12 Giardia intestinalis

A 24-year-old man went on a 3-month backpacking trip across India. He drank bottled water and reportedly ate well-cooked food in hotels and restaurants. While in India, his stools were looser than normal. In the week before his return he developed frequent watery, non-bloody diarrhea. This settled enough for him to fly home. He immediately went to his doctor and a stool culture grew *Campylobacter*. His bowels improved over 10 days without treatment but 2 weeks after his return he developed more diarrhea, with loss of appetite, bloating, and flatulence. For the first time, his stools failed to flush away completely in the toilet and were particularly offensive in smell. He began to lose weight. His doctor requested three stool specimens for culture and also microscopy for ova, cysts, and parasites. One out of three specimens contained *Giardia* cysts. He was treated with a course of metronidazole and his symptoms improved.

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

CAUSATIVE AGENT

Giardia is a protozoan consisting of six species that infect mammals, amphibians, and birds. The only species that infects humans is *Giarda intestinalis* (alt. *lamblia* and *duodenalis*). It has two stages to its life cycle (**Figure 12.1**): (a) a trophozoite (feeding and pathology-causing stage) that is flagellated (with four pairs of flagellae), pear-shaped, with two nuclei, a ventral "sucking" disk, and median bodies. It also has a rigid cytoskeleton composed of microtubules and microribbons. It measures 9–21 µm long by 5–15 µm wide; (b) a cyst, with a highly resistant wall that enables it to remain viable outside the body of the host for long periods. The cyst is smooth-walled and oval in shape, measuring 8–12 µm long by 7–10 µm wide. The genome of the parasite has five chromosomes of different sizes and variation of the number of genome equivalents (ploidy) occurs during the life cycle: trophozoite >cyst>excyzoite>trophozoite. The genome ploidy is important in gene regulation and differentiation. *Giardia* is the oldest known extant eukaryote, having prokaryotic characteristics: no mitochondria and metabolism similar to prokaryotes.

G. intestinalis is a multispecies complex with at least eight recognized assemblages or genotypes (A–H) based on a number of clinical samples. The two genotypes A and B are the major human pathogens. Molecular analysis of 2800 samples indicates that genotype B accounts for around 58% giardiasis cases with genotype A found in around 37% of cases worldwide. There are, however, differences in percentages of these in different countries. For example in Spain, there were 27.4% of A and 72% of B recorded in Madrid. A and B genotypes were equally represented in Rioja. In Spain, children also appear to be more commonly infected with the B phenotype than adults.

ENTRY INTO THE BODY

Cysts are ingested from contaminated water or food and having passed through the stomach, begin to open up at one end (excystation), releasing trophozoites into the intestine lumen, which then divide within 12 hours (**Figure 12.1**). They settle in the small intestine (predominantly in the mid-jejunum). A minimum of 10–25 cysts are necessary to produce an infection. The trophozoites attach to the intestinal wall through their ventral "sucking" disk and feed on nutrients (**Figure 12.2**). They increase in number by binary fission and colonize large areas of epithelial surface causing diarrhea and damage to the epithelium (see Section 2). At regular intervals and following detachment and movement down toward the colon (and probably exposure to biliary secretions), some of the trophozoites become encysted (encystation), with each trophozoite forming a single cyst. Both trophozoites and cysts pass out of the body in the feces.

SPREAD WITHIN THE BODY

Penetration of the epithelial surface by the trophozoites is very rare, as is migration of the trophozoites to systemic sites. Invasion of the gallbladder, pancreas, and urinary tract have been reported but the trophozoites normally remain in the intestine/colon and do not cross the mucosal barrier.

