



## **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.**

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## Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa, and, if symptomatic, the infection typically causes diarrhea. *Cryptosporidium* can also infect other gastrointestinal and extraintestinal sites, especially in individuals whose immune systems are suppressed. Advanced immunosuppression—typically CD4 T lymphocyte cell (CD4) counts <100 cells/mm<sup>3</sup>—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis.<sup>1</sup> The three species that most commonly infect humans are *Cryptosporidium hominis*, *Cryptosporidium parvum*, and *Cryptosporidium meleagridis*. Infections are usually caused by one species, but a mixed infection is possible.<sup>2,3</sup>

Cryptosporidiosis remains a common cause of chronic diarrhea in patients with AIDS in developing countries, with up to 74% of diarrheal stools from patients with AIDS demonstrating the organism.<sup>4</sup> In developed countries with low rates of environmental contamination and widespread availability of potent antiretroviral therapy, the incidence of cryptosporidiosis has decreased. In the United States, the incidence of cryptosporidiosis in patients with HIV is now <1 case per 1,000 person-years.<sup>5</sup>

Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with humans or animals infected with *Cryptosporidium*, particularly those with diarrhea. *Cryptosporidium* oocysts can contaminate recreational water sources, such as swimming pools and lakes, and public water supplies and may persist despite standard chlorination. Person-to-person transmission of *Cryptosporidium* is common, especially among sexually active men who have sex with men.

## Clinical Manifestations

Patients with cryptosporidiosis most commonly have acute or subacute onset of watery diarrhea, which may be accompanied by nausea, vomiting, and lower abdominal cramping. Disease severity can range from asymptomatic to profuse, cholera-like diarrhea.<sup>6</sup> More severe symptoms tend to occur in immune-suppressed patients, whereas transient diarrhea alone is typical in patients with competent immune systems. Fever is present in approximately one-third of patients, and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium*, leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low CD4 counts.<sup>7</sup> Pulmonary *Cryptosporidium* infections also have been reported, and may be under-recognized.<sup>8,9</sup>

## Diagnosis

Diagnosis of cryptosporidiosis has traditionally been made by microscopic identification of the oocysts in stool with acid-fast staining or direct immunofluorescence, which offers higher sensitivity.<sup>10</sup> Concentration methods (e.g., formalin-ethyl acetate) may facilitate diagnosis of cryptosporidiosis. Other diagnostic methods are being increasingly used. Antigen-detection by enzyme-linked immunosorbent assay or immunochromatographic tests also is useful; depending on the specific test, sensitivities reportedly range from 66% to 100%. However, some immunochromatographic tests are plagued by false-positive results.<sup>11</sup> Multiplex molecular methods are increasingly used for diagnosis, and can identify a greater number of cases than microscopic methods.<sup>10,12</sup> Cryptosporidial enteritis also can be diagnosed from small sections of tissue from intestinal biopsy.

A single stool specimen is usually adequate to diagnosis cryptosporidiosis in individuals with profuse diarrheal illness, whereas repeat stool sampling is recommended for those with milder disease.

## Preventing Exposure

Individuals with HIV should be educated and counseled about the different ways that *Cryptosporidium* can be transmitted (**BIII**). Modes of transmission include direct contact with people, including diapered children, and animals infected with *Cryptosporidium*; swallowing contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Scrupulous handwashing can reduce the risk of diarrhea in individuals with HIV, including diarrhea caused by *Cryptosporidium*.<sup>13</sup> Patients with HIV should be advised to wash their hands after potential contact with human feces (including after diapering small children). Handwashing also should be recommended in association with the following activities: after handling pets or other animals, after gardening or any other contact with soil, before preparing food or eating, and before and after sex (**BIII**). Individuals with HIV should avoid unprotected sex, especially practices that could lead to direct (e.g., oral-anal sex) or indirect (e.g., penile-anal sex) contact with feces. They should be advised to use prophylactic barrier methods such as condoms and dental dams during sex to reduce such exposures (**BIII**).

Individuals with HIV—particularly those with CD4 counts <200 cells/mm<sup>3</sup>—should avoid direct contact with diarrhea or stool from pets (**BIII**). They should wear gloves when handling feces or cleaning areas that might have been contaminated by feces from pets (**BIII**). Individuals with HIV should also limit or avoid direct exposure to calves and lambs (**BII**). Paying attention to hygiene and avoiding direct contact with stool are important when visiting farms or petting zoos or other premises where animals are housed or exhibited.

