

# HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE OPPORTUNISTIC INFECTIONS IN PATIENTS WITH HIV AND AIDS Fungal and Parasitic Infections

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**ABSTRACT :** Since the advent of highly active anti-retroviral therapy (HAART), the incidence of specific fungal and parasitic opportunistic infections as observed in HIV disease has been in decline. However, in many parts of the world, and in areas where access to HAART is limited, these specific opportunistic infections are still observed in HIV patients. In this manuscript, we review the epidemiology, clinical manifestations, diagnosis, and treatment of common fungal and parasitic opportunistic infections.

## 1. PNEUMOCYSTIS PNEUMONIA

*Pneumocystis jiroveci*, previously known as *Pneumocystis carinii*, is a ubiquitous organism that is currently classified as a fungus, but which shares many characteristics with that of protozoal organisms. Exposure and primary infection from this organism usually occur within the first few years of life. Reactivation or primary infection in the immunocompromised host can lead to development of its most common presentation, *Pneumocystis pneumonia* (PCP).

The incidence of PCP has decreased since the advent of PCP prophylaxis regimens and highly active anti-retroviral therapy (HAART). Nevertheless, it remains one of the most common opportunistic infections. The main risk factor for development of PCP in patients with HIV is a CD4 T-lymphocyte count of  $< 200/\mu\text{L}$ , as up to 90% of cases of PCP occur in this setting. Other risk factors include previous history of PCP, oral candidiasis, other history of an AIDS-defining illness, and history of unexplained fever for  $> 2$  weeks [1].

Patients with HIV infection should receive prophylaxis against PCP if they have history of oropharyngeal candidiasis, or if they have a T-lymphocyte count  $< 200/\mu\text{L}$ . Trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for primary prophylaxis of PCP in patients infected with HIV [2]. Common regimens include one double-strength tablet of TMP-SMX daily or

three times weekly. Daily administration also has benefit in protection against toxoplasmosis. Alternative prophylactic regimens are included in Table I.

The clinical manifestations of PCP are widespread and nonspecific, and include nonproductive cough, fever, and substernal chest discomfort, and symptoms of progressive dyspnea on exertion [3]. Symptoms usually develop slowly and are progressive. Physical examination findings are nonspecific. Rales may be auscultated during episodes of tachypnea or after exertion [4].

Specific laboratory information may help in diagnosis of PCP. Arterial blood gas reveals hypoxemia with an elevated alveolar-arterial gradient. Chest X-ray findings may include diffuse bilateral interstitial infiltrates, often progressing to an alveolar pattern. However, in approximately 10% of cases, chest X-ray findings may be normal. A characteristic "ground-glass" appearance is noted on high-resolution computer tomography scanning [3].

Definitive diagnosis relies upon histopathologic demonstration of *P. jiroveci* organisms directly from lung tissue, bronchoalveolar lavage, and induced sputum specimens [4]. Bronchoalveolar lavage (BAL) is currently the procedure of choice in recovery of organisms, with sensitivity of approximately 90-99%. Spontaneously produced sputum has very low sensitivity. Sensitivity utilizing induced sputum specimens may approach approximately 50-95%, depending on collection technique and skill of the microbiologist or pathologist interpreting the specimen [3-4]. The sensitivity of both BAL and induced sputum techniques may be decreased in patients who have received primary prophylaxis [3].

Monoclonal antibody direct immunofluorescence (DIF) staining is specific for *P. jiroveci* cysts and trophozoites, thus helping to distinguish the organism from other morphologically similar organisms such as *Candida* species. In resource-poor settings, wet mount preparations of BAL fluid samples may detect characteristic "honeycomb" structures with direct microscopy, having a sensitivity of approximately 80% [5]. Molecular amplification techniques via polymerase chain reaction (PCR) are becoming more available, however, these techniques also may produce false positive results in asymptomatic carriers [3].

