, 14, 44, 45]. Single daily doses offer better compliance (tinidazole has a longer half-life than metronidazole and is well tolerated if taken during meals) [1, 14]. Poor compliance can lead to drug resistance, and while anecdotal evidence of metronidazole resistance exists, further studies on the genetic mechanisms of resistance, and assemblage-linked sensitivity to metronidazole, as well as the development of multi-drug resistance are required [1]. Albendazole offers a more palatable alternative to the nitroimidazoles, particularly for children, but multiple doses are required [1, 45].

It has been proposed that probiotic therapy may be useful in preventing infection or as an adjunct for treating infection [46]. It was found that commensal bacteria can determine susceptibility and resistance to *Giardia* infection in mice [1, 5, 47]. It has also been shown that probiotic lactobacilli release a low molecular weight, heat-sensitive factor that inhibits proliferation of *Giardia* trophozoites in vitro culture [48]. Such novel therapeutic strategies warrant further investigation [1, 5], and may prove to be more applicable and useful than drugs for treating children in endemic areas.

The control of *Giardia* infections in endemic situations where the frequency of re-infections is high because of environmental contamination and poor hygiene represents the biggest challenge. The children who are infected in such environments, particularly in developing countries and among disadvantaged groups, represent the most important group in terms of the clinical impact of *Giardia* [1, 2, 7]. Under such circumstances, it is debatable whether the regular use of drugs is of any benefit. This is in contrast to the situation with gastrointestinal helminths such as hookworm, where regular mass chemotherapy has been shown to have great benefit in control [24, 26, 45]. For example, a sustained, community-based control program that used a regular 5-day treatment regimen of 400 mg albendazole over 6.5 years in an isolated community effectively controlled hookworm (*Ancylostoma duodenalis*) but had no sustained effect on the prevalence of *Giardia* and *Hymenolepis* [24, 45]. Although *Giardia* was well suppressed by multiple doses of albendazole, regular 6-monthly single doses of albendazole did not suppress the parasite over the long-term. Re-infection with *Giardia* by the fecal–oral route is rapid in such environments in which cyst survival is possible, negating any transient benefits of chemotherapy without concurrent behavioral changes [24, 45]. Mass treatment must be combined with appropriate education programs designed to prevent re-infection [1, 24].

**Conclusions**

In theory, the prevention and control of intestinal protozoan infections is now more feasible than ever before [1], but whether it is a practical proposition remains de-
batable. Molecular epidemiology has recently had an enormous impact on the taxonomy of *Giardia* and the characterization of the etiological agents of giardiasis in humans and, as such, we are in a much better position to evaluate risk factors for public health in terms of our understanding of transmission patterns and sources of infection. There is a need to undertake molecular epidemiological studies in localized, well-defined endemic foci, particularly in developing countries and among disadvantaged groups. Our understanding of the pathogenesis of infections with *Giardia* has improved and we are a little closer to being able to say why clinical disease occurs in some individuals but may not be apparent in others. However, studies are required to better understand the strain-dependent outcomes of infection, particularly in children. Drugs are available to treat infections with *Giardia* but the question is when to use them, and it is essential that their use be complemented by basic health education strategies designed to limit the frequency of fecal-oral transmission. In this regard, such interventions will require the cooperation of government agencies to improve basic infrastructure in disadvantaged communities.

It has also been proposed that training courses on important intestinal protozoa such as *Giardia* should be undertaken for health workers and courses on the usefulness of molecular methods for detecting such protozoa should be encouraged for primary health and daycare workers and diagnostic laboratory staff [1]. More effective diagnoses carried out in clinics and laboratories globally will enhance the targeting of treatment and lead to a reduction in morbidity [1]. In addition, providing accurate surveillance statistics are collected, the view of the importance of intestinal protozoal diseases held by governments, national and international NGOs, and advocacy groups will be more realistic, and lead to correct targeting of aid and research funds [1].

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