

Initiation and discontinuation of prophylaxis for Opportunistic Infections can be found in *Prevention of Secondary Disease: Preventive Medicine*.

I. PNEUMOCYSTIS JIROVECHII

Pneumocystis jirovecii pneumonia (PCP), or pulmonary pneumocystosis and formerly *P. carinii* pneumonia, is classified as a fungus based upon its genome. However, it is included here with the parasitic infections because the treatment considerations for PCP are similar to those for parasitic infections.

PCP can cause severe pneumonia in HIV-infected individuals, and although PCP is highly preventable, it is still encountered in the HIV-infected population. In patients who are not yet receiving care, PCP may be seen as the HIV/AIDS-presenting illness. For patients receiving PCP prophylaxis, PCP can result from failure of or non-adherence to the prophylactic regimen.

A. Presentation

RECOMMENDATION:

Clinicians should place all hospitalized HIV-infected patients with respiratory symptoms and/or abnormal chest x-rays in respiratory isolation in a negative pressure room until active pulmonary tuberculosis is excluded or an alternative diagnosis that accounts for the abnormalities is established. (I)

Between 60% and 80% of patients with AIDS will develop PCP if they are not receiving prophylaxis. Predictors of risk for PCP include current CD4 cell counts <200 cells/mm³ or $\leq 14\%$ of total lymphocytes. PCP may be seen in patients with higher CD4 counts who have thrush or unexplained fever of at least 2 weeks' duration.

Characteristics of PCP include several days to weeks of progressive dyspnea on exertion and/or nonproductive cough often accompanied by fever. Auscultation of the chest is usually normal. Chest x-ray typically demonstrates diffuse bilateral interstitial infiltrates usually without consolidation; however, normal chest x-rays may be seen in up to 30% of patients. Computed tomographic (CT) scan of the chest may help detect PCP in patients with a normal chest x-ray with "ground glass" appearance.

PCP may be complicated by bullous disease and pneumothorax. The degree of hypoxemia at presentation is of prognostic value; it establishes the severity of the illness and dictates the treatment modality (see Section C: *Treatment*).

Pulmonary tuberculosis in HIV-infected persons often presents in an atypical fashion that may mimic PCP. Patients presenting with these symptoms or any other respiratory signs or symptoms should be placed in appropriate respiratory isolation until results from concentrated acid-fast bacillus (AFB) smears from either sputum or bronchoalveolar lavage (BAL) fluid are negative or alternative diagnosis is established.

B. Diagnosis

RECOMMENDATIONS:

Clinicians should obtain evidence of the characteristic organisms in induced sputum, bronchoalveolar lavage fluid, or tissue specimen. (III)

Clinicians should obtain a bronchoalveolar lavage if induced sputum is negative or unavailable. (III)

Laboratory abnormalities include hypoxemia, especially exercise-induced oxygen desaturation measured by pulse oxymetry or arterial blood gases. Serum lactate dehydrogenase (LDH) is usually elevated. Neither of these findings, however, is specific for PCP. Definitive diagnosis requires demonstration of the organism in induced sputum, BAL, or lung tissue. Visualization of the cysts may be accomplished by silver stain or fluorescent antibody, or trophozoites may be visualized with modified Giemsa or Hemacolor stains. Monoclonal fluorescent antibody techniques may improve sensitivity. PCR of clinical specimens may also support the diagnosis. Induced sputum is less invasive than BAL, and most clinicians would obtain induced sputum when available before BAL, unless the patient is very ill and prompt diagnosis is required. Protocols for adequate sputum induction with hypertonic saline should be followed, and obtained specimens should be processed within 2 hours of collection. Both BAL and induced sputum induction should be performed using respiratory precautions against transmission of airborne pathogens including tuberculosis.

BAL is highly sensitive in patients who are not receiving PCP prophylaxis and is the preferred diagnostic procedure. However, empiric treatment for mild disease may be reasonable for patients who can successfully complete treatment and for whom close clinical follow-up is available. Occasionally, transbronchial biopsy or open-lung biopsy is required to make the diagnosis, particularly in patients treated with aerosolized pentamidine prophylaxis in whom BAL may yield no organisms. Negative results of induced sputum do not exclude the diagnosis of PCP and should be followed by bronchoscopy for definitive diagnosis. This has become increasingly important because clinical and technical confidence in the diagnosis of PCP has diminished as its incidence has declined.

