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section 8 Infectious diseases 1378 treatment is amphotericin B 0.6 mg/kg per day intravenously for 2 weeks, followed by itraconazole 400 mg/day orally for 10 weeks. Patients with less severe disease can be initially treated with oral itraconazole for 12 weeks. In the latter case, itraconazole 600 mg/ day in 2–3 divided doses may be considered in the first 3 days be- fore reducing to 400 mg/day. Most patients respond well, with reso- lution of fever and other signs of infection, and clearance of fungus from bloodstream within the first 2 weeks. In patients with severe immunodeficiency (i.e. CD4+ cell count <50 cells/µl), antiretroviral therapy should be initiated as soon as possible. After successful pri- mary treatment, HIV-infected patients should be given 200 mg/day of itraconazole orally as secondary prophylaxis for life or until im- mune recovery after antiretroviral therapy (i.e. CD4+ cell counts of 200 cells/µl or above for at least 6 months). For HIV-uninfected indi- viduals, the optimal duration of treatment and the role of secondary prophylaxis remain unknown. FURTHER READING Chaiwarith R, et al. (2007). Discontinuation of secondary prophylaxis against penicilliosis marneffei in AIDS patients after HAART. AIDS, 21, 365–7. Deng Z, et al. (1998). Infection caused by Penicillium marneffei in China and Souhtheast Asia: review of eighteen published cases and report of four more Chinese cases. Rev Infect Dis, 10, 640, 52. Kawila R, et al. (2013). Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infec- tion in Northern Thailand: a retrospective study. BMC Infect Dis, 13, 464. Le T, et al. (2011). Epidemiology, seasonality, and predictors of out- come of AIDS-associated Penicillium marneffei in Ho Chi Minh City, Vietnam. Clin Infect Dis, 52, 945–52. Sirisanthana T, Supparatpinyo K (1998). Epidemiology and manage- ment of penicilliosis in human immunodeficiency virus-infected patients. Int J Infect Dis, 3, 48–53. Supparatpinyo K, et al. (1994). Disseminated Penicillium marneffei infection in Southeast Asia. Lancet, 344, 110–13. Supparatpinyo K, et al. (1998). A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients in- fected with the human immunodeficiency virus. N Engl J Med, 339, 1739–43. 8.7.7 Microsporidiosis Louis M. Weiss ESSENTIALS Microsporidia are obligate intracellular eukaryotic pathogens re- lated to the Fungi that can infect both vertebrates and inverte- brates. They were first identified about 150 years ago as the cause of pebrine, a disease of silkworms, with the description of Nosema bombycis in these economically important insects. They were first described in mammalian tissue samples about 75 years ago and starting 30 years ago they were recognized as pathogenic organ- isms responsible for a diarrhoeal syndrome in patients with AIDS. In addition to the gastrointestinal tract, it is now appreciated that microsporidia can infect virtually any organ system. The phylum Microsporidia contains about 1400 species, distributed in 200 genera, and 15 microsporidian species have been reported in human infections. Microsporidia are found in surface water and it appears that at least some cases are due to ingestion of spores of the

causative organism in water or food. In addition, many of the species seen in humans are also seen in various animals, sug- gesting that zoonotic transmission of this infection occurs. Clinical manifestations are most frequently reported in patients with ad- vanced immune suppression, such as patients with HIV infection, and include diarrhoea and wasting syndrome. This is usually due to infection of the small intestinal mucosa by either Enterocytozoon bieneusi or Encephalitozoon intestinalis. Microsporidia also cause
keratoconjunctivitis in both immune competent and immune compromised hosts. These corneal infections have been most commonly caused by either Encephalitozoon hellem or Vittaforma corneae. Other reported manifestations of infection include acalculous cholecystitis, sinusitis, cough/dyspnoea, urethritis, myositis, and encephalitis. Gastrointestinal microsporidiosis is diagnosed by microscopic examination of faecal specimens, after appropriate staining for microsporidian spores, or by detection of microsporidian DNA in faecal specimens. Aside from sup- portive care, albendazole is an effective drug for treating infec- tion due to Encephalitozoonidae. Ent. bieneusi does not respond to albendazole and fumagillin is an effective drug for diarrhoeal syndromes due to this pathogen, although it is not commercially available for humans. Topical fumagillin solutions have been used successfully to treat microsporidian keratoconjunctivitis. In HIV- infected patients, remission of microsporidiosis can be achieved by immune restoration due to antiretroviral drug treatment. As transmission can occur via food or water, prevention can be achieved by safe food and water practices, such as boiling water. As microsporidian spores are minuscule, water filtration methods need to be able to remove organisms that are 1 to 3 μm in size to be an effective preventative measure. Introduction The class or order Microsporidia was elevated to the phylum Microspora by Sprague in 1977 and in 1998 Sprague and Becnel suggested that the term Microsporidia instead be used for the phylum name. While microsporidia were historically considered ‘primitive’ protozoa, molecular phylogenetic analysis has led to the recognition that these organisms are not primitive but degenerate, and that they are related to the Fungi, either as a basal branch of the Fungi or as a sister group. Microsporidia infect almost all animal phyla, including other protists. They are important agricultural parasites in insects, fish, laboratory rodents, and mammals. Several species of microsporidia are used as biological control agents for destructive species of insects. In their hosts, most microsporidia in- fect the digestive tract, but infections of almost all organ systems have been documented. Microsporidiosis occurs in both immune