Individuals with HIV should not drink water directly from lakes or rivers (**AIII**). Waterborne infection also can result from swallowing water during recreational activities. Individuals with HIV should be cautioned that lakes, rivers, salt-water beaches, some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium*. They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water (**BIII**).

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations in which a community boil water advisory is issued, boiling water for at least 1 minute will eliminate the risk for cryptosporidiosis (**AIII**). Using submicron personal-use water filters (home or office types) or bottled water also may reduce the risk of infection from water from a municipal source or a well (**BII**).

For persons with low CD4 counts, the magnitude of the risk of acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain but is likely small. Available data are inadequate to recommend that all persons with HIV boil water or avoid drinking tap water in non-outbreak settings. However, individuals with HIV may consider drinking only filtered water (**CIII**), despite the complexities involved in selecting appropriate water filters, the lack of enforceable standards for removal of *Cryptosporidium* oocysts, the costs of the products, and the difficulty of using the products consistently. Note that ice made from contaminated tap water also can be a source of infection.

Patients with HIV with low CD4 counts should be cautious about eating raw oysters because cryptosporidial oocysts can survive in oysters for >2 months and have been found in oysters harvested from certain commercial oyster beds (**CIII**). In the hospital setting, standard precautions for use of gloves and for handwashing after removal of gloves should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible individual with HIV (**BIII**). Because of the potential for fomite transmission, some specialists recommend that patients with HIV, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis (**CIII**).

Individuals with HIV who travel to developing countries should be warned to avoid drinking tap water or using tap water to brush their teeth (**BIII**). They should also avoid using ice that is not made from bottled water and consuming raw fruits or vegetables that may have been washed in tap water (**BIII**).

Individuals with HIV also should avoid other sources of *Cryptosporidium* oocysts as much as possible (**BIII**). This includes avoiding directly working with people with diarrhea; with farm animals such as cattle and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, gloves should be worn, and good hand hygiene observed.

## Preventing Disease

Because chronic cryptosporidiosis occurs primarily in patients with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent this disease (**AII**). Rifabutin and possibly clarithromycin taken for *Mycobacterium avium complex* prophylaxis have been found to protect against cryptosporidiosis.<sup>14,15</sup> Rifaximin, which is used for prevention of travelers' diarrhea, also has been used to treat cryptosporidial diarrhea. However, it is unclear whether rifaximin can protect against cryptosporidiosis.<sup>16</sup> Data are insufficient, however, to warrant a recommendation to use rifaximin, rifabutin, or clarithromycin as chemoprophylaxis for cryptosporidiosis.

## Treating Disease

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/mm<sup>3</sup> usually leads to resolution of clinical cryptosporidiosis<sup>17-20</sup> and is the mainstay of treatment. Patients not already taking antiretrovirals who develop cryptosporidiosis should be started on ART as part of the initial management of cryptosporidiosis (**AII**). Management should also include symptomatic treatment of diarrhea with anti-motility agents (**AIII**). Tincture of opium may be more effective than loperamide (**CIII**). Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved to treat secreting tumor-induced diarrhea, is no more effective than other oral antidiarrheal agents and **is usually not recommended** (**CII**).<sup>21</sup> Because diarrhea can cause lactase deficiency, patients should avoid milk products (**CIII**).

Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Stool volume in patients with AIDS with severe diarrhea can exceed 10 L/day; managing the diarrhea often requires intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions (**AIII**). Most patients can be treated with enteral nutrition; total parenteral nutrition is rarely indicated (**CIII**).

Patients with biliary tract involvement may require endoscopic retrograde cholangiopancreatography for diagnosis. They may also benefit from sphincterotomy, stenting, or both.<sup>7,22</sup>

Several agents, including nitazoxanide, paromomycin, and spiramycin, have been investigated in small, randomized controlled clinical trials of adults with HIV. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.<sup>23</sup>