The treatment of choice for PCP is TMP-SMX, even for those patients who develop the disease while on primary prophylaxis with the drug. Those patients with mild-to-moderate disease can safely receive oral outpatient therapy. Patients with moderate-to-severe disease, defined as a room air  $\text{pO}_2 < 70$  mmHg or an alveolar-arterial gradient  $> 35$  mmHg should also receive corti-

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**TABLE I**  
ALTERNATIVE PCP PROPHYLACTIC REGIMENS FOR PATIENTS UNABLE TO TOLERATE TMP-SMX [2-4]

ALTERNATIVE PROPHYLACTIC REGIMEN	Remarks
■ DAPSONE	Inexpensive as compared to atovaquone or aerosolized pentamidine
■ DAPSONE + PYRIMETHAMINE	Confers more protection against toxoplasmosis than aerosolized pentamidine
■ ATOVAQUONE SUSPENSION	May be more tolerable than dapsone Expensive as compared to TMP-SMX or dapsone
■ AEROSOLIZED PENTAMIDINE	Once per month administration Expensive as compared to TMP-SMX or dapsone

costeroids concurrently, preferably initiated within 72 hours of starting TMP-SMX therapy [4].

Secondary prophylaxis with TMP-SMX can be safely discontinued when CD4 T-lymphocyte count is > 200/ $\mu$ L for at least 3 months after immune reconstitution with HAART. Secondary prophylaxis should be re-initiated if CD4 T-lymphocyte count becomes < 200/ $\mu$ L or if the patient develops recurrent PCP with a CD4 T-lymphocyte count > 200/ $\mu$ L [4-6].

Emergence of *P. jiroveci* resistance to sulfa medications through point mutations in the dihydropteroate-synthase (DHPS) gene has been documented, however, the clinical significance of these mutations is uncertain [3].

## 2. TOXOPLASMA ENCEPHALITIS

*Toxoplasma gondii* is a protozoal organism that infects a wide range of hosts. Although infection can occur in almost any organ, in HIV-infected patients, the most common manifestation of *T. gondii* infection is encephalitis [7]. Similarly to other opportunistic infections, the incidence of *T. gondii* encephalitis has decreased dramatically since the advent of HAART regimens.

Transmission of *T. gondii* organisms occur as domestic cats shed oocysts into the environment [7]. Humans acquire infection through ingestion of contaminated water and food, typically undercooked or raw meat [8]. Once *T. gondii* oocysts or tissue cysts are ingested, they are phagocytosed by intestinal epithelial cells or directly invade through intestinal mucosa. Direct human-to-human transmission, other than from mother to fetus, has not been recorded [7].

Disease is caused almost exclusively through reactivation of latent tissue cysts. *T. gondii* encephalitis usually occurs in patients with CD4 T-lymphocyte counts < 50/ $\mu$ L. The clinical presentation of *T. gondii* encephalitis is varied, and may include headache, fever, and acute mental status change [4]. Headache is usually bilateral, severe, and persistent, responding poorly to analgesics [7]. Focal neurologic signs include hemiparesis, speech abnormalities, cranial nerve abnormalities, and cerebellar findings. Meningeal signs are rare [8]. Progression of disease may lead to convulsions and coma [7].

*Toxoplasma* encephalitis is the most common cause of focal CNS lesions in AIDS patients [9]. Other etiolo-

gies of focal neurologic lesions must be considered, including *Cryptococcus neoformans*, *Aspergillus* species, *M. tuberculosis*, *Nocardia* species, bacterial brain abscess, lymphoma, and progressive multifocal leukoencephalopathy [8].

*T. gondii* infection is diagnosed in a variety of ways. Detection of IgG antibody against *T. gondii* should be pursued in all immunocompromised patients. It must be noted that a positive IgG antibody is not helpful, as most HIV patients are seropositive. A negative IgG antibody may help to rule out *T. gondii* infection when viewed in conjunction with other clinical data [4]. Specific techniques for detection of antibody to *T. gondii* include indirect fluorescent antibody assay (IFA), direct and latex agglutination tests (LAT), enzyme-linked immunosorbent assay (ELISA), and immunosorbent agglutination assay test (IAAT). IFA, IAAT, and ELISA also detect IgM antibodies, indicating recent infection [7]. It may take up to seven days after reactivation of infection for IgM to become positive.