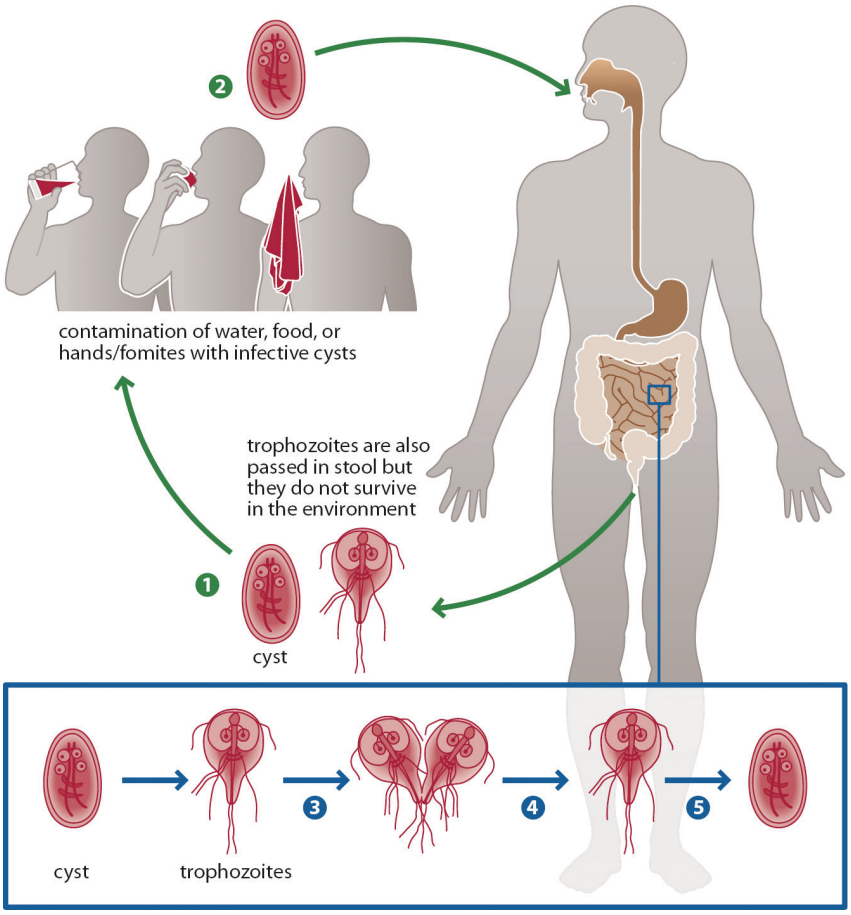

Figure 12.1 The life cycle of *G. intestinalis*. Both cysts and trophozoites are found in feces (1). The cysts are hardy and can survive 2–3 months or more in cold water. Cysts in contaminated water, food, or by the fecal-oral route (hands or fomites) cause infection (2). In the small intestine, the cysts give rise to trophozoites (each cyst producing two trophozoites) (3). The trophozoites multiply by binary fission and remain in the lumen of the small bowel where they can be free in the mucus or attached to the epithelial cells by their ventral sucking disk (4). Trophozoites encyst on transit toward the colon. The cyst is the stage found most commonly in non-diarrheal feces (5). The cysts are infectious when passed in the stool or shortly afterward and, if ingested by another person, the cycle begins again. *Courtesy of the Centers for Disease Control, Atlanta, Georgia. Image is found in the Public Health Image Library #3394. Additional photo credit is given to Alexander J. da Silva, PhD, and Melanie Moser who created the image in 2002.*

PERSON-TO-PERSON SPREAD

Cysts can remain dormant for up to 3 months in cold water. Spread is through ingestion of contaminated food and also via the **fecal–oral** route (hands and **fomites**), although water is probably the main source. Contamination of public-drinking supplies has led to giardiasis epidemics. When children become infected, up to 25% of their family members also become infected. Individuals can shed cysts in their feces and remain symptom-free but are an important source of person-to-person transmission (see Section 3). Sexual transmission of *Giardia* has been described in men who have sex with men. *Giardia* is found in a wide variety of different animal species and has been regarded as a **zoonosis**, although there is little evidence for animals being a significant source of human giardiasis.

EPIDEMIOLOGY

Giardiasis is one of the most common water-borne diseases that infect humans and the most common enteric protozoal infection worldwide, with 280 million cases a year and up to 33% of individuals infected. Prevalence rates vary from 4% to 42%. It affects nearly 2% of adults and 8% of children in developed countries. Infection is linked to poor hygiene and sanitation and is more prevalent in warm climates.

The prevalence within the US is estimated to be roughly 1.2 million, with the majority of cases not identified due to the carrier being asymptomatic. In 2012, the CDC reported 15223 cases. The most affected are children 0 to 4 years of age, with the largest percentage of cases being in the northwest US. Infection is most common in late summer and early fall due to outdoor water activities.