Gallium scan has been used to assist in the diagnosis of PCP. However, pulmonary uptake of gallium indicates lung inflammation and is not specific for *P. jirovecii* infection. In addition, patients with mild PCP may have minimal or no uptake. This test may be useful in patients with baseline chronic lung disease with abnormal baseline blood gases and who have worsening respiratory symptoms.

Generally, the yield of organisms is reduced after initiation of effective therapy. Diagnostic specimens should be obtained within 72 hours of initiating presumptive therapy. Empiric treatment for mild disease may be reasonable for patients for whom adherence to therapy and close clinical follow-up can be ensured. In most cases, however, a definitive diagnosis should be sought. Definitive diagnosis is especially important for patients in whom a diagnosis of PCP

would be an AIDS-defining illness, when adjunctive steroids are indicated, and for patients without an alternative diagnosis who did not respond to empiric treatment for PCP.

C. Treatment

RECOMMENDATIONS:

Clinicians should treat PCP with trimethoprim/sulfamethoxazole administered either parenterally or orally, depending on the severity of the illness and likelihood of adherence. A total of 21 days of therapy should be completed. Dosing regimens are listed in Table 1. (I)

Clinicians should hospitalize patients with severe disease, as defined by initial room air pO₂ of <70 mmHg or an arterial-alveolar oxygen gradient of >35 mmHg, and administer parenteral treatment with the most effective agent and steroids. (I)

If PCP fails to improve within 7 to 10 days of treatment, clinicians should consider an alternative diagnosis and a change in PCP therapy, generally from trimethoprim/sulfamethoxazole to intravenously administered pentamidine. (II)

Clinicians should administer adjunctive steroids to persons with PCP who have significant hypoxia (see Table 1). (I)

Clinicians should initiate secondary prophylaxis to prevent recurrence of PCP immediately after completion of the treatment regimen. (II)

Trimethoprim/sulfamethoxazole (TMP/SMX) provides additional activity against bacteria, which can occasionally cause mixed infection with PCP. Although intravenous pentamidine is an effective alternative for treatment of PCP, there is no oral formulation available, it possesses no antibacterial activity, and it has greater potential toxicity than TMP/SMX. For patients who are not receiving TMP/SMX, a standard antibacterial regimen for bacterial pneumonia should be used (see *Bacterial Infections*) if bacterial infection is also present or strongly suspected.

TABLE 1
TREATMENT OF PCP IN HIV-INFECTED INDIVIDUALS

Clinical Status	Preferred Regimen	Alternatives
<i>Patient acutely ill</i> <p align="center">pO₂ <70 mmHg <i>or</i> A-a gradient >35 mmHg</p>	TMP/SMX: 15 to 20 mg/kg* IV, based on TMP, divided q6h or q8h <p align="center"><i>plus</i></p> Prednisone: 40 mg PO bid, days 1-5 40 mg PO qd, days 6-10 20 mg PO qd, days 11-21	<ol style="list-style-type: none"> 1. Pentamidine isethionate: 3 to 4 mg/kg/day IV, infused over 90 minutes <p align="center"><i>plus</i></p>Prednisone as in the preferred regimen <p align="center"><i>or</i></p> 2. Clindamycin: 900 mg IV q8h† <p align="center"><i>plus</i></p>Primaquine base: 15 to 30 mg PO qd <p align="center"><i>plus</i></p>Prednisone as in the preferred regimen
<i>Patient able to take medication orally</i> <p align="center">pO₂ ≥70 mmHg <i>or</i> A-a gradient ≤35 mmHg</p>	TMP/SMX: 15 to 20 mg/kg qid based on weight	<ol style="list-style-type: none"> 1. Dapsone: 100 mg PO qd‡ <p align="center"><i>plus</i></p>TMP: 5 mg/kg tid <p align="center"><i>or</i></p> 2. Clindamycin: 450 mg PO q8h <p align="center"><i>plus</i></p>Primaquine: 15 mg base PO qd <p align="center"><i>or</i></p> 3. Atovaquone suspension: 750 mg PO bid (with a fatty meal to maximize absorption)

* The dose of 15 mg /kg is as effective as the dose of 20 mg/kg and has less hematological toxicity.

† The efficacy of clindamycin has not been established for the treatment of severe disease.

‡ Check G6PD screen prior to initiation. Hemolytic anemia may occur in some cases of G6PD deficiency.

More than 50% of patients who receive one of these antipneumocystis regimens have significant adverse effects (see Table 2), which usually occur 7 to 14 days after initiation of treatment. An alternative treatment (see Table 1) may be required if adverse events occur.

