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

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Microsporidiosis (Last updated December 15, 2016; last reviewed December 15, 2016)

Panel's Recommendations

I. In children with HIV infection, what are the best interventions (compared with no intervention) to treat microsporidiosis?

- Effective antiretroviral therapy (ART) is the primary initial treatment for microsporidiosis in HIV-infected children **(strong, very low)**.
- Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided **(expert opinion)**.
- Albendazole, in addition to ART, is also recommended for initial therapy of microsporidiosis caused by microsporidia other than *Enterocytozoon bieneusi* and *Vittaforma corneae* **(strong, low)**.
- Systemic fumagillin (where available), in addition to ART, is recommended for microsporidiosis caused by *E. bieneusi* and *V. corneae* **(strong, moderate)**.
- Topical therapy with fumagillin eye drops, in addition to ART, is recommended in HIV-infected children with keratoconjunctivitis caused by microsporidia **(strong, very low)**.
- Oral albendazole can be considered in addition to topical therapy for keratoconjunctivitis due to microsporidia other than *E. bieneusi* and *V. corneae* **(expert opinion)**.

II. In HIV-infected children who have been treated for microsporidiosis, when can treatment (secondary prophylaxis) be safely discontinued?

Clinicians may consider continuing treatment for microsporidiosis until improvement in severe immunosuppression is sustained (more than 6 months at Centers for Disease Control and Prevention immunologic category 1 or 2) and clinical signs and symptoms of infection are resolved **(weak, very low)**.

Rating System:

Strength of Recommendation: Strong, weak

Quality of Evidence: High; Moderate; Low; or Very Low

Introduction/Overview

Epidemiology

Microsporidia are obligate, intracellular, spore-forming organisms that primarily cause moderate to severe diarrhea. They are ubiquitous and infect most animal species. They are classified as fungi and defined by their unique single polar tube that coils around the interior of the spore.[1] Many microsporidia have been reported as pathogens in humans, but *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common microsporidia that cause infection in HIV-infected patients. Other microsporidia, such as *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* spp., *Pleistophora ronneeafiei*, *Vittaforma (Nosema) corneae*, *Mycobacterium africanum*, *Mycobacterium ceylonensis*, *Nosema ocularum*, *Tubulinosema acridophagus*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, and *Anncaliia* (syns *Brachiola/Nosema*) *algerae* also have been implicated in human infections. The organisms develop in enterocytes and are excreted in feces. They are transmitted by the fecal-oral route, including through ingestion of contaminated food or water, and, possibly, through contact with infected animals.[2,3] Vertical transmission from an infected mother to her child has not been demonstrated in humans but it does occur in animals.[3]

Prior to the era of antiretroviral therapy (ART), prevalence rates for microsporidiosis were reported to be as high as 70% in HIV-infected adults with diarrhea.[1,4-6] The role of microsporidiosis in chronic diarrhea was questioned early in the HIV epidemic but is now believed to be causal.[7,8] The incidence of microsporidiosis has declined with the widespread use of effective ART, but it is still observed in HIV-infected individuals who are not receiving effective ART.[9] Among HIV-uninfected individuals, microsporidiosis is increasingly recognized in children, travelers, organ transplant recipients, contact lens wearers, and the elderly.[10]

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Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal (GI) tract infection. Microsporidia-associated diarrhea is intermittent, copious, watery, and non-bloody. It may be accompanied by crampy abdominal pain; fever is uncommon. Chronic severe diarrhea can result in dehydration, malnutrition, and failure to thrive. Microsporidia species have been found to cause disease in multiple other organs besides the GI tract, as well as disseminated disease.[4,11] Different infecting species may result in different clinical manifestations. *E. bieneusi* is associated with malabsorption, diarrhea, pulmonary disease, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, peritonitis, keratoconjunctivitis, sinusitis, osteomyelitis, pulmonary disease, and disseminated disease. *Encephalitozoon* (syn *Septata*) *intestinalis* is associated with diarrhea, cholangitis, dermatitis, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, nephritis, urethritis, cystitis, and disseminated infection. *Nosema*, *Vittaforma*, and *Microsporidium* spp. are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* spp. are associated with myositis. *Trachipleistophora* spp. are also associated with encephalitis, cardiac disease, and disseminated disease.