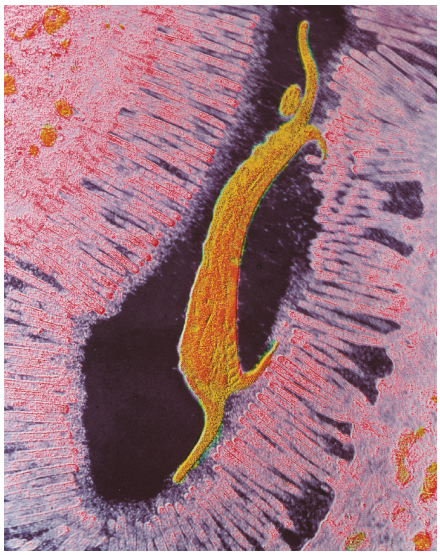

Figure 12.2 *G. intestinalis* attached to microvilli in the small intestine. This colored TEM (transmission electron micrograph) shows a *G. intestinalis* trophozoite attached by means of its ventral sucking disks to microvilli in the human small intestine. *From CNRI / Science Photo Library, with permission.*

Water-borne outbreaks appear to be the most common source of infection. In Canada, in 2016, there were 3818 reported cases of giardiasis with a similar seasonal variation to that seen in the US. In the Western world, giardiasis is more likely to be diagnosed as a cause of diarrhea that occurs or persists after travel to a developing country. This is due to its relatively long incubation period and persistent symptoms. Thus, the organism is a cause of "traveler's diarrhea", also called "backpacker's diarrhea" and "beavers' fever" (since it was originally believed to be transmitted from beavers to man).

It is not unusual for outbreaks of *Giardia* to occur on cruise ships.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

In a study of prison "volunteers" in the 1950s given the same infectious dose, 50% of subjects developed asymptomatic infections, 35% self-limiting symptomatic infections, and 15% troublesome persistent diarrhea. Given that they received the same dose and strain this illustrates the impact of host susceptibility and resistance. However, host defenses against *G. intestinalis* are not well characterized but they are believed to involve both non-immunologic mucosal processes and immune mechanisms.

HOST DEFENSES

Non-Immunologic Defenses

Intestinal epithelial cells are shed and replaced every 3–5 days and therefore the trophozoites need to constantly detach and reattach to new epithelial surfaces. The mucus produced by the goblet cells impedes access of the trophozoites to the epithelium. It has been proved that certain commensal bacterial species enable mice to be resistant against *Giardia* colonization suggesting that differences in microbiotic composition between individuals and species could explain the variability in pathology and susceptibility to infection (see later).

IMMUNE RESPONSES

There appears to be little or no mucosal inflammation in human *Giardia* infection, which indicates that local defense must be occurring without systemic recruitment. Most of the data on immune responses to *Giardia* come from experimental animal models.

INNATE IMMUNITY

Antimicrobial peptides such as **defensins** and **cathelicidins** secreted by intestinal epithelial cells have anti-giardial activity *in vitro* and may have activity *in vivo*. Nitric oxide (NO) produced by gut epithelial cells inhibits growth, encystation, and excystation *in vitro*, but has no effect on viability. However, *Giardia* has developed strategies to evade this host defense mechanism. Trophozoites down-regulate expression of iNOS in intestinal epithelial cells. This probably leads to the reduced expression of iNOS reported in pediatric patients infected with *Giardia*. Although monocytes/macrophages and polymorphs can kill trophozoites *in vitro* by oxidative mechanisms, very few are found in the human intestinal lumen during infection. Mast cells are currently recognized as effector cells of the immune response against several parasites. Interestingly, in tissues from the small intestine that have been infected with *G. intestinalis*, the most strongly induced transcripts are mast-cell proteases. Mast cells and NO could act together to induce peristalsis. The maturation and activation of dendritic cells (DCs) can be induced through *Giardia* lysates, excretory secretory products, and other specific proteins. This is seen as an increase in pro-inflammatory cytokines, for example IL-6, TNFα and IL-12 and of surface molecules such as CD80, CD86, and MHC class II. *Giardia* may activate the maturation and migration of DCs to the site of infection with their subsequent release of immunomodulatory cytokines. The production of IL6 by DCs seems to be of major importance in the clearance of *Giardia*.

ADAPTIVE IMMUNITY

T-Cell Responses

IL-6 produced by DC is important for T-cell differentiation and may determine the type of T-cell response that ensues. In both humans and animals, *Giardia* infection induces a strong protective adaptive immune response, in which the main player is CD4+ T lymphocytes. This includes Th-1, Th-2, and Th-17 cells. Recent findings in a murine model of *Giardia* has shown local elevations in the ratio between Th-17 and Treg lymphocytes within the small intestinal lamina propria and Peyer's patches related to their increased resistance to infection. Interestingly, duodenal mucosal lymphocyte alterations are maintained for many months after the onset of infection in human patients. Th-17 cells producing IL-17 have been found in the blood of humans infected with *Giardia*. The evidence is clear that CD4+ T cells are important protection against *Giardia* infection and specific depletion of **CD4**+ T cells results in the development of chronic giardiasis. CD8+ T cells appear to play no role in host protection against *Giardia*.