Whereas PCR testing is very specific for *T. gondii*, sensitivity is low (< 50%) when testing is performed on cerebrospinal fluid [4]. False negative results may also occur if empiric treatment for *T. gondii* infection is initiated before a specific sample is obtained. If brain biopsy is pursued, PCR testing may not differentiate between *T. gondii* encephalitis and chronic dormant infection [8].

Visualization of tachyzoite forms in tissue or cerebrospinal fluid smears can also aid in histologic diagnosis. Immunoperoxidase staining, using specific antisera to *T. gondii*, is both sensitive and specific for the organism [8].

MRI and/or CT imaging is useful in diagnosis of *T. gondii* encephalitis. These imaging modalities should be considered even if the patient does not display focal neurologic deficits. Characteristic radiologic findings include multiple brain abscesses. Pathologically, *T. gondii* causes focal necrosis of brain matter, and thus these areas of necrosis may become calcified, leading to characteristic "ring-enhancing" lesions on neuroimaging. The cerebral hemispheres are almost universally involved in AIDS patients with *T. gondii* encephalitis, and predilection for the basal ganglia has also been noted on autopsy of AIDS patients [8].

It is accepted clinical practice to begin empiric treatment for *T. gondii* encephalitis for patients with multiple

**TABLE II**  
ALTERNATIVE *TOXOPLASMA* ENCEPHALITIS TREATMENT REGIMENS [4, 8]

ALTERNATIVE TREATMENT REGIMEN	Remarks
■ PYRIMETHAMINE + CLINDAMYCIN + LEUCOVORIN	Utilized in patients unable to tolerate sulfonamides or who fail first-line therapy
■ TMP-SMX	May be equivalent in efficacy to pyrimethamine/sulfadiazine as shown in a small randomized trial

“ring-enhancing” lesions on MRI in those patients with a CD4 T-lymphocyte count < 200/μL, with subsequent observation for clinical and radiographic improvement. For those patients with a single “ring-enhancing” lesion on MRI, a negative IgG antibody result, or without radiologic or clinical improvement on empiric treatment, brain biopsy should be considered [9].

The initial treatment of choice for presumed *T. gondii* encephalitis is a combination of pyrimethamine/sulfadiazine. Leucovorin is used in conjunction with this regimen to counteract myelosuppression caused by pyrimethamine. Alternative treatment regimens are described in Table II.

This acute phase treatment should be continued for at least six weeks, noting radiographic and clinical improvement. A longer treatment course may be required if there is an incomplete response after six weeks of therapy. Maintenance therapy in the form of secondary prophylaxis is usually instituted at half the dose of acute phase treatment. Secondary prophylaxis should be discontinued when the patient’s CD4 T-lymphocyte count is > 200/μL and HIV peripheral blood viral load has been controlled for at least 6 months [8]. Of note, anti-convulsants should only be instituted if the patient has a history of seizure, and should be continued at least through the acute phase treatment [4].

### 3. OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

Oropharyngeal (OPC) and esophageal candidiasis are common opportunistic infections in patients with HIV infection. Similar to most opportunistic infections, the incidences of both conditions have declined dramatically since the advent of HAART regimens [10]. *C. albicans* is the most common *Candida* species isolated from the mucous membranes of HIV-infected patients [11].

OPC is a marker for advanced immunosuppression and usually occurs in patients with CD4 T-lymphocyte counts < 200/μL [4]. Elevated plasma HIV-1 RNA levels appear to be a better predictor of HIV-related OPC than CD4 T-lymphocyte counts in the early stages of HIV disease [11]. Many patients are asymptomatic, but altered taste sensation can occur.

