Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Giardiasis (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

- Giardiasis can be prevented by practicing good hygiene, avoiding drinking or swimming in water that may be contaminated, and not eating food that may be contaminated **(AIII)**.
- Antiretroviral treatment of HIV-infected children to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric giardiasis **(AII*)**.
- Combination antiretroviral therapy should be part of primary initial treatment for giardiasis in HIV-infected children **(AII*)**.
- Dehydration and electrolyte abnormalities should be corrected **(AIII)**.
- Patients with chronic diarrhea should be monitored for malabsorption leading to malnutrition **(AIII)**.
- Tinidazole **(AII)** and nitazoxanide **(AI)** are preferred and metronidazole **(AI)** is the alternative recommended treatment for giardiasis in children.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Giardia intestinalis has a worldwide distribution and, among nationally reportable intestinal parasites, is the most commonly identified in public health laboratories in the United States.[1] Surveillance data show a bimodal age distribution, with the greatest number of reported cases occurring in children aged 1 to 9 years and adults aged 35 to 44 years. In the United States, most cases are reported between early summer and early fall and are associated with recreational water activities and camping.[1]

Humans are the principal reservoir of *G. intestinalis* (also known as *Giardia lamblia* or *Giardia duodenalis*) infection. The parasite is found in many animals species, although the role of zoonotic transmission is still being unraveled.[2] It is a flagellated protozoan with two forms: trophozoites and cysts. The infectious and environmentally resistant form is the cyst. After ingestion, each *Giardia* cyst produces two trophozoites in the proximal portion of the small intestine. Detached trophozoites pass through the intestinal tract, and form smooth, oval-shaped, thin-walled infectious cysts that are passed in feces. Duration of cyst excretion is usually self-limited but can vary and excretion may last for months. Studies in adults have shown that ingestion of as few as 10 to 100 fecally derived cysts is sufficient to initiate infection.[3] *Giardia* cysts are infectious immediately upon being excreted in feces and remain viable for at least 3 months in water at 4°C.[4] Freezing does not eliminate infectivity completely, whereas heating, drying, or submersing in seawater are likely to do so.[4,5]

G. intestinalis is more common in certain high-risk groups, including children, employees of childcare centers, patients and staff of institutions for people with developmental disabilities, men who have sex with men, people who ingest contaminated drinking water or recreational water, travelers to disease-endemic areas of the world, close contacts of infected people, and people exposed to infected domestic and wild animals (i.e., dogs, cats, cattle, deer, and beavers).[6] There is a paucity of information on giardiasis in HIV-infected children, although *Giardia* has been associated with diarrhea in children with AIDS.[7,8]

Infection with *Giardia* can occur directly by the fecal-oral route or indirectly via ingestion of contaminated

water or food, but water contaminated with cysts appears to be the major reservoir and vehicle for spread of the parasite.[1] Most waterborne outbreaks have been related to ingestion of surface water treated by inadequate purification systems.[9] Drinking untreated mountain stream water is a risk for hikers. Person-to-person spread occurs frequently in childcare centers and in families of children with diarrhea.[10,6] Antigiardial host defenses are B-cell dependent, with secretory immunoglobulin A playing a major role in immunity. Humoral immunodeficiencies, such as X-linked agammaglobulinemia and hypogammaglobulinemia, predispose to chronic symptomatic disease.[11]

Symptoms of giardiasis in HIV-infected individuals appear to be no more severe than those in HIV-negative individuals, and giardiasis is not typically considered a major cause of enteritis in HIV-infected patients.[12] However, with progressive immunosuppression and reduced CD4 T lymphocyte (CD4) cell counts, the risk of symptomatic *Giardia* infections increases. Studies in adults have demonstrated that enteritis due to *G. intestinalis* is a frequent event among AIDS patients, especially in the most advanced stage of disease.[13] Research in HIV-infected adults from countries where giardiasis is endemic demonstrate that risk of *Giardia* infections and severity of disease increased with increasing immunosuppression and lower CD4 cell counts.[14,15] In a study of 75 HIV-infected adults in India, *G. intestinalis* was the most commonly isolated parasite, and patients with lower CD4 cell counts presented with significantly more enteric disease and chronic diarrhea.[16] In another study of 43 adults naive to combination antiretroviral therapy (cART), *G. intestinalis* was detected in one-third of patients and was significantly associated with lower CD4 cell counts (OR = 3.0 for CD4 counts $\leq$100 cells/mm^3).[17] A case-control study comparing giardiasis in HIV-infected adults in Brazil before and after the era of cART demonstrates that the incidence of enteric diseases caused by *Giardia* decreased after initiation of such treatment.[14] Given the evidence, it is reasonable to recommend initiation of cART and immune reconstitution as a primary mode of prevention **(AII*)**.

