THERAPY FOR HUMAN GASTROINTESTINAL MICROSPORIDIOSIS

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Abstract. Gastrointestinal microsporidiosis is a major cause of diarrhea and wasting in persons with acquired immune deficiency syndrome (AIDS). Microsporidia demonstrate properties of both true eukaryotes and prokaryotes. The biology of microsporidia makes its elimination from the gastrointestinal tract therapeutically challenging. This organism depends greatly on the host for its energy needs and reproduction; microsporidal spores are impervious to the elements. Microsporidal infection of the gastrointestinal tract, principally with Enterocytozoon bieneusi and Encephalitozoon intestinalis in patients with AIDS has been treated with different medical regimens with variable success. The less common pathogen, E. intestinalis, responds well to albendazole, making it excellent first-line therapy, but such is not the case for E. bieneusi. None of the benzimidazoles has been demonstrated to be efficacious for E. bieneusi. On the other hand, E. bieneusi has shown excellent clinical therapeutic response to either direct action with fumagillin or its analogue, TNP-470, or indirectly by immune enhancement by suppression of the HIV virus with more aggressive, highly effective antiretroviral therapy. Further work is necessary to fully establish proper therapeutic protocols and manage side effects of the treatments. Other promising forms of therapy such as polyamine inhibitors and thalidomide demonstrate certain effectiveness in treatment of microsporidian in vivo (polyamine inhibitors) and in selected cases in vitro (thalidomide). Lack of either sufficiently suggestive or definitive human studies prevents the endorsement of these modes of therapy for treatment of gastrointestinal microsporidiosis at this time.

INTRODUCTION

The importance of microsporidia (Enterocytozoon bieneusi and Encephalitozoon intestinalis) as serious human gastrointestinal pathogens came into focus with the advent of acquired immune deficiency syndrome (AIDS). Therapy of human microsporidial disease has been the subject of active investigation with limited success. The objective of this article is to review and clarify the status of various regimens proposed for the treatment of gastrointestinal microsporidiosis. These regimens are evaluated for their usefulness, and where possible, the proposed mechanism of action is explained.

Biology. Microsporidia demonstrate properties of both true eukaryotes and prokaryotes. Eukaryotic features consist of nuclei surrounded by or enclosed within a nuclear envelope, an intracytoplasmic membrane system, and chromosome separation on mitotic spindles. Prokaryotic features are also present in that microsporidia contain a small subunit RNA of prokaryotic size. Microsporidia also lack mitochondria, peroxisomes, and Golgi apparatus, features which are characteristic of eukaryotes. Certain molecular comparisons described by Keeling and Doolittle, such as the alpha and beta tubulin found in microsporidia, as well as chitin in the spore wall suggest a possible relationship to fungi. Microsporidial development and proliferation are exclusively intracellular using host cells’ synthetic and energetic systems; only the dormant cyst stage is present extracellularly. No evidence of an intermediate host or of a vector transmitting developmental stages of microsporidia has been documented in human infection. Through the environmental triggering of the sporoplasm into the target cell through a polar tube, transmission of spore material takes place. The life cycle of microsporidia is unique with a proliferative mesogonic stage, followed by a sporogonic stage with distinctive spores. These spores consist of a proteinaceous exospore, chitin endospore, and an inner plasma membrane. Spore function enhances survival of the microsporidia in the extra-intestinal environment, with viability of up to 10 years demonstrated in the spores of certain species (i.e., Nozema bombicis). Certain microsporidia develop intracellularly in direct contact with the cytoplasm of the target cells (E. bieneusi) while others have sporophorous vesicles or parasitophorous membranes separating them from the cellular cytoplasm (E. intestinalis).

Intestinal mucosal injury ascribed to microsporidia ranges from normal histologic appearance to gross villous atrophy with chronic inflammation. Enterocytozoon bieneusi preferentially localizes to the apical ¼ to ½ of the villi, while E. intestinalis infects intestinal villous and crypt cells and submucosal macrophages. Parasites are seen in the supranuclear subapical region of the enterocyte near the Golgi apparatus and mitochondria of the host. Decline in mucosal brush-border membrane enzymes has been described. No definitive evidence of cytokines as a factor in the production of diarrhea and cellular injury has been established. In most cases, elevated cytokine levels were not detected in either tissue or intestinal effluent. No discreet cytotoxin has been detected in microsporidia that might be responsible for its pathological or clinical effects.