8.7.7 Microsporidiosis 1379 compromised and immune competent hosts. These pathogens can be transmitted by food or water and are likely zoonotic. Several different genera and species of microsporidia cause disease in hu- mans. The genera infecting humans include Nosema, Vittaforma Pleistophora, Encephalitozoon, Enterocytozoon, Trachipleistophora, Anncaliia, Tubulonosema, Endoreticulatus, and Microsporidium. Diagnosis can be made by finding characteristic spores in body fluids (e.g. stool, urine, conjunctival scraping, and so on) using stains, such as chromotrope 2R or Uvitex 2B. Definitive identifica- tion of the microsporidia causing an infection can be done using ultrastructural examination or molecular techniques. Historical perspective Before the HIV/AIDS pandemic, most of the literature on microsporidian infections dealt with such infections in nonhuman hosts (e.g. silk moths, honeybees, fish, and rabbits). Microsporidia were first described in 1959 as being human pathogens when they were found in a child with encephalitis. In the immune suppressed host, for example, those treated with immune suppressive drugs or infected with human immunodeficiency virus (particularly those at advanced stages of the disease), microsporidia can produce a wide range of clinical diseases. Reports of diarrhoeal syndromes

associ- ated with microsporidiosis and HIV infection were first reported in 1985, and the number of articles describing human disease increased rapidly after 1990. Since the advent of combination antiretroviral therapy, the incidence of microsporidiosis has declined in the HIV infected population. In addition to gastrointestinal tract involvement, immune compromised patients with encephalitis, ocular infection, sinusitis, myositis, and disseminated infection are well described in the literature. The burgeoning literature on human microsporidiosis in HIV-infected individuals has been recently complemented by an increasing awareness of microsporidia infections in immune compe- tent people, most notably infections resulting in keratoconjunctivitis. Although initially regarded as rare, microsporidia are now believed to be common enteric pathogens that cause self-limited or asymp- tomatic infections in most immune competent hosts. Aetiology, pathogenesis, and pathology Microsporidia are obligate intracellular parasites, whose lifecycle comprises an extracellular stage (spore) and reproductive stages occurring in host cells. They are eukaryotes containing a nucleus with a nuclear envelope, an intracytoplasmic membrane system, chromosome separation on mitotic spindles, vesicular Golgi, and a mitochondrial remnant organelle called a mitosome. Microsporidia are ubiquitous in the environment and infect almost all inverte- brates and vertebrates. They form characteristic unicellular spores (Fig. 8.7.7.1) which are environmentally resistant. Microsporidia are currently classified based on their ultrastructural features, including the size and morphology of the spores, number of coils of the polar tube, developmental life cycle, and host-parasite relation- ship. The microsporidia infecting humans have spores that range from 1.0 to 4.0 µm in size and are usually ovoid. Spore structure is characteristic of the phylum; consisting of an electron-dense, pro- teinaceous exospore, an electronlucent endospore composed of chitin and protein, and an extrusion apparatus that consists of a polar tube attached to the inside of the anterior end of the spore by an anchoring disc and, depending on the species, the polar tube has 4 to approximately 30 coils within the spore. Spores induce in- fection by a high velocity extrusion of their polar tube bringing the sporoplasm into intimate contact with the host cell thereby forming a channel for delivering sporoplasm (spore contents) into its target host cell. The overall process of germination, formation of the polar tube and delivery of the sporoplasm into the host cell functions es- sentially like a hypodermic needle. Replication of the parasite and subsequent production of spores occurs in host cells. When spores are phagocytosed they can also germinate infecting adjacent cells. Microsporidia can invade and survive in macrophages and den- dritic cells allowing their dissemination within the host. Microsporidia were historically considered ‘primitive’ protozoa. Molecular phylogenetic data, however, indicate that microsporidia are related to the Fungi (either as a basal branch of the Fungi or as a sister group within the Cryptomycota) and are not primitive but degenerate eukaryotes. Molecular phylogeny has also led to the rec- ognition that traditional phylogeny based on structural observations may not reflect the relationships among the various microsporidian species and genera. The genome size of the microsporidia varies from 2.3 to 19.5 Mbp, with the genomic size of the Encephalitizoonidae being under 3.0Mbp, making them among the smallest eukaryotic nuclear genomes so far identified. There are almost no introns in the compact genome of Enc. cuniculi, the gene density is high, and proteins are shorter than the corresponding genes in Saccharomyces cerevisiae. Genome data for the Microsporidia are available on MicrosporidiadB (http://microsporidiadb.org/micro/), which is part of the EuPathdB (http://eupathdb.org/ eupathdb/) website. In HIV-infected patients, diarrhoea is the clinical feature that has been most frequently associated with microsporidiosis. In par- ticular, this symptom has been historically associated with infections by either Ent. bieneusi or Enc. intestinalis. The diarrhoea reported in these infections is a consequence of infection of the mucosa of the small intestine and, in advanced HIV disease, is often associated with a wasting syndrome and