Clinical Manifestations

The incubation period usually lasts 1 to 2 weeks and averages 7 days.[6] Symptomatic infection with *G. intestinalis* can cause a broad spectrum of clinical manifestations. Children usually present with short-lasting, acute watery diarrhea with or without low-grade fever, nausea, anorexia, and abdominal pain. Others have a more protracted intermittent course, characterized by foul-smelling stools associated with flatulence, abdominal distension, and anorexia. Malabsorption combined with anorexia can lead to significant weight loss, failure to thrive, and anemia in children. Stools can be profuse and watery initially and later become greasy and foul smelling. Blood, mucus, and fecal leukocytes are absent. Varying degrees of malabsorption can occur, and abnormal stool patterns can alternate with periods of constipation and normal bowel movements. Post-*Giardia* infection lactose intolerance can occur in 20% to 40% of patients.[18] This syndrome may take several weeks to resolve and can contribute to malnutrition in children.

Asymptomatic infection is common.[19] Extraintestinal invasion is unusual, but trophozoites occasionally migrate into bile or pancreatic ducts. Reactive arthritis has been associated with giardiasis.[20]

Diagnosis

Although performance of diagnostic tests has not been evaluated in HIV-infected children, it is expected to be similar to other populations. A definitive diagnosis is established by detection of *Giardia* trophozoites or cysts in stool specimens, duodenal fluid or small-bowel tissue by microscopic examination using staining methods such as trichrome; direct fluorescent antibody (DFA) assays; by detecting soluble stool antigens using enzyme immunoassays (EIA); or, by using molecular techniques including polymerase chain reaction.[21,22] Identification of both trophozoites and cysts can be made on direct smears of concentrated specimens of stool. Appropriately conducted direct examination of stool establishes the diagnosis in up to 70% of patients with a single examination and in 85% with a second examination. Identification of *Giardia* can be difficult because of intermittent excretion of cysts. Stool specimens should be examined within 1 hour after being passed. Trophozoites are more likely to be present in unformed stools as a result of rapid bowel transit time. Cysts, but not trophozoites, are stable outside the gastrointestinal (GI) tract.

When giardiasis is suspected and stool specimens are negative, aspiration, biopsy, or both, of the duodenum or upper part of the jejunum should be performed. In a fresh specimen, trophozoites usually can be visualized on direct wet mount. The commercially available Entero-Test is an alternative method for obtaining duodenal fluid directly.[23] Duodenal biopsy is the optimal method for diagnosis in patients with clinical characteristics but negative stool and duodenal fluid samples.

Use of polyclonal antisera or monoclonal antibodies against *Giardia*-specific antigens has improved diagnostic testing. Studies comparing EIA kits for detecting *Giardia* antigen in stool showed a sensitivity of 87% to 100% and specificity of 100%. All fluorescent antibody tests had 100% sensitivity and specificity.[24] These rapid diagnostic tests can be positive before and after detection of organisms by microscopic examination. DFA and EIA were equally sensitive, and both were more sensitive than microscopy of permanently stained smears after concentration in formalin ethyl acetate.[25] Most experts recommend use of DFA testing and microscopy instead of microscopy alone **(AIII)**. Specific antibodies to *Giardia* have been detected and quantified by immunodiffusion, hemagglutination, immunofluorescence, and EIA, but a serologic test is not available commercially.