The biology of microsporidia makes its elimination from the gastrointestinal tract therapeutically challenging. Spores that are impervious to the elements and the organism, microsporidia itself, which employs much of the host for its energy requirements and reproduction present serious obstacles to its clearance and has challenged our best efforts. Successful therapy must exploit some of these more unique aspects of microsporidial physiology.

Therapy. Various types of medicinal regimes have been used to treat gastrointestinal microsporidiosis. Success has varied from ineffective to very promising. These therapies will be discussed here.

Albendazole. Albendazole is a benzimidazole derivative with broad-spectrum antihelminthic and antifungal activity. Albendazole interferes with tubulin polymerization and binds to the colchicine-binding site of beta tubulin. Biochemical and genetic analyses have identified the beta tu-
bulin subunit as the primary benzimidazole target. Beta tubulin residues Cys 165, Phe 167, Glu 198, Phe 200, Arg 242, and Val 268 are predictive of benzimidazole sensitivity. Benzimidazole sensitive microsporidia such as Encephalitozoon hellem, Encephalitozoon cuniculi, and E. intestinalis share a high degree of beta tubulin homology with amino acid sequences which confer sensitivity, primarily Glu gastrointestinal ty.

Clinical studies have demonstrated that albendazole is effective in clearing E. intestinalis from the gastrointestinal tract of AIDS patients, but albendazole is less effective against E. bieneusi, demonstrating only decreased parasite burden and degenerative changes to the parasite. The suggestion was made that albendazole has a parasitostatic effect on E. bieneusi with an incomplete inhibition of microsporidian reproduction. At the present time, the sequencing of the alpha and beta tubulin genes of E. bieneusi has not been accomplished, denying the necessary information that could confirm that resistance is due to amino acid changes in the protein primary sequence, important to impart benzimidazole sensitivity to the organism.

Hepatic metabolism of albendazole proceeds primarily through the production of albendazole sulfoxide, a metabolite 1.7-fold more biologically active, as well as less toxic through the production of albendazole sulfoxide, a metabolite to impart benzimidazole sensitivity to the organism. Other benzimidazoles have been investigated and determined to be either highly active, but poorly absorbed (mebendazole); highly active but highly toxic (nocodazole and parbendazole); or poorly active but highly absorbed (thiabendazole). A drug of potential interest was fenbendazole, which was rapidly absorbed after oral ingestion and quickly metabolized to oxfendazole. Both fenbendazole and oxfendazole were highly active against E. intestinalis, yet not significantly toxic to the cell culture system, e.g., green monkey kidney cells, used for investigation.

In light of the limited effectiveness of albendazole on E. bieneusi infection, extrapolation of the potential effect of the other benzimidazoles on E. bieneusi is problematic. Given the diversity of benzimidazole activity, metabolism, and pharmacokinetics, a derivative with improved anti-E. bieneusi activity may exist or could potentially be developed.

Metrizidazole. Metrizidazole (Flagyl), another benzimidazole first used to treat trichomoniasis and later amebiasis, giardiasis, and anaerobic infections, has been used to treat microsporidiosis. Metrizidazole is administered in an inactive form and enters cells by passive diffusion. The drug is then activated in cells via electron transfer from ferredoxin to its nitro group, resulting in the therapeutically active intermediate. He and others noted that at a concentration of 10 μM, metrizidazole significantly inhibited E. intestinalis spore germination in calcium containing H2O2 germination medium. Potentiation of this effect was noted with the calcium channel blocker nifedipine. The mode of action of metrizidazole on microsporidians is uncertain, but a slowed to inhibited intracellular parasite proliferation and differentiation is seen in vitro with E. intestinalis in cell culture. This suggests that the effect of metrizidazole may be more complex than just inhibiting spore germination of the organism. No in vitro data are available on E. bieneusi.