Antibody Responses

Although *Giardia* trophozoites do not usually cross the mucosal barrier, some antigenic *Giardia* products antigens must penetrate the barrier. This might be through the M cells of Peyer's patches or the DCs with intraepithelial processes into the gut lumen. Antibodies to *Giardia* are found in both mucosal secretions and serum and it has been established that antibodies, particularly of the IgA isotype, contribute to the maintenance of protective immunity against giardiasis. Anti-*Giardia* secretory IgA can be detected in human saliva and breast milk. Antibodies of up to 16 immunogenic proteins in infected patients have been identified by serum IgG. These include variant-specific surface proteins (VSP: see below), cytoskeletal proteins unique to *Giardia* (α- and β-tubulin, α- and β-giardin), and enzymes (e.g. arginine deaminase, orthinine carbamoyl transferase, and enolase) are found (see below). These enzymes have been found to be induced following contact of the parasite with the intestinal epithelial cells. **IgG** antibodies to *Giardia* have been shown to kill *Giardia* trophozoites *in vitro* through complement. Although it is unlikely that this mechanism could occur in the intestinal lumen, it might be one explanation as to why *Giardia* does not invade.

GIARDIA-SPECIFIC ANTIGENS AND ANTIGENIC VARIATION

Each trophozoite expresses only one of many highly immunogenic variant-specific surface proteins (VSP) on *Giardia*. The trophozoites being able to switch the VSPs in their surface coats. The mechanism of this variation is believed to be through interference RNA (iRNA) and mRNA. Disruption of this pathway generates trophozoites that simultaneously express numerous VSP. It is likely that the variation is driven by antibody. This **antigenic variation** (at least in mice) is thought to be a mechanism whereby the trophozoites can avoid the immune system. An alternative, but not mutually exclusive, biological explanation for antigenic variation is their adaptation to different intestinal environments. There is some evidence for this possibility in that different VSPs have different susceptibility to proteases.

Interestingly, the repertoire of VSP antigens is much smaller than that seen in trypanosomes (see Case 37) and the mechanisms leading to their "switching" are different.

PATHOGENESIS

The mechanisms by which giardiasis causes diarrhea and malabsorption are incompletely understood. Several have been postulated and include damage to the endothelial brush border, enterotoxins, immunologic reactions, changes in gut motility, and fluid hypersecretion via increased adenylate cyclase activity. Direct attachment of trophozoites to the epithelium has been demonstrated to cause increased epithelial permeability. *Giardia*-induced loss of intestinal brush border surface area, villus flattening, inhibition of disaccharidase activities, and eventual overgrowth of enteric bacterial flora appear to be involved in the pathophysiology of giardiasis but have yet to be causatively linked to the disease's clinical manifestations. There is little evidence of any exotoxins producing epithelial damage. Regarding the damage to the brush border, which provides a large surface area for absorption, biopsies from only 3% of patients with infection showed villus shortening and there was little inflammation. In experimental infection of 10 human volunteers with *Giardia* type B genotype, only five individuals developed symptoms and only two of these showed any change to the brush border. Thus, microvillus shortening and inflammation are not directly correlated with the symptoms and indeed clearance of the organism from the intestinal tract. From *in vitro* studies, there is some evidence for *Giardia* inducing a change in the cytoskeleton of human duodenal cells with increased **apoptosis** and disruption of tight junctions in monolayers of intestinal cells. Cysteine proteases secreted by *G. intestinalis* may disrupt intestinal epithelial cell junctional complexes and degrade chemokines. Although disruption of tight junctions has not been confirmed by clinical observation, there is evidence for a correlation of infection with impairment of both absorption and digestive functions. In fact, there are varying degrees of malabsorption of sugars (e.g. xylose, disaccharides), fats, and fat-soluble vitamins (e.g. vitamins A and E) but these might contribute to substantial weight loss. Although CD8+ T cells do not contribute to protection against *Giardia*, there is some suggestion that they are involved in enterocytic damage.

Giardia infections can produce symptoms that persist long after infection although, again, the mechanisms for this are unclear.

Recent research has emphasized the importance of the intestinal microbiota in *Giardia* pathogenicity. Conventional, germ-free, or germ-free mice that were reconstituted with duodenal microbes from patients with symptomatic giardiasis,

were infected with *G. lamblia* trophozoites. The infected non-reconstituted conventional mice showed the intestinal pathology among the three groups, with the reconstituted germ-free mice showing moderate pathology. The infected germ-free mice, however, did not develop intestinal pathology compared with the other groups, suggesting a requirement for intestinal microbes to stimulate pathology.