Although some patients with PCP will initially worsen before improvement is noted, most patients improve after 7 to 10 days of treatment. Failure to improve in this time period is an indication to switch the treatment regimen or reevaluate for an alternative diagnosis. Patients with severe disease (initial room air pO₂ of <70 mmHg and/or the A-a gradient >35 mmHg) require hospitalization, parenteral treatment with the most effective agent, and steroids. The addition of corticosteroids within 72 hours of initiating therapy in patients with significant hypoxia decreases the risk of death and the need for mechanical ventilation. Patients with mild to moderate disease, indicated by an initial room air pO₂ ≥70 mmHg and A-a gradient of ≤35 mmHg, do not require steroids and may be treated with oral regimens if appropriate.

TABLE 2
DRUG TOXICITY ASSOCIATED WITH PCP TREATMENT

TMP/SMX
Potential toxicity: Cytopenias, rash, increased serum liver enzymes, hyperkalemia, interstitial nephritis, nausea, vomiting, fever
Monitoring: CBC with differential, creatinine, serum liver enzymes, and electrolytes once or twice per week during acute therapy
Clindamycin
Potential toxicity: Nausea, diarrhea, rash, fever
Monitoring: <i>Clostridium difficile</i> toxin assay if diarrhea occurs
Dapsone
Screening before initiation: Screen G6PD prior to initiating
Potential toxicity: Hemolysis in G6PD deficiency, methemoglobinemia, rash, fever
Monitoring: Monitor CBC during routine visits and obtain haptoglobin and peripheral blood smear if hemolytic anemia is suspected
Pentamidine (iv)
Potential toxicity: Hypotension, renal insufficiency, hypoglycemia, hyperglycemia, hypocalcemia hypomagnesemia, cardiac arrhythmias, pancreatitis (can be a delayed phenomenon)
Administration: Administer over 90 minutes with a saline load
Monitoring: <ul style="list-style-type: none"> • Glucose—monitor before, daily during therapy, and after therapy (every other day may be reasonable) • Frequent electrolytes, including calcium and magnesium at least three times a week • Avoid concomitant nephrotoxic agents, including amphotericin and foscarnet. Measure blood urea nitrogen and creatinine before and daily during therapy (every other day monitoring may be reasonable unless other nephrotoxic agents are used) • CBC, differential, platelet count, and calcium—monitor before and periodically during therapy • Monitor electrocardiogram before and during treatment. If new QT prolongation or arrhythmia develops, daily cardiograms or continuous cardiac monitoring are warranted • Frequent monitoring of amylase and lipase
Primaquine
Screening before initiation: Screen G6PD prior to initiating
Potential toxicity: Thrombocytopenia, hemolysis in G6PD deficiency, methemoglobinemia
Monitoring: Monitor CBC during routine visits and obtain haptoglobin and peripheral blood smear if hemolytic anemia is suspected
Atovaquone
Potential toxicity: Rash, nausea, diarrhea, vomiting, elevated liver enzymes
Monitoring: Generally well tolerated, no laboratory monitoring required

D. Prevention

RECOMMENDATIONS:

Clinicians should initiate PCP prophylaxis in patients with CD4 cell counts <200 cells/mm³, or ≤14% of total lymphocytes, and in patients with higher CD4 counts who have a history of PCP, thrush, or unexplained constitutional symptoms of >2 weeks' duration (I).

TMP/SMX is the preferred prophylactic agent for PCP (I). See Table 3 for specific recommendations.

Clinicians should discontinue primary and secondary PCP prophylaxis when patients have responded to HAART with a sustained CD4 cell count of ≥200 cells/mm³ for ≥3 months. (I)

PCP has become a relatively uncommon respiratory infection in patients with advanced HIV disease who are receiving prophylaxis. Current prophylactic medications vary in their ability to prevent PCP; however, TMP/SMX is clearly the most effective. Although several dosage recommendations exist for TMP/SMX, daily rather than thrice-weekly dosing is most often successfully maintained by the patient. Daily TMP/SMX is the only prophylactic regimen for which breakthrough with PCP rarely occurs even when CD4 counts decline to <50 cells/mm³.