Clinical studies on the effectiveness of metrizidazole in vitro have been largely disappointing. Eefinck-Schattenkerk and others (unpublished data) treated 19 HIV-positive patients with microsporidian-associated diarrhea with 500 mg of orally administered metrizidazole three times daily. Diarrhea improved in ten and completely resolved in five patients. Twelve of the 15 respondents relapsed within four weeks after the discontinuation of the drug. The effect was considered symptomatic because duodenal biopsies showed microsporidia regardless of the response to therapy. Hing and others (unpublished data) noted that eight E. bieneusi-infected, HIV-positive patients who were treated with metronidazole (400 mg, three times a day, for four to six weeks) had mixed results: one had a sustained and complete response with cessation of diarrhea; two patients had a partial response but relapsed within three months; and five patients failed to respond. Other groups have also reported a lack of therapeutic efficacy with metronidazole. Paromycyn. In vitro examination of paromycyn against the parasite Encephalitozoon cuniculi revealed that it was ineffective against the parasite.

Azithromycin. Hing and others (unpublished data) attempted treatment of microsporidial infections with macrolide azithromycin. The results were unsatisfactory, as azithromycin was not seen as an effective form of therapy. In vitro evaluation of azithromycin against the microsporidian E. cuniculi, a human pathogen closely related to E. intestinalis showed no efficacy in the eradication of the parasite.

Sulfonamides. Trimethoprim-sulfamethoxazole is a potent and widely used antibiotic and antiparasitic agent commonly used against a variety of protozoal organisms especially Pneumocystis carinii. In a study of 97 AIDS patients, Albrecht and others found 21 had microsporida (18 E. bieneusi and 3 E. intestinalis). Fourteen of 18 E. bieneusi infected patients were started on pentamidine as Pneumocystis carinii pneumonia (PCP) prophylaxis and 3 on trimethoprim-sulfamethoxazole for the same reason. Of the 62 patients without microsporida, 19 received trimethoprim-sulfamethoxazole. The prophylaxis results revealed an insignificantly lesser incidence of microsporidiosis with trimethoprim-sulfamethoxazole compared to pentamidine or no prophylaxis. Trimethoprim-sulfamethoxazole displays minimal activity against E. bieneusi and E. intestinalis. In an in vitro system using Maden-Darby canine kidney (MDCK) cells, effectiveness of sulfonamides was evaluated against E. cuniculi. Sulfadiazine and sulfaguanadine were ineffective against E. cuniculi growth and proliferation at both normal pharmacologic and suprapharmacologic concentrations.

Atovaquone. This antiprotozoal drug has been used to treat mild to moderate Pneumocystis carinii infection, as well as ocular and cerebral toxoplasmosis in AIDS patients intolerant to more standard therapies. The mode of action of this drug, while not fully elucidated, may rest with the selective inhibition of mitochondrial electron transport (cytochrome bc1 complex) with inhibition of de novo pyrimidine synthesis. Some protozoa may be unable to salvage preformed pyrimidines like mammalian cells, thus demonstrating preferential susceptibility of the parasite to the drug; bioavailability is low. A marked lipophilicity is noted, and there is a prominent enterohepatic biliary excretion and uptake of the drug. Drug levels in AIDS patients have been noted to be approximately 1/5 to 1/2 that of normal HIV-positive controls.
In a study of eight AIDS patients with diarrhea and microsporidiosis, each was given 750 mg of atovaquone three times a day. Four patients were documented to have *E. bieneusi* by electron microscopy. Patients noted a 9.5-pound weight gain after 1 to 6 months of therapy and a mean decrease in number (mean ± standard deviation [SD]) of daily stools from 10 ± 2.5 to 3 ± 1 over the same time period. Fecal examination showed decreased numbers of microsporidial spores but failed to demonstrate their clearance even with prolonged administration of the drug. Changes in parasite morphology were noted in the jejunal biopsy of one patient; fewer parasites were present in the jejunal biopsy of another. In three other patients, no change in parasite concentration was seen.

Beauvais and others evaluated the effectiveness of atovaquone *in vitro* against *E. cuniculi* grown in cultures with MDCK cells. Atovaquone was ineffective in either altering parasite morphology or eliminating or slowing the growth or proliferation of the microsporidia.

**Furazolidone.** The effectiveness of furazolidone was studied in six patients with *E. bieneusi*-associated diarrhea and AIDS. A course of treatment of 100 mg orally four times a day for 20 days was undertaken in three patients and 100 mg five times per day for 18 days in the other three patients. This drug was well tolerated and neither noticeable clinical side effects nor adverse changes in laboratory parameters were noted. A cessation of diarrhea was noted in all six patients within two weeks along with either cessation (one) or decrease in shedding (five) of parasites in stools. There was a recurrence of symptomatic microsporidiosis in one patient who was initially cleared of infection; retreatment in two cases failed to produce parasite clearances from the stool. Symptomatic relief correlated with decreased fecal shedding of spores and long-term follow-ups was complicated by HIV-related deaths in five of the six patients between 15 to 120 days post-treatment.