*Candida* species are normal inhabitants of the gastrointestinal tract. Thus, most disease is caused by overgrowth of organisms in the setting of an immunosuppressed state [10]. Diagnosis of OPC is usually made

by its characteristic appearance, consisting of painless white plaques of the tongue and buccal mucosa, and occasional erythematous plaques on the palate and tongue. Angular cheilosis may also be noted. In contrast to oral hairy leukoplakia, the plaques observed in OPC can usually be scraped off of the oral mucosa with a tongue blade or other device [4]. Recovery of organisms in diagnosis of OPC is not essential.

Patients with esophageal candidiasis usually have concurrent OPC, although isolated cases may occur. Symptoms of esophageal candidiasis include dysphagia, odynophagia, retrosternal burning pain, and fever, although up to 40% of patients may be asymptomatic [10]. A presumptive diagnosis of esophageal candidiasis may be made if these symptoms are present in the setting of OPC.

Confirmation of diagnosis can be made with upper endoscopy, revealing white plaques which may progress to superficial ulceration of the esophageal mucosa [4]. Endoscopy is not required unless a patient fails to improve with appropriate anti-candidal therapy, and in this case, direct examination may help to rule out other causes of esophagitis, such as CMV. As in the case of OPC, histologic examination and culture from endoscopic specimens may be useful in identifying azole resistant *Candida* species [10].

Treatment options for OPC are included in Table III. Treatment of esophageal candidiasis involves utilization of systemic therapy. A therapeutic trial with oral fluconazole is acceptable, observing for resolution of symptoms within seven days of therapy [12]. If symptoms are refractory to this initial treatment, endoscopy may be warranted to rule out other common causes of esophagitis. Total duration of therapy is typically 14-21 days, but may be needed indefinitely [11]. As observed in OPC, itraconazole and ketoconazole capsules are inferior to oral fluconazole, whereas itraconazole solution appears to be equivalent in efficacy [12].

### 4. CRYPTOCOCCAL MENINGITIS

*Cryptococcus neoformans* is an environmental fungus which is found worldwide in soil that has been contaminated with pigeon and other bird stool. Serological studies have shown that most individuals are likely exposed to *C. neoformans* within the first 2 years of life. The route of acquisition appears to be through the inhalation of small yeast forms or basidiospores via environmental

exposure. A primary pulmonary infection may subsequently develop, leading to eventual eradication or containment of organisms within pulmonary granulomata. Some patients with this initial infection may be asymptomatic, whereas others may develop a severe pneumonia. Depending on specific host factors, *C. neoformans* may also subsequently disseminate with predilection for the brain and meninges [13].

The most common manifestation of cryptococcosis in HIV patients is cryptococcal meningitis. Similarly to other opportunistic infections, the incidence of cryptococcal meningitis has decreased dramatically due to the advent of HAART.

The majority of cases of cryptococcal meningitis occur in HIV patients with a CD4 T-lymphocyte count of < 100/ $\mu$ L [14]. Clinical features include headache, fever, malaise, lethargy, and altered mental status, presenting over a course of several days to several weeks [13]. Classic meningeal signs of meningismus and photophobia occur in approximately one fourth to one third of cases [4]. Other signs may include papilledema due to increased intracranial pressure, cranial nerve palsies, vision or hearing loss, and gait ataxia [13].

There are no pathognomonic findings on brain imaging. Computed tomography imaging of the brain may reveal hydrocephalus, cerebral edema, or meningeal enhancement. Single or multiple intracranial nodules, known as cryptococcomas, may also be visualized within the brain parenchyma, basal ganglia, midbrain, and meninges on CT imaging or MRI [13].