Diagnosis

To diagnose microsporidia GI infection, thin smears of unconcentrated stool-formalin suspension or duodenal aspirates can be stained with modified trichrome stain. Microsporidia spores are small (1–5 µm diameter) and ovoid; they stain pink to red with modified trichrome stain and contain a distinctive equatorial belt-like stripe. They can also be visualized with hematoxylin-eosin, Giemsa, and acid-fast staining but are often overlooked because of their small size. Chemofluorescence agents such as chromotrope 2R, calcofluor-white (a fluorescent brightener), or Uvitex 2B are useful as selective stains for microsporidia in stool and other body fluids.

Urine sediment examination by light microscopy can be used to identify microsporidia spores causing disseminated disease (such as *Encephalitozoonidae* or *Trachipleistophora*). Transmission electron microscopy, staining with species-specific antibodies, or polymerase chain reaction (PCR) (using specific primers) is needed for speciation.

Endoscopic biopsy should be considered for all patients with chronic diarrhea of longer than 2 months duration and negative stool examinations. Touch preparations are useful for rapid diagnosis (i.e., within 24 hours). The organisms can be visualized with Giemsa, tissue Gram stain, calcofluor-white or Uvitex 2B, Warthin-Starry silver staining, or chromotrope 2R.[12] Immunofluorescent antibody assays using monoclonal and/or polyclonal antibodies are also available. Sensitive assays using PCR amplification of DNA sequences extracted from stool or biopsy specimens have been developed for *E. bieneusi*, *E. intestinalis*, *E. hellem*, and *E. cuniculi*[13,14] and can be performed at the Centers for Disease Control and Prevention (CDC).

Primary Prevention

Preventing Exposure

Because microsporidia are most likely transferred from contaminated water, food, or contact with an infected individual or animal, direct contact should be avoided. Untreated water sources (drinking water that has not been chemically treated, filtered, or boiled to eliminate infectious agents) should also be avoided. Fresh fruit and vegetables should be thoroughly washed or peeled prior to eating. This recommendation is especially important for individuals with severe immunosuppression. Hand-washing after exposure to potentially contaminated material or contact with infected individuals or animals also is recommended.

In a hospital, standard precautions (e.g., 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 individual. However, contact precautions should be used in the case of a diapered or incontinent child.

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Preventing Disease

No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Immune reconstitution resulting from ART often results in clearance of microsporidia infections. Effective ART is the primary initial treatment for these infections in HIV-infected children and adults.[15] Interestingly, some protease inhibitors, but not others, may have direct inhibitory activity against microsporidia.[16] Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Albendazole has activity against many species of microsporidia,[17-19] but it is not effective against *Enterocytozoon* infections or *V. corneae*.[20,21] Albendazole, in addition to ART, is recommended for initial therapy of microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae*.

Fumagillin (Sanofi-Synthelabo Laboratories, Gentilly, France) (a water-insoluble antibiotic made by *Aspergillus fumigatus*) and its synthetic analog, TNP-470,[22] have both been used to treat microsporidiosis in animals and humans. In a placebo-controlled study of immunocompromised adults (10 of 12 of whom were HIV-infected adults) with *E. bieneusi* microsporidiosis, fumagillin (20 mg/dose orally 3 times daily for 2 weeks) was associated with decreased diarrhea and clearance of microsporidia spores, which was not observed in placebo recipients.[23] Placebo recipients received fumagillin at the conclusion of the trial and all 6 demonstrated clearance of microsporidia. Thrombocytopenia occurred in 2 of the 6 patients randomized to receive fumagillin. No data are available on use of fumagillin or TNP-470 in HIV-infected children, and neither drug is available for systemic use in the United States. Despite the lack of experience using these agents in children, fumagillin and TNP-470 (where available), in addition to ART, are recommended based on demonstration of efficacy in adults. Consultation with an expert is recommended.