**Itraconazole.** This antifungal agent has been used with success in both human and animal (invertebrate) microsporidial infections. In *vitro* experimental models using itraconazole for the human microsporidian *Encephalitozoon hellem* revealed an inhibition of the extension of the spore polar filament. This filament is important in the transfer of the sporoplasm from the spore to the target cell to initiate parasite replication and spore formation. The site of action of itraconazole appears to be a disruption of the integrity of the plasma membrane. Studies have yet to establish a role for itraconazole as a treatment for gastrointestinal microsporidiosis caused by either *E. bieneusi* or *E. intestinalis*. In one case reported by Albrecht and Stillbrink, an AIDS patient developed *E. bieneusi* intestinal infection while on itraconazole therapy for *Histoplasma capsulatum*. Itraconazole was demonstrated to be neither curative nor preventative for intestinal microsporidiosis.

**Polyamines.** Polyamines play an important role in the proliferation and differentiation of pathogenic protozoa. These quaternary ammonium compounds (putrescine, spermidine, and spermine) are important in nucleic acid and protein synthesis. The ornithine decarboxylase (ODC) inhibitor D-L-alpha difluoromethyl ornithine (DFMO) has been effective in the treatment of African sleeping sickness. Polyamine analogues were found to deplete cellular polyamines and to affect their metabolism in pathogenic protozoa.

Coyle and others performed *in vitro* drug inhibition studies using the human microsporidial pathogen *Encephalitozoon cuniculi* grown in RK-13 cells found that the polyamines analogue N,N′-bis (ethyl) norspermine (BE-3-3-3) completely inhibited microsporidial growth. This agent is known to induce spermidine spermine N-acetyl transferase (SSAT) and down-regulation of polyamine metabolism. *Encephalitozoon cuniculi* displayed the ability to not only synthesize polyamines but also to salvage them from the environment. This antagonism of BE-3-3-3 suggests that the salvage pathway is particularly important in the growth and development of *Encephalitozoon cuniculi in vitro*. The ability to effectively block this pathway with a chemical agent suggests a possible therapeutic avenue. While data related to *E. intestinalis* and *E. bieneusi* are lacking, the efficacy of interference of cellular polyamine metabolism in *in vitro* *E. cuniculi* and *in vitro* *Trypanosoma cruzi* with inhibition of the growth and development of the parasites and the improvement in disease status, suggest the possibility that the manipulation of polyamine metabolism in the treatment of these parasites may be a feasible form of clinical therapy.

**Octreotide.** Octreotide is a synthetic cyclic octapeptide analogue of somatostatin. It has been reported effective in the treatment of refractory secretory diarrhea caused by pancreatic cholera syndrome (vipoma) and carcinoid syndrome. Investigators have described its usefulness in the control of AIDS-associated diarrhea.

Specific attention to the role of octreotide therapy in microsporidial diarrhea was addressed by Simon and others in the description of two AIDS patients with diarrhea caused by *E. bieneusi*. One of the two patients responded with reduction of stool frequency and production of a more formed stool; the other patient showed no such response. No gross changes in the presence of the parasite were noted. More extensive data as to the effectiveness of octreotide in the treatment of microsporidia-associated diarrhea in AIDS patients are lacking at the present time.

**Nifedipine.** Calcium has been noted to be a significant component in the germination process of microsporidia. The calcium ion appears to be released from either the polaroplast area of the microsporidial spore as it swells and the polar filament is extruded or via influx from the spore coat. The addition of the calcium channel blocker nifedipine in nanomolar concentration inhibits germination of *Encephalitozoon hellem* and *E. intestinalis* spores *in vitro*. This suggests that voltage-gated calcium channels play a key role in the extrusion of the polar filament. The site of this inhibitory action is believed to be at the cell membrane level. The effect of the Nifedipine is reversible with the washing of the spores overnight which restores their ability to germinate.