Direct or indirect identification of *C. neoformans* or its antigenic constituents is the mainstay of diagnosis of cryptococcal meningitis. India ink staining is positive upon direct CSF examination in approximately 80% of patients [15]. In contrast, cryptococcal antigen testing of both serum and CSF samples have a sensitivity and specificity > 95% in patients with cryptococcal meningitis [16]. A serum titer of > 1:4 is very specific for the organism, and testing typically results in higher titers [13, 16].

Examination of CSF may reveal a low to normal white cell count, elevated CSF total protein, and low

CSF glucose levels. Culture of CSF or serum may result in white mucoid colonies within 48-72 hours of sampling [13]. Sensitivity of culture of *C. neoformans* approaches 75% [4].

The treatment of choice for patients with cryptococcal meningitis includes an induction regimen consisting of intravenous amphotericin B in combination with oral flucytosine for a 2-week course [11, 16]. Most experts recommend an amphotericin B dosage of 0.7 mg/kg/day [14], with a recommended flucytosine dosage of 100 mg/kg divided into four total doses per day [16]. Amphotericin B lipid complex formulations have been shown to be at least as efficacious as standard amphotericin B preparations, with the added benefit of reduced toxicity [14].

After induction therapy is complete, consolidation therapy with oral fluconazole 400 mg daily is initiated for an additional 8 weeks or until CSF cultures are sterile [16]. After this treatment course is completed, secondary prophylaxis is continued with oral fluconazole 200 mg daily [14].

Current recommendations suggest that it may be safe to discontinue secondary prophylaxis if patients remain asymptomatic after primary treatment and have a sustained increase in CD4 T-lymphocyte count > 100-200/ $\mu$ L after HAART [4].

Itraconazole appears to be less efficacious than fluconazole in both consolidation therapy and in secondary prophylaxis regimens, and is only recommended if fluconazole is intolerable [16]. This may be in part due to the fact that plasma drug concentrations of itraconazole have been shown to be uniformly lower than that of fluconazole in comparison, and that itraconazole has relatively low penetration into the CSF of humans [17].

Control of increased intracranial pressure is generally advocated [14, 16]. Initial intervention includes daily percutaneous lumbar puncture, followed by cerebrospinal fluid shunting if refractory to these measures. Medical treatment with mannitol or acetazolamide has not been shown to be effective in managing increased intracranial pressure [13].

**TABLE III**  
TREATMENT REGIMENS FOR OROPHARYNGEAL CANDIDIASIS [4, 11, 12]

TREATMENT REGIMEN	Remarks
■ NYSTATIN LOZENGES OR SUSPENSION	Topical modalities
■ CLOTRIMAZOLE TROCHES	Relapse may occur sooner as opposed to oral fluconazole
■ AMPHOTERICIN B SUSPENSION	
■ ORAL FLUCONAZOLE	Is at least equal in efficacy and may be superior to topical therapy May be better tolerated than topical therapy Often first-line agent
■ ITRACONAZOLE CAPSULES	Inferior in efficacy as compared to oral fluconazole due to variable absorption
■ KETOCONAZOLE CAPSULES	
■ ITRACONAZOLE SOLUTION	Equivalent in efficacy as compared to oral fluconazole Less well-tolerated as compared to oral fluconazole

## 5. CRYPTOSPORIDIOSIS

*Cryptosporidium* species are intracellular parasites which infect the gastrointestinal epithelium to produce diarrhea in both immunocompetent and immunosuppressed individuals [18]. *C. parvum* and *C. hominis* are the most common of the cryptosporidial species which infect patients with HIV [19]. As observed in patients with clinical manifestations of diarrhea, cryptosporidiosis has been noted to be the cause in approximately 14% of HIV patients in developed countries, and approximately 24% of HIV patients in developing countries [18].

Human-to-human spread of oocysts, particularly via the fecal-oral route, is a frequent mode of transmission. Approximately 1-3% of the general population in developed countries, and up to 10% of the general population in developing countries can be excreting oocysts at any given time. Zoonotic transmission is also common, with sheep and cattle being the most important reservoirs of human disease [18].