Keratoconjunctivitis caused by microsporidia in HIV-infected adults responds to topical therapy with investigational fumagillin eye drops prepared from Fumidil B® (fumagillin bicyclohexylammonium, a commercial product used to control a microsporidia disease of honeybees) in saline to achieve a concentration of 70 µg/mL of fumagillin.[24-27] Topical therapy with investigational fumagillin eye drops, in addition to ART, is recommended for HIV-infected children with keratoconjunctivitis caused by microsporidia. The addition of oral albendazole to topical fumagillin can be considered for keratoconjunctivitis due to microsporidia other than infections with *Enterocytozoon* or *V. corneae*, because microsporidia may persist systemically despite clearance from the eye with topical therapy alone.[28,29] Children with suspected keratoconjunctivitis that is unresponsive to antibacterial or antiviral therapy should be referred to a pediatric ophthalmologist for evaluation for possible microsporidiosis.

Other agents, including nitazoxanide, atovaquone, metronidazole, and fluoroquinolones, have been reported to reduce diarrhea associated with microsporidia infection. However, metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis. The role of alternative agents or the use of combination regimens for initial therapy is unknown; albendazole remains the preferred therapy for GI tract and disseminated infection caused by microsporidia other than *E. bieneusi* and *V. corneae*.[21,30,31]

Monitoring and Adverse Events (Including IRIS)

Patients with 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.

Albendazole side effects are rare, but hypersensitivity (e.g., rash, pruritus, fever), neutropenia (reversible),

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central nervous system effects (e.g., dizziness, headache), GI disturbances (e.g., abdominal pain, diarrhea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Dose-related bone marrow toxicity is the principal adverse effect of systemic fumagillin, with reversible thrombocytopenia and neutropenia being the most frequent adverse events; topical fumagillin has not been associated with substantial side effects.

There has been one report of immune reconstitution inflammatory syndrome (IRIS) following initiation of ART in a patient with *E. bieneusi* infection,[32] but IRIS has not been described in association with treatment for non-*E. bieneusi* microsporidiosis. Concern for IRIS should not delay institution of ART in the presence of microsporidia infection.

Managing Treatment Failure

The only feasible approaches to managing treatment failure are supportive treatment and optimization of ART to achieve full virologic suppression. The roles of alternative and combination therapy are unknown.

Secondary Prevention

No pharmacologic interventions are known to be effective in preventing recurrence of microsporidiosis. However, the use of ART alone in patients with microsporidiosis has resulted in clearance of infection and symptoms,[15] suggesting that improvements in the immune system after successful ART are critical to recovery and may prevent recurrence. Continued albendazole therapy after treatment for an acute episode of GI or disseminated infection caused by microsporidia other than *E. bieneusi* and *V. corneae* may be considered in those with severe immunosuppression (CDC immunologic category 3) until immune recovery is observed (longer than 6 months at CDC immunologic category 1 or 2).

For keratoconjunctivitis, discontinuation of fumagillin and albendazole treatment may be considered after resolution of infection in patients and immune recovery is observed (longer than 6 months at CDC immunologic category 1 or 2). Therapy should be continued indefinitely if severe immunosuppression (CDC immunologic category 3) persists because recurrence or relapse may follow treatment discontinuation.

Discontinuing Secondary Prophylaxis

Discontinuation of secondary prophylaxis can be considered when immune recovery is observed (longer than 6 months at CDC immunologic category 1 or 2).

Recommendations

Treatment

I. In children with HIV infection, what are the best interventions (compared with no intervention) to treat microsporidiosis?

- Effective ART is the primary initial treatment for microsporidiosis in HIV-infected children **(strong, very low)**.

  An observational study of four adults with documented *E. bieneusi* infection followed stool samples and duodenal biopsy pre-ART, then 1–3 and 6 months post-ART.[15] Results demonstrated that if the patient responded to ART, symptoms related to microsporidiosis improved within 1 month and evidence of eradication of the organism occurred at 6 months. Unfortunately, there are no comparable data for children.

- Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided **(expert opinion)**.

  There are no studies that address this specific management issue in microsporidiosis. However,

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recognition and management of hydration status and electrolyte imbalance are key to management of infectious diarrhea.

- Albendazole, in addition to ART, is also recommended for initial therapy of microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(strong, low)**.

  Albendazole has activity against many species of microsporidia but it is not effective against *E. bieneusi* or *V. corneae*. Small observational cohort studies in adults have demonstrated improvement in symptoms and resolution of diarrhea as well as clearance of the organism in some patients following albendazole treatment.[17,18] A large randomized, open-label study in immunocompetent children in Costa Rica demonstrated clinical improvement in 95% of children receiving albendazole within 48 hours of initiation of therapy compared with only 30% who received supportive care only.[19] Case reports suggest that albendazole therapy is not effective in cases of infection with *E. bieneusi* and *V. corneae*.[20] In these cases, systemic fumagillin therapy, where available, is recommended.