Nitazoxanide is an orally administered nitrothiazole benzamide with *in vivo* activity against a broad range of helminths, bacteria, and protozoa. Nitazoxanide is approved by the Food and Drug Administration for treatment of cryptosporidiosis in children and adults. Nitazoxanide 500 mg administered twice daily for 3 days to adults without HIV with cryptosporidiosis resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.<sup>24,25</sup> In one study, adults with HIV with cryptosporidiosis with CD4 counts >50 cells/mm<sup>3</sup> were treated with nitazoxanide 500 mg to 1,000 mg twice daily for 14 days; the nitazoxanide treatment group had substantially higher rates of parasitological cure and resolution of diarrhea than the placebo group.<sup>26</sup> Efficacy of nitazoxanide for the treatment of cryptosporidial diarrhea in children with HIV was not confirmed, however, in two randomized trials in children.<sup>27,28</sup> Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts < 50 cells/mm<sup>3</sup>, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment.<sup>29</sup> Adverse events associated with nitazoxanide are limited and typically mild, and no important drug-drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, many experts will institute a trial

of nitazoxanide or paromomycin in conjunction with ART, but never instead of ART, despite the paucity of evidence that such antiparasitic therapy is beneficial **(CIII)**.

Paromomycin is a non-absorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. Paromomycin in high doses is effective for the treatment of cryptosporidiosis in animal models. A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, there were few cures, relapses were common, and long-term success rates were only 33%.<sup>22</sup> Two randomized trials comparing paromomycin with placebo demonstrated limited effectiveness of the drug among patients with AIDS and cryptosporidiosis.<sup>23,30,31</sup> One case series suggested a better response rate in patients receiving paromomycin along with ART.<sup>32</sup> Paromomycin may be used instead of nitazoxanide in conjunction with ART, but never instead of ART **(CIII)**.

### ***Special Considerations with Regard to Starting ART***

As noted above, patients with cryptosporidiosis should be offered ART as part of the initial management of cryptosporidiosis **(AII)**. *In vitro* and in animal models, PIs can inhibit *Cryptosporidium*, but there is no clinical evidence that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.<sup>33,34</sup>

### ***Monitoring of Response to Therapy and Adverse Events (including IRIS)***

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte imbalance, weight loss, and malnutrition. Immune reconstitution inflammatory syndrome (IRIS) has been described in association with 3 cases of extra-intestinal cryptosporidiosis.<sup>35</sup>

### ***Managing Treatment Failure***

Supportive treatment and optimization of ART to achieve full virologic suppression are the main approaches to managing treatment failure **(AIII)**. The clinical response rather than results of stool tests should be used to guide the response to therapy. Some authorities advocate adding anti-parasitic drugs **(CIII)**, such as nitazoxanide or paromomycin alone or in combination with azithromycin, as well as optimizing ART in patients with treatment failure and cryptosporidiosis.<sup>36,37</sup>

## **Preventing Recurrence**

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

## **Special Considerations During Pregnancy**

Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in non-pregnant women **(AII)**. Pregnancy should not preclude the use of ART and in fact is always an indication for ART. Nitazoxanide is not teratogenic in animals but no data on use in human pregnancy are available. Nitazoxanide can be used in pregnancy after the first trimester in women with severe symptoms **(CIII)**. Limited information is available about the teratogenic potential of paromomycin, but oral administration is associated with minimal systemic absorption, which may minimize potential risk. Paromomycin can be used in pregnancy after the first trimester in women with severe symptoms **(CII)**. Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, one study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.<sup>38</sup> Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII)**. Loperamide is the preferred anti-motility agent in late pregnancy **(CIII)**. Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal, therefore tincture of opium **is not recommended** in late pregnancy **(AIII)**.<sup>38</sup>

## Recommendations for Preventing and Managing Cryptosporidiosis

### Preventing Chronic Cryptosporidiosis

- Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease **(AII)**.

### Managing Cryptosporidiosis

#### Preferred Management Strategies:

- Aggressive oral and/or IV rehydration and replacement of electrolyte loss **(AIII)**, and
- Symptomatic treatment of diarrhea with anti-motility agent **(AIII)**; tincture of opium may be more effective than loperamide **(CIII)**, and
- Initiation or optimization of ART for immune restoration to CD4 count >100 cells/mm<sup>3</sup> **(AII)**

#### Consider:

- Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for 14 days **(CIII)** plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, or
- Paromomycin 500 mg PO four times a day for 14 days–21 days **(CIII)** plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement

### Other Considerations:

- Because diarrhea can cause lactase deficiency, patients should avoid milk products **(CIII)**.

**Key:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IV = intravenous; PO = orally

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