

Microsporidiosis

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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. Phylogenetic studies now place microsporidia with the Cryptomycota as the basal branch of the fungal kingdom (or alternatively as a sister phylum).¹ The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon* (syn *Septata*) *intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* species, *Pleistophora ronneafiei*, *Vittaforma* (syn *Nosema*) *corneae*, *Tubulonosema acridophagus*, *Endoreticulatus* sp., *Nosema ocularum*, *Anncaliia* (syns *Brachiola*/*Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, *Anncaliia* (syns *Brachiola*/*Nosema*) *algerae*, and *Microsporidium* sp.²⁻⁸ In the pre-antiretroviral therapy (ART) era, reported prevalence rates of microsporidiosis varied between 2% and 70% among people with HIV/AIDS with diarrhea, depending on the diagnostic techniques employed and the population described.^{3-5,8} The incidence of microsporidiosis has declined with the widespread use of effective ART, but it continues to occur among people with HIV who are unable to obtain ART or to remain on it.⁹ Microsporidiosis is increasingly recognized among people without HIV, including children, travelers, organ transplant recipients, contact lens wearers, and the elderly. In people with immune suppression, clinical signs related to microsporidiosis^{3-5,8} are most commonly observed when CD4 T lymphocyte (CD4) cell counts are <100 cells/mm³.

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.^{3-5,8}

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*, *Vittaforma*, 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 mm), 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.⁷

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.⁷ 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.^{7,10} The assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

People with HIV who have CD4 counts <200 cells/mm³ should avoid untreated water sources **(AIII)**. Additional recommendations include increasing 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)**.¹¹ The precautions described in the section on cryptosporidiosis also are applicable to microsporidiosis.

Preventing Disease

Preventing Chronic Microsporidiosis
<ul style="list-style-type: none">Because chronic microsporidiosis occurs primarily in people with advanced immunodeficiency, initiate ART before severe immunosuppression occurs (AII).

Key: ART = antiretroviral therapy

Because chronic microsporidiosis occurs primarily in people with advanced immunodeficiency, appropriate initiation of ART before severe immunosuppression should prevent this disease **(AII)**. No specific chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treating Disease

Managing Microsporidiosis
<ul style="list-style-type: none">Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm³ (AII).Manage severe dehydration, malnutrition, and wasting with fluid support (AII) and nutritional supplements (AIII).Antimotility agents can be used for diarrhea control, if required (BIII). <p><i>GI Infections Caused by Enterocytozoon bienersi</i></p> <ul style="list-style-type: none">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) (unavailable in the United States)

- Nitazoxanide 500 mg twice daily for at least 14 days may resolve chronic diarrhea and is a reasonable alternative if fumagillin is not available (CIII), but the effect appeared to be minimal in people with low CD4 counts.

*Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than *E. bieneusi* and *Vittaforma corneae**

- Albendazole is recommended only for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* (AII). Albendazole 400 mg PO twice daily (AII) for at least 14 days; continue therapy until the CD4 count is >200 cells/mm³ after initiation of ART (BIII).

*Disseminated Disease Caused by *Trachipleistophora* or *Anncaliia**

- Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily (CIII)

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 four times daily (investigational use only in the United States; needs to be prepared by a compounding pharmacy) (BII), and
- Albendazole 400 mg PO twice daily for management of systemic infection (BIII)
- For people with CD4 count >200 cells/mm³, therapy can be discontinued after ocular infection resolves (CIII).
- For people with CD4 count ≤200 cells/mm³, therapy should be continued indefinitely as recurrence or relapse may occur when therapy is discontinued (BIII).