The role of calcium is complex in that its removal from the incubation medium inhibits germination in some microsporidial species, while increasing the incubation medium calcium concentration inhibits germination in others. *In vitro* data exist at the present time regarding the use of calcium channel blockers in human AIDS-associated microsporidial disease. Toxic interaction between calcium channel blockers and protease inhibitors used in anti-HIV therapy makes such studies problematic.
**Thalidomide.** Thalidomide has been used for its immuno-suppressive effect in controlling erythema nodosum leprosum and in other immune-mediated diseases, including Behcets, rheumatoid arthritis, and chronic graft versus host reaction. A suppressive effect on HIV replication in monocytes in vitro has been demonstrated. The mechanism of action of thalidomide is uncertain, but a well-described study demonstrates inhibition of tumor necrosis factor alpha (TNF-α) from mononuclear cells by enhancing TNF-α messenger RNA (mRNA) degradation. Elevated TNF-α has been described in diarrhea effluent from AIDS patients with microsporidiosis; other groups have not found this to be the case. Sharpstone and others, in a study of 18 HIV-positive patients with chronic diarrhea caused by *E. bieneusi* and one with *E. intestinalis* gave each patient 100 mg of thalidomide orally at night for 1 month. Seven of the *E. bieneusi* patients had a full remission judged by stool frequency (less than three per day or greater than 70% reduction in stool frequency and solid or semisolid as-similated bowel movement). Three other patients had a partial response as judged by a 50% or greater reduction in baseline stool frequency but with continued weight loss. Villus height-crypt depth ratio improved with therapy. A statistically significant decrease in fecal TNF-α from 17.2 to 8.9 ng/ml and no real evidence of a decrease in the intensity of infection, clinical response, or number of abnormal forms of *E. bieneusi* was noted after treatment. Close evaluation demonstrated microscopic abnormalities in individual microsporidia with the presence of vacuolated nuclei and cytoplasm, megaspores, and meganuclei. An apparent injury to the microsporidia was documented. No injury to the mucosa of the small bowel was noted. The exact mode of action, whether it was antiparasitic or anti-inflammatory, was not readily apparent from the study. At the present time, no other in-depth or long-term studies are available that establish a specific role for thalidomide in microsporidial disease.

**Fumagillin and TNP-470.** Fumagillin, an angiogenesis factor consisting of a water-insoluble antibiotic extracted from *Aspergillus fumigatus* has been noted to inhibit the replication of *E. cuniculi* in vitro and topically to treat ocular infections due to *E. hellem* or *E. intestinalis*. This agent was also thought to inhibit RNA synthesis. In a study of ten drug regimens used in the treatment of *E. bieneusi*, only patients treated with 20 mg fumagillin three times daily resolved their infection on both stool and intestinal biopsy evaluation. Clear-cut benefit was not seen in three of the four patients taking fumagillin due to co-infections with *Cryptosporidium parvum*, *Isospora belli*, and Cytomegalovirus. One patient received mild relief of symptoms, while the fourth not only resolved the infection and the diarrhea, but also gained weight back to baseline. Important to note was that all patients receiving fumagillin developed thrombocytopenia with Week 2, becoming more severe by Week 3, but completely resolved in 8–14 days following cessation of therapy. No bleeding or purpura was noted during the period of thrombocytopenia; two patients experienced neutropenia as well. A similar finding has been seen in cancer patients treated with fumagillin in doses ranging from 400 to 3,550 mg. This adverse effect is felt to be a direct toxic effect on the megakaryocyte. None of the patients received HIV-protease inhibitors associated with immune-mediated microsporidial clearance.

An analog of fumagillin, TNP-470, has been active in the inhibition of tumor growth by anti-angiogenesis in vitro but is less toxic in vivo in laboratory animals. Didier examined the role of TNP-470 as an antimicrosporidal agent against the microsporidia *E. intestinalis* and *Vittaforma corneae*. MIC₅₀ in *E. intestinalis* and *V. corneae* were 0.35 ± 0.21 and 0.38 ± 0.11 ng/ml, respectively. The mechanism of action of TNP-470 on microsporidial replication is based upon its binding to methionine aminopeptidases and inhibition of RNA synthesis. In tumor cells treated with TNP-470, mRNA encoding for cyclin D1 was significantly lower than in non-treated human umbilical cells. Whether this effect depends either directly on the microsporidia or indirectly through the host cell is yet to be determined. *In vivo* studies have shown that TNP-470 does not cause a decline in CD4 T cells or a rise in human immunodeficiency virus p24 levels. Larger *in vivo* studies are needed to evaluate its efficacy against microsporidial disease in human systems.