historically with an elevated mortality rate. Parasitization of the intestinal mucosa can be seen on micro- scopic examination of biopsy specimens. Microsporidia that infect human subjects are listed in Table 8.7.7.1. Human infections with microsporidia other than with Ent. bieneusi, Encephalitozoon spe- cies, or Vittaforma corneae have been reported in only a few case reports for each organism. Polaroplast membranes Nucleus Endospore Exospore Anchoring disc (polar sac) Straight part of polar tube Polar tube coil Plasmalemma Fig. 8.7.7.1 Diagram of a microsporidian spore, showing internal structure. Courtesy of Professor Elizabeth U. Canning. Modified from Canning EU, Hollister WS (1992). Human infections with microsporidia. Rev Med Microbiol, 3, 35–42, with permission.

section 8 Infectious diseases 1380 The immune suppressive states (e.g. AIDS and transplantation) associated with microsporidiosis in humans are those that inhibit cell-mediated immunity. In mice, interferon-γ and interleukin-12 (IL-12) contribute to protective immunity against Enc. intestinalis and Enc. cuniculi infections. Adoptive transfer of sensitized syn- geneic T-enriched spleen cells protects athymic or severe com- bined immunodeficiency (SCID) mice against lethal Enc. cuniculi infection. The major killing mechanism exhibited by CD8+ T cells in murine microsporidosis models is due to the perforin pathway (e.g. mice lacking perforin die when infected with Enc. cuniculi). Infection with Enc. cuniculi in many mammals re- sults in chronic infection with persistently high antibody titres and ongoing inflammation (e.g. persistent encephalitis in rabbits and chronic renal disease and congenital transmission in foxes). Transmission of infection to transplant recipients by kidneys used in renal transplantation suggests that chronic infection is also seen in humans. Epidemiology Most infections due to microsporidia are transmitted by oral inges- tion of spores, with the site of initial infection being the gastrointes- tinal tract. Microsporidian spores are commonly found in surface water, and human pathogenic species have been found in muni- cipal water supplies, tertiary sewage effluent, and ground water. Water contact has been found to be an independent risk factor for microsporidiosis (e.g. an outbreak of V. corneae keratoconjunctivitis was associated with hot spring exposure). Risk factors for Ent. bieneusi infection, in a population of HIV-infected patients sur- veyed in France, included swimming in a pool in the 12 months before the survey. In rural Mexican households, faecal excretion of Encephalitozoon spores was associated with the use of unboiled water for drinking and for preparing food. Spores are viable for a long time in water, but can be killed by boiling. Microsporidia are also foodborne pathogens, for example, an outbreak of foodborne Ent. bieneusi infection (characterized by abdominal pain, nausea, and diarrhoea) occurred in Sweden in 2009. Viable infective spores of Microsporidia are present in several body fluids (e.g. stool, urine, respiratory secretions) during infection, suggesting that person-to-person transmission can occur. Heavy parasitization of respiratory tract epithelial cells with Enc. hellem, in at least one HIV-infected patient examined at autopsy, raises the possibility that some microsporidian infections can be acquired by inhaling spores. Congenital transmission has been seen in many mammals, but has not been reported in humans. Many microsporidia are also probably zoonotic infections in hu- mans. Spores and/or DNA of potentially human-infective strains of Ent. bieneusi and of Enc. hellem have been found in faecal samples and intestinal contents from pigeons. In addition, spores and/or DNA of Encephalitozoon spp. have been identified in faecal samples of aquatic animals. Spores of Enc. intestinalis have been identified in faecal specimens from dogs, pigs, goats, cows, and donkeys. Ent. bie neusi has been identiied in faecal samples from dogs, cats, pigs, goats, cows, horses, and rhesus monkeys. House mice in central Europe have been found to be infected with Ent. bieneusi, Enc. hellem, and Enc. cuniculi. Genotyping of microsporidia is beginning to shed light on possible interspecies transmissibility of