TABLE 3 PROPHYLACTIC REGIMENS FOR PCP	
Drug	Dose
TMP/SMX* (preferred)	1 DS tablet daily† <i>or</i> 1 SS tablet daily <i>or</i> 1 DS tablet three times/week
Dapsone‡	100 mg PO qd <i>or</i> 50 mg PO daily <i>plus</i> pyrimethamine 50 mg weekly <i>plus</i> leucovorin 25 mg PO weekly§ <i>or</i> 200 mg <i>plus</i> pyrimethamine 75 mg <i>plus</i> leucovorin 25 mg weekly
Atovaquone¶	1500 mg PO qd (or 750 mg bid)
Pentamidine isethionate (aerosolized pentamidine)	300 mg in 6 cc sterile water via Respirgard II nebulizer once a month

DS, double strength; SS, single strength.

* There is an increased risk of prophylaxis failure with advancing immunosuppression, especially for non-TMP/SMX regimens.

† 1 DS tablet TMP/SMX is effective for prophylaxis against toxoplasmosis as well. Lower doses might also provide such protection.

‡ Exclude G6PD deficiency before initiating. Hemolytic anemia may occur in some cases of G6PD deficiency.

§ This regimen is effective prophylaxis against toxoplasmosis in individuals who are intolerant to TMP/SMX.

¶ Results from CPCRA/ACTG 277 showed that atovaquone in suspension, at the dose of 1500 mg PO daily is comparable to dapsone for PCP prophylaxis. No overall differences in the rate of adverse effects were noted in this study. Although some patients may better tolerate dapsone, the relative risk for discontinuation was greater with this agent than with atovaquone. Atovaquone is significantly more expensive.

The occurrence of rash is an adverse effect of TMP/SMX. Mild rash should be tolerated; symptomatic treatment with antihistamines may be useful prior to each dose. Desensitization to sulfa, using a dose-escalation regimen of TMP/SMX over a period of 10 to 14 days, has been shown to help patients better tolerate the drug. This method is safe and effective in approximately 50% of patients with previous mild TMP/SMX rash without previous Stevens-Johnson syndrome or other systemic symptoms such as fever or hepatitis. Dapsone is a safe and well-tolerated alternative for most patients with mild to moderate TMP/SMX-associated rash.

II. *TOXOPLASMA GONDII*

A. Presentation

Toxoplasma gondii, a protozoan found throughout the world, is acquired through ingestion of oocysts from contaminated soil, inadequately cooked meat, or cat feces. With primary infection, which is generally asymptomatic, trophozoites disseminate to tissues including the brain, muscle, and retina, where they subsequently encyst. Symptomatic toxoplasmosis is usually seen only in patients with advanced HIV disease. Toxoplasma encephalitis is the most common manifestation of reactivation and most often presents as sudden or gradual onset of a local neurologic abnormality, such as new onset of seizure, focal weakness, or speech deficit. Alternatively, it may present as a change in personality or cognitive status. Contrast CT scans generally reveal multiple ring-enhancing lesions scattered throughout the brain, located at the junction of the white and gray matter, often with associated mass effect. Contrast-enhanced MRI is often a more sensitive imaging modality. *Toxoplasma* retinitis is an infrequent complication.

B. Diagnosis

RECOMMENDATIONS:

Although the definitive diagnosis of toxoplasma encephalitis requires a brain biopsy, clinicians should use the following presumptive criteria to diagnose cerebral toxoplasmosis (II):

- **Multiple ring-enhancing central nervous system mass lesions demonstrated by an imaging study; MRI is more sensitive than a contrast-enhanced CT scan**
- **Positive serum IgG to *T. gondii***
- **CD4 count <100 cells/mm³**
- **Lack of toxoplasmosis prophylaxis**

Clinicians should consider alternative diagnoses if there is an absence of serum IgG antibodies to *T. gondii*. (III)

Clinicians should obtain a brain biopsy to establish a definitive diagnosis if the patient fails to clinically and radiographically respond to therapy within 10 to 14 days or the presentation is unusual enough to make the diagnosis uncertain. (III)

Most cases of toxoplasmosis in persons with AIDS occur in individuals with serum antibodies to *T. gondii*. A negative IgG serum antibody result is uncommon in a patient with reactivated toxoplasmosis and should prompt the clinician to consider alternative diagnoses that explain the clinical presentation. If available, DNA amplification testing of cerebrospinal fluid for evidence of *T. gondii* DNA may support the diagnosis of toxoplasmosis.