Discontinuation of Chronic Maintenance Therapy for Non-Ocular Manifestations (BIII)

- No longer have signs and symptoms of microsporidiosis, and
- Sustained increase in CD4 count >200 cells/mm³ for ≥3 months after ART

Pregnancy Considerations

- Albendazole is not recommended for use during the first trimester (BIII); use in later pregnancy should be considered only if benefits outweigh potential risks (CIII).
- Fumagillin has an antiangiogenic effect and should not be used systemically during pregnancy (AIII). Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate (CIII).
- Nitazoxanide has not been associated with adverse outcomes in pregnancy; however, data are very limited on its use during pregnancy (CIII).
- Azole antifungals should be avoided during the first trimester (BIII).
- Loperamide should be avoided in the first trimester unless benefits outweigh potential risks of congenital malformations (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).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; GI = gastrointestinal; PO = orally

Data suggest that treatment with ART enables a person's own defenses to eradicate microsporidia,^{12,13} and administration of ART with immune restoration (an increase in CD4 count to >100 cells/mm³) is associated with resolution of symptoms of enteric microsporidiosis, including illness caused by *E. bieneusi*.¹²⁻¹⁵ Everyone, therefore, should be offered ART as part of the initial management of microsporidial infection (AII), and they should be given fluid support if they have signs of diarrhea and dehydration (AII). People 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. bieneusi* infection. Based on results from a controlled clinical trial, oral fumagillin (60 mg/day), a water-insoluble antibiotic made from *Aspergillus fumigatus* **(BII)**,^{16,17} or to its synthetic analog, TNP-470 can be administered **(BIII)**.¹⁸ Fumagillin and TNP-470 are not commercially available for systemic use in the United States, and Sanofi in France no longer produces FLISINT (fumagillin). One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART;¹⁹ however, the effect appeared to be minimal among people with low CD4 counts. Based on the professional experience of several experts who have treated diarrhea caused by *E. bieneusi* with nitazoxanide in organ transplant recipients, nitazoxanide is a reasonable alternative for the treatment of diarrhea due to *E. bieneusi* if fumagillin is not available **(CIII)**.²⁰

Albendazole, a benzimidazole that binds to β -tubulin, has activity against many species of microsporidia, but it is not effective against *E. bieneusi* or *V. corneae* infections. The tubulin genes of both *E. bieneusi*²¹ and *V. corneae*²² have amino acid residues associated with albendazole resistance. Albendazole is recommended only for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII)**.²³⁻²⁵

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 people with HIV with persistent diarrhea and *E. bieneusi* infection **(CIII)**²⁶; 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)**.

People with ocular infections caused by microsporidia should be administered topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve a concentration of 70 μ g/mL of fumagillin) **(BII)**.²³ Topical fumagillin solution needs to be made by a compounding pharmacy because it is not commercially available 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, people with HIV should be offered ART as part of the initial management of microsporidial infection, as well as fluid support if they have signs of diarrhea and dehydration **(AII)**. Data suggest that treatment with ART, which results in immune reconstitution, enables a person's own defenses to eradicate microsporidia.^{12,13}

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 after stopping the drug.

One report of immune reconstitution inflammatory syndrome (IRIS) has been described in a person with HIV treated with ART in the setting of *E. bieneusi* infection;²⁷ 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 use 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/mm³), treatment should be discontinued after ocular infection resolves **(CIII)**; treatment should be continued indefinitely if CD4 counts fall below 200 cells/mm³ 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 those who no longer have signs and symptoms of microsporidiosis and have a sustained increase in their CD4 counts to >200 cells/mm³ for 3 to 6 months after ART **(BIII)**.¹³

Special Considerations During Pregnancy

During pregnancy, rehydration and initiation of ART are the preferred initial treatment of microsporidiosis as for all people with HIV **(AII)**. In rats and rabbits, albendazole is embryotoxic and teratogenic at exposure levels less than those 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.²⁸

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 outweigh potential risks **(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 during pregnancy **(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 furazolidone-exposed pregnancies.²⁹ Nitazoxanide has not been associated with adverse outcomes in pregnancy; however, data are very limited on its use during pregnancy **(CIII)**. Case reports exist of birth defects in infants exposed to itraconazole, but prospective cohort studies of >300 women with first-trimester exposure did not show an increased risk of malformation.^{30,31} 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, specifically hypospadias, among 683 women with exposure to loperamide in early pregnancy.³² Therefore, loperamide should be avoided in the first trimester unless benefits 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)**.

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