these organisms. For example, Ent. bieneusi organisms excreted by rhesus monkeys in a public park in China included genotypes known to infect human subjects. Contact with pigs is a risk factor for infection by a porcine- associated genotype of Ent. bieneusi, among human inhabitants of a rural area of China. Several human pathogenic microsporidia (e.g. Anncaliia algerae and Trachipleistophora hominis), can also infect mosquitoes, suggesting that vector borne transmission might also occur for some of the human pathogenic microsporidia. Although initially regarded as rare, microsporidia are now be- lieved to be common enteric pathogens that cause self-limited or asymptomatic infections in normal hosts. Cases of microsporidiosis have been identified from all continents except Antarctica. Surveys of pathogens seen in stool samples in Africa, Asia, South America, and Central America have demonstrated that microsporidia are often found during careful stool examinations. In immune deficient hosts, most reported cases have manifested as diarrhoea with wasting syndrome and disseminated infection. Microsporidiosis prevalence rates varied between 2% and 70%, in 25 studies conducted on pa- tients with HIV infection from 1989 to 1998, before the widespread use of combination highly active antiretroviral therapy. The rates varied depending on the symptoms of the population studied and the diagnostic techniques used. Overall, these studies identified 375 E. bieneusi infections among 2400 patients with chronic diar- rhoea, for a prevalence of 15% in this population. The aggregate data Table 8.7.7.1 Species of microsporidia that infect humans Species Reported sites of infection Enterocytozoon bieneusi Small intestinal epithelium, gallbladder epithelium, rarely in respiratory tract and maxillary sinus Encephalitozoon (formerly Septata) intestinalis Intestinal epithelium, gallbladder epithelium, paranasal sinuses, respiratory tract, liver, kidney, pituitary, conjunctiva. Encephalitozoon hellem Corneal epithelium, respiratory tract, kidney, paranasal sinuses Encephalitozoon cuniculi Kidney, urinary bladder, duodenal mucosa, conjunctiva, respiratory tract, adrenal glands, brain, heart, spleen, lymph nodes, cerebrospinal fluid Vittaforma corneae (formerly Nosema corneum) Corneal stroma, urinary tract Trachipleistophora hominis Skeletal muscle, conjunctiva, corneal stroma, nasopharynx Trachipleistophora anthropophthera Brain, kidney, heart, pancreas, thyroid, parathyroid glands, liver, spleen, lymph nodes, bone marrow, cornea Pleistophora ronneafiei Skeletal muscle Anncaliia algeraea Skeletal muscle, skin, corneal stroma Anncaliia vesicularuma Skeletal muscle Anncaliia connoria Generalized Tubulinosema sp. Skeletal muscle Tubulinosema acridophagus Generalized Nosema ocularum Corneal stroma ‘Microsporidium ceylonensis’ Corneal stroma ‘Microsporidium africanum’ Corneal stroma a Organisms in the genus Anncaliia were formerly designated by the generic names Brachiola and Nosema.

