Cystoisosporiasis (Formerly Isosporiasis)

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Epidemiology

Cystoisosporiasis, also known as Isosporiasis, is a protozoan gastrointestinal infection that occurs worldwide but is more common in tropical and subtropical regions. Immunocompromised people, including those who have HIV, are at increased risk for chronic, debilitating illness.[1-7] Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.[8] Although *Cystoisospora (Isospora) belli* completes its life cycle in humans, oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective when ingested. Available data suggest that the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.[2] For complete lifecycle, see the Centers for Disease Control and Prevention Cystoisosporiasis webpage.

C. belli is frequently found in tropical and subtropical regions including the Caribbean, Central and South America, Africa, India, and Southeast Asia.[9] However, cases of *C. belli* can also occur in resource-rich countries like the United States due to travel and immigration, especially when individuals are exposed to contaminated food or water sources.[10] This parasitic infection is more commonly observed in people with HIV (especially, but not exclusively in those with low CD4 T lymphocyte [CD4] cell counts), and outbreaks among institutionalized groups have also been reported.[11-13]

Clinical Manifestations

The most common manifestation of cystoisosporiasis is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, lasting several weeks or more, particularly in people with HIV or other immunocompromising conditions. This kind of diarrhea often results in severe dehydration, electrolyte abnormalities (e.g., hypokalemia), weight loss, and malabsorption.[6,7,14-18] Extraintestinal infection—such as in the biliary tract, lymph nodes, spleen, and liver—has been documented in postmortem examinations of people with HIV.[2,19-21] Acalculous cholecystitis/cholangiopathy[2,22-24] and reactive arthritis[25] also have been reported.

Diagnosis

Typically, infection is diagnosed by detecting *Cystoisospora (Isospora)* oocysts (dimensions, 23–36 μm by 12–17 μm) in fecal specimens.[2] Oocysts may be shed intermittently and at low levels, even by individuals with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and ultraviolet fluorescence microscopy, under which there is autofluorescence.[2,26] The microbiology/parasitology laboratory should be notified of the patient's immunodeficiency status to ensure appropriate testing is done. Infection can also be diagnosed by detecting oocysts in duodenal

aspirates or mucus, or by identifying developmental stages of the parasite in intestinal biopsy specimens or using the string test (Entero-Test).[2,16]

Polymerase chain reaction (PCR) methods are increasingly used to detect *C. belli* for diagnosis, as supported by existing literature.[10] These molecular quantitative PCR or qPCR techniques offer such advantages as faster detection and the ability to detect multiple parasites simultaneously, making them more efficient than traditional microscopy.[27] PCR methods have demonstrated a sensitivity ranging from 87% to 100% and a specificity ranging from 88% to 100% for detecting *C. belli*.[27] However, it is important to note that the availability of PCR may be limited in certain settings.

A distinguishing feature of *C. belli* is eosinophilia.[28] However, other helminths, certain fungi (e.g., coccidioidomycosis, histoplasmosis, cryptococcosis), and certain protozoan parasites (e.g., *Dientamoeba fragilis*, *Sarcocycstis*) should be part of the differential diagnosis as these can also cause eosinophilia in the blood.

Preventing Exposure

C. belli is acquired by ingesting contaminated water or food. Hand washing with soap, avoiding potentially contaminated food (e.g., salads) or water in cystoisosporiasis-endemic areas, and proper food preparation (peeling fruits and cooking vegetables) can help prevent infection.

Water filtration using certified filters is effective (absolute one micron or less, National Sanitation Foundation/American National Standards Institute [ANSI] Standard 53 or Standard 58 for cyst removal or cyst reduction by an ANSI-accredited certification organization).[29] Filters that may **not** be designed to safely remove *C. belli* and other protozoans include those with a nominal pore size of one micron or smaller, filters labeled as "Effective against Giardia" or "Effective against parasites," carbon filters, active carbon filters, chlorinated filters, ultraviolet light filters, water purifiers, and filters labeled as "U.S. Environmental Protection Agency (EPA) approved" or "EPA registered" (note: the EPA does not test, certify, or register filters based on their ability to remove *Cystoisospora* and other protozoans).