Prevention Recommendations

Preventing Exposure

Because *Giardia* organisms are most likely transferred from contaminated water, food, or contact with an infected person or animal, avoidance of untreated water sources is recommended **(AIII)**. This recommendation is especially important in individuals with severe immunosuppression. Hand washing with soap and water after exposure to potentially fecally contaminated material or contact with an infected person or animal is also recommended **(AIII)**. Alcohol-based gels are ineffective against the cysts of *Giardia* and should not be substituted for hand washing when exposure to *Giardia* is a concern.

In a hospital, standard precautions (i.e., use of gloves and hand washing after removal of gloves) should be sufficient to prevent transmission from an infected patient to a susceptible HIV-infected person.

When traveling where water may be contaminated or where the safety of drinking water is in doubt, travelers, hikers, and campers should be advised of methods to make water safe for drinking. These measures include using bottled water, disinfecting water by heating it to a rolling boil for 1 minute, or using a filter that has been tested and rated by National Safety Foundation Standard 53 or Standard 58 for cyst and oocyst reduction. Waterborne outbreaks can be prevented with a combination of adequate filtration of water sources, chlorination, and maintenance of water distribution systems.[1,9] Travelers should also be advised of the potential for transmission of giardiasis during use of contaminated recreational water (e.g., lakes, rivers, inadequately treated swimming pools).

Preventing First Episode of Disease

No chemoprophylactic regimens are known to be effective in preventing giardiasis. However, because the risk of acquisition of giardiasis and the severity of infection increase with the severity of immunosuppression, cART is a primary modality for prevention in HIV-infected children to prevent or reverse severe immunodeficiency **(AII*)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided **(AIII)**. Effective cART and anti-parasitic therapy are the primary initial treatments for these infections in HIV-infected children and adults **(AII*)**.[14] Antimotility agents should be used with caution in

young children **(CIII)**.

Tinidazole **(AII)**. The therapeutic efficacy against *Giardia* of metronidazole led to development of other nitroimidazole derivatives, such as tinidazole and secnidazole. These agents have the advantage of longer half-lives, making them suitable for single-daily-dose therapies. A single, 2-g dose (or the equivalent pediatric dosing of 50 mg/kg in a single dose) of tinidazole has demonstrated cure rates ranging from 80% to 100%, and is also associated with improved compliance.[26-28] Tinidazole is approved for use in children aged 3 years and older. The drug is available in tablets, which can be crushed in flavored syrup for patients unable to swallow tablets.

Nitazoxanide **(AI)** is approved in the United States for treatment of infections due to *G. intestinalis* in patients aged 1 year or older. Two randomized, controlled clinical trials in HIV-uninfected children demonstrated nitazoxanide's efficacy against placebo and its comparability with metronidazole and mebendazole in treating giardiasis in children, with eradication rates for *G. intestinalis* of 71% to 94% with nitazoxanide treatment.[29]

Metronidazole **(AI)** was determined to be therapeutic against giardiasis in 1962. Since then, metronidazole and other nitroimidazoles have been used by clinicians as the mainstay of therapy of giardiasis. Metronidazole is the drug most often used for treatment worldwide. Children have been included in many of the clinical trials, with outcomes similar to those in adults (median efficacy, 94%) for the 5- to 10-day regimens.[30] Metronidazole is not available in a standard liquid form, but a suspension can be prepared by thoroughly crushing metronidazole tablets, using glycerin as a lubricant, and suspending the mixture in cherry syrup.[31] In spite of its widespread and accepted use against *Giardia*, the U.S. Food and Drug Administration has never approved it for this indication.

Quinacrine is usually used in combination therapy for cases in which treatment failure is suspected.[32] The severity of side effects has prevented clinicians from using it as an initial therapeutic choice or first-line alternative, particularly in children. A bitter taste and vomiting have led to lower efficacy in children, probably due to low compliance. Yellow/orange discoloration of the skin, sclerae, and urine affects 4% to 5% of those taking quinacrine, beginning about 1 week after starting treatment, and can last up to 4 months after discontinuation of therapy. Other common side effects include nausea, vomiting, headache, and dizziness. Quinacrine can precipitate hemolysis in glucose-6-phosphate dehydrogenase (G6PDH)-deficient individuals.[33] Quinacrine is no longer available in the United States and has been discontinued by the manufacturer.[34]

Monitoring and Adverse Events (Including IRIS)

Patients with chronic diarrhea should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. In severely ill patients, total parenteral nutrition may be indicated **(BIII)**.