Contaminated water is also an important reservoir in transmission of cryptosporidiosis. Oocysts are resistant to the most common methods of water treatment, even chlorine-treated and filtered drinking water [18]. Particular attention to proper preparation of drinking water is thus a main focus in prevention of cryptosporidiosis [19].

Humans are infected through the ingestion of cryptosporidium oocysts [4]. These oocysts subsequently release sporozoites, which invade gastrointestinal epithelium, particularly in the jejunum and terminal ileum. Depending upon the isolate, infection may occur from ingestion of as few as 9 to 1024 oocysts. Extraintestinal infection, particularly of the biliary tract, is more common in patients with AIDS than in immunocompetent individuals. Biliary cryptosporidiosis is particularly observed in AIDS patients with a CD4 T-lymphocyte count < 50/ $\mu$ L [20].

Intestinal cryptosporidiosis is associated with impaired absorption and enhanced secretion, leading to a profuse watery diarrhea. The diarrhea typically contains mucous but rarely contains blood or leukocytes. The frequency of stools, depending on severity of disease, may be up to 10 per day [18]. Associated symptoms include crampy abdominal pain, nausea, vomiting, and anorexia. Fever, malaise, and weight loss may also occur [20].

There are four main clinical patterns of intestinal cryptosporidiosis in patients with AIDS. Approximately 4% of patients have no change in bowel habits. A fulminant infection, characterized by passage of at least two liters of watery stool per day, is present in approximately 8% of AIDS patients. Fulminant infection only occurs in patients with a CD4 T-lymphocyte count < 50/ $\mu$ L [18].

A transient infection occurs in approximately 29% of patients. These patients typically have diarrhea for less than two months, after which *cryptosporidium* species become absent from stool specimens and clinical symp-

toms resolve. A majority of AIDS patients (60%) will develop a chronic diarrhea that is present for at least two months, in which the organism is persistently detected in stool specimens [18].

Diagnosis of intestinal cryptosporidiosis involves detection of oocysts or antigenic components in clinical specimens. A modified acid-fast stain can differentiate oocysts from stool yeasts which are similar in shape and size [4]. This test should be specifically requested, as it is not typically performed with routine ova and parasite examination [20]. Enzyme-linked immunosorbent assays or direct immunofluorescence methods have improved sensitivity and specificity of detection of oocysts [18].

Preventative measures should also be utilized in AIDS patients. They should be advised to boil and subsequently cool drinking water, even if the original source of the water is bottled [19]. Immunocompromised patients are advised to use extensive handwashing techniques, and to avoid stool from animals or humans [20].

Infection of the biliary tract by *cryptosporidium* species can occur in up to 26% of AIDS patients with intestinal cryptosporidiosis. Symptoms of biliary cryptosporidiosis may include right upper quadrant pain, nausea, emesis, and fever. Alkaline phosphatase is usually elevated. Ultrasonography of the biliary tree may aid in diagnosis. In approximately 50 to 60% of patients, ERCP will reveal intrahepatic sclerosing cholangitis, with or without associated papillary stenosis. If papillary stenosis is observed, decompression via sphincterotomy may provide symptomatic relief [18].

The preferred treatment for intestinal cryptosporidiosis is immune reconstitution with HAART [4]. Utilization of protease inhibitors as a component of HAART may also have some benefit independent of immune reconstitution, as these agents reduce *C. parvum* sporozoite host cell invasion and parasite development *in vitro* [19]. Supportive treatment with control of diarrheal symptoms and rehydration should be initiated in addition to HAART [4].

There is no reliable medical treatment for cryptosporidiosis, as a number of agents have been evaluated without success [18]. Nitazoxanide, an antiparasitic agent, has been studied in AIDS patients with a CD4 T-lymphocyte count > 50/ $\mu$ L. Depending on dosage used, a randomized controlled study has shown parasite clearance rates of 63-67% as compared to placebo [21].