**Antiretroviral therapy.** The subject of antiretroviral therapy with reverse transcriptase inhibitors and the newer group of drugs, the protease inhibitors, has presented not only the potential for opportunistic infection prophylaxis by enhancement of immune competency, or at least its preservation, by HIV suppression, but possibly a therapy as well. Coquel and others noted a remission of intestinal microsporidiosis in AIDS patients placed on highly active antiretroviral therapy.

In a small study of five patients with chronic microsporidiosis—three patients with cryptosporidiosis and one with a mixed infection—Carr and others noted promising results with aggressive retroviral therapy. All microsporidia patients ceased having diarrhea, gained a median of 15 kg in weight, and became biopsy negative for the parasite. A question of dense CD8 lymphocyte and macrophage infiltration in these patients may presage potential relapse with falling CD4 counts and progression of the patients’ HIV disease. In a larger study, Benhamou and others (unpublished data) evaluated the course of chronic intestinal microsporidiosis and cryptosporidiosis in patients undergoing protease inhibitor adjunctive therapy to two nucleoside analogues using either ritonavir or indinavir. Fifteen patients, nine with cryptosporidiosis and six with microsporidiosis, were followed between two to 24 months before the initiation of protease inhibitory therapy. Patients were under triple therapy for a mean time of 3.8 ± 1.4 months; of the thirteen patients, diarrhea disappeared in 12 with this therapy. Mean CD4 lymphocyte counts increased from 56 ± 56/μl to 115 ± 80/μl (*P < 0.01*); HIV viral levels in nine patients declined from 312,745 ± 482,856 copies/ml to 5,788 ± 9,283 copies/ml (*P < 0.05*). Clearance of *C. parvum* and microsporidia was noted in 85% of the cases, with their disappearance correlating with clinical improvement.

In a study of 37 patients with microsporidiosis, Conteas and others found a remission rate of over 40%. Correlation with remission was seen with a CD4 lymphocyte count greater than 100/μl, greater than two anti-HIV medications, and the use of a protease inhibitor. The available HIV viral loads obtained from patients who cleared their infection were low, consistent with good viral suppression. A large
A epidemiological study of AIDS patients with diarrhea in the Southern California area revealed a remarkable decline from 1993 to 1996, in prevalence of microsporidia in these patients. Temporally, the greatest drop was noted in 1995 and 1996 which is a period significant for both widespread use of multidrug, anti-HIV therapy, and the introduction of, wide acceptance of, and use of protease inhibitors. These studies further validated the importance of HIV virus suppression and immune preservation for the clearance of this parasite.

CONCLUSIONS

Microsporidal infection of the gastrointestinal tract primarily with *E. bieneusi* and *E. intestinalis* in patients with acquired immunodeficiency syndrome has long been considered untreatable, progressive, and often fatal. The less common pathogen, *E. intestinalis*, responds well to albendazole, making it excellent first-line therapy, but such is not the case for *E. bieneusi*. None of the benzimidazoles has been demonstrated to be efficacious for *E. bieneusi*. On the other hand, *E. bieneusi* has shown excellent clinical therapeutic response either to the direct action of fumagillin or its analogue, TNP-470, or indirectly by immune enhancement by suppression of the HIV virus with more aggressive, highly effective antiretroviral therapy. These therapies hold the greatest promise in eradicating *E. bieneusi* and either are the standard of care for microsporidal therapy (antiretroviral therapy), or will be (fumagillin TNP-470). Further work is necessary to fully establish proper therapeutic protocols and manage side effects of these treatments. Other forms of promising therapy such as polyamine inhibitors and thalidomide demonstrate a certain effectiveness in treatment of microsporidia in vitro (polyamine inhibitors) and in selected cases in vivo (thalidomide). Lack of sufficiently suggestive or definitive human studies prevent the endorsement of these modes of therapy in treating gastrointestinal microsporidiosis at this time. Our description of the falling prevalence of gastrointestinal microsporidiosis in Southern California may complicate the quest for definitive antimicrosporidal therapy, while at the same time demonstrating the importance of antiretroviral therapy for not only HIV infection but microsporidial infections as well.

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REFERENCES