The differential diagnosis of CNS mass lesions is broad and includes primary CNS lymphoma and pyogenic brain abscess. Positron emission tomography (PET) or thallium-201 single-photon emission CT (TI-201 SPECT) may help to differentiate toxoplasma encephalitis lesions from lymphoma. Uptake of glucose and methionine on PET scans and of thallium on SPECT scans is generally greater in the setting of lymphoma than toxoplasmosis. However, false-positive scans have been reported in partially treated lesions, particularly in lesions near areas of normally high activity, such as base of skull or scalp. The value of TI-201 in patients receiving HAART may be reduced due to an increase in uptake in patients receiving medications regardless of the etiology of the lesions. This decrease in positive predictive value suggests that in patients receiving HAART, this test should be combined with other diagnostic modalities.

PET uses other highly specific radiolabeled substrates such as fluorodeoxyglucose (FDG PET). Increased activity (glycolysis) occurs in lymphoma lesions, whereas toxoplasmosis is characterized by cold lesions (decreased activity). Progressive multifocal leukoencephalopathy is a nonmalignant lesion that can cause increased metabolic activity, but this is relatively uncommon (8%) and has a characteristic radiologic appearance. PCR for toxoplasma can be performed in the cerebrospinal fluid if there are no contraindications for a lumbar puncture. In the setting of primary CNS lymphomas, PCR for Epstein-Barr virus is often positive in the cerebral spinal fluid.

C. Treatment

RECOMMENDATION:

Clinicians should continue acute therapy for toxoplasmosis until there is clinical improvement and radiographic evidence of reduction in size and number of lesions (for 4 to 6 weeks) and should follow with suppressive therapy. (III)

Patients may require adjuvant treatment with corticosteroids to reduce accompanying brain edema. Antiseizure medications may also be required.

TABLE 4 TREATMENT OF ACUTE TOXOPLASMOSIS IN HIV-INFECTED PATIENTS	
Preferred regimen	Alternative
Sulfadiazine 1-1.5 g PO q6h <i>plus</i> Pyrimethamine 200 mg PO loading dose followed by 50-100 mg PO qd <i>plus</i> Leucovorin 10-20 mg PO qd	<ol style="list-style-type: none"> Clindamycin 600-1200 mg IV q12h <i>plus</i> Pyrimethamine 200 mg PO loading dose followed by 50-100 mg PO qd <i>plus</i> Leucovorin 10-20 mg PO qd <i>or</i> 2. Pyrimethamine 200 mg PO loading dose followed by 50-100 mg PO qd <i>plus</i> Leucovorin 10-20 mg PO qd <i>plus</i> Azithromycin 1200-1500 mg/day <i>or</i> Clarithromycin 500-1000 mg/day <i>or</i> Atovaquone 750 mg qid

TABLE 5 PREVENTION OF RECURRENT TOXOPLASMOSIS IN HIV-INFECTED PATIENTS	
Preferred Regimen	Alternative
Sulfadiazine 1 g PO bid <i>plus</i> Pyrimethamine 50 mg PO qd <i>plus</i> Leucovorin 10 mg PO qd	<ol style="list-style-type: none"> Clindamycin 300 mg PO q6h <i>plus</i> Pyrimethamine 50 mg PO qd <i>plus</i> Leucovorin 10 mg PO qd 2. Sulfadiazine 1 g PO bid <i>plus</i> Pyrimethamine 50 mg PO <i>plus</i> Leucovorin 10 mg PO Entire regimen given thrice weekly 3. Atovaquone 750 mg bid or qid

D. Prevention

RECOMMENDATIONS:

Clinicians should initiate prophylaxis for toxoplasmosis when a patient's CD4 count decreases to <100 cells/mm³ and the patient is toxoplasma IgG positive (I). TMP/SMX is the preferred prophylactic agent for toxoplasmosis (I).

Clinicians should discontinue primary toxoplasmosis prophylaxis when patients have responded to HAART with a sustained (≥ 3 months) increase in CD4 cell count (>200 cells/mm³). (I)

Clinicians should counsel HIV-infected toxoplasma-seronegative patients to avoid undercooked meats and to carefully wash hands after handling cat litter boxes and after gardening. (III)

Although less common than PCP, toxoplasma encephalitis is an extremely serious clinical condition that may be prevented in the toxoplasma-seropositive individual by the use of prophylactic antibiotics. Toxoplasma-seronegative individuals should be counseled to avoid undercooked meat and to carefully wash their hands after handling cat litter boxes and after gardening. When possible, cat owners should have litter boxes changed by a non-HIV-infected, non-pregnant individual.