## 6. ISOSPORIASIS, CYCLOSPORIASIS, AND MICROSPORIDIOSIS

*Isoospora belli* is an obligate intracellular parasite which infects solely humans [22-23]. Transmission is assumed to occur through ingestion of infective oocysts from contaminated food and water [22]. Isoosporiasis is observed worldwide in patients with AIDS, but is particularly concentrated in developing countries [24].

Isoosporiasis is characterized by an intermittent chron-

ic secretory diarrhea lasting approximately three days to three weeks. The clinical manifestations are indistinguishable from cryptosporidiosis, and may also include abdominal pain, nausea, emesis, and fever [24]. Prolonged courses of illness are associated with dehydration and malabsorption. Despite treatment, recurrence of the infection in AIDS patients is common, particularly if immune reconstitution is not established [22].

Diagnosis of isosporiasis involves identification of oocysts in stool through acid-fast staining or wet mount techniques. Because oocyst shedding is intermittent, several stool examinations may be necessary for diagnosis. The treatment of choice for isosporiasis is a seven- to ten-day course of trimethoprim-sulfamethoxazole (TMP-SMX), one double-strength tablet per day [24]. Fluoroquinolones, typically ciprofloxacin, can be used for patients intolerant of TMP-SMX. Nitazoxanide may also be an alternative treatment. Because of the high relapse rate in AIDS patients, secondary prophylaxis with TMP-SMX is recommended until immune reconstitution is achieved (23).

*Cyclospora cayatanensis* is a protozoan parasite that is typically observed with fruit-associated foodborne outbreaks, but which also causes diarrheal illness in immunocompromised patients. It is thought to be transmitted through contaminated water. Infection usually occurs during warm and rainy seasons [22].

Clinical symptoms of cyclosporiasis are similar to that observed in isosporiasis and cryptosporidiosis, including an explosive, watery diarrhea occurring one to 11 days after ingestion of oocysts. Diarrhea in AIDS patients, unlike in immunocompetent individuals, may be prolonged and recurrent. Infection of the biliary system may also occur [24]. Associated symptoms include abdominal cramping, fatigue, anorexia, nausea, emesis and weight loss [22].

As in isosporiasis, identification of *Cyclospora* cannot be obtained through routine stool ova and parasite examination. A modified acid fast staining technique, auramine-phenol, or modified trichrome are usually required for diagnosis [23]. Infection in immunocompromised patients usually responds to a seven-day course of TMP-SMX, one double-strength tablet per day. Alternative regimens for patients intolerable to TMP-SMX include a ten-day course of ciprofloxacin 500 mg twice daily [24].

Microsporidia are a group of intracellular parasites [22-23]. The species *Enterocytozoon bienewisi* causes the majority of infection in association with HIV disease. Infection occurs most often in patients with a CD4 T-lymphocyte count < 50/μL [25].

Acquisition of the organism is thought to occur through ingestion of microsporidia spores, typically from contaminated water or zoonotic sources. Clinical symptoms of microsporidiosis are varied, depending upon the infecting species. In the case of *E. bienewisi* infection, manifestations typically include a chronic diarrhea and cholangitis [4]. Asymptomatic carrier states

also exist [25]. Disseminated disease and involvement of other organs has also been reported.

Microsporidiosis is primarily diagnosed through examination of stool and urine specimens by light microscopy. Definitive diagnosis requires ultrastructural examination via electron microscopy or molecular techniques such as PCR. Endoscopy and small intestinal biopsy may be required if stool examination is negative and if symptoms continue [25].

There is no effective antimicrosporidial treatment that is proven and established. *E. bienewisi* microsporidiosis is difficult to eradicate, and the treatment of choice is immune reconstitution with HAART. Fumagillin and albendazole have shown some minimal activity in clinical trials [22]. A 60-day course of nitazoxanide has also recently been studied as a possible alternative treatment, however, response was poor in patients with low CD4 T-lymphocyte count [4]

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