Cryptosporidiosis

Updated: January 18, 2023
Reviewed: January 10, 2024

Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infects 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 (CD4) cell counts <100 cells/mm^3—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis.[1] The three species that most commonly infect humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Infections are usually caused by one species, but a mixed infection is possible.[2,3]

Cryptosporidiosis remains a common cause of chronic diarrhea in people with HIV and AIDS in low- and middle-income countries.[4] In high-income countries with low rates of environmental contamination and widespread availability of potent antiretroviral therapy (ART), the incidence of cryptosporidiosis in people with HIV has decreased. In the United States, the incidence of cryptosporidiosis in people with HIV is now <1 case per 1,000 person-years.[5]

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 public water supplies and recreational water sources—such as swimming pools and lakes—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 present with 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, watery, voluminous diarrhea.[6] More severe symptoms tend to occur in immunosuppressed people, whereas transient diarrhea alone is typical in people 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 people with prolonged disease and low CD4 counts.[7] Pulmonary *Cryptosporidium* infections also have been reported and may be under-recognized.[8,9]

Diagnosis

Diagnosis of cryptosporidiosis was traditionally made by microscopic identification of the oocysts in stool with acid-fast staining or direct immunofluorescence, which offers higher sensitivity.[10] Concentration methods (e.g., formalin-ethyl acetate) may facilitate diagnosis of cryptosporidiosis. However, these methods are insensitive, and 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 produce frequent false-positive results.[11] Polymerase chain reaction and multiplex molecular methods are increasingly used for diagnosis and can identify a greater number of cases than microscopic methods.[10,12] Cryptosporidial enteritis also can be diagnosed from small sections of tissue from intestinal biopsy.

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

Preventing Exposure

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

Scrupulous handwashing can reduce the risk of diarrhea, including diarrhea caused by *Cryptosporidium*, in individuals with HIV.[13] People 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).**

People with HIV—particularly those with CD4 counts <200 cells/mm^3—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).** People 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.

People 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, saltwater beaches, some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium*. *Cryptosporidium* oocysts are extremely chlorine resistant and thus may persist even in chlorinated recreational water.[14,15] 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 people 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 people with HIV boil water or avoid drinking tap water in non-outbreak settings. However, people 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.

People 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 people with HIV, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII).**

People with HIV who travel to low- and middle-income 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).**

People 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

Recommendations for Preventing Cryptosporidiosis
Preventing Chronic Cryptosporidiosis • Because chronic cryptosporidiosis occurs primarily in people with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease (AII).

Key: ART = antiretroviral therapy

Because chronic cryptosporidiosis occurs primarily in people with HIV with advanced immunodeficiency, initiation of ART before they become severely immunosuppressed should prevent the disease **(AII).** Rifabutin and possibly clarithromycin taken for *Mycobacterium avium* complex prophylaxis have been found to protect against cryptosporidiosis.[16,17] Rifaximin, which is used for prevention of traveler's diarrhea, also has been used to treat cryptosporidial diarrhea. However, it is unclear whether rifaximin can protect against cryptosporidiosis.[18] Data are insufficient, however, to warrant a recommendation to use rifaximin, rifabutin, or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treating Disease

Recommendations for Treating Cryptosporidiosis

Managing Cryptosporidiosis
• Preferred Management Strategies
  o Aggressive oral and/or IV rehydration and replacement of electrolyte loss (AIII), *and*
  o Symptomatic treatment of diarrhea with antimotility agents (AIII); tincture of opium may be more effective than loperamide (CIII).
  o People with HIV not taking ART should initiate ART to achieve immune restoration to CD4 count >100 cells/mm^3 (AII).
• General Considerations
  o Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for at least 14 days (CIII) plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or*
  o Paromomycin 500 mg PO four times a day for at least 14 days to 21 days (CIII) plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement
Pregnancy Considerations
• Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in nonpregnant people (AII).
• 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).
• Loperamide is the preferred antimotility agent in late pregnancy (CIII). Loperamide should be avoided in the first trimester unless benefits are felt to outweigh potential risks (CIII).
• Nitazoxanide (CIII) and paromomycin (CIII) can be used in pregnancy after the first trimester.

Other Considerations
• Because diarrhea can cause lactase deficiency, people with cryptosporidiosis should avoid milk products (CIII).

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

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/mm^3 usually leads to resolution of clinical cryptosporidiosis[19-22] and is the mainstay of treatment. People with HIV 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 antimotility 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).**[23] Because diarrhea can cause lactase deficiency, people with HIV and cryptosporidiosis should avoid milk products **(CIII).**

Rehydration and repletion of electrolyte losses by either oral or intravenous route are important. Stool volume in patients with HIV and 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.[7,24]

Several agents—including nitazoxanide, paromomycin, clofazimine, and spiramycin—have been investigated in small, randomized controlled clinical trials of adults with HIV.[25] No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[26]

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 U.S. Food and Drug Administration for treatment of cryptosporidiosis in children over 1 year of age and adults. Nitazoxanide 500 mg administered twice daily for 3 days to adults without HIV but with cryptosporidiosis resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.[27,28] In one study, adults with HIV with cryptosporidiosis and CD4 counts >50 cells/mm^3 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.[29] Efficacy of nitazoxanide for the treatment of cryptosporidial diarrhea in children with HIV, however, was not confirmed in two randomized trials in children.[30,31] 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^3, 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.[32] Adverse events associated with nitazoxanide are 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 **(CIII).**

Paromomycin is a nonabsorbable 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%.[24] Two randomized trials comparing paromomycin with placebo demonstrated limited effectiveness of the drug among patients with AIDS and cryptosporidiosis.[33,34] One case series suggested a better response rate in patients receiving paromomycin along with ART.[35] 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 animal and *in vitro* models, HIV protease inhibitors (PI) can inhibit *Cryptosporidium*, but there is no clinical evidence that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII).**[36,37]

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 three cases of extraintestinal cryptosporidiosis.[38]

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 antiparasitic 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.[39,40]

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 nonpregnant people **(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 people 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 people with severe symptoms **(CIII).** 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.[41] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII).** Loperamide is the preferred antimotility 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).**[42]

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