



Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Epidemiology

Microsporidia are protists related to fungi, defined by the presence of a unique invasive organelle consisting of a single polar tube that coils around the interior of the spore. They are ubiquitous organisms and are likely zoonotic and/or waterborne in origin. The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon (syn Septata) intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* species, *P. ronneafiei*, *Vittaforma (syn Nosema) corneae*, *Microsporidium* sp, *Nosema ocularum*, *Anncaliia (syns Brachiola/Nosema) connori*, *Anncaliia (syn Brachiola) vesicularum*, and *Anncaliia (syns Brachiola/Nosema) algerae*.¹⁻⁷ In the pre-antiretroviral (ART) era, reported prevalence rates of microsporidiosis varied between 2% and 70% among HIV-infected patients with diarrhea, depending on the diagnostic techniques employed and the patient population described.^{2-4,7} The incidence of microsporidiosis has declined with the widespread use of effective ART, but continues to occur among HIV-infected patients who are unable to obtain ART or to remain on it.⁸ Microsporidiosis is increasingly recognized among HIV-uninfected persons, including children, travelers, organ transplant recipients, contact lens wearers, and the elderly. In patients with immune suppression, clinical signs related to microsporidiosis are most commonly observed when CD4 T lymphocyte cell (CD4) counts are <100 cells/ μ L.^{2-4,7}

Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection have also been described.^{2-4,7}

Clinical syndromes can vary by infecting species. *E. bieneusi* is associated with malabsorption, diarrhea, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Anncaliia* and *Trachipleistophora* are associated with keratoconjunctivitis. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

Diagnosis

Effective morphologic demonstration of microsporidia by light microscopy can be accomplished with staining methods that produce differential contrast between the spores of the microsporidia and the cells and debris in clinical samples such as stool. In addition, because of the small size of the spores (1–5 μ m), magnification up to 1,000 times is required for visualization. Chromotrope 2R and the fluorescent brighteners calcofluor white and Uvitex 2B are useful as selective stains for microsporidia in stool and other body fluids.⁶

In biopsy specimens, microsporidia can be visualized with Giemsa, tissue Gram stains (Brown-Hopps Gram stain), calcofluor white or Uvitex 2B (fluorescent brighteners) staining, Warthin-Starry silver staining, or Chromotrope 2A.⁶ In gastrointestinal disease, examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool examination is negative and microsporidiosis is suspected, a small bowel biopsy may be useful. If the etiologic agent is *Encephalitozoon* or *Trachipleistophora* sp., examination of urine often also reveals the organism. Determination of the species of microsporidia causing disease can be made by the morphology of the organism demonstrated by transmission electron microscopy, by staining with species-specific antibodies, or by polymerase chain

reaction using species- or genus-specific primers.^{6,9} Assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

Patients with AIDS who have CD4 counts <200 cells/ μ L should avoid untreated water sources (**AIII**). Additional recommendations include general attention to hand washing and personal hygiene, avoiding eating undercooked meat or seafood, and limiting exposure to animals known to be infected with microsporidia (**BIII**).¹⁰ The precautions described in the section on cryptosporidiosis also are applicable to microsporidiosis (see also [Appendix: Food and Water-Related Exposures](#)).

Preventing Disease

Because chronic microsporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of combination ART before the patient becomes severely immunosuppressed should prevent this disease (**AII**). No specific chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treating Disease

Data suggest that treatment with ART enables a patient's own defenses to eradicate microsporidia,^{11,12} and administration of ART with immune restoration (an increase in CD4 count to >100 cells/ μ L) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *E. bienewisi*.¹¹⁻¹⁴ All patients therefore should be offered ART as part of the initial management of microsporidial infection (**AII**). They should be given fluid support if they have signs of diarrhea and dehydration (**AII**). Patients with malnutrition and wasting should be treated with nutritional supplementation (**AIII**). Antimotility agents can be used if required for diarrhea control (**BIII**).

No specific therapeutic agent is available for *E. bienewisi* infection. A controlled clinical trial suggested that *E. bienewisi* infection may respond to oral fumagillin (60 mg/day), a water-insoluble antibiotic made by *Aspergillus fumigatus* (**BII**),^{15,16} or to its synthetic analog, TNP-470 (**BIII**).¹⁷ However, fumagillin and TNP-470 are not available for systemic use in the United States. One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bienewisi* in the absence of ART,¹⁸ however, the effect appeared to be minimal among patients with low CD4 cell counts. Therefore, this drug **cannot be recommended** with confidence (**CIII**).

Albendazole, a benzimidazole that binds to β -tubulin, has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* infections or *V. corneae*. The tubulin genes of both *E. bienewisi*¹⁹ and *V. corneae*²⁰ have amino acid residues associated with albendazole resistance. Albendazole is only recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bienewisi* and *V. corneae* (**AII**).²¹⁻²³

Itraconazole may be useful in disseminated disease when combined with albendazole, especially in infections caused by *Trachipleistophora* or *Anncaliia* (**CIII**). Treatment with furazolidone (an agent that is not currently available in the United States) combined with albendazole was reported to improve clinical signs in four HIV-infected patients with persistent diarrhea and *E. bienewisi* infection (**CIII**);²⁴ however, furazolidone has not been demonstrated to be active in other case reports. Metronidazole and atovaquone are not active *in vitro* or in animal models and **should not be used** to treat microsporidiosis (**AII**).