 available have demonstrated microsporidia demonstrate strength of association, coherence, and reproducibility with respect to being causative for a diarrhoeal syndrome. Studies have demonstrated that asymptomatic carriage can occur in immune compromised patients. There are numerous reports of microsporidiosis in patients who have undergone kidney, liver, heart-lung, pancreas, or bone marrow transplantation. There has been speculation that microsporidiosis in immune deficient subjects might sometimes reflect activation of microsporidian infection acquired before the onset of immunodefi- ciency. Three recipients of transplanted organs (lung and kidneys) from one donor developed Enc. cuniculi infection caused by an iden- tical genotype of this organism; an archival serum sample from the organ donor had a high titre of antibody to Enc. cuniculi, suggesting that the donated organs were the source of the infection seen in the recipients. The phylum Microsporidia (Microspora) contains at least 1400 species distributed into over 200 genera, of which the following have been demonstrated in human disease (Table 8.7.7.1): Nosema (N. corneum renamed Vittaforma corneae; N. algerae reclassi-

fied initially as Brachiola algerae and now as Anncaliia algerae), Pleistophora, Encephalitozoon, Enterocytozoon, Septata (re- classified as Encephalitozoon1), Trachipleistophora, Brachiola Anncaliia, Tubulonosema, Endoreticulatus, and Microsporidium. Microsporidium is a nontaxonomic genus created for microsporidia of unclear identity. Encephalitozoon hellem (Enc. hellem) has been associated with superficial keratoconjunctivitis, sinusitis, respira- tory disease, prostatic abscesses, and disseminated infection. Encephalitozoon cuniculi (Enc. cuniculi) has been associated with hepatitis, encephalitis, and disseminated disease. Encephalitozoon (Septata) intestinalis is associated with diarrhoea, disseminated in- fection, and superficial keratoconjunctivitis. Nosema, Vittaforma, and Microsporidium have been associated with stromal keratitis associated with trauma. Pleistophora, Anncaliia, Tubulonosema, Endoreticulatus, and Trachipleistophora have been associated with myositis sometimes with associated disseminated disease. Trachipleistophora has been associated with encephalitis, keratitis, and disseminated disease. Enterocytozoon bieneusi (Ent. bieneusi), originally described in humans, is associated with malabsorption, diarrhoea, and cholangitis. Prevention There are limited data on effective preventative strategies for microsporidiosis, however, the most effective prophylaxis for im- mune compromised patient is restoration of immune function. There are no data that demonstrate an effective prophylactic medi- cation that prevents infection in humans. It is probable that the usual sanitary measures that prevent contamination of food and water will decrease the chance of infection; these measures for water include boiling water, the use of bottled water, ultraviolet treatment, chlor- ination, or the use of filters that remove particles of at least 1 μm in size. Both immune capture and molecular methods have been de- veloped to evaluate the presence of microsporidia in water samples. Hand washing and general hygienic habits reduce the chance of con- tamination of conjunctiva and cornea with microsporidian spores. Spores can be rendered noninfectious by a 30-minute exposure to most common disinfectants, so the procedures used to clean most hospital rooms should be sufficient to limit infection. Spores are also killed by the methods commonly used for sterilization. Given the presence of microsporidia in the respiratory secretions of pa- tients with disseminated microsporidiosis, it is reasonable to isolate infected patients from contact with immune suppressed patients to prevent transmission. It is reasonable to screen close contacts of pa- tients with microsporidiosis for the presence of these organisms. Clinical features Clinical features of microsporidian infections reflect the anatomical site colonized by the microsporidia (Table 8.7.7.1). Watery diar- rhoea, weight loss, and fat malabsorption have been reported in HIV- infected patients with intestinal microsporidiosis. Microsporidian infection of the gallbladder and billiary system can result in acalculous cholecystitis, which might necessitate cholecystectomy, or sclerosing cholangitis or AIDS cholangiopathy. Infection of the paranasal sinuses and respiratory tract can result in symptoms of si- nusitis, cough, and dyspnoea. Symptomatic urethritis and prostatitis have been ascribed to Encephalitozoon spp. infection. Encephalitis with mass lesions has been seen with both Encephalitozoon and Trachipleistophora infections associated with headache, cognitive impairment, nausea, vomiting, focal neurological deficit, and epi- leptic seizures. Both Trachipleistophora and Anncaliia have been re- ported in cases of myositis with muscle pain, tenderness, weakness, and wasting. Disseminated microsporidiosis can present as a fever of unknown origin with negative blood cultures. Hepatitis with liver function abnormalities can be seen in disseminated infection. There have been case reports of microsporidian infections causing nodular skin lesions. Microsporidian infection of the conjunctiva and corneal epi- thelium causes symptoms of keratoconjunctivitis (e.g. foreign body sensation in the eye, ocular discomfort and redness, photo- phobia, blurred vision, and sometimes reduced visual acuity). Microsporidian infections of the corneal stroma lead to reduced visual acuity, with or without corneal ulceration.