Medication	Dose
TMP/SMX	1 DS PO daily (preferred) <i>or</i> 1 SS PO daily
Dapsone* <i>plus</i> Pyrimethamine <i>plus</i> Leucovorin	50 mg PO daily 50 mg PO weekly 25 mg PO weekly
Dapsone* <i>plus</i> Pyrimethamine <i>plus</i> Leucovorin	200 mg weekly 75 mg weekly 25 mg weekly
Atovaquone	1500 mg once a day

DS, double strength; SS, single strength.

* Exclude G6PD deficiency before initiating.

III. CRYPTOSPORIDIOSIS

A. Presentation

RECOMMENDATION:

Clinicians should include cryptosporidiosis in the differential diagnosis of diarrhea, especially large-volume diarrhea. (I)

Cryptosporidium parvum is a waterborne, foodborne, and fecally transmitted protozoan. It causes large-volume (>250 mL/day), watery diarrhea often associated with profound weight loss and prostration. Significant fever is unusual and should prompt a search for other conditions (e.g., cytomegalovirus colitis). In approximately 20% of cases of intestinal cryptosporidiosis, cholangitis also occurs.

B. Diagnosis

RECOMMENDATIONS:

Clinicians should specifically request acid-fast staining or immunofluorescent antibody testing of the stool to establish a diagnosis of cryptosporidiosis. (I)

Clinicians should specifically alert the laboratory to look for cryptosporidia if this diagnosis is suspected (III).

Diagnosis of cryptosporidiosis is established by immunofluorescence stain using monoclonal antibodies to test for the presence of antigen in the stool. Light microscopic examination of stool is less sensitive, although this latter method is readily available and also identifies pathogens other than cryptosporidia. The laboratory should be specifically alerted to look for cryptosporidia if this diagnosis is suspected. Cryptosporidiosis is reportable in New York State.

C. Treatment

RECOMMENDATION:

Clinicians should prescribe a combination of paromomycin 1 g bid plus azithromycin 600 mg PO daily for 4 weeks, followed by paromomycin maintenance therapy. (III)

Treatment for cryptosporidiosis is primarily supportive and includes the use of antidiarrheal agents and electrolyte/fluid replacement. Paromomycin, an oral aminoglycoside, in doses of 250 to 500 mg qid has been shown to reduce both the excretion of cysts as well as symptoms. Azithromycin 1250 mg PO daily, nitazoxanide 0.5 to 1.0 g PO bid, or atovaquone 750 mg PO bid have been reported as alternative effective treatments for a minority of patients. Refractory diarrhea may prompt a trial of octreotide 100 to 500 µg SC tid for symptomatic relief, although the efficacy of this agent has not been established.

D. Prevention

RECOMMENDATION:

Clinicians should counsel patients to:

- **Avoid contact with human and animal feces, pets with diarrhea, dogs or cats <6 months of age**
- **Avoid drinking water from lakes, streams, or rivers, unless it has been adequately boiled**
- **Boil water for 1 minute when public health agencies issue a boil-water advisory during waterborne outbreaks of cryptosporidiosis**

Swimming (including in pools) and consumption of tap water may pose a small risk of acquiring cryptosporidiosis.

IV. *ISOSPORA BELLI*

A. Presentation

Isospora belli, another protozoan cause of watery diarrhea, is predominantly seen in patients living outside of the United States or in individuals from developing countries. Because this organism is found only in humans, the mode of dissemination is thought to be enteric through fecal-oral transmission and through contamination of food and water.

B. Diagnosis

RECOMMENDATION:

Because *Isospora belli* is shed intermittently in the stool, clinicians should request multiple stool specimens for modified acid-fast stool staining. (I)

Peripheral blood eosinophilia in the setting of diarrhea suggests the possibility of *I. belli*.

C. Treatment

RECOMMENDATIONS:

Clinicians should treat *Isospora belli* with TMP/SMX DS PO four times daily for at least 10 days. (I)

Clinicians should consider using pyrimethamine 50 to 75 mg/day for 10 days in patients allergic to sulfa, followed by leucovorin 5 to 10 mg/day. (III)

Clinicians should consider discontinuing isosporiasis prophylaxis for patients who are asymptomatic and have sustained CD4 >200 cells/mm³ for ≥3 months. (III)

Isosporiasis is associated with a high-relapse rate when treatment is stopped. Recurrent disease can be prevented with suppressive TMP/SMX DS PO three times weekly.