Colonization by *Giardia* in mice causes a dysbiosis with an increase of the *Proteobacteria* and a decrease in the *Firmicutes*. Segmented filamentous bacteria (SFB), found in many animals including humans, are present in the small intestine near the terminal ileum and are responsible for stimulating IL-17 production. Resistance to *Giardia* in mice occurs with a high intestinal density of SFBs and susceptibility with a low density. In humans, SFBs are scarce in neonates, who are prone to infection, and are more common in adults. A reduction in *Clostridia* has also been noted in infected animals and the presence of the organism is linked to effective Treg responses.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

Most persons infected with *G. intestinalis*, on a global basis, are either asymptomatic or minimally symptomatic. The clinical effects of *Giardia* infection range from asymptomatic carrier status to severe malabsorption (see Section 2). Factors contributing to the variations in presentation include the **virulence** of particular *Giardia* strains (see Section 2), their genotype (A or B), the numbers of cysts ingested, the age of the host, and the state of the immune system (see later). Asymptomatic carriers often have a large number of cysts in their stools.

If symptoms are present, they occur about 1–3 weeks after ingestion of the parasite. These include:

- watery offensive-smelling diarrhea with abdominal cramps;
- severe flatulence;
- nausea with or without vomiting;
- fatigue;
- and possibly fever.

A slower onset may occur with development of yellowish loose, soft and foul-smelling stools – often floating due to the high lipid content. Stools may be watery or even constipation can occur. Initial symptoms usually last 3–4 days or can become chronic leading to recurrent symptoms, severe malabsorption and debilitation may occur. Other symptoms include anorexia, malaise, and weight loss.

Children with malabsorption associated with *Giardia* infection often show failure to thrive and **protein-losing enteropathy** can be a complication leading to stunted growth of children, commonly seen in Africa. Reduced uptake of lipids across the gut epithelium causes deficiency in lipid-soluble vitamins, which is an additional problem for children.

Poor nutrition can also contribute to an increased risk of a person having symptoms with the infection. More serious infections, which can lead to death, are seen in people with a weakened immune system, such as patients with HIV/AIDS, cancer, transplant patients, and the elderly. *Helicobacter pylori* may predispose to *Giardia* due to **hypochlorhydria**. Patients may develop lactose intolerance.

Giardia infection has also been associated with development of post-infectious complications including irritable bowel syndrome and chronic fatigue syndrome. Changes in the intestinal microbiota profile in children with *Giardia* might contribute to some of these complications.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

Clinical diagnosis is often difficult because the same symptoms can occur with a number of intestinal parasites. Giardiasis is therefore diagnosed by the identification of cysts (**Figure 12.3**) or trophozoites (**Figure 12.4**) in the feces, and this is still regarded as the gold standard method. Due

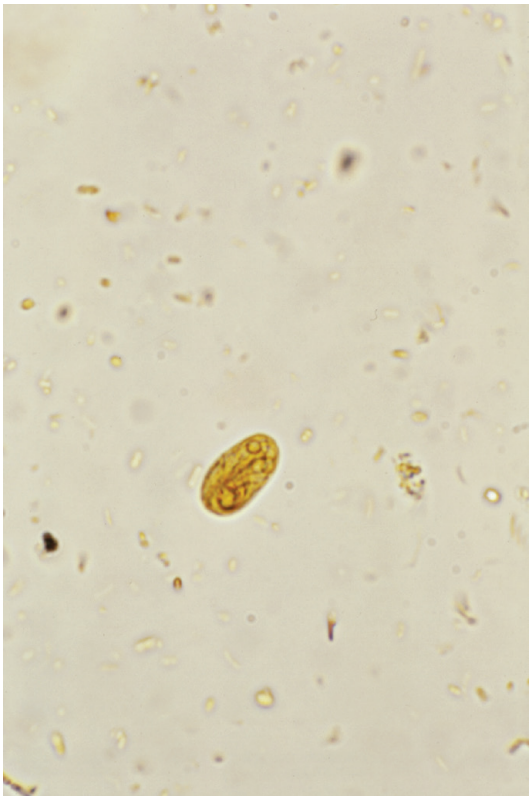

Figure 12.3 *G. intestinalis* cyst in a wet mount stained with iodine. *Courtesy of the Centers for Disease Control, Atlanta, Georgia. Image is found in the Public Health Image Library #3741. Additional photo credit is given to Dr Mae Melvin who took the photo in 1977.*