Preventing Disease

Recommendations for Preventing First Episode of *Cystoisospora belli* Infection (Primary Prophylaxis)
Indication
• Individuals with CD4 count <200 cells/mm^3 living in or traveling to regions endemic for *Cystoisospora belli* (CII).
Preferred Therapy
• TMP-SMX (160 mg/800 mg) PO three times weekly (AI), *or*
• TMP-SMX (160 mg/800 mg) PO daily (AI)
Criteria for Discontinuation of Primary Prophylaxis
• Sustained increase in CD4 count to ≥200 cells/mm^3 for >6 months in response to ART (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally; TMP-SMX = trimethoprim-sulfamethoxazole

Several studies have found that chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is associated with a lower incidence or prevalence of cystoisosporiasis.[1,3,4,30] In a randomized,

placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against cystoisosporiasis in people with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).[1] In an observational study,[3] the incidence of cystoisosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in individuals with CD4 counts <50 cells/mm^3. In that study, multivariable analysis found the relative hazard for *C. belli* infection was 6.2 in individuals with CD4 counts between 50 and 199 cells/mm^3 and 15.9 for individuals with CD4 counts <50 cells/mm^3. After adjustment for the CD4 count, the risk of cystoisosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles County AIDS surveillance registry during the pre-ART era, the prevalence of cystoisosporiasis was lower in people with a history of *Pneumocystis* pneumonia (PCP) compared to those without PCP; indirect evidence of a protective effect from the use of TMP-SMX for PCP treatment and secondary prevention.[4] Given the substantially increased risk of infection in individuals with low CD4 counts, we recommend ensuring that individuals with CD4 counts <200 cells/mm^3 are started and maintained on TMP-SMX if they are living in or traveling to regions endemic for *C. belli* **(CII)**. Primary prophylaxis can be discontinued for people with a sustained increase in CD4 count to ≥200 cells/mm^3 for >6 months in response to ART **(BIII).** Data on alternative medications for primary prophylaxis for people with sulfa intolerance are limited. The primary approach to prevention of cystoisosporiasis is to reduce the risk of acquisition by avoiding potentially contaminated food or water in cystoisosporiasis-endemic areas via regular hand washing, proper food preparation (peeling fruits, cooking vegetables), and use of certified water filters of 1 micron or less.

Treating Disease

Recommendations for Treating *Cystoisospora belli* Infection
General Management Considerations
• Fluid and electrolyte support in patients with dehydration (AIII)
• Nutritional supplementation for people who are malnourished (AIII)
Preferred Therapy for Acute Infection
• TMP-SMX (160 mg/800 mg) PO (or IV) four times daily for 10 days (AII), *or*
• TMP-SMX (160 mg/800 mg) PO (or IV) twice daily for 7 days (BI), *or*
o In patients with persistent or worsening symptoms while on TMP-SMX (160 mg/800 mg) twice daily, consider increasing the daily dose and/or extending the duration to 3–4 weeks (BIII).
Note: IV TMP-SMX may be used for patients with potential or documented malabsorption.
Alternative Therapy for Acute Infection (For Patients With Sulfa Intolerance [AIII])
• Pyrimethamine 50–75 mg PO daily plus leucovorin 10–25 mg PO daily for 4 weeks (BIII), *or*
• Ciprofloxacin 500 mg PO or 400 mg IV (for those who cannot tolerate PO) twice daily for 7 days (CI)
Chronic Maintenance Therapy (or Secondary Prophylaxis) (In People With HIV and CD4 Count <200 cells/mm^3)
Preferred Therapy
• TMP-SMX (160 mg/800 mg) PO three times weekly (AI), *or*
• TMP-SMX (160 mg/800 mg) PO daily (AIII)

Alternative Therapy

- TMP-SMX (320 mg/1,600 mg) PO three times weekly (BIII), *or*
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (BIII), *or*
- Ciprofloxacin 500 mg PO three times weekly (CI) as a second-line alternative

Criteria for Discontinuation of Chronic Maintenance Therapy

- Sustained increase in CD4 count ≥200 cells/mm^3 for >6 months in response to ART and without evidence of active *C. belli* infection (BIII)

Other Considerations

- TMP-SMX double-strength tablets are (160 mg/800 mg).
- Ciprofloxacin can increase QTc and has been associated with tendon rupture and aortic aneurysms.
- Due to concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection (CIII), unless it is needed for PCP prophylaxis. Clinicians should consider giving supplemental folic acid 4 mg/day to women of childbearing potential on TMP-SMX prior to pregnancy or as soon as possible in their first trimester (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IV = intravenously; PCP = *Pneumocystis* pneumonia; PO = orally; QTc = QT corrected for heart rate; TMP-SMX = trimethoprim-sulfamethoxazole

Clinical management includes fluid and electrolyte support for people with dehydration **(AIII)** and nutritional supplementation for people who are malnourished **(AIII).** TMP-SMX is the antimicrobial agent of choice for treatment of cystoisosporiasis **(AII).** It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for people with documented sulfa intolerance **(AIII)** or in whom treatment fails **(BIII).**

Three studies in people with HIV in Haiti have demonstrated the effectiveness of various TMP-SMX treatment regimens.[6,7,31] Participants in these studies were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not reported. Based on the initial studies,[6,7] the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily **(AII).**[7,32] In another study, TMP-SMX (160/800 mg) administered twice daily for seven days was also effective **(BI).**[31] Although published experience using twice-daily TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but increase the daily dose and/or the duration of therapy (up to 3 to 4 weeks)[6,16] if symptoms worsen or persist **(BIII).** Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption or for those who cannot tolerate oral medications.