Microsporidian keratoconjunctivitis, in individuals without HIV infection, has been recognized increasingly in Asia. Exposure to mud after recent rain- fall appears to be a risk factor for this microsporidian eye infection. In India, Vittaforma corneae DNA has been demonstrated (by poly- merase chain reaction testing) in corneal scrapings from patients with keratitis. This organism has been described as a cause of kera- titis resulting from bathing in hot springs in Taiwan, and has also caused keratoconjunctivitis in rugby football players in Singapore. Laboratory diagnosis Intestinal microsporidiosis can be diagnosed by microscopic exam- ination of faecal samples. The spores (which are ovoid) can be de- tected by microscopy after staining with chromotrope 2R or with optical brighteners such as Uvitex 2B or Calcofluor White M2R (which bind to chitin in the spores, resulting in fluorescence), or with fluorescent antibodies directed against the spores. In a study that examined 50 electron microscopy-proven microsporidia-positive stool specimens, both the chromotrope 2R and optical brighteners identified 100% of specimens if at least fifty 100× objective fields

section 8 Infectious diseases 1382 were examined. The limit of detecting microsporidia by these tech- niques appears to be 50 000 organisms/ml. Spores of Ent bieneusi are 1.5 µm × 0.9 µm whereas those of Encephalitozoonidae are larger, ca. 2.5 µm × 1.5 µm. Definitive identification of a microsporidium causing an infection can be done by ultrastructural examination (Fig. 8.7.7.2) or molecular techniques. Patients with diarrhoea or keratoconjunctivitis should have urine examined to look for dis- seminated infection. This has therapeutic implications because microsporidia that disseminate, such as Encephalitozoon spp, are sensitive to albendazole, whereas those that do not dissem- inate, such as Ent. bieneus), are resistant to albenazole. Species specific diagnosis can be obtained by electron microscopy or by molecular tests. Generally, it is easier to identify microsporidian spores in body fluids other than in stool because of the absence of bacteria and debris, which can be confused with microsporidian spores. Because these infections usually involve mucosa or epithe- lium, cytologic preparations that have been useful for diagnosing infection include intestinal and biliary epithelium, epithelium of the cornea and conjunctivae, epithelium of the sinonasal and tracheobronchial regions, renal tubular epithelium, and urothelium. Histologically, microsporidia can be seen in sections prepared from tissue fixed using routine procedures by employing a modified tissue chromotrope 2R (Fig. 8.7.7.3), tissue Gram stain (Brown–Hopp or Brown–Brenn) or Luna stain. Serology has not proven useful for the diagnosis of active infection. Several molecular diagnostic tests have been developed for pathogenic microsporidia and these tests are available from some reference laboratories. Treatment and prognosis Among the compounds tested in vitro and in vivo for treatment of microsporidiosis, fumagillin and albendazole have demonstrated the most consistent activity and have been demonstrated to have clinical efficacy in human infections with various microsporidia. Encephalitozoonidae infections can be treated with albendazole. In contrast, albendazole is not an effective treatment for Ent. bie neusi infection. In a small controlled trial, HIV-infected patients with Enc. intestinalis infection were treated with albendazole (400 mg orally twice daily) or with placebo. Albendazole treatment led to clearance of gastrointestinal Enc. intestinalis infection in this study. Uncontrolled trials and anecdotal case reports describe par- tial or complete resolution of symptoms (diarrhoea, sinusitis, and keratoconjunctivitis) in patients with Enc. intestinalis, Enc. hellem, or Enc. cuniculi infection following albendazole treatment. Pregnancy is a contraindication to albendazole treatment. Microsporidiosis is seen most commonly in immune compromised hosts, particularly in those with HIV infection and CD4+ cell counts lower than 50/µl. Clinical studies have demonstrated that improved immune function can result in the clinical response of patients with