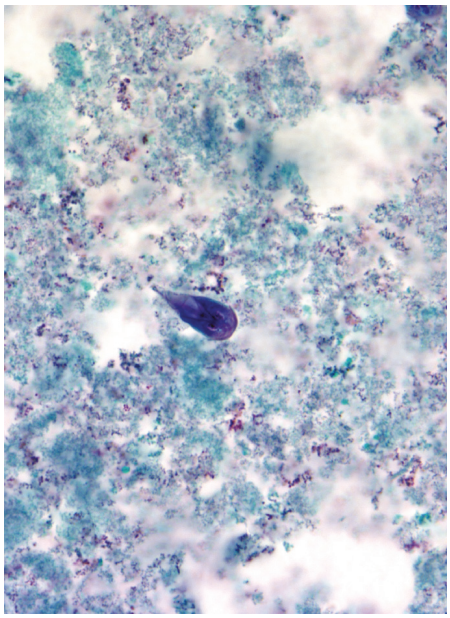

Figure 12.4 *G. lamblia* trophozoite stained with trichrome. *Courtesy of the Centers for Disease Control, Atlanta, Georgia. Image is found in the Public Health Image Library #7833. Additional photo credit is given to DPDX / Melanie Moser who created the original image.*

to the intermittent and low levels of cysts, the fecal samples are usually concentrated before direct examination of wet mounts under the microscope. A number of methods have been used including formalin-ether and sucrose gradients for concentration. Samples can be stained with iodine, methylene blue or trichrome.

Alternate methods for detection of the parasite in the stool samples include antigen detection tests by **ELISA** and by a direct fluorescence assay (DFA) (**Figure 12.5**). Commercial kits for both of these are available.

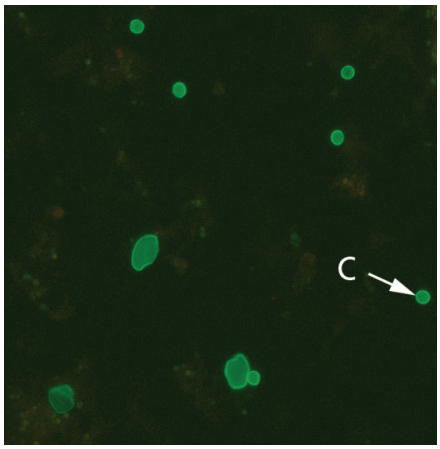

Figure 12.5 Identification of cysts of *G. intestinalis* by fluorescent-labeled *Giardia* antibodies. A formalin-fixed preparation stained with commercially available fluorescent antibodies to *Giardia* and visualized under a fluorescence microscope. Cysts of *Giardia* are seen as large green ovoid objects (labeled C). Oocysts of *Corynebacterium parvum* are also seen in this preparation. *Courtesy of the Centers for Disease Control, Atlanta, Georgia. Image is found in the Laboratory Identification of Parasites of Public Health Concern.*

A "string" test (entero-test) can also be performed. This involves swallowing a weighted gelatine capsule on a piece of string. After the gelatine dissolves in the stomach, the weight carries the string into the duodenum. The string is left for 4–6 hours or overnight while the patient is fasting and then examined for bilious staining. This indicates successful passage into the duodenum and mucus from the string can be examined for trophozoites after fixation and staining.

The **polymerase chain reaction** (**PCR**) detection of *Giardia* DNA is often restricted to laboratory use and mostly for subtyping of *G. intestinalis* (see Section 1).

A duodenal biopsy can be taken and this may be the most sensitive test. This is often taken in cases of unexplained diarrhea.

DIFFERENTIAL DIAGNOSIS

Other causes of gastroenteritis need to be considered including amebiasis, bacterial overgrowth syndromes, Crohn ileitis, *Cryptosporidium* enteritis, irritable bowel syndrome, celiac sprue, tropical sprue, strongyloidiasis, viral gastroenteritis, and lactose intolerance.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

MANAGEMENT

With mild infection, giardiasis can resolve in 6 weeks or so. However, there are several drugs used in the treatment of giardiasis. They include:

1. Nitroimidazole derivatives (metronidazole (Flagyl®), tinidazole, secnidazole, ornidazole,): most frequently used first-line drugs, especially metronidazole.
2. Benzimidazoles (albendazole and mebendazole): these widely used anti-helminthic drugs are used to treat giardiasis but with variable efficacy.
3. Nitrofuran derivatives (furazolidone): these have been reported to have high efficacy in first-line therapy.
4. Acridine compounds (mepacrine and quinacrine): mechanism of action unknown but has been shown to be efficient in therapy.
5. Aminoglycoside: the oral aminoglycoside paromomycin is the drug of choice for pregnant women as it is poorly absorbed and has no systemic effects.
6. Nitazoxanide: in controlled studies efficacies of between 44% and 91% have been reported.