Some data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.[2,15,16,33,34] However, the combination of pyrimethamine plus sulfadoxine **is not typically recommended (CIII),** due to associations with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,[35] and slow clearance from the body after therapy is discontinued. In addition, sulfadoxine is not commercially available in the United States.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of cystoisosporiasis.[3,36,37] Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) for 4 weeks may be an effective treatment alternative option for sulfa-intolerant patients **(BIII).** The leucovorin is given to prevent myelosuppression from pyrimethamine.

Ciprofloxacin is a second-line agent that can be used for individuals with sulfa allergy and an inability to obtain pyrimethamine **(CI).** In a randomized, controlled trial in Haiti, ciprofloxacin 500 mg orally (PO) twice daily for 7 days was less effective than PO TMP-SMX but may have modest activity against *C. belli*.[31]

Special Considerations With Regard to Starting ART

There are limited data on the effectiveness of ART for *C. belli* infection in the setting of HIV coinfection.[3,23,30] Immune reconstitution with ART may result in fewer relapses of cystoisosporiasis, and immune reconstitution inflammatory syndrome (IRIS) has not been reported. Therefore, for people with HIV and cystoisosporiasis, TMP-SMX therapy and ART should both be started as soon as possible, and ART initiation should not be deferred **(AIII).**

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

People treated for cystoisosporiasis should be monitored for clinical response and adverse events. In people with HIV, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, elevated transaminase levels, and hyperkalemia. For ciprofloxacin, side effects beyond gastrointestinal issues include prolong QT intervals and tendonitis and tendon rupture. For pyrimethamine, side effects include bone marrow suppression. As noted earlier, IRIS has not been described in this population.

Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of nonadherence, malabsorption, and concurrent other gastrointestinal infections or enteropathies should be considered and the TMP-SMX regimen (daily dose, duration, and mode of administration) should be reevaluated **(AIII).**[38] For people with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered **(BIII).**

The effectiveness of albendazole,[37,39,40] nitazoxanide,[41,42] doxycycline,[43] and the macrolides roxithromycin and spiramycin,[33,44,45] have not been substantiated. Metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone appear to be ineffective.[14,33,34,36,44]

Preventing Recurrence

People with HIV with CD4 counts <200 cells/mm^3 should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX **(AI),** which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections. Based on observational studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy. These relapses rapidly responded to retreatment and secondary prophylaxis decreased the risk of another relapse.[6,7,31] In a randomized, placebo-controlled trial in Haiti, no symptomatic recurrences were noted in people who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) **(AI).**[7] Daily TMP-SMX (160/800 mg) **(AIII)** and thrice-weekly TMP-SMX (320/1600 mg) have been effective **(BIII)**[5,16]; however, clinical and parasitological relapses despite maintenance TMP-SMX therapy and ART have been reported.[23] Many of these studies were conducted in the pre-ART era. It is unclear if recurrent *Cystoisospora* infections are due to relapse or reinfection.

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used **(BIII).**[36] Based on limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative, although some data question whether it is efficacious at all **(CI).**[31]

When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in individuals without evidence of active *C. belli* infection who have a sustained increase in the CD4 count to levels ≥200 cells/mm^3 for >6 months after initiation of ART **(BIII).**

Special Considerations During Pregnancy

TMP-SMX is the agent of choice for treatment as well as primary and secondary prophylaxis during pregnancy. Although first-trimester exposure to TMP has been associated with a small increase in the risk of birth defects,[46-49] TMP-SMX therapy should be provided in the setting of maternal symptomatic *C. belli* infection. Due to concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection, unless TMP-SMX is needed for PCP prophylaxis **(CIII).** Most members of the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV recommend that clinicians give supplemental folic acid 4 mg/day to women who are on TMP-SMX if they are capable of becoming pregnant, or as soon as possible in their first trimester **(BIII).**[48-50] Additional details regarding the use of TMP-SMX during pregnancy are provided at *Pneumocystis* Pneumonia. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.[51] Long-term therapy with pyrimethamine should be used only if the potential benefit outweighs the potential risk. Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities, but efficacy against *C. belli* has been questioned.[52] Both TMP-SMX and ciprofloxacin are category C for pregnancy.

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