Ocular infections caused by microsporidia should be treated with topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve a concentration of 70 μ g/mL of fumagillin) (**BII**).²¹ Topical fumagillin is the only formulation available for treatment in the United States and is investigational. Although clearance of microsporidia from the eye can be demonstrated, the organism often is still present systemically and can be detected in urine or in nasal smears. Therefore, the use of albendazole as a

companion systemic agent to fumagillin is recommended in ocular infections (**BIII**).

Special Considerations with Regard to Starting ART

As noted above, all patients should be offered ART as part of the initial management of microsporidial infection and also fluid support if they have signs of diarrhea and dehydration (**AII**). Data suggest that treatment with ART, which results in immune reconstitution, enables a patient's own defenses to eradicate microsporidia.^{11,12}

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

Although side effects with albendazole are rare, hepatic enzymes should be monitored because elevations have been reported. Albendazole is not known to be carcinogenic or mutagenic. Topical fumagillin has not been associated with substantial side effects. Oral fumagillin has been associated with thrombocytopenia, which is reversible on stopping the drug.

One report of immune reconstitution inflammatory syndrome (IRIS) has been described in an HIV-infected patient treated with ART in the setting of *E. bienersi* infection;²⁵ however, no IRIS reactions have been reported with other species of microsporidia or with other cases of *E. bienersi*. Concerns about IRIS should not alter therapy or the institution of ART (**AIII**).

Managing Treatment Failure

Supportive treatment and optimization of ART to attempt to achieve full virologic suppression are the only currently feasible approaches to managing treatment failure (**AIII**).

Preventing Recurrence

In individuals with relatively competent immune systems (>200 CD4 cells/ μ L blood), treatment can probably be discontinued after ocular infection resolves (**CIII**), but it should be continued indefinitely if CD4 counts fall below 200 cells/ μ L blood because recurrence or relapse may occur after treatment discontinuation (**BIII**). Whether it is safe to discontinue treatment for other manifestations after immune restoration with ART is unknown. Based on experience with discontinuation of secondary prophylaxis for other opportunistic infections, it is reasonable to discontinue chronic maintenance therapy in patients who no longer have signs and symptoms of microsporidiosis and have a sustained increase in their CD4 counts to levels >200 cells/ μ L for 6 months after ART (**BIII**).¹²

Special Considerations During Pregnancy

Rehydration and initiation of ART should be the mainstays of initial treatment of cryptosporidiosis during pregnancy, as in nonpregnant women (**AII**). In rats and rabbits, albendazole is embryotoxic and teratogenic at exposure levels less than that estimated with therapeutic human dosing. There are no adequate and well-controlled studies of albendazole exposure in early human pregnancy. A recent randomized trial in which albendazole was used for second-trimester treatment of soil-transmitted helminth infections found no evidence of teratogenicity or other adverse pregnancy effects.²⁶

Based on these data, albendazole **is not recommended** for use during the first trimester (**BIII**); use in later pregnancy should be considered only if benefits are felt to outweigh potential risk (**CIII**). Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, because of the antiangiogenic effect of fumagillin, this drug **should not be used** systemically in pregnant women (**AIII**). Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate (**CIII**). Furazolidone is not teratogenic in animal studies, but human data are limited to a case series that found no association between first-trimester use of furazolidone and birth defects in 132 exposed pregnancies.²⁷ Case reports exist of birth defects in infants exposed to itraconazole, but prospective cohort studies of more than

300 women with first-trimester exposure did not show an increased risk of malformation.^{28,29} In general, however, azole antifungals should be avoided during the first trimester (**BIII**). Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, a recent study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.³⁰ 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**).

Recommendations for Managing Microsporidiosis

Preventing Chronic Microsporidiosis

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

Managing Microsporidiosis

- Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm³ (**AII**).
- Severe dehydration, malnutrition, and wasting should be managed by fluid support (**AII**) and nutritional supplements (**AIII**).
- Anti-motility agents can be used for diarrhea control, if required (**BIII**).

For Gastrointestinal Infections Caused by Enterocytozoon bienewisi

- The best treatment option is ART and fluid support (**AII**).
- No specific therapeutic agent is available for this infection.
- Fumagillin 60 mg PO daily (**BII**) and TNP-470 (**BIII**) are two agents that have some effectiveness, but neither agent is available in the United States.
- Nitazoxanide may have some effect, but the efficacy is minimal in patients with low CD4 cell count, and cannot be recommended (**CIII**).

For Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than E. bienewisi and Vittaforma corneae:

- Albendazole 400 mg PO BID (**AII**), continue until CD4 count >200 cells/mm³ for >6 months after initiation of ART (**BIII**)

For Disseminated Disease Caused by Trachipleistophora or Anncaliia

- Itraconazole 400 mg PO daily + albendazole 400 mg PO BID (**CIII**)

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) (**BII**), plus albendazole 400 mg PO BID for management of systemic infection (**BIII**)
- For patients with CD4 count >200 cells/mm³, therapy can probably be discontinued after ocular infection resolves (**CIII**).
- For patients with CD4 count ≤200 cells/mm³, therapy should be continued until resolution of ocular symptoms and CD4 count increases to >200 cells/uL for at least 6 months in response to ART (**BIII**)

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; PO = orally, QID = four times daily

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