Different countries may have a preference for the use of different types of drugs. In addition, from a worldwide perspective, albendazole (a benzimidazole compound) is used, which has a much broader range of action than metronidazole and the other agents listed. It kills *Giardia* very well, but also

Entamoeba, *Ascaris*, *Enterobius*, and hookworms, and can do this in one single dose. In developing countries, a single-dose albendazole is being given to schoolchildren and has been associated with improved school attendance and educational attainment. They feel better for being cleared of protozoa and helminths.

TREATMENT OF REFRACTORY GIARDIASIS

In general, efficacy of treatment with nitroimidazoles is 90%. However, nitroimidazole failure (especially with metronidazole) has been reported in up to 50% giardiasis cases in both travelers and in high endemic countries. A number of studies have indicated the use of a different class of drug, combination therapy or repeated courses with increased dose/duration of the same drug can be used with variable efficacy.

Pregnant Patients

Treatment of pregnant patients with *Giardia* is difficult because of the potential adverse effects of anti-*Giardia* agents on the fetus. If possible, drug treatment should be avoided during the first trimester. Mildly symptomatic women should have their treatment delayed until after delivery. If left untreated, however, adequate nutrition and hydration maintenance is important. Paromomycin is now the only anti-*Giardia* drug considered completely safe during early pregnancy (see different drugs used to treat *Giardia* above).

PREVENTION

- Good hygiene is very important.
- Contaminated water should be avoided: untreated water should not be consumed. Outbreaks of giardiasis in developed countries are often traced back to breakdown in filtration systems of drinking water supplies.
- Individuals traveling to warm climates where Giardia is found should take extra care with drinking water and consumption of raw food – boil drinking water, and so forth.
- There is no known chemoprophylaxis for humans.
- There is no vaccine for humans yet although there is an effective killed vaccine for dogs (Giardiavax®).

SUMMARY

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

- *Giardia* is a protozoan flagellate. It has two stages – a trophozoite and a cyst with a highly resistant wall.
- *Giardia* consists of six species. Only one species infects humans and this is variously referred to as *G. intestinalis*, *lamblia* or *duodenalis*. There are at least eight genotypes or assemblages (A–H). Only A and B are human pathogens, with B being the most frequent globally. Other genotypes are seen in other mammals and birds.
- The main infectious stage is the cyst; cysts are ingested in contaminated water or food. They lose their cell wall in the duodenum and emerge as trophozoites, which attach to the intestinal wall through their ventral "sucking" disk and feed. They colonize large areas of epithelial surface. They rarely invade the epithelium and spread systemically. They become encysted again and both trophozoites and cysts pass out of the body in stools.
- Contamination of public drinking supplies has led to giardiasis epidemics. When children become infected, up to 25% of their family members also become infected. Individuals can shed cysts in their feces and remain symptom-free. Sexual transmission of *Giardia* has been described in homosexual males.
- *Giardia* is found in a wide variety of different animal species and has been regarded as a zoonosis, although there is little evidence for animals being a significant source of human giardiasis.
- Giardiasis is one of the most common causes of diarrhea worldwide. There are around 280 million cases a year. It is more commonly found in children where, in developing countries, it is estimated that up to 20% are infected.
- *Giardia* is widespread in the US, with a prevalence of an estimated 1.2 million with the majority not identified due to the carrier being asymptomatic. Infection is most common in late summer and early fall due to outdoor water activities. Similar seasonal variation is seen in Canada.
- In the Western world, giardiasis is a cause of diarrhea that occurs or persists after travel to a developing country – "traveler's diarrhea", "backpacker's diarrhea", and "beavers' fever".

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

- The host defenses are clearly effective since individuals infected with *Giardia* are often asymptomatic and some are able to clear the organism without treatment.
- Host defenses are not well characterized but include both non-immunologic and immunologic mechanisms.
- Mucus prevents immediate access of trophozoites. The intestinal microbiota may also play a role in preventing attachment/inhibiting proliferation.
- Antimicrobial peptides such as defensins and cathelicidins secreted by intestinal epithelial cells have anti-giardial activity *in vitro* and may have activity *in vivo*. Monocytes/macrophages and polymorphs can kill trophozoites *in vitro* by oxidative mechanisms but very few are found in the human intestinal lumen during infection IL-6 produced by dendritic cells appears to be of major importance in the clearance of *Giardia*.