V. MICROSPORIDIA SPECIES

A. Presentation

Microsporidia organisms cause prolonged watery diarrhea in persons with advanced HIV disease and occasionally disseminate to other organs, especially conjunctiva and cornea with *Encephalitozoon* species.

B. Diagnosis

The routine diagnostic stool evaluation is often negative. Small (1-2 μm in diameter) gram-positive spores, according to Gram, Brown-Hopps, or modified Warthin-Starry stain, can be visualized in intestinal tissue specimens and in concentrated stool specimens as well. Electron microscopy of biopsy material may increase diagnostic yield.

C. Treatment

Albendazole 400 mg PO bid may control symptoms but does not eradicate the parasite.

VI. CYCLOSPORA

Cyclospora is an intracellular parasite that shares the subclass Coccidia with *Cryptosporidium*, *Isospora*, and *Toxoplasma*.

Infection with *Cyclospora* has been reported worldwide, and it is endemic in Nepal, Haiti, and Peru. The prevalence of *Cyclospora* infections in the United States is unknown. Most documented cases in the United States are seen in overseas travelers. *Cyclospora* is transmitted by ingestion of oocysts that occur as a result of fecal contamination. It is unknown whether animals or humans serve as sources of infection for humans. Transmission via contaminated drinking water has been implicated in two outbreaks. Reports have suggested an association between eating fresh fruits, raspberries in particular, and clinical illness.

A. Presentation

The incubation period for cyclosporiasis ranges from 1 to 11 days. In patients with AIDS, chronic unremitting or relapsing diarrhea is a common presentation. Nausea, vomiting, bloating, anorexia, and weight loss may also be present. Additionally, cholangitis has been reported.

B. Diagnosis

RECOMMENDATION:

Clinicians should base the diagnosis of cyclosporiasis on microscopic detection of oocysts in stool. (I)

Like *Cryptosporidium* and *Isospora*, *Cyclospora* oocysts are acid fast; thus identification is facilitated by using acid-fast techniques. These techniques, however, are not very sensitive and require a laboratory technician with expertise to identify the parasite.

C. Treatment

RECOMMENDATION:

Clinicians should prescribe oral TMP/SMX 160 mg/800 mg four times a day for 10 days, followed by secondary prophylaxis with TMP/SMX three times a week to treat *Cyclospora* infection in HIV-infected patients. (I)

VII. GIARDIA

Giardia lamblia is a flagellated protozoan that may cause diarrheal illness (giardiasis). Giardiasis is perhaps the most commonly reported parasitic infection in the United States. Although usually waterborne, it may also be transmitted by contaminated uncooked foods or by person-to-person contact in families, nurseries, and daycare centers. This protozoan may also be transmitted by sexual practices that enable fecal-oral transmission.

A. Presentation

The incubation period ranges from 1 to 8 weeks, and symptoms often precede fecal shedding of the parasites. The most characteristic symptoms include diarrhea of more than 10 days' duration, cramping, bloating, flatulence, and weight loss. Nausea, vomiting, and fever may also occur. *Giardia*-induced diarrhea is usually noninflammatory, with only rare tissue invasion; however, proctitis and vaginitis with this organism have been described.

B. Diagnosis

Giardia is often diagnosed by examining one to three fresh or concentrated stool specimens. A monoclonal antibody reagent for direct fluorescence detection of *Giardia* cysts has high

sensitivity and specificity and is usually used instead of the direct stool examination. A monoclonal antibody combination reagent for direct fluorescence detection of *Giardia* and *Cryptosporidium* is often available and used as a diagnostic tool for these two entities. Differentiation between both protozoans is based on size.

C. Treatment

RECOMMENDATIONS:

Clinicians should treat *Giardia* with metronidazole 250 mg PO tid for 5 to 10 days. (I)

Clinicians should educate *Giardia*-infected patients regarding improved hygienic measures. (III)

Single doses of metronidazole of 1.6 to 2 g for 2 to 3 days may be as effective as 250 mg tid for 5 to 10 days but may cause more gastrointestinal side effects. Other nitroimidazole derivatives, including tinidazole (2 g PO qd), are effective and have fewer side effects.

VIII. AMEBIASIS

Amebiasis is caused by pathogenic strains of *Entamoeba histolytica*. This protozoan is acquired through fecal-oral contamination and may occur by waterborne or foodborne transmission, as well as by person-to-person transmission. It is endemic in many countries in the developing world, particularly in the tropics, causing both intestinal and extraintestinal disease. Outbreaks also occur in the developed world, particularly among men who have sex with men, institutionalized individuals, and travelers returning from endemic areas.