Adverse effects reported with tinidazole are not as common as with metronidazole but do include bitter taste, vertigo, and GI upset.[30]

Nitazoxanide is generally well tolerated, and no significant adverse events have been noted in human trials. Adverse events have been mild and transient and principally related to the GI tract, such as abdominal pain, diarrhea, and nausea. Nitazoxanide has been well tolerated up to the maximum dose of 4 g when taken with or without food, but the frequency of GI side effects increases significantly with the dose level.[29]

The most common side effects of metronidazole treatment include headache, vertigo, nausea, and a metallic taste in the mouth. Nausea occurs in 5% to 15% of patients given standard multiday courses. In addition, pancreatitis, central nervous system toxicity at high doses, and transient, reversible neutropenia have been attributed to metronidazole.[30]

Immune reconstitution inflammatory syndrome has not been associated with giardiasis or its treatment.

Managing Treatment Failure

The most important steps for management of treatment failure are supportive treatment, optimization of cART to achieve full virologic suppression, and modification of antiparasitic therapy **(AII*)**. Treatment failures have been

reported with all of the common anti-*Giardia* agents. It is important for clinicians to differentiate between resistance to treatment and reinfection, which is common in endemic regions and situations of poor fecal-oral hygiene. Resistance to most anti-*Giardia* agents has been documented but there is no consistent correlation between *in vitro* resistance and clinical failure.[30] Clinically resistant strains have been treated with longer repeated courses or higher doses of the original agent or a drug from a different class to avoid potential cross-resistance. Combination regimens using metronidazole-albendazole, metronidazole-quinacrine, or other active drugs or giving a nitroimidazole plus quinacrine for at least 2 weeks have proven successful against refractory infection. In AIDS patients with severe giardiasis, prolonged or combination therapy may be necessary **(BII*)**.[32,35]

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing recurrence of giardiasis **(CIII)**. Reinfection is frequent in endemic areas, in situations of poor hygiene, or inadequate treatment of contaminated water (e.g., private wells). This can be prevented by practicing good hand hygiene everywhere, but particularly after toilet use and handling of soiled diapers. Hand hygiene should also be practiced before food preparation and ingestion. To reduce risk of disease transmission, children with diarrhea should be excluded from child care settings until the diarrhea has stopped. Children with giardiasis should not use recreational water venues for 2 weeks after symptoms resolve. Additional information about recreational water illnesses and how to stop them from spreading is available at http://www.cdc.gov/healthywater/swimming.

Discontinuing Secondary Prophylaxis

Not applicable.

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Dosing Recommendations for Prevention and Treatment of Giardiasis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	cART to avoid advanced immunodeficiency	N/A	N/A
Secondary Prophylaxis	N/A	N/A	N/A

Treatment	• Tinidazole, 50 mg/kg by mouth, administered as 1 dose given with food (maximum 2 g). **Note:** Based on data from HIV-uninfected children
	• Nitazoxanide. **Note:** Based on data from HIV-uninfected children
	  • 1–3 years: 100 mg by mouth every 12 hours with food for 3 days
	  • 4–11 years: 200 mg by mouth every 12 hours with food for 3 days
	  • ≥12 years: 500 mg by mouth every 12 hours with food for 3 days
		Metronidazole 5 mg/kg by mouth every 8 hours for 5-7 days.
		Note: Based on data from HIV-uninfected children
			Tinidazole is approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed.
			Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. It is not FDA-approved for the treatment of giardiasis.
			Supportive Care:
			• Hydration
			• Correction of electrolyte abnormalities
			• Nutritional support
			Antimotility agents (e.g., loperamide) should be used with caution in young children.

Key to Abbreviations: cART = combination antiretroviral therapy; FDA = U.S. Food and Drug Administration