Continued...

Continued...

- Most information on immune responses to *Giardia* infections comes from animal models. CD4+ T cells including Th-1, Th-2, and Th-17 appear to play a role in *Giardia* infections in mice but their exact protective role in humans is unclear. CD8+ T cells do not play a role.
- Antibody responses to human *Giardia* do have some protective role. Specific IgA antibodies in human saliva and breast milk can protect children against infection in early life. Immunodominant antigens include VSPs, cytoskeletal structures, giardin, and enzymes. Serum antibodies of IgG class to 16 immunogenic proteins of *Giardia* have been seen in humans,
- *Giardia* shows antigenic variation with each trophozoite expressing one VSP expressed and switching of these probably providing escape from the immune system.
- The mechanisms by which giardiasis causes diarrhea and malabsorption are unclear but have been postulated that include damage to the endothelial brush border, enterotoxins, immunologic reactions, changes in gut motility, and fluid hypersecretion via increased adenylate cyclase activity. Malabsorption of sugars (e.g. xylose, disaccharides), fats, and fat-soluble vitamins (e.g. vitamins A and E) might contribute to substantial weight loss.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

- The clinical effects of *Giardia* infection range from asymptomatic carrier status to severe malabsorption.
- Factors contributing to the variations in presentation include the virulence of particular *Giardia* strains, their genotype (A or B), the numbers of cysts ingested, the age of the host, and the state of the immune system. Carriers often have a large number of cysts in their stools.
- If symptoms are present, they occur about 1–3 weeks after ingestion of the parasite. These include: watery diarrhea with abdominal cramps, severe flatulence, nausea with or without vomiting, fatigue, and possibly fever.
- Infection can become chronic leading to recurrent symptoms, severe malabsorption, and debilitation. Other symptoms include anorexia, malaise, and weight loss. Children with malabsorption syndrome often show failure to thrive. Patients may develop lactose intolerance.
- Patients with a weakened immune system such as patients with HIV/AIDS, cancer, transplant patients or the elderly can develop more severe infections.
- Infection has been associated with development of post-infectious complications including irritable bowel syndrome and chronic fatigue syndrome.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

- Giardiasis is diagnosed by the identification of cysts or trophozoites in the feces which is still the "gold standard". Direct mounts for microscopy as well as concentration procedures may be used. Samples can be stained with iodine or trichrome.
- Commercial kits are available for antigen detection tests by ELISA and by immunofluorescence. PCR testing for *Giardia* DNA can also be used but is usually restricted to laboratory use.
- A "string" test (entero-test) can also be performed.
- Differential diagnosis for other causes of gastroenteritis includes amebiasis, bacterial overgrowth syndromes, Crohn ileitis, *Cryptosporidium* enteritis, irritable bowel syndrome, celiac sprue, and tropical sprue.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

- Drugs used: nitroimidazole derivatives (e.g. metronidazole, tinidazole, ornidazole, and secnidazole); benzidamazoles (albendazole and mebendazole) nitrofuran derivatives (e.g. furazolidone), acridine compounds (e.g. mepacrine and quinacrine) aminoglycoside (especially for pregnant women) and nitazoxanide.
- Metronidazole is the most common antibiotic treatment for giardiasis but more and more refractory cases are being described.
- Aminoglycoside is the drug of choice for pregnant patients since it avoids the potential adverse effects of the other anti-*Giardia* agents on the fetus.
- Prevention should include: good hygiene, avoidance of contaminated food and water, extra care during traveling to warm climates, boiling water, etc.
- No known chemoprophylaxis and no human vaccine as yet. There is an effective vaccine for dogs.

FURTHER READING

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WEBSITES

Centers for Disease Control and Prevention, Parasites – Giardia: https://www.cdc.gov/parasites/giardia/index.html

European Centre for Disease Prevention and Control, Giardiasis: https://www.ecdc.europa.eu/en/giardiasis/facts

WebMD, Giardiasis, 2020: https://www.webmd.com/digestive-disorders/giardiasis-overview

Students can test their knowledge of this case study by visiting the Instructor and Student Resources: [www.routledge.com/cw/lydyard] where several multiple choice questions can be found.