- Systemic fumagillin (where available) in addition to ART is recommended for microsporidiosis caused by *E.bieneusi* and *V. corneae* **(strong, moderate)**.

  In a placebo-controlled study of immunocompromised adults (10 of 12 of whom were HIV-infected adults) with *E. bieneusi* microsporidiosis, fumagillin (20 mg/dose orally 3 times daily for 2 weeks) was associated with decreased diarrhea and clearance of microsporidia spores, which was not observed in placebo recipients.[23] Placebo recipients received fumagillin at the conclusion of the trial and all 6 demonstrated clearance of microsporidia.

- Topical therapy with fumagillin eye drops, in addition to ART, is recommended in HIV-infected children with keratoconjunctivitis caused by microsporidia **(strong, very low)**.

  Improvements have been demonstrated in a small number of reported cases of topical fumagillin treatment of microsporidial keratoconjunctivitis. Treatment with this agent is complicated by lack of a licensed preparation in the United States.[24-27]

- Oral albendazole can be considered in addition to topical therapy for keratoconjunctivitis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(expert opinion)**.

  The addition of oral albendazole to topical fumagillin can be considered for keratoconjunctivitis caused by microsporidia other than *E. bieneusi* or *V. corneae* because microsporidia may persist systemically despite clearance from the eye with topical therapy alone.[28,29]

Secondary Prevention

II. In HIV-infected children who have been treated for microsporidiosis, when can treatment (secondary prophylaxis) be safely discontinued?

Clinicians may consider continuing treatment for microsporidiosis until improvement in severe immunosuppression is sustained (more than 6 months at CDC immunologic category 1 or 2) and clinical signs and symptoms of infection are resolved **(weak, very low)**.

Recurrence of microsporidiosis has been documented following discontinuation of treatment in severely immunosuppressed patients.[24] However, discontinuation of therapy following immune restoration resulting from initiation of ART was successful in a small number of patients.[15]

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Dosing Recommendations for Preventing and Treating Microsporidiosis

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Primary Prophylaxis	N/A	N/A	Not recommended
Secondary Prophylaxis	Disseminated, Non-Ocular Infection or GI Infection Caused by Microsporidia Other Than *E. bieneusi* or *V. corneae*: • Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily Ocular Infection: • Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) **plus**, for infection attributed to microsporidia other than *E. bieneusi* or *V. corneae*, albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily for management of systemic infection	N/A	Criteria for Discontinuing Secondary Prophylaxis: • After initiation of ART, resolution of signs and symptoms and sustained immune reconstitution (more than 6 months at CDC immunologic category 1 or 2)
Treatment	Effective ART Therapy: • Immune reconstitution may lead to microbiologic and clinical response. For Disseminated (Not Ocular) and Intestinal Infection Attributed to Microsporidia Other Than *E. bieneusi* or *V. corneae*: • Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily (in addition to ART) *Treatment Duration:* • Continue until sustained immune reconstitution (longer than 6 months at CDC immunologic category 1 or 2) after initiation of ART and resolution of signs and symptoms For *E. bieneusi* or *V. corneae* Infections: • Fumagillin (where available) adult dose 20 mg by mouth 3 times daily, *or* • TNP-470 (a synthetic analogue of fumagillin; where available) recommended for treatment of infections caused by *E. bieneusi* in HIV-infected adults (in addition to ART) For Ocular Infection: • Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) **plus**, for microsporidial infection other than *E. bieneusi* and *V. corneae*, albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily for management of systemic infection (in addition to ART) *Treatment Duration:* • Continue until sustained immune reconstitution (longer than 6 months at CDC immunologic category 1 or 2) after initiation of ART and resolution of signs and symptoms.	N/A	• Supportive care (e.g., hydration, correction of electrolyte abnormalities, nutritional support) • Fumagillin for systemic use is unavailable in the United States and data on dosing in children are unavailable. Consultation with an expert is recommended.

Key to Acronyms: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; GI = gastrointestinal; QID = 4 times a day

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