gastrointestinal microsporidiosis, with elimination of the organism and normalization of the intestinal architecture. In HIV-infected pa- tients with Ent. bieneusi infection, remission of this microsporidian in- fection can be achieved by treatment of the HIV disease with effective antiretroviral therapy that leads to restoration of immune competence, as evidenced by a raised CD4+ count and reduced HIV load. Clinical trials and case reports in patients with AIDS or organ transplantation Fig. 8.7.7.2 Transmission electron micrograph of jejunal biopsy from a patient with AIDS and Encephalitozoon intestinalis infection. The microvillus border (epithelial surface) is at the top of the photograph. Epithelial cells and lamina propria leukocytes are heavily infected with Enceph. intestinalis (arrows). Courtesy of the Electron Microscopy and Histopathology Unit, London School of Hygiene and Tropical Medicine. From Croft SL, Williams J, McGowan I (1997). Intestinal microsporidiosis. Semin Gastrointest Dis, 8, 45–55, with permission. Fig. 8.7.7.3 Light micrograph of intestinal villus biopsy (plastic section) from a patient with a gastrointestinal infection with Encephalitozoon intestinalis. Note the presence of spores (arrows) on the apical and basal side of the epithelial cells as well as in the lamina propria. From Wittner M and Weiss LM (eds.) The Microsporidia and Microsporidiosis. American Society of Microbiology, Washington, DC, 1999; with permission.

8.7.7 Microsporidiosis 1383 have demonstrated that fumagillin (20 mg orally thrice daily) is ef- fective for the treatment gastrointestinal infection with Ent. biene usi. Fumagillin is also active against other microsporidia including Encephalitozoonidae. The major limiting toxicity of systemic therapy with fumagillin has been thrombocytopenia which has been reversible on stopping treatment. Transient clinical remission has been reported in Ent. bieneusi with furazolidone or nitazoxanide (1000 mg twice daily) treatment. Individual patients infected with Trachipleistophora hominis, Anncaliia vesicularum, or Anncaliia algerae have demon- strated clinical improvement after treatment with albendazole com- bined with azoles (e.g. itraconazole or voriconazole). A solutions of the soluble salt fumagillin bicylohexylammonium (3 mg/ml which is equivalent to fumgaillin, 70 µg/ml) applied topic- ally has been demonstrated to be nontoxic to the cornea and effective for the treatment of ocular microsporidiosis. It should be appreci- ated that ocular infection can be associated with systemic infection and if microsporidia are demonstrated in urine or nasal smears then oral albendazole should also be administered. Successful treat- ment of microsporidian keratoconjunctivitis has also been reported with voriconazole eye drops. In a study of the natural history of microsporidian keratoconjunctivitis in India in immune competent hosts it was observed that this infection resolves spontaneously in many patients. HIV-negative patients with microsporidian infection of the cor- neal stroma have been treated by corneal transplantation, with results that have ranged from failure (opacification of the transplant) to apparent success, as judged by transparency of the graft 6 months after transplantation. FURTHER READING Didier ES, Weiss LM (2011). Microsporidiosis: not just in AIDS pa- tients. Curr Opin Infect Dis, 24, 490–5. Didier ES, et al. (2005). Therapeutic strategies for human microsporidia infections. Expert Rev Anti Infect Ther, 3, 419–34. Field AS (2002). Light microscopic and electron microscopic diag- nosis of gastrointestinal opportunistic infections in HIV-positive patients. Pathology, 34, 21–35. Franzen C (2008). Microsporidia: a review of 150 years of research. The Open Parasitology Journal, 2, 1–34. Ghosh K, Weiss LM (2009). Molecular diagnostic tests for micro sporidia. Interdiscip Perspect Infect Dis, 2009, 926521. Ghosh K, Weiss LM (2012). T cell response and persistence of the microsporidia. FEMS Microbiol Rev, 36, 748–60. Molina JM, et al. (2002). Fumagillin treatment of intestinal micro sporidiosis. N Engl J Med, 346, 1963–69. Sharma S, et al. (2011). Microsporidial keratitis: need for increased awareness. Surv Ophthalmol, 56, 1–22. Weiss LM, Becnel JJ (eds) (2014). Microsporidia: pathogens of oppor tunity. Wiley-Blackwell, Chichester.

Revision #1
Created 2026-01-22 16:46:03 UTC by Omar Ayman
Updated 2026-01-22 16:46:03 UTC by Omar Ayman