A. Presentation

The clinical manifestations of intestinal amebiasis are usually of gradual onset (1-3 weeks). Symptoms vary from mild diarrhea, sometimes alternating with constipation, to severe invasive intestinal disease causing rectocolitis with visible blood and mucus in the stool, tenesmus, abdominal pain, and fever. Colonic perforation can also occur. Fulminant disease may be seen in patients who are debilitated or receiving corticosteroids.

Trophozoites may travel through the portal vein, causing necrosis of the liver and leading to abscess formation. Amebic liver abscesses often cause prolonged fevers, malaise, anorexia, and weight loss. Dull right, upper-quadrant pain may also be present. Concomitant diarrhea is uncommon, but cysts may be found in stool. Dissemination to the lungs may occur as a result of rupture of liver abscess and erosion through the diaphragm. Spread to the genitourinary tract may result in fistula formation. Cerebral amebiasis has also been described.

B. Diagnosis

RECOMMENDATION:

Clinicians should obtain at least three stool specimens before excluding the diagnosis of amebiasis. (II)

1. Intestinal Amebiasis

The identification of motile trophozoites in fresh stool samples is characteristic of intestinal amebiasis. However, unless trophozoites are observed with ingested red blood cells, it is difficult to differentiate, based on morphology alone, the pathogenic *E. histolytica* from the nonpathogenic *E. dispar*. A single stool sample may only diagnose one-third of infected patients. Therefore, serial stool samples are often required to establish the diagnosis. Antigen testing, PCR, and immunoassay techniques allow proper identification of pathogenic amoebas. The presence of trophozoites may coincide with the presence of cysts, especially in endemic areas. Endoscopy may be needed to establish the diagnosis if *E. histolytica* is suspected but the stool examination is negative or if there is need for prompt diagnosis.

Cysts may be seen in asymptomatic individuals and commonly are secondary to *E. dispar*. It is crucial to distinguish amebiasis from acute exacerbation of inflammatory bowel disease because treatment with corticosteroids exacerbates intestinal amebiasis.

2. Extraintestinal Amebiasis

Amebic liver abscess is usually diagnosed with the use of abdominal ultrasound or tomography. Single lesions on the right lobe of the liver are frequent. Elevated alkaline phosphatase is common and mild transaminitis may also be seen. Typically, the erythrocyte sedimentation rate is markedly elevated. Fine-needle aspiration under ultrasound guidance yields yellow-brown odorless fluid that is usually sterile. Amebic serology is almost always positive.

C. Treatment

RECOMMENDATIONS:

Clinicians should initiate treatment of *E. histolytica* when trophozoites with ingested red blood cells are present in the stool. One of the following regimens should be used (II):

- metronidazole 750 mg tid for 10 days or 2.4 g qd for 3 days
- tinidazole 2 g PO qd for 3 days followed by paromomycin 500 mg tid for 7 days
- iodoquinol 650 mg tid for 20 days

Clinicians should treat patients with asymptomatic *E. histolytica* infection with one of the following regimens (II):

- paromomycin 500 mg tid for 7 days
- iodoquinol 650 mg tid for 20 days

- **diloxanide furoate 500 mg tid for 10 days**

Clinicians should treat extraintestinal disease with metronidazole 750 mg tid for 10 days or 2.4 g qd for 3 days (II).

Patients presenting with clinical symptoms and positive stool examinations showing trophozoites with ingested red blood cells should be treated with either metronidazole (750 mg tid for 10 days or 2.4 g qd for 3 days) or tinidazole 2 g PO qd for 3 days followed by paromomycin 500 mg tid for 7 days or iodoquinol 650 mg tid for 20 days.

Asymptomatic cyst passers should be treated because of the potential for invasive disease and risk of transmission to others. Paromomycin 500 mg tid for 7 days, iodoquinol 650 mg tid for 20 days, or diloxanide furoate 500 mg tid for 10 days should be used.

Extraintestinal disease should be treated with metronidazole (750 mg tid for 10 days or 2.4 g qd for 3 days). Needle aspiration of liver abscess is not necessary for treatment, but aspiration may be used to aid in the diagnosis. Aspiration has also been used to drain large liver abscess of the left lobe to prevent rupture into the